# WHO 2022 Update on the Classifications of Prostate Cancer

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**University of Alabama at Birmingham**

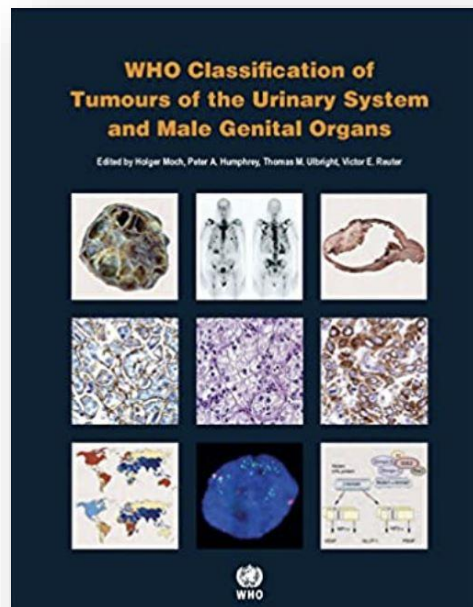# WHO Classification of the Urinary and Male Genital Tumours
## *5th edition series*

- WHO *5th edition series* **structural reorganization**

- Refinements of **terminology** and **classification**

- Precursor lesions **(HGPIN; IDC-P; AIP)**

- **Grading / computational pathology (AI)**

- Advances in **molecular pathways** (targets of therapy)

# WHO Classification of the Urinary and Male Genital Tumours
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**WHO Classification of Tumours of the Urinary System and Male Genital Organs**

Edited by Holger Moch, Peter A. Humphrey, Thomas M. Ulbright, Victor E. Reuter

*Tumours of the prostate*

| | |
|---|---|
| **Epithelial tumours** | |
| *Glandular neoplasms* | |
| Acinar adenocarcinoma | 8140/3 |
|   Atrophic | |
|   Pseudohyperplastic | |
|   Microcystic | |
|   Foamy gland | |
|   Mucinous (colloid) | 8480/3 |
|   Signet ring–like cell | 8490/3 |
|   Pleomorphic giant cell | |
|   Sarcomatoid | 8572/3 |
| Prostatic intraepithelial neoplasia, high-grade | 8148/2 |
| Intraductal carcinoma | 8500/2 |
| Ductal adenocarcinoma | 8500/3 |
|   Cribriform | 8201/3 |
|   Papillary | 8260/3 |
|   Solid | 8230/3 |
| Urothelial carcinoma | 8120/3 |
| *Squamous neoplasms* | |
|   Adenosquamous carcinoma | 8560/3 |
|   Squamous cell carcinoma | 8070/3 |
| Basal cell carcinoma | 8147/3 |
| | |
| **Neuroendocrine tumours** | |
| Adenocarcinoma with neuroendocrine differentiation | 8574/3 |
| Well-differentiated neuroendocrine tumour | 8240/3 |
| Small cell neuroendocrine carcinoma | 8041/3 |
| Large cell neuroendocrine carcinoma | 8013/3 |
| | |
| **Mesenchymal tumours** | |
| Stromal tumour of uncertain malignant potential | 8935/1 |
| Stromal sarcoma | 8935/3 |
| Leiomyosarcoma | 8890/3 |
| Rhabdomyosarcoma | 8900/3 |
| Leiomyoma | 8890/0 |
| Angiosarcoma | 9120/3 |
| Synovial sarcoma | 9040/3 |
| Inflammatory myofibroblastic tumour | 8825/1 |
| Osteosarcoma | 9180/3 |
| Undifferentiated pleomorphic sarcoma | 8802/3 |
| Solitary fibrous tumour | 8815/1 |
| Solitary fibrous tumour, malignant | 8815/3 |
| Haemangioma | 9120/0 |
| Granular cell tumour | 9580/0 |
| | |
| **Haematolymphoid tumours** | |
| Diffuse large B-cell lymphoma | 9680/3 |
| Chronic lymphocytic leukaemia / small lymphocytic lymphoma | 9823/3 |
| Follicular lymphoma | 9690/3 |
| Mantle cell lymphoma | 9673/3 |

| | |
|---|---|
| Acute myeloid leukaemia | 9861/3 |
| B lymphoblastic leukaemia/lymphoma | 9811/3 |
| | |
| **Miscellaneous tumours** | |
| Cystadenoma | 8440/0 |
| Nephroblastoma | 8960/3 |
| Rhabdoid tumour | 8963/3 |
| Germ cell tumours | |
| Clear cell adenocarcinoma | 8310/3 |
| Melanoma | 8720/3 |
| Paraganglioma | 8693/1 |
| Neuroblastoma | 9500/3 |
| | |
| **Metastatic tumours** | |

*Tumours of the seminal vesicles*

| | |
|---|---|
| **Epithelial tumours** | |
| Adenocarcinoma | 8140/3 |
| Squamous cell carcinoma | 8070/3 |
| | |
| **Mixed epithelial and stromal tumours** | |
| Cystadenoma | 8440/0 |
| | |
| **Mesenchymal tumours** | |
| Leiomyoma | 8890/0 |
| Schwannoma | 9560/0 |
| Mammary-type myofibroblastoma | 8825/0 |
| Gastrointestinal stromal tumour, NOS | 8936/1 |
| Leiomyosarcoma | 8890/3 |
| Angiosarcoma | 9120/3 |
| Liposarcoma | 8850/3 |
| Solitary fibrous tumour | 8815/1 |
| Haemangiopericytoma | 9150/1 |
| | |
| **Miscellaneous tumours** | |
| Choriocarcinoma | 9100/3 |
| Seminoma | 9061/3 |
| Well-differentiated neuroendocrine tumour / carcinoid tumour | 8240/3 |
| Lymphomas | |
| Ewing sarcoma | 9364/3 |
| | |
| **Metastatic tumours** | |

The morphology codes are from the International Classification of Diseases for Oncology (ICD-O) {917A}. Behaviour is coded /0 for benign tumours; /1 for unspecified, borderline, or uncertain behaviour; /2 for carcinoma in situ and grade III intraepithelial neoplasia; and /3 for malignant tumours. The classification is modified from the previous WHO classification {756A}, taking into account changes in our understanding of these lesions.

## WHO Classification of the Urinary and Male Genital Tumours
### 4th edition series

*Tumours of the prostate*

**Epithelial tumours**
*Glandular neoplasms*
Acinar adenocarcinoma — 8140/3
  Atrophic
  Pseudohyperplastic
  Microcystic
  Foamy gland
  Mucinous (colloid) — 8480/3
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Acute myeloid leukaemia — 9861/3
B lymphoblastic leukaemia/lymphoma — 9811/3

**Miscellaneous tumours**
Cystadenoma — 8440/0
Nephroblastoma — 8960/3
Rhabdoid tumour — 8963/3
Germ cell tumours
Clear cell adenocarcinoma — 8310/3
Melanoma — 8720/3
Paraganglioma — 8693/1
Neuroblastoma — 9500/3

**Metastatic tumours**

*Tumours of the seminal vesicles*

**Epithelial tumours**
Adenocarcinoma — 8140/3
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**Mixed epithelial and stromal tumours**
Cystadenoma — 8440/0

**Mesenchymal tumours**
Leiomyoma — 8890/0
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**Miscellaneous tumours**
Choriocarcinoma — 9100/3
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Lymphomas
Ewing sarcoma — 9364/3

**Metastatic tumours**

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## WHO Classification of the Urinary and Male Genital Tumours
### 5th edition series

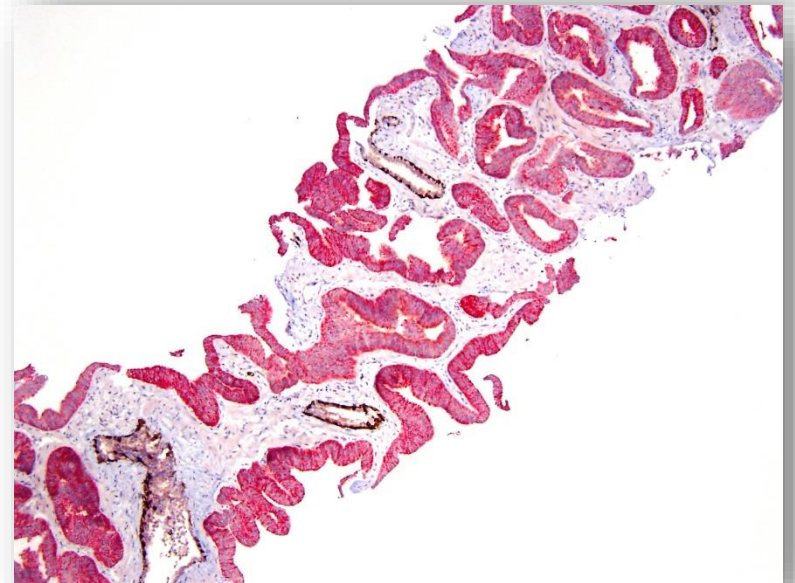| | |
|---|---|
| *Tumours of the prostate* | 6.0 |
| Introduction | 6.0.0.1 |
| **Epithelial tumours of the prostate** | |
| Glandular neoplasms of the prostate | |
| Prostatic cystadenoma | 6.1.1.6 |
| High-grade prostatic intraepithelial neoplasia | 6.1.1.1 |
| Intraductal carcinoma of the prostate | 6.1.1.2 |
| Prostatic acinar adenocarcinoma | 6.1.1.3 |
| Prostatic ductal adenocarcinoma | 6.1.1.4 |
| Treatment-related neuroendocrine prostatic carcinoma | 6.1.1.5 |
| Squamous neoplasms of the prostate | |
| Adenosquamous carcinoma of the prostate | 6.1.2.1 |
| Squamous cell carcinoma of the prostate | 6.1.2.2 |
| Adenoid cystic (basal cell) carcinoma of the prostate | 6.1.2.3 |
| Mesenchymal tumours unique to the prostate | |
| Stromal tumours of the prostate | |
| Prostatic stromal tumour of uncertain malignant potential | 6.2.1.1 |
| Prostatic stromal sarcoma | 6.2.1.2 |
| | |
| *Tumours of the seminal vesicle* | 15.0 |
| Tumours of the seminal vesicle: Introduction | 15.0.0.1 |
| Epithelial tumours of the seminal vesicle | |
| Glandular neoplasms of the seminal vesicle | |
| Cystadenoma of the seminal vesicle | 15.1.1.1 |
| Adenocarcinoma of the seminal vesicle | 15.1.1.2 |
| Squamous neoplasms of the seminal vesicle | |
| Squamous cell carcinoma of the seminal vesicle | 15.1.2.1 |
| Other tumours of the seminal vesicle | |
| Mixed epithelial and stromal tumours of the seminal vesicle | 15.2.0.1 |

# WHO Classification of the Urinary and Male Genital Tumours
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- WHO *5th edition series* **structural reorganization**

- Refinements of **terminology** and **classification**

- Precursor lesions **(HGPIN; IDC-P; IAP)**

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WHO Classification of the Urinary and Male Genital Tumours
5th edition series

**Terminology scheme across the WHO 5th edition**:

- *The term **"subtype"** to replace **"variant"** for a distinct clinical or morphologic category within a **tumour type***
- *The term **"variant"** is reserved for **genomic rather than morphologic** alterations*

Subtypes of prostate acinar adenocarcinoma are **morphologically distinct and have prognostic significance** (management implications)

| **WHO URO 4** | **WHO URO 5** |
|---|---|
| **Epithelial tumours**<br>*Glandular neoplasms*<br><br>Acinar adenocarcinoma<br><br>*Histologic Variants*<br>Atrophic variant<br>Pseudohyperplastic variant<br>Microcystic variant<br>Foamy gland variant<br>Mucinous (colloid) variant<br>Signet ring-like cell variant<br>Pleomorphic giant cell variant<br>Sarcomatoid variant | **Epithelial tumours of the prostate**<br>*Glandular neoplasms of the prostate*<br><br>Prostatic acinar adenocarcinoma<br><br>*Unusual Histological Patterns*<br>Atrophic adenocarcinoma (including aberrant p63 +)<br>Pseudohyperplastic adenocarcinoma<br>Microcystic adenocarcinoma<br>Foamy gland adenocarcinoma<br>Mucinous (colloid) adenocarcinoma<br><br>*Subtypes*<br>Signet ring-cell like adenocarcinoma<br>Pleomorphic giant cell adenocarcinoma<br>Sarcomatoid carcinoma<br>→ PIN-like carcinoma |

## PIN-like carcinoma

- Uncommon
- Resembles **HGPIN or Ductal** adenocarcinoma:
    - large (cystic) discrete glands with flat or stubby tufts/short papillae architecture
    - pseudostratified epithelium with elongated nuclei

- DDx
  **HGPIN:** crowded glands and lack of basal cells (HMWCK/p63)
  **Ductal adenocarcinoma:** absence of complex papillae, cribriform glands or necrosis

- Generally favorable prognosis; assigned **Gleason score 3+3 = 6**
  (3+4=7 ? if thin pap projection)

- Molecular Alteration: frequent activating mutations in the **RAF/RAS pathway**

*Paulk A, Giannico G, Epstein JI. Am J Surg Pathol. 2018*
*Kaur HB .. Lotan T. Histopathology. 2021*
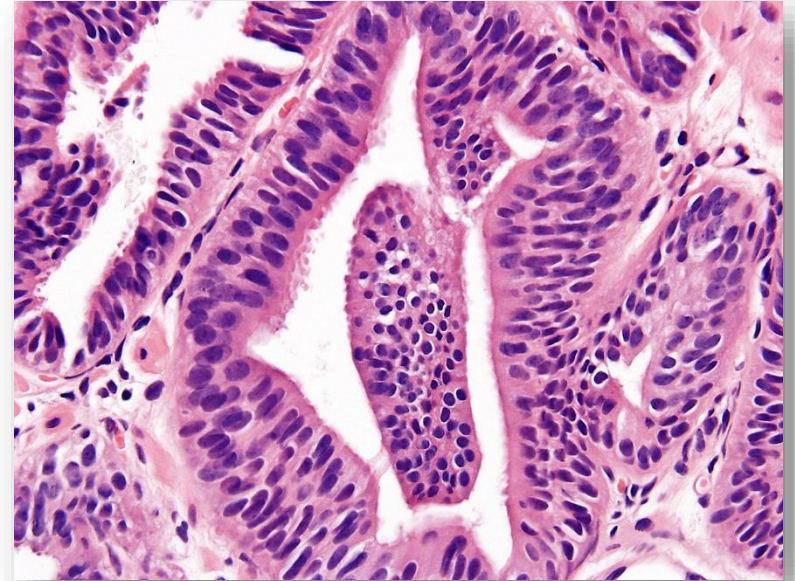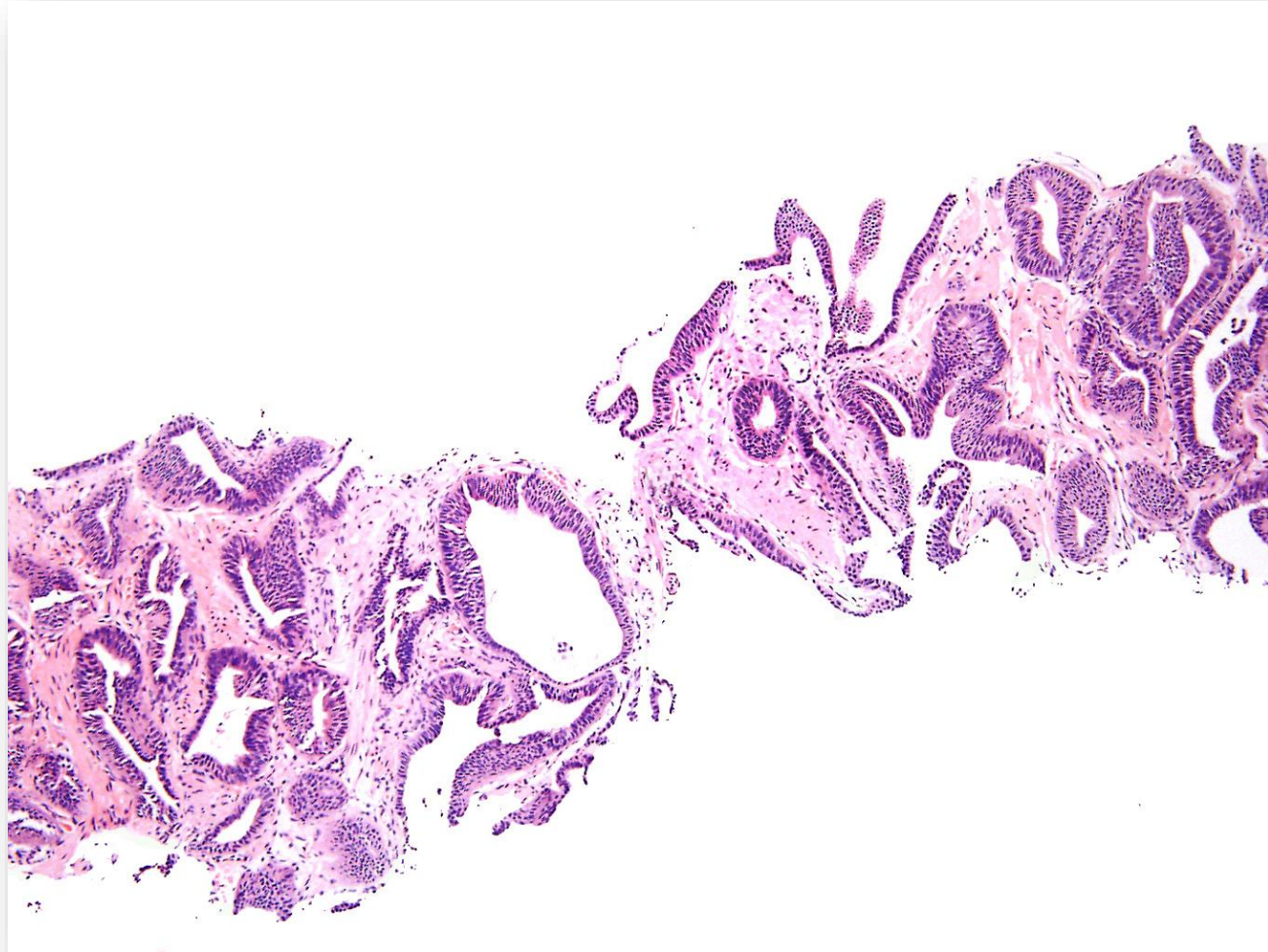
**PIN-Like Carcinoma**

**PIN-Like Carcinoma**

# Radical Prostatectomy
## PIN-Like Carcinoma

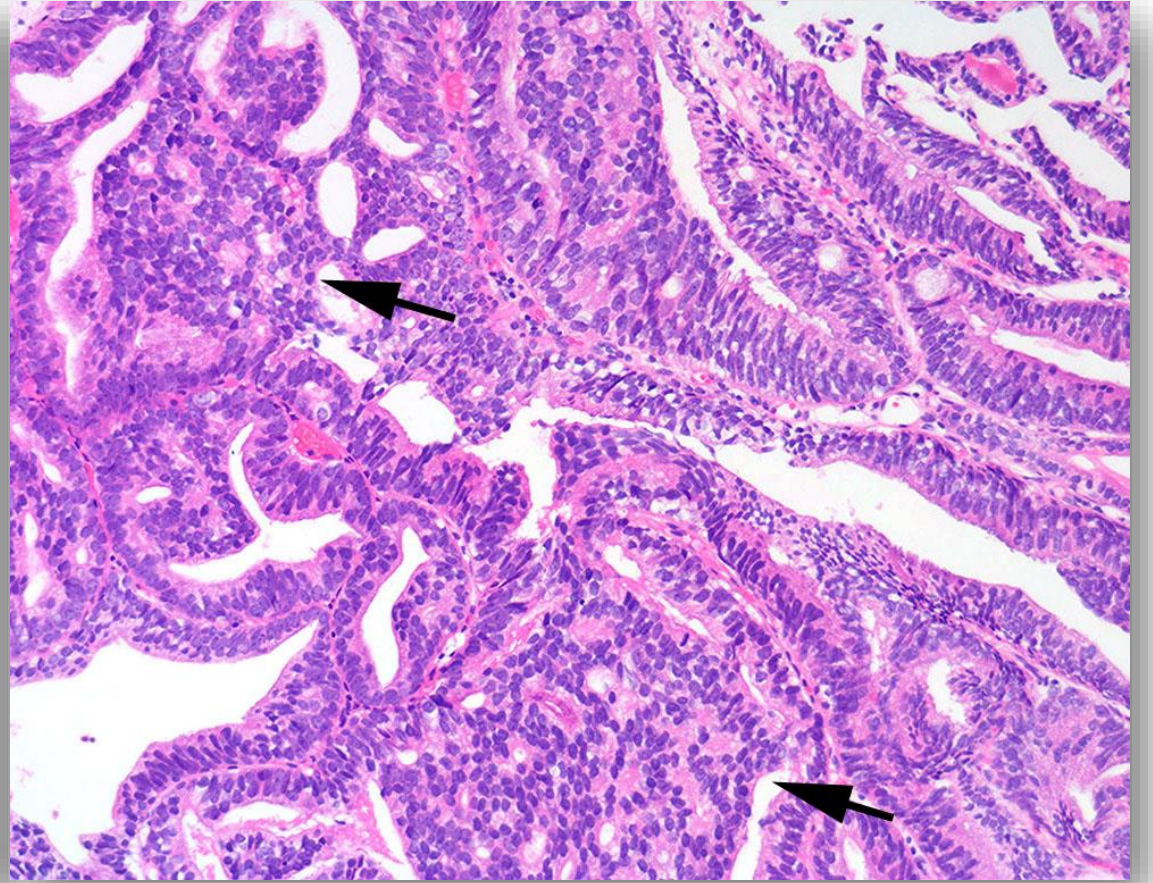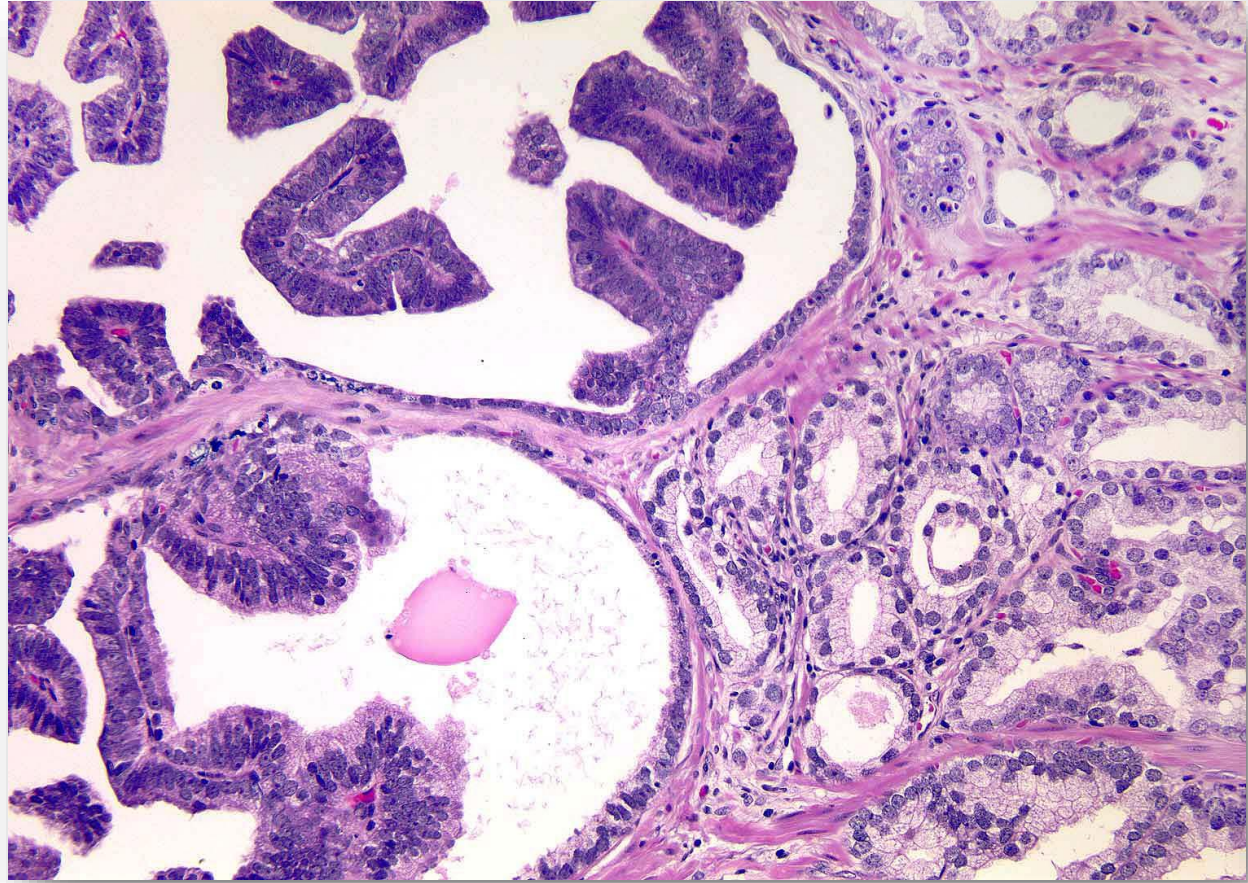# WHO Classification of the Urinary and Male Genital Tumours
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# Ductal Adenocarcinoma

**Should ductal adenocarcinoma become a subtype of acinar ?**

- Overwhelming majority **admixed** with acinar component (exception central ductal)
- Genomic studies; **clonally related** to concurrent acinar adenocarcinoma

- Relatively enriched for germline or somatic pathogenic alterations in **DNA repair genes** (HRR, MSI)
- Ductal histologic features are often preserved **in metastatic sites**

- **Reporting**
  RP: ? > 50% or pure
  NBx**:** even pure ductal should be reported as adenocarcinoma of prostate **with ductal features** (accounts for in grade)

**Consensus:** Keep ductal adenocarcinoma as a **type** of in WHO 5th edition
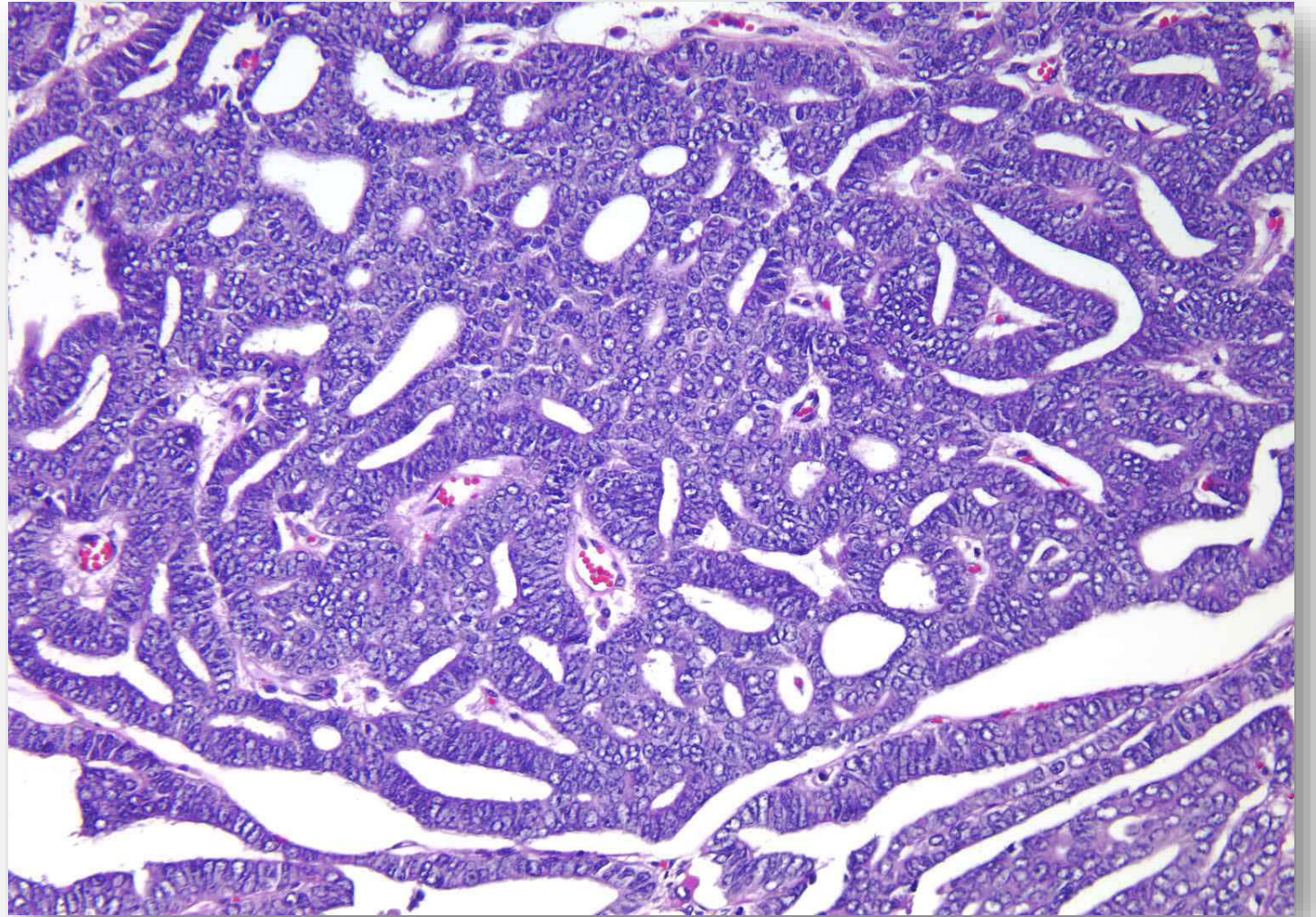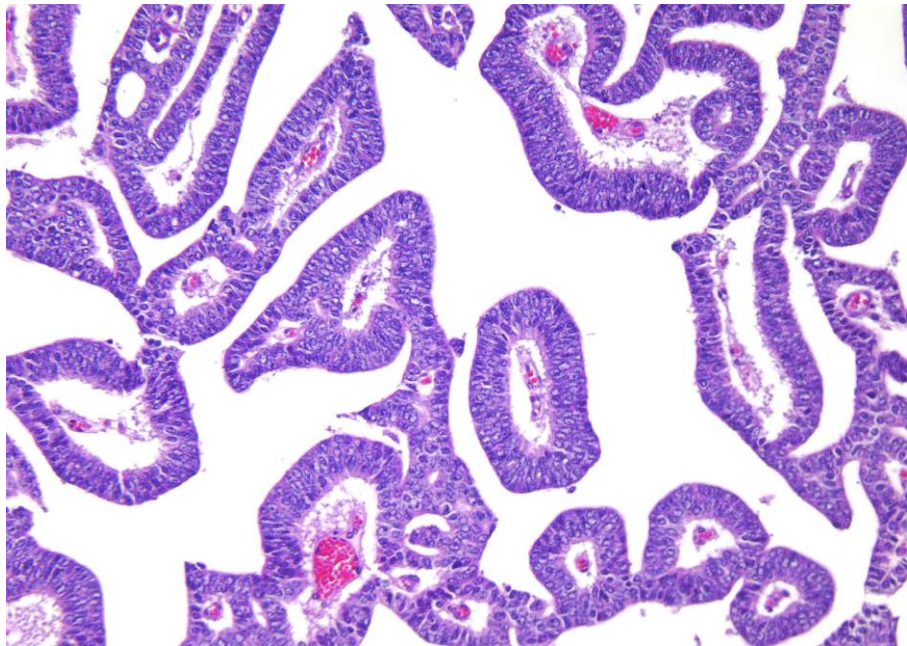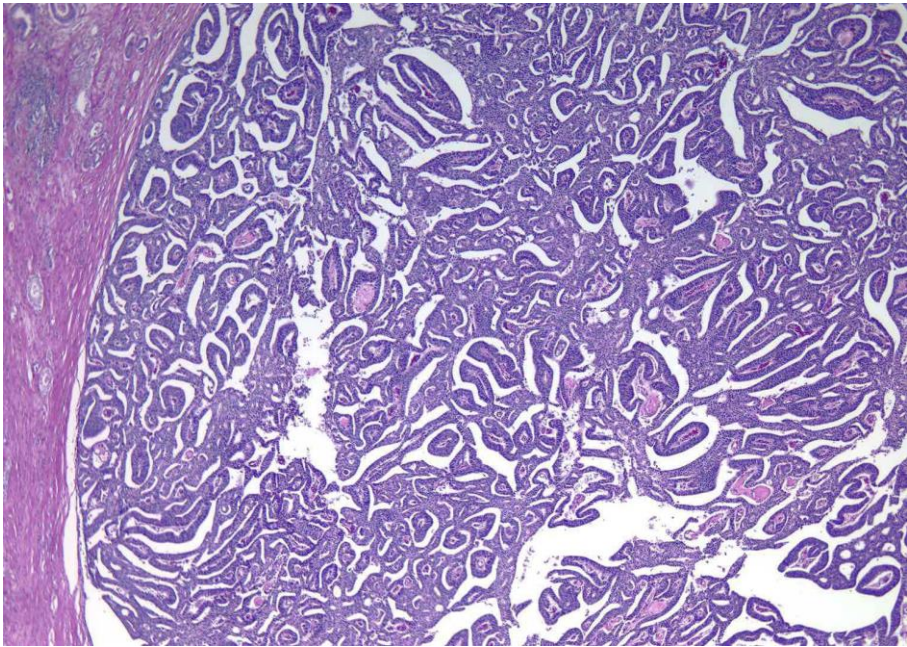
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## Precursor Lesions of Prostate Adenocarcinoma

**HGPIN**
- Earliest histologically recognizable precursor
- **Low Grade PIN** is no longer recognized as an entity
- Patterns: tufted > micropapillary > flat
- **cribriform HGPIN** controversial, diagnosis not recommended
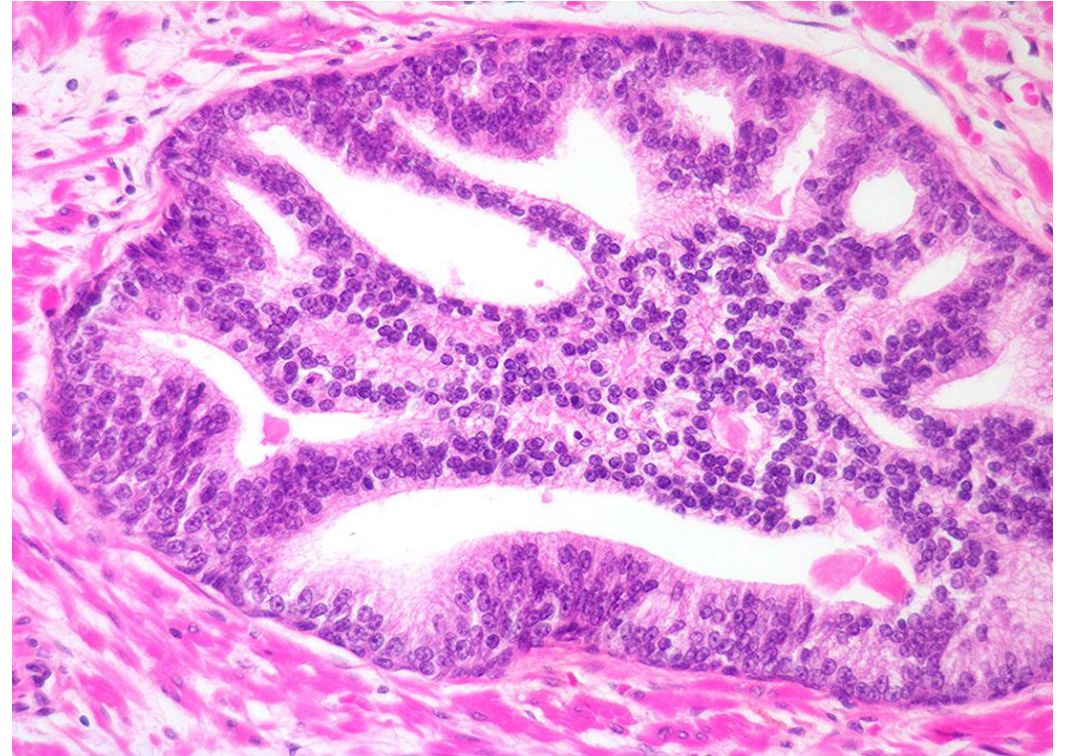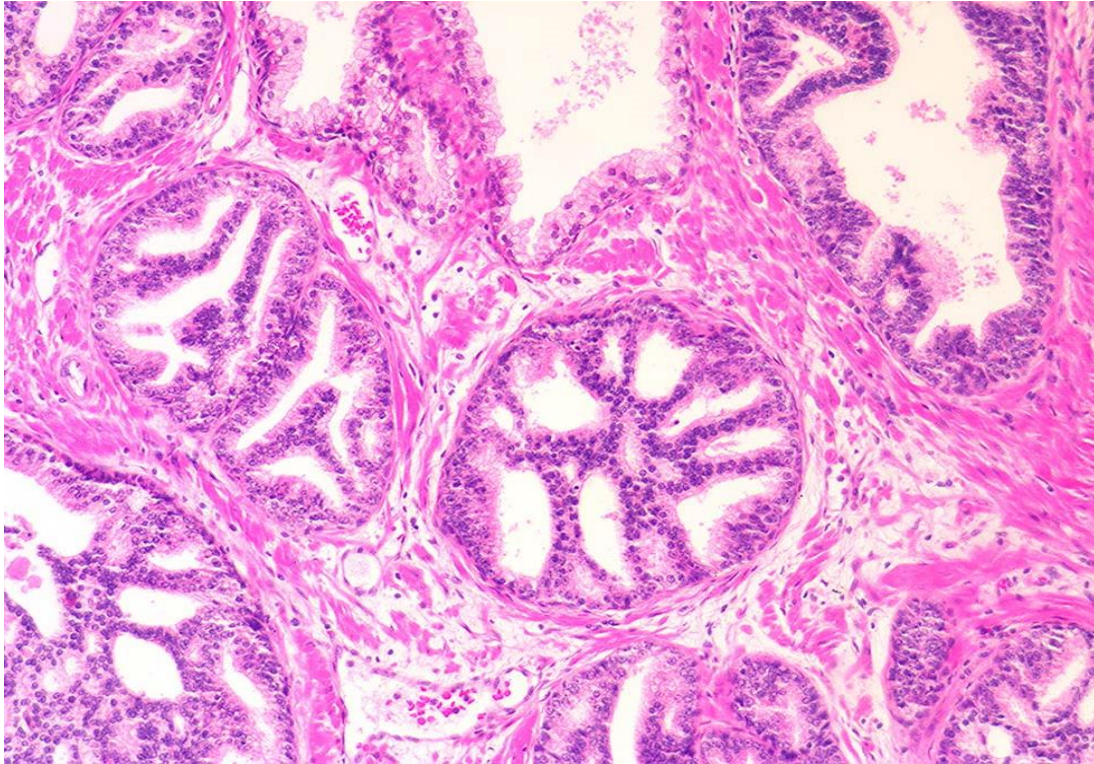
*Epstein JI et al APLM 2020 (GUPS White Paper)*

**IDC-P**

➡ **Intraductal precursors** with architectural and cytological features short of IDC-P
    atypical cribriform proliferation (ACP)
    atypical intraductal proliferation (AIP)
    atypical intraductal proliferation, suspicious for IDC-P (ASID)

HGPIN
Tufted / Micropapillary
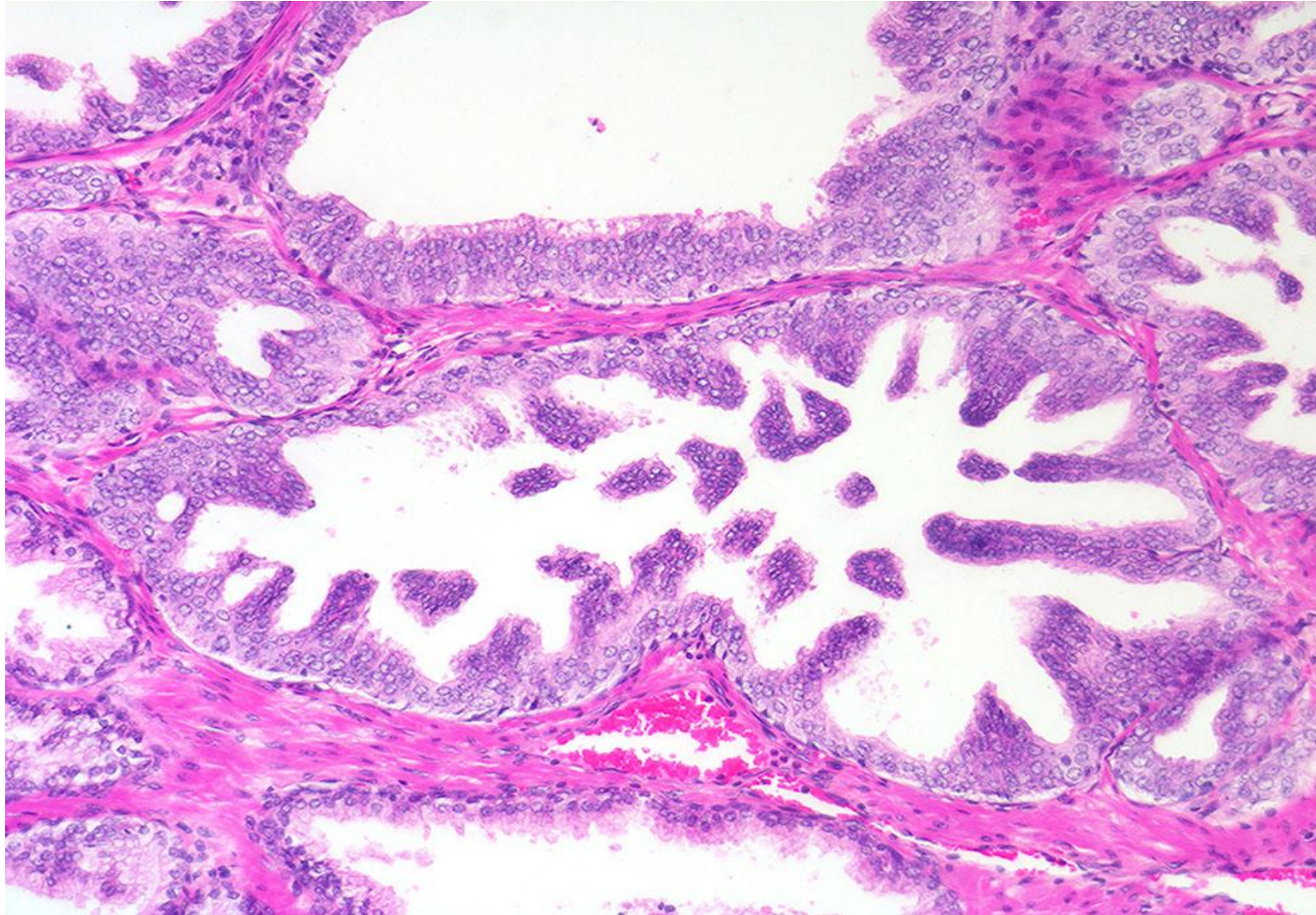
Atypical Intraductal Proliferation
**AIP**

# Intraductal Carcinoma of Prostate

## IDC-P

**Disease-specific survival of patients with invasive cribriform and intraductal prostate cancer at diagnostic biopsy**

Charlotte F Kweldam[1], Intan P Kümmerlin[1], Daan Nieboer[2], Esther I Verhoef[1], Ewout W Steyerberg[2], Theodorus H van der Kwast[3], Monique J Roobol[4] and Geert J van Leenders[1]

[1]Department of Pathology, Erasmus Medical Centre, Rotterdam, The Netherlands; [2]Department of Public Health, Erasmus Medical Centre, Rotterdam, The Netherlands; [3]Laboratory Medicine Program, University Health Network, Toronto, ON, Canada and [4]Department of Urology, Erasmus Medical Centre, Rotterdam, The Netherlands

**Modern Pathology 2016**

**Prostate cancer outcomes of men with biopsy Gleason score 6 and 7 without cribriform or intraductal carcinoma**

Charlotte F. Kweldam [a,*], Intan P. Kümmerlin [a], Daan Nieboer [b], Esther I. Verhoef [a], Ewout W. Steyerberg [b], Luca Incrocci [c], Chris H. Bangma [d], Theodorus H. van der Kwast [e], Monique J. Roobol [d], Geert J. van Leenders [a]

# IDC-P
## Historic Perspective

- *Kovi J et al. ; Cancer 1985*
  "ductal permeation by carcinoma the basement membrane remained intact "


- *McNeal JE and Yemoto CE; AJSP 1996*
  "complete spanning of ductal/acinar lumen by several trabeculae of malignant epithelial cells"

**Intraductal carcinoma of the prostate on needle biopsy: histologic features and clinical significance**

*Modern Pathology 2006*

Charles C Guo[1] and Jonathan I Epstein[1,2,3]

27 cases of isolated IDC-P in Needle Bx

**IDC-P Definition**

- Malignant epithelial cells filling large acini and ducts
- Preservation of basal cells: H&E or IHC
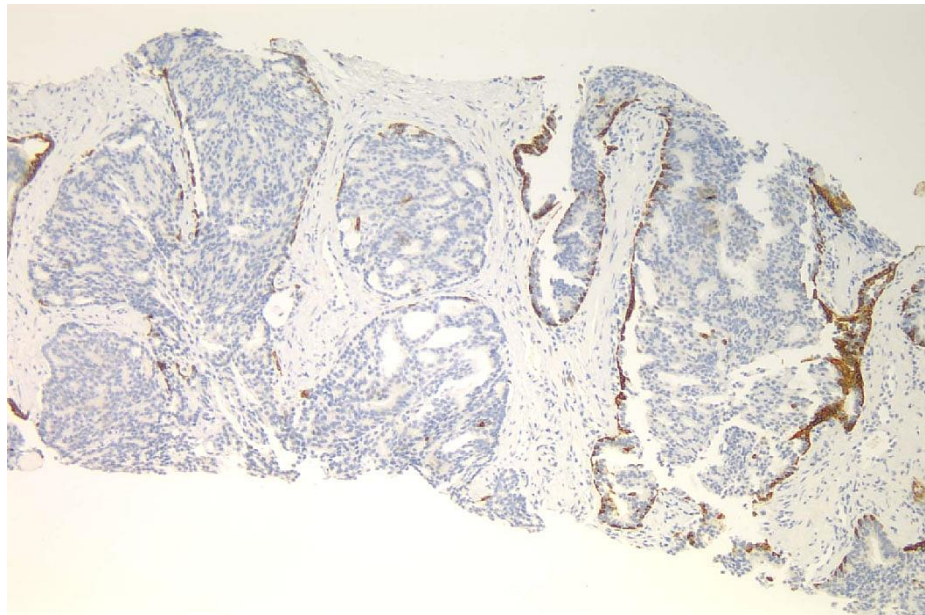
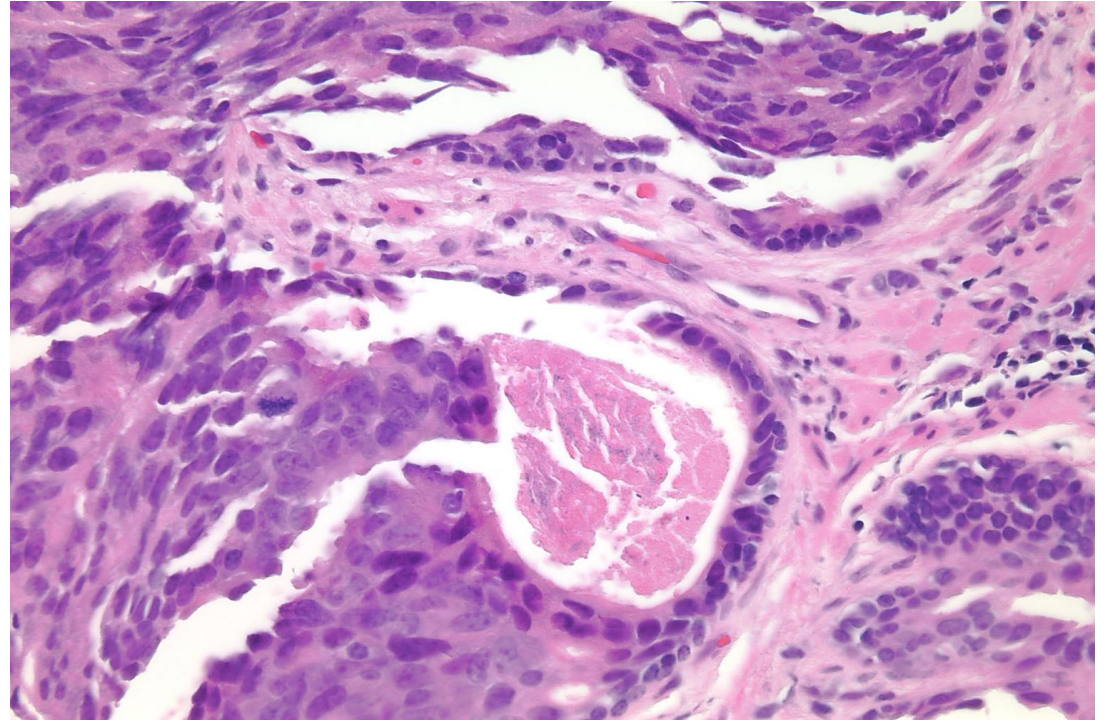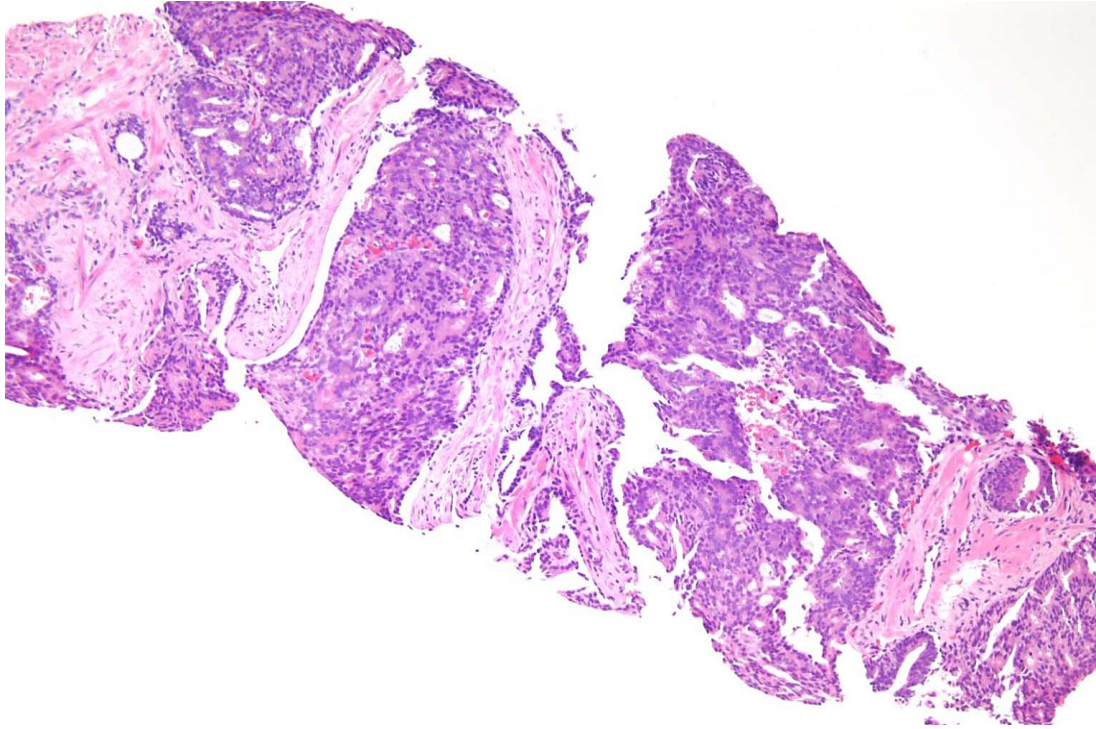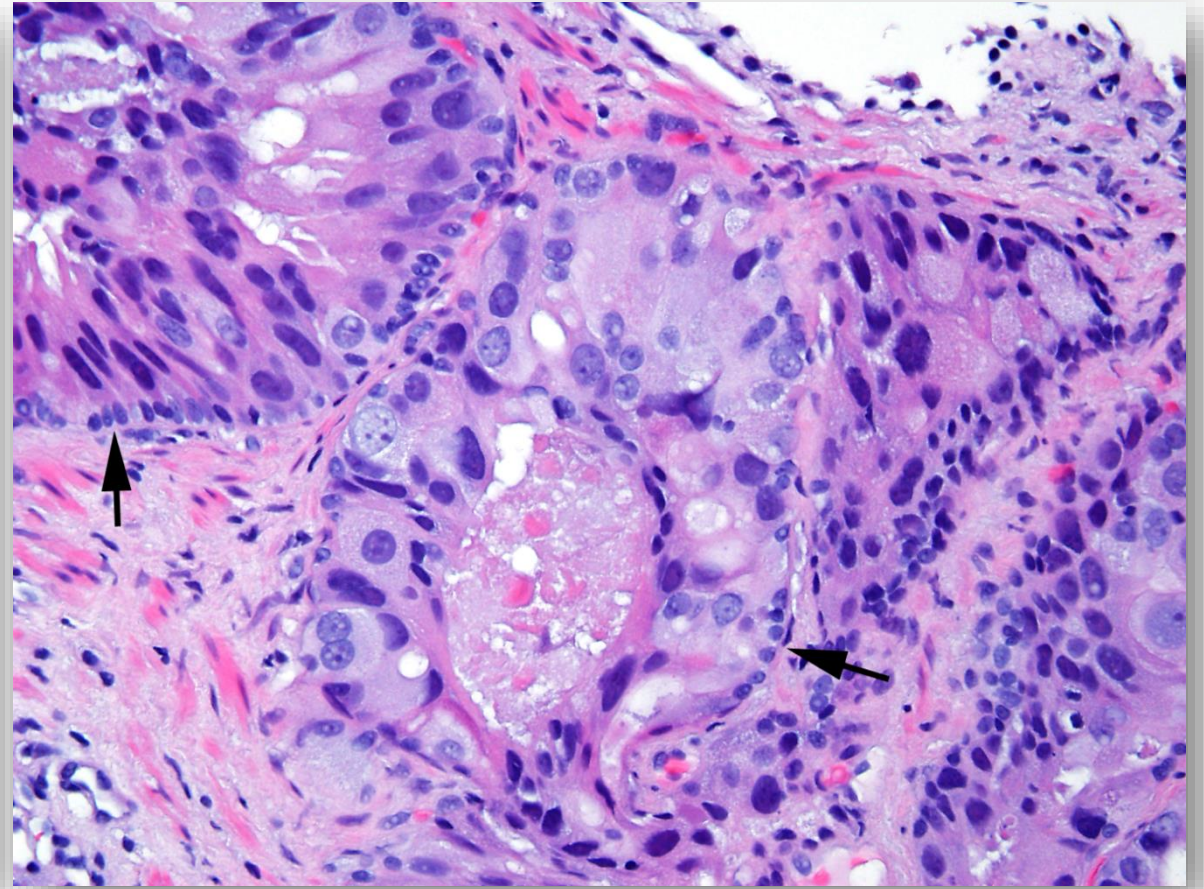- **solid** or **dense cribriform** patterns
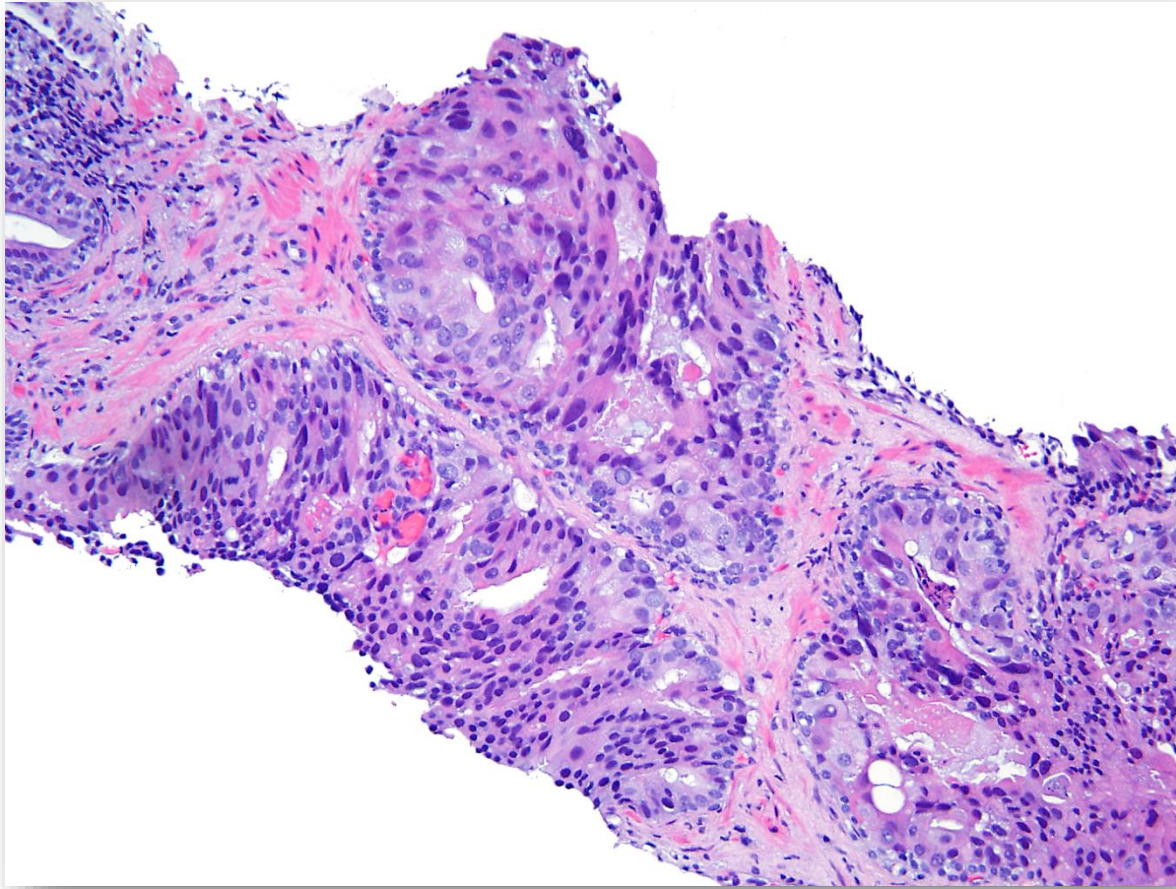
- **loose cribriform or micropapillary patterns**

**+**

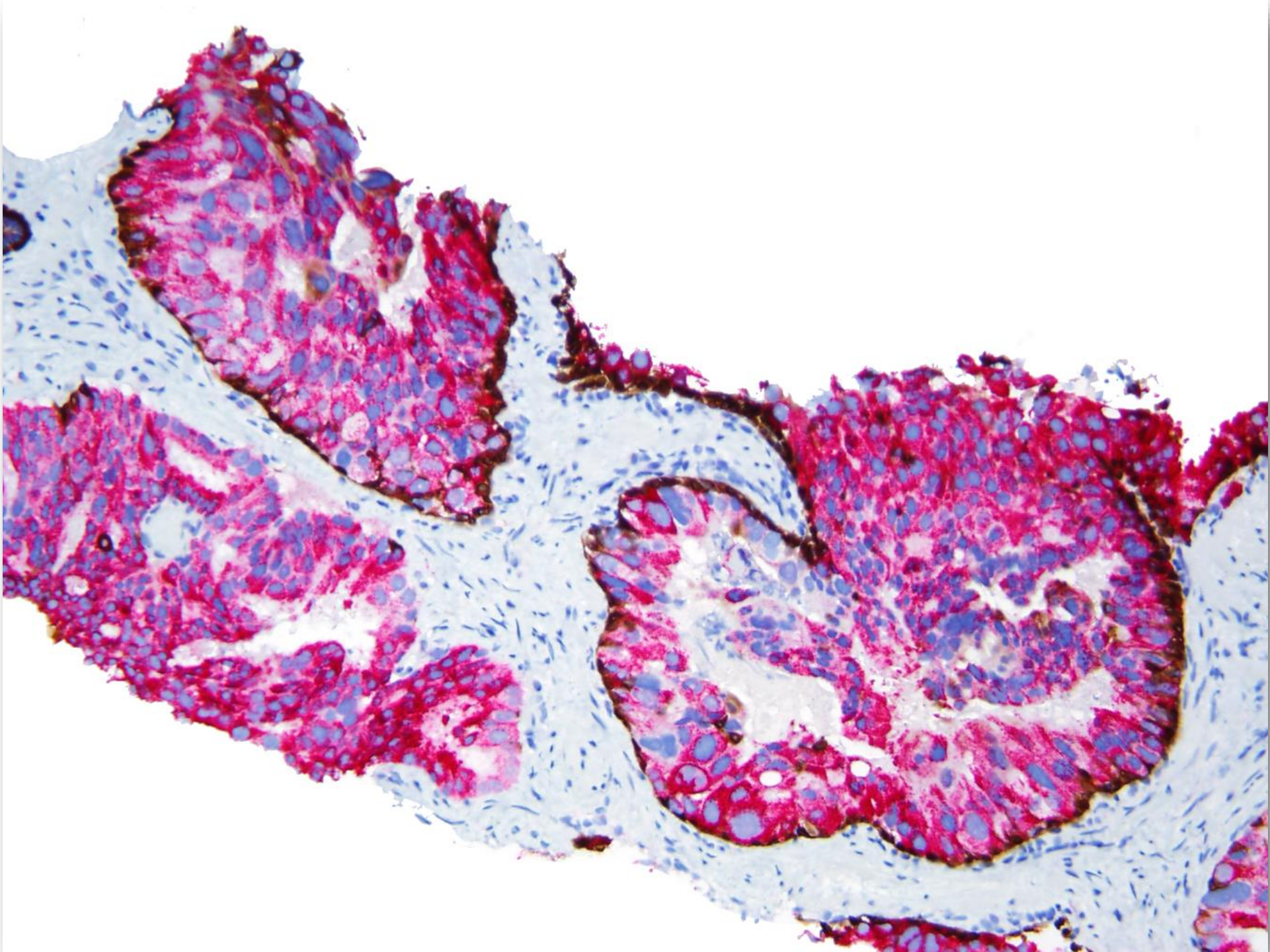marked **nuclear atypia** (≥ 6 x normal) or **comedonecrosis**
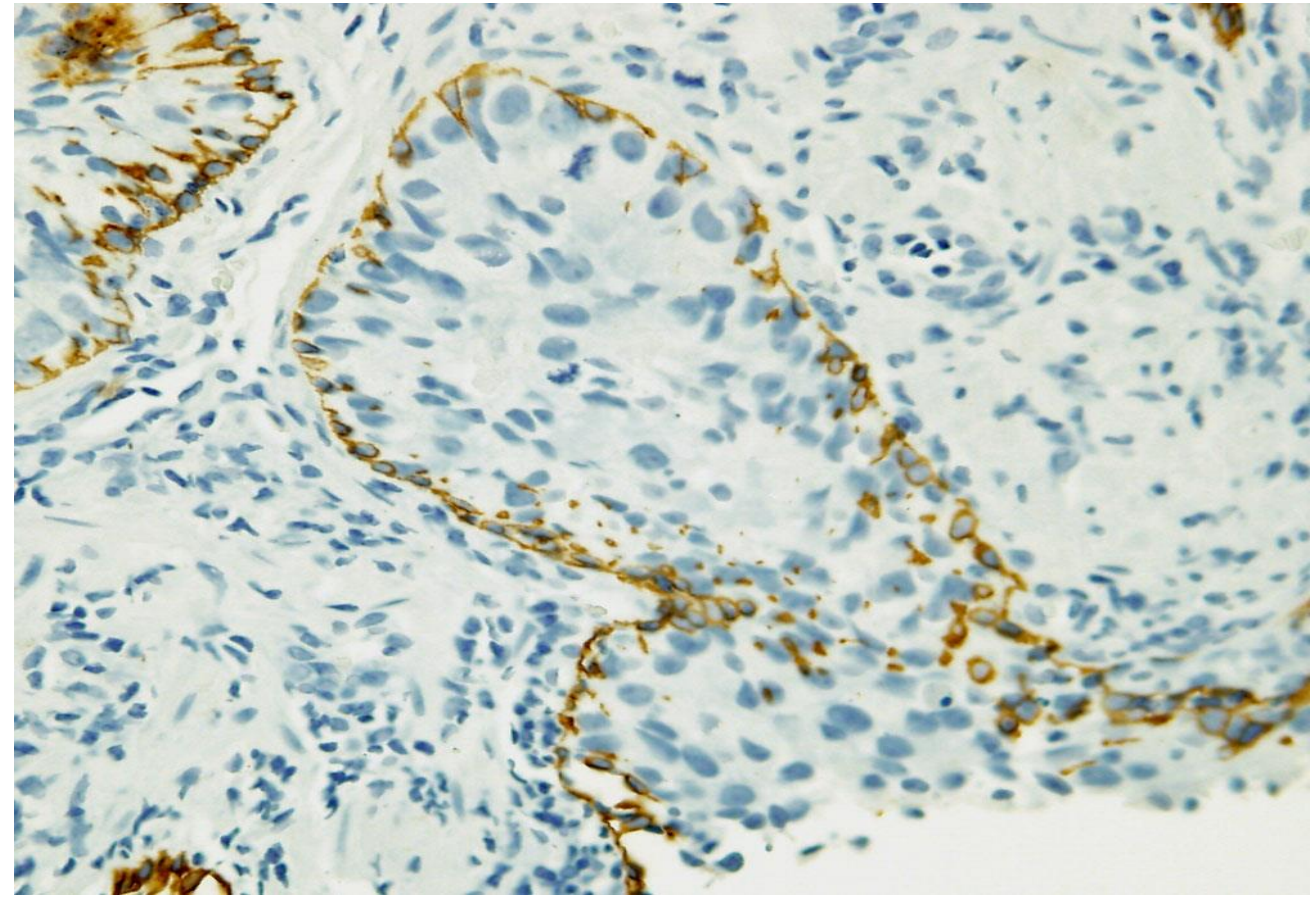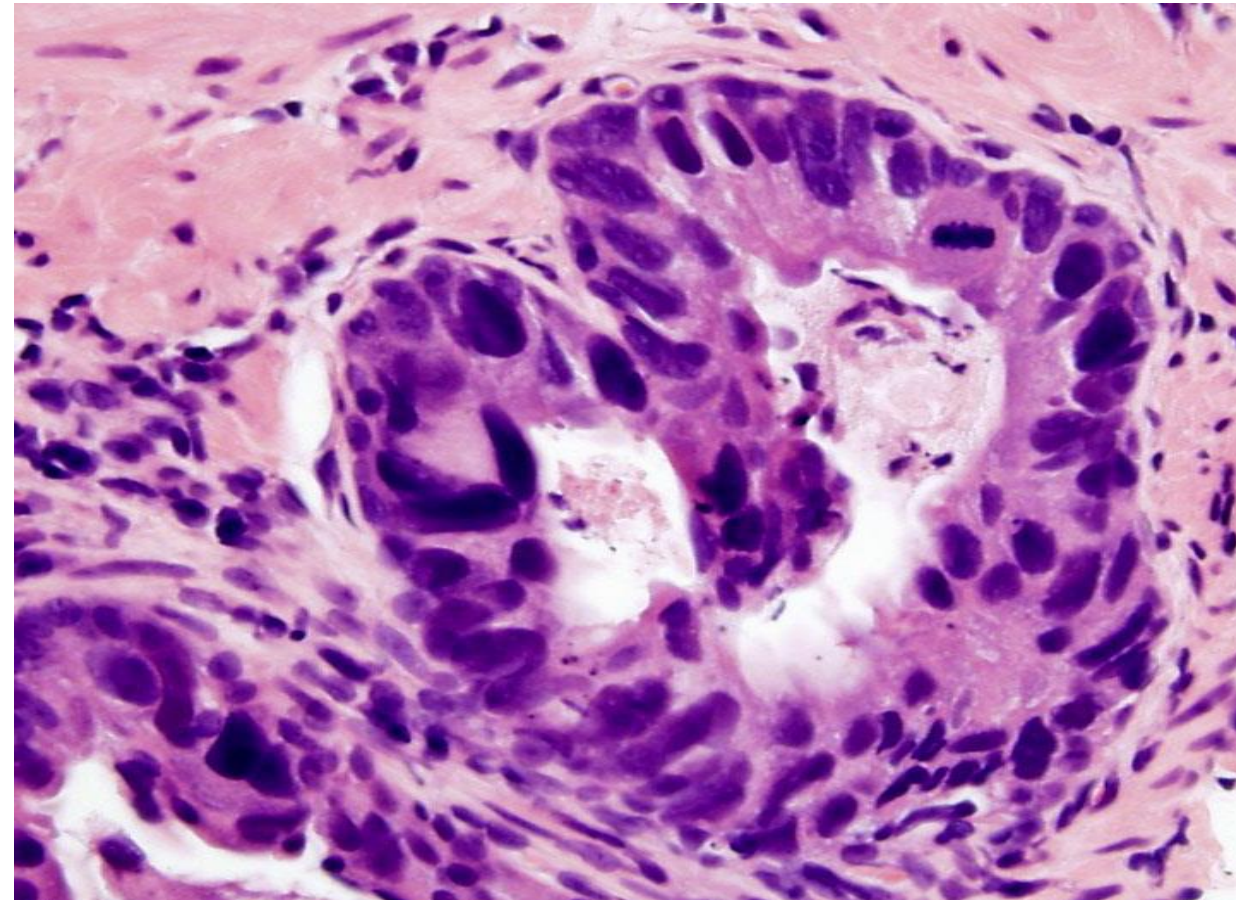
**Outcome**

- 6 RP
  - Gleason score 8 or 9 with 5 cases with prominent IDC-P
  - Non-focal EPE in 5/6 and LVI in 2/6
- 3/16 pts without RP developed bone metastases
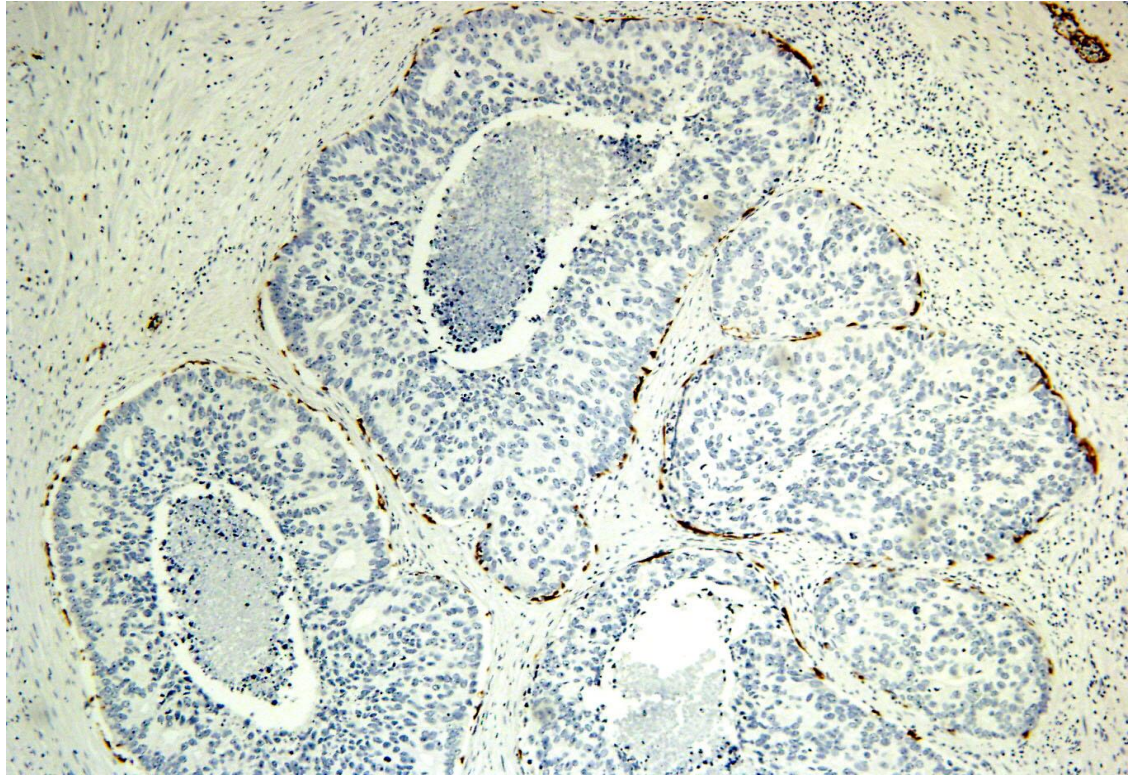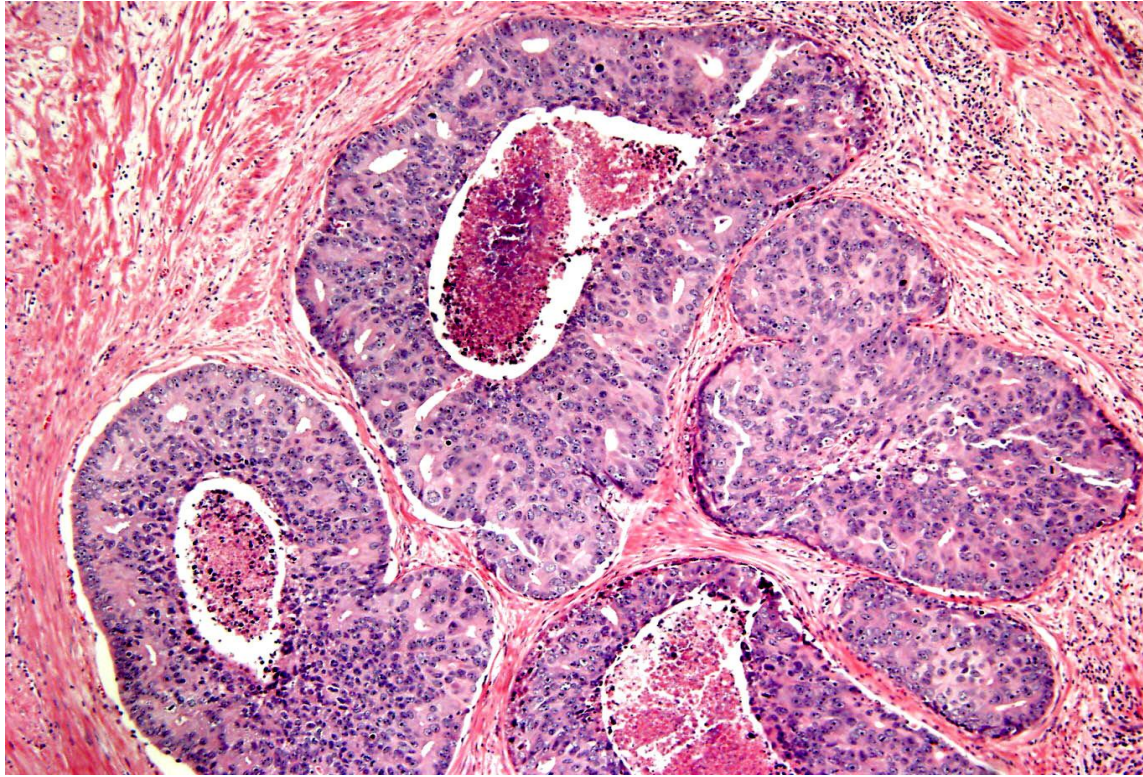
# Incidence of IDC-P

**RP**
- 15 to 30%
- vast majority with invasive cancer
- Incidence correlates with **GG**, volume and PCA **risk categories**
- Isolated IDC-P (without invasive cancer) exceedingly rare!

**Prostate Bx**
- 2.8% of all Bx
- 14% of Bx with invasive cancer
- Isolated IDC-P in 0.06-0.26% of Bx

*Khani F et al. J Pathol. 2019*
*Rijstenberg LL et al. Histopathology. 2020*
*Watts K, Li J, Magi-Galluzzi C, Zhou M. Histopathology. 2013*
*Porter LH et al. Eur Urol. 2017*

# Prostatic Intraductal Carcinoma (IDC-P)

- An **advanced stage of tumor progression** with <u>intraductal spread </u>of tumor **(mostly)**

- **Justified to treat patients** with intraductal carcinoma on biopsy even in the absence of documented infiltrating cancer

# Differential Diagnosis of IDC-P

- **HGPIN**
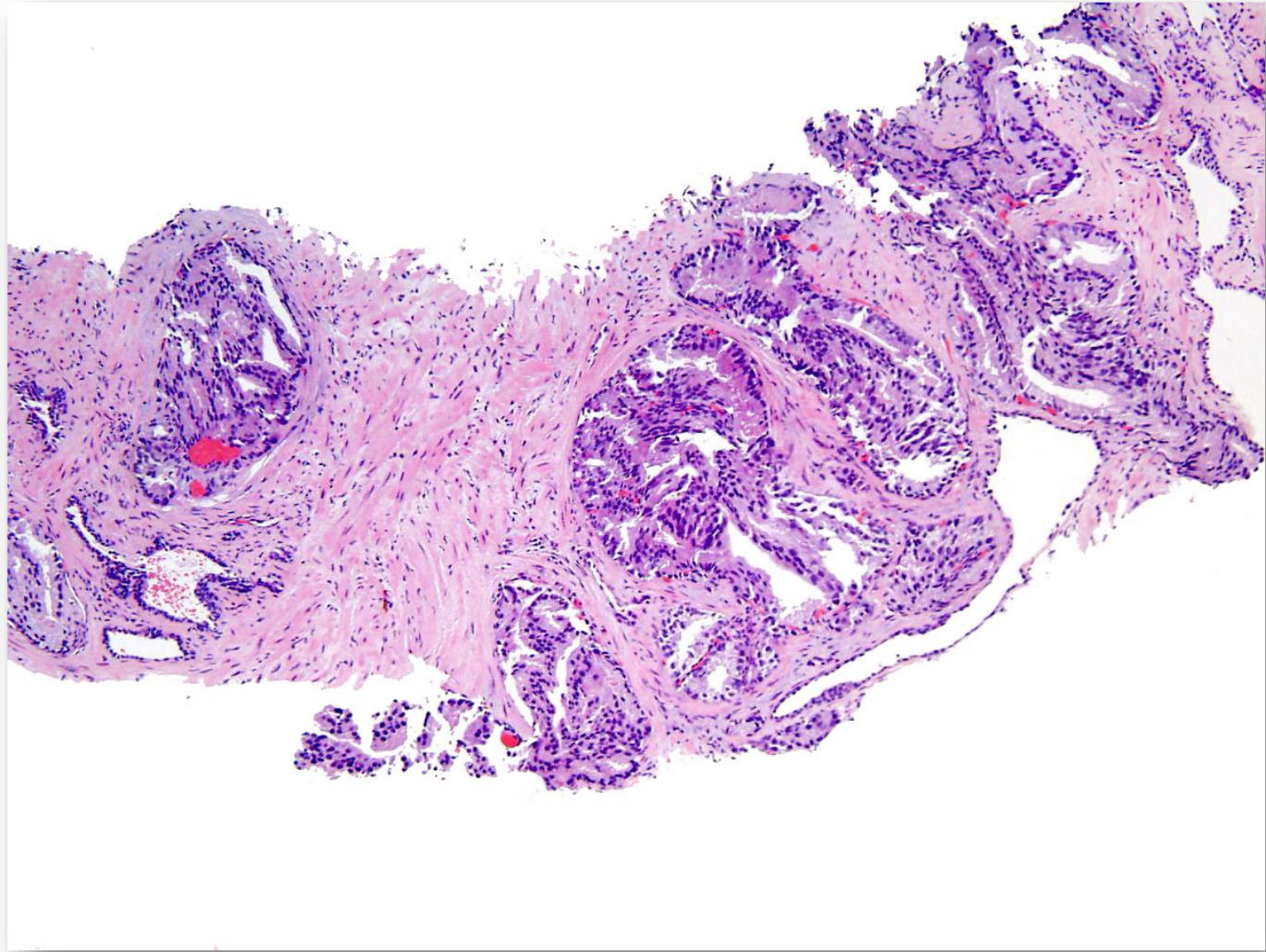- **Cribriform acinar adenocarcinoma**
- **Ductal adenocarcinoma**
- **Intraductal spread of HGTCC**
- Cribriform Hyperplasia (Central zone)
- Basal Cell Hyperplasia

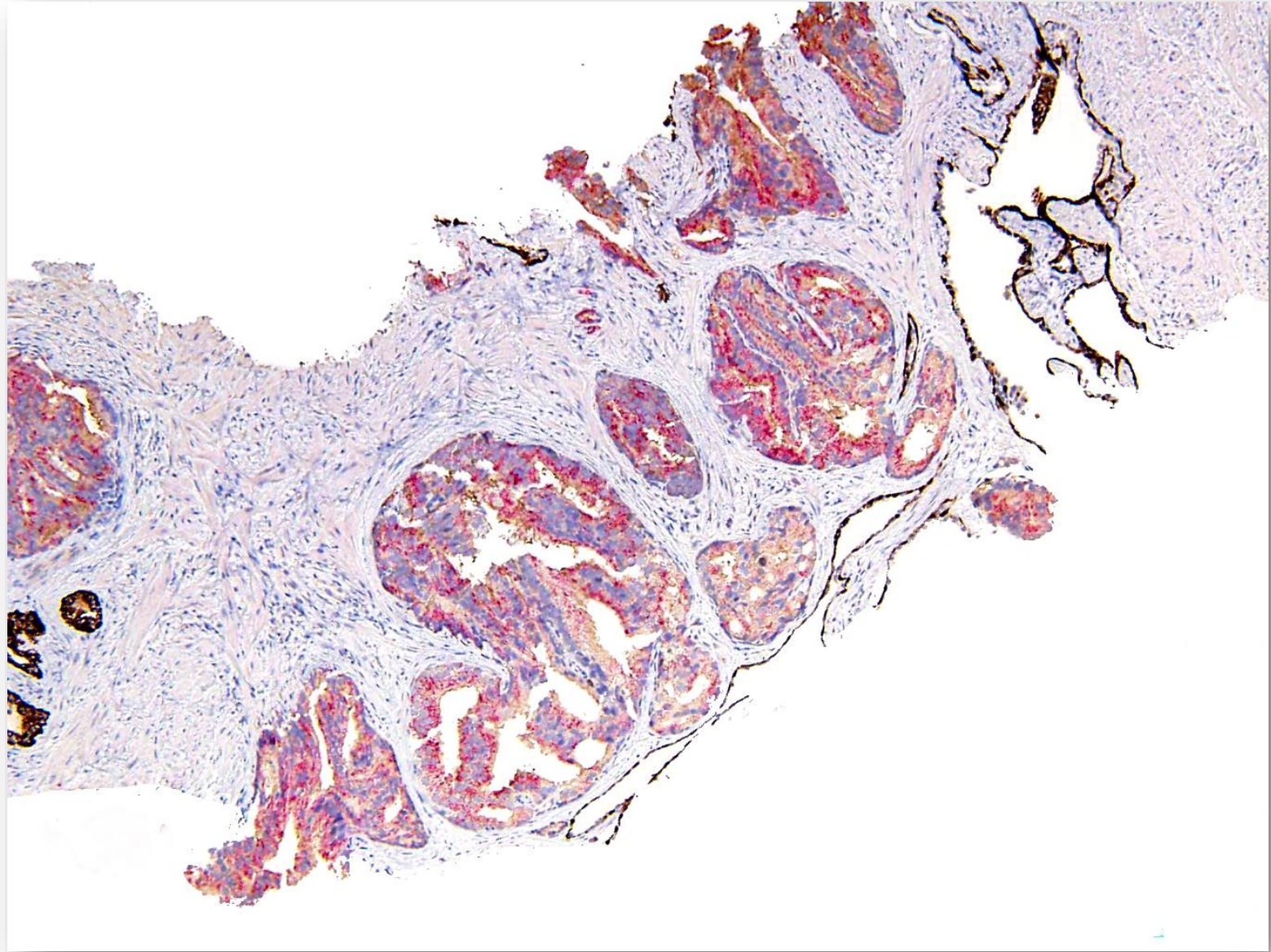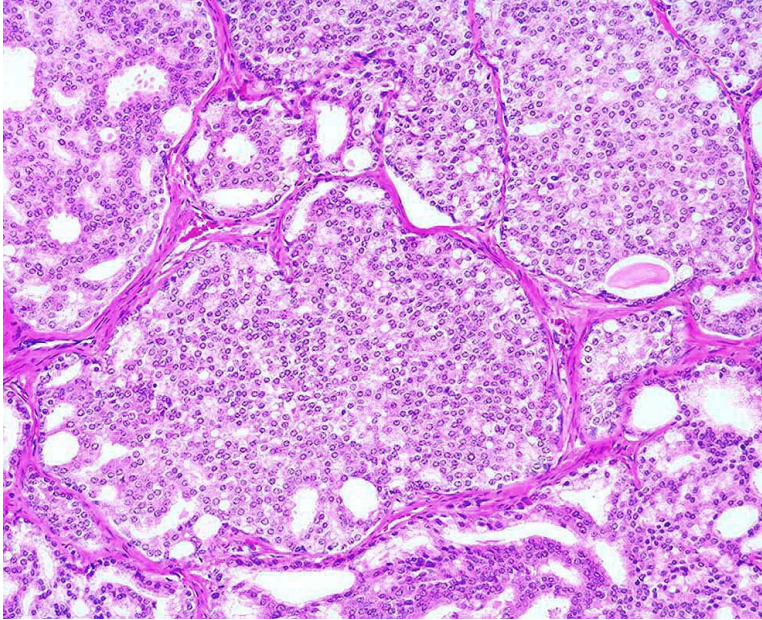# Cribriform Acinar Adenocarcinoma
*vs*
# IDC-P
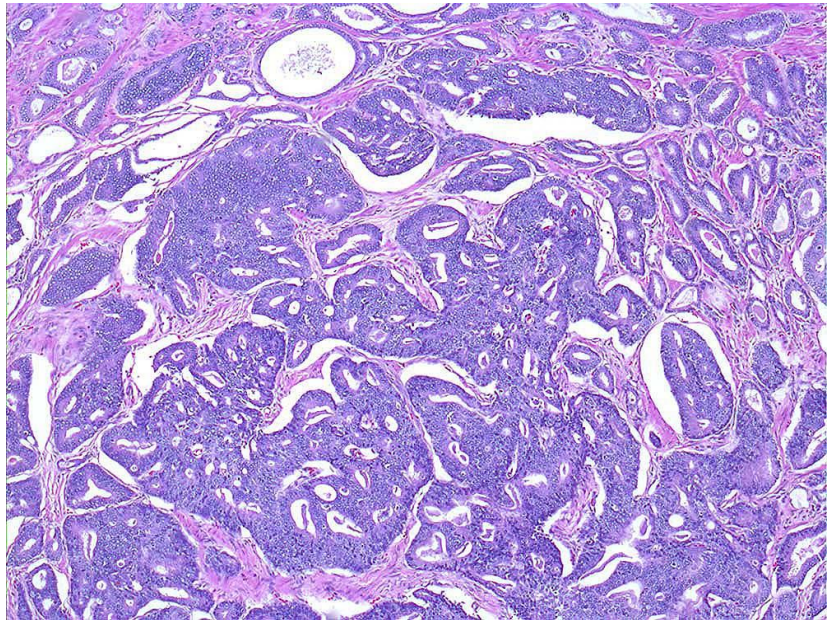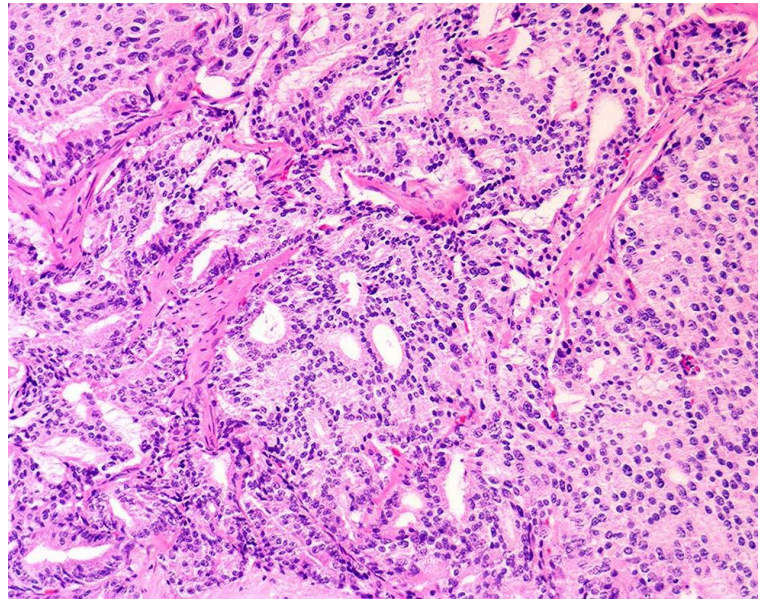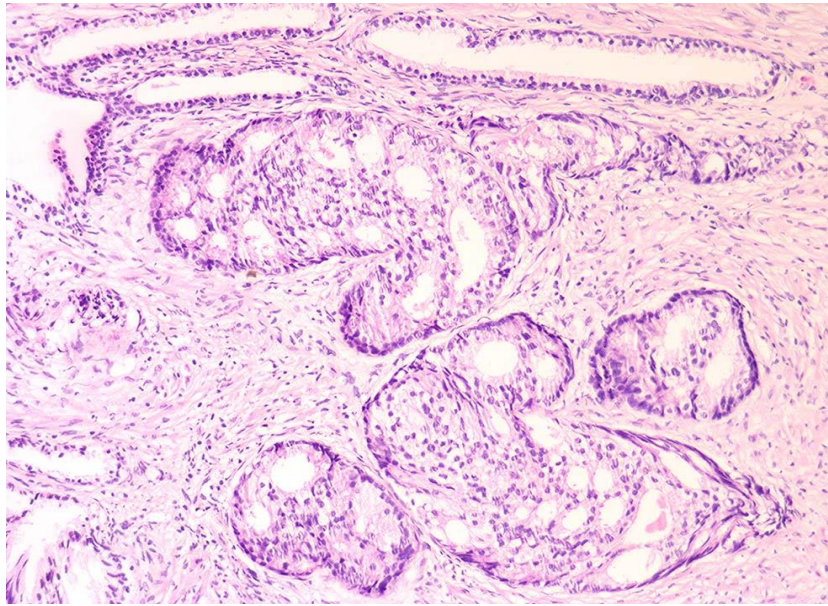
**Intraductal Carcinoma (IDC-P)**

**VS**

**Prostatic Intraepithelial Neoplasia (HGPIN)**
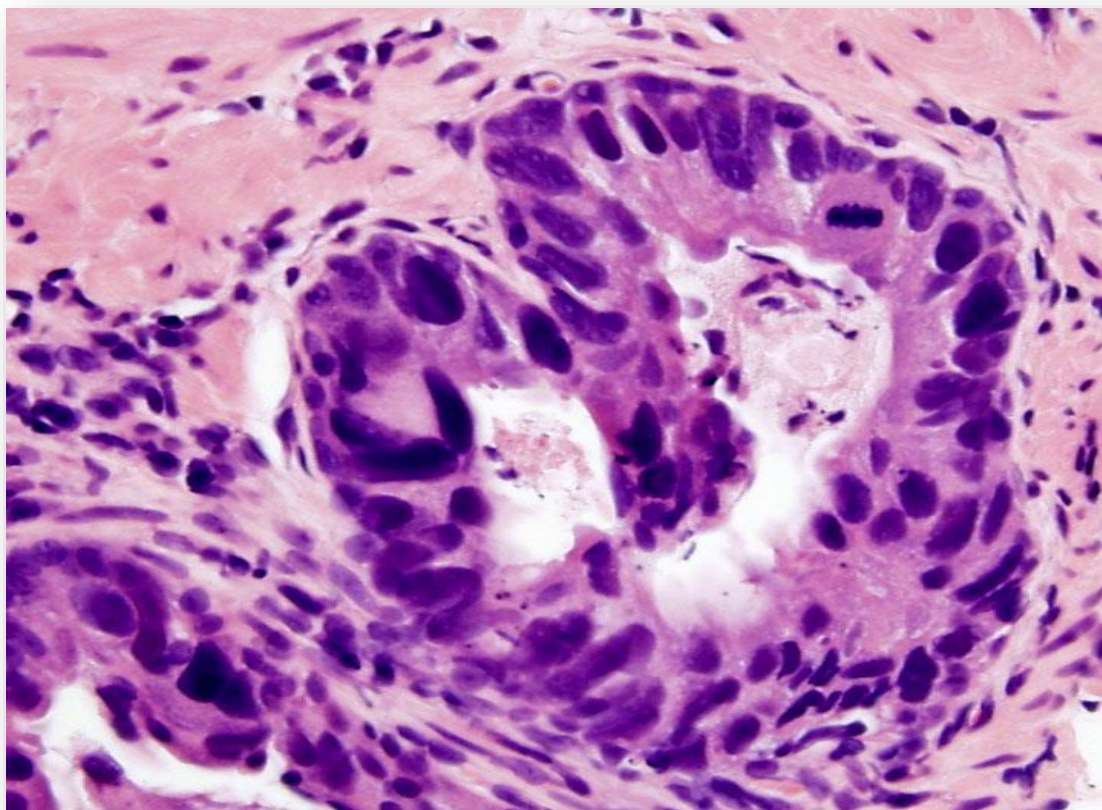
IDC-P
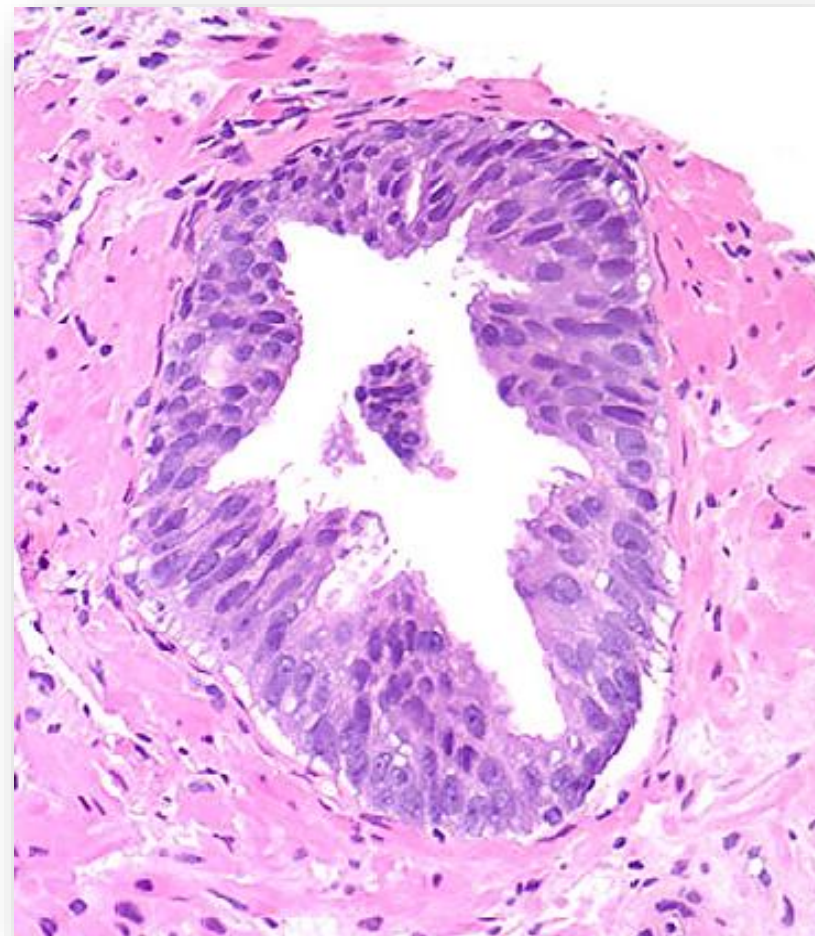
HGPIN
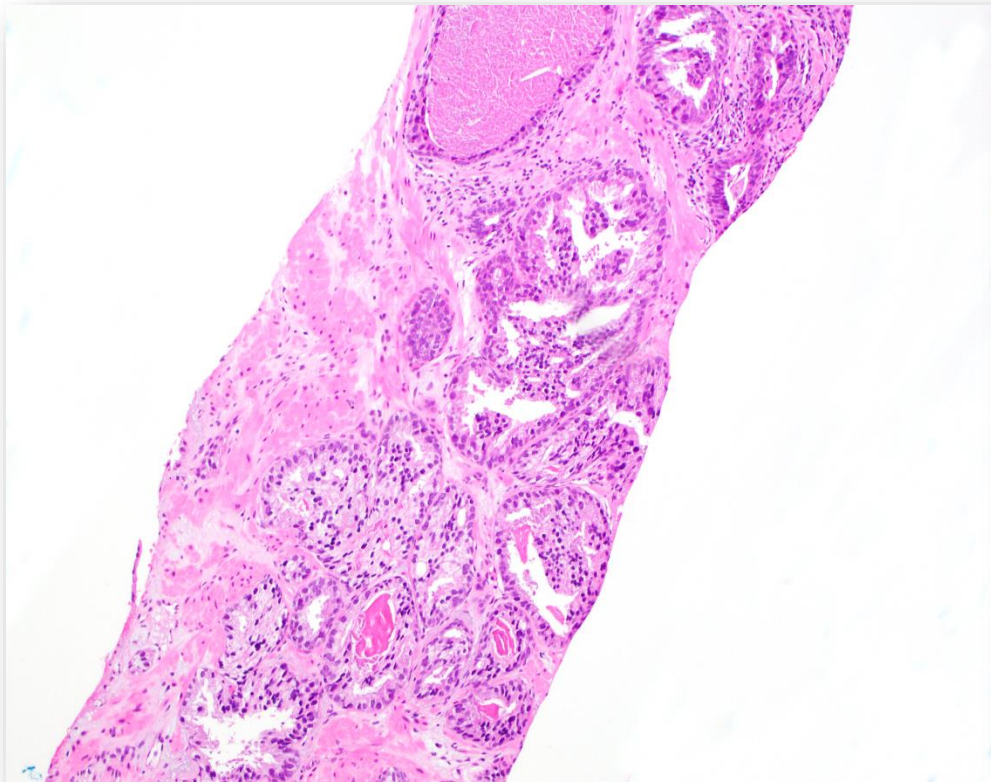
PIN *vs* DCIS (R/O IDC-P)
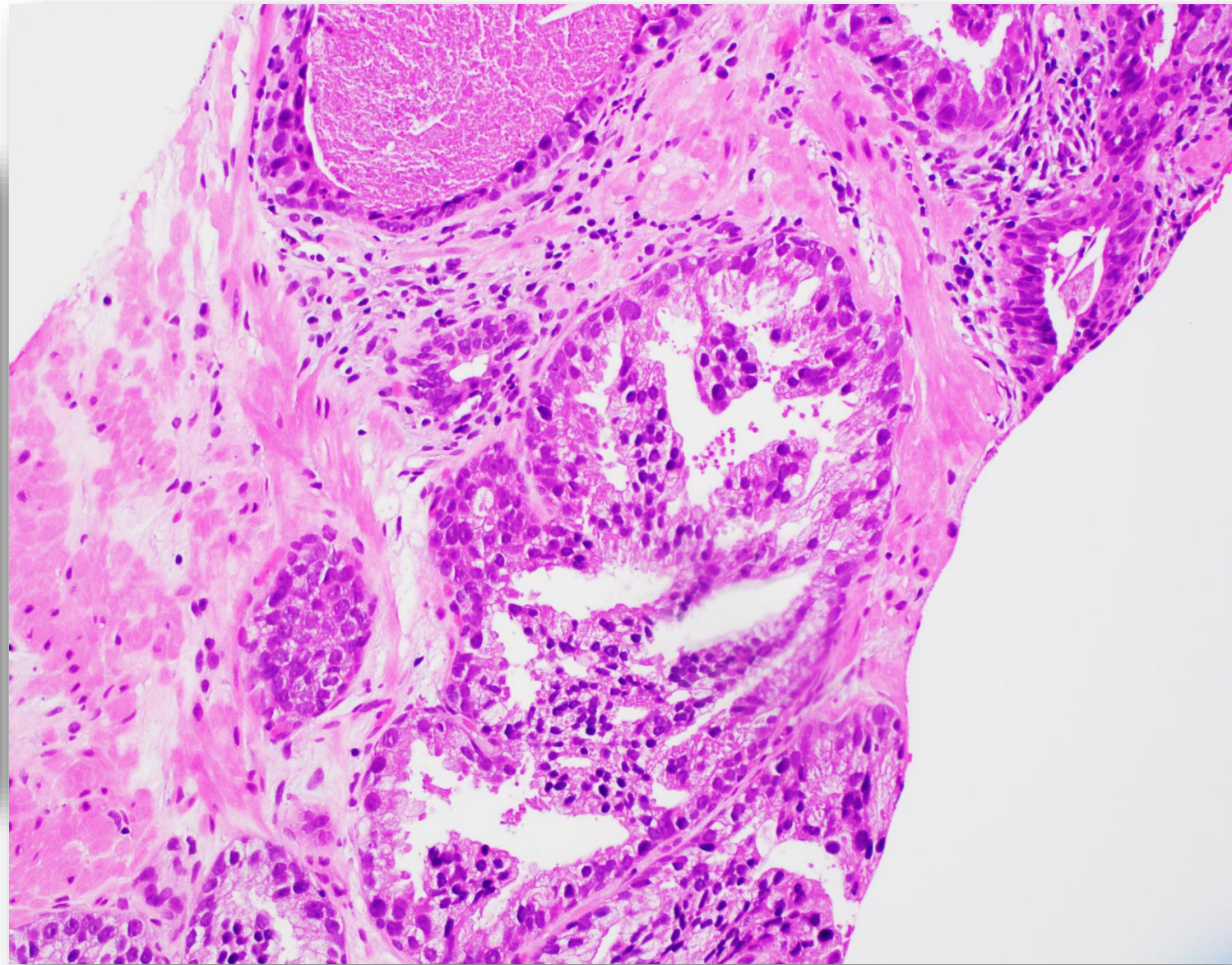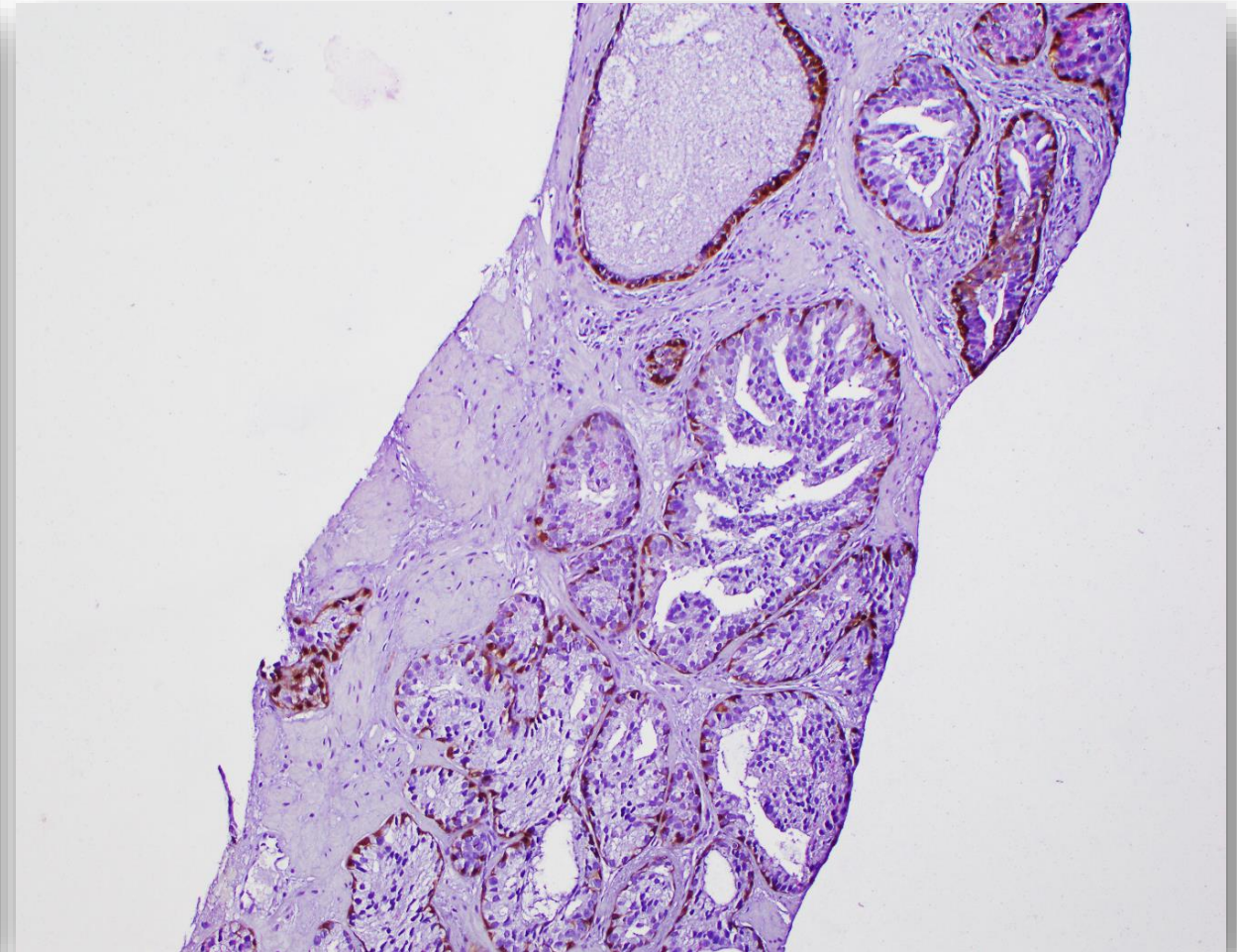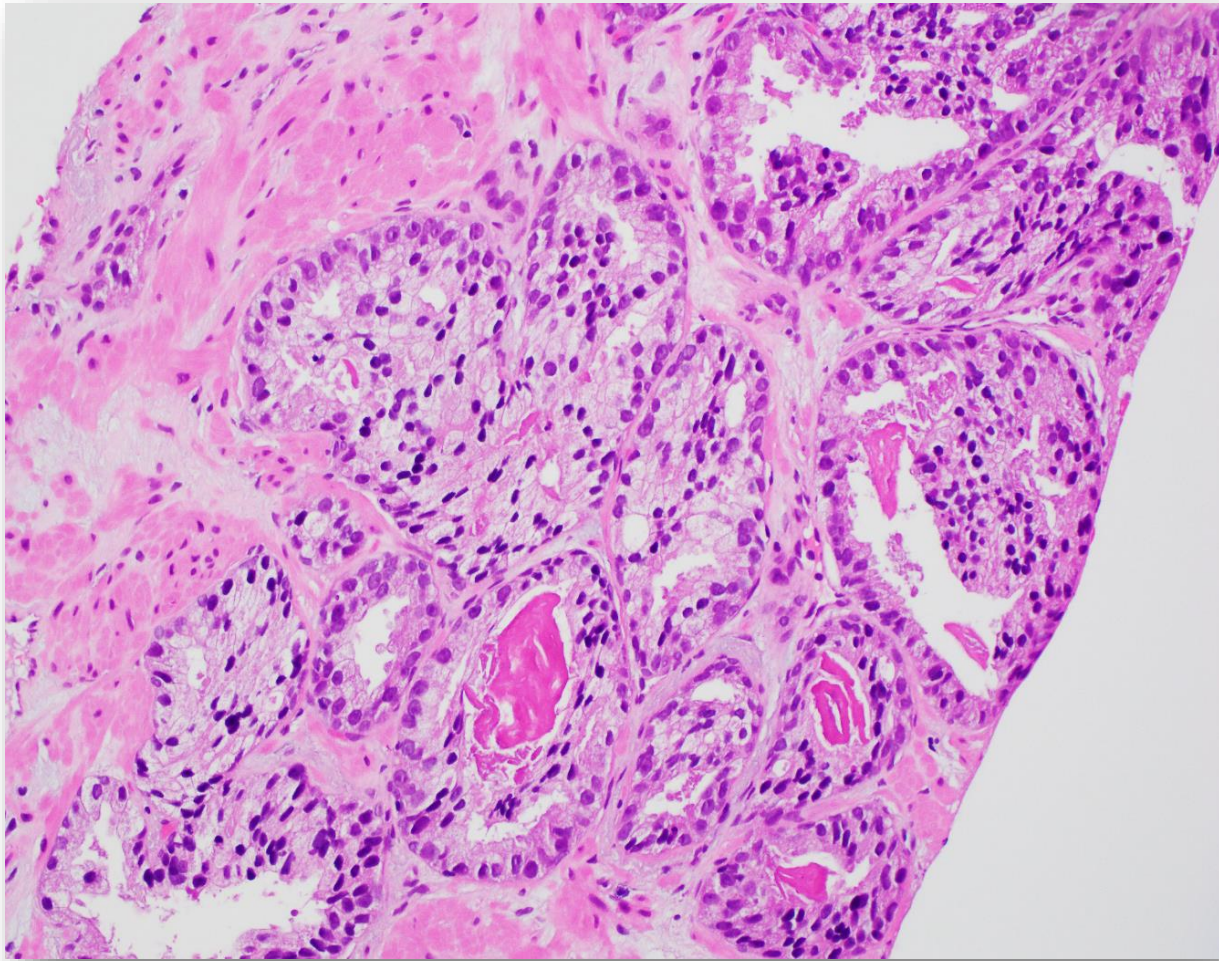
PIN *vs* DCIS (R/O IDC-P)

Atypical Intraductal Proliferation (AIP)

**Atypical intraductal proliferation and intraductal carcinoma of the prostate on core needle biopsy: a comparative clinicopathological and molecular study with a proposal to expand the morphological spectrum of intraductal carcinoma**

Rajal B Shah,[1,2] Jiyoon Yoon,[1] Gang Liu[3] & Wei Tian[1]
[1]Division of Pathology, Miraca Life Sciences, Irving, TX, USA, [2]Department of Pathology, Baylor College of Medicine, Houston, TX, USA, and [3]University of Toledo, Toledo, OH, USA

**Atypical Intraductal Proliferation (AIP)**
*Histologically worse than HGPIN but lacks the diagnostic criteria of IDC-P*

- 106 of 1480 consecutive and 22 retrospectively
  - AIP only (2.4%),
  - IDC-P only (1.3%)
  - IDC-P coexisting with AIP (2%)

- PCa in 96% and 97% cases of AIP and IDC-P, respectively

**Atypical intraductal proliferation and intraductal carcinoma of the prostate on core needle biopsy: a comparative clinicopathological and molecular study with a proposal to expand the morphological spectrum of intraductal carcinoma**

Rajal B Shah,[1,2] Jiyoon Yoon,[1] Gang Liu[3] & Wei Tian[1]
[1]*Division of Pathology, Miraca Life Sciences, Irving, TX, USA,* [2]*Department of Pathology, Baylor College of Medicine, Houston, TX, USA,* and [3]*University of Toledo, Toledo, OH, USA*

- **IDC-P** associated PCa more **aggressive pathology** compared to AIP
  - highest GS (GS ≥ 4 + 3; GG 3 and higher)
  - Largest extent PCa involvement
- **AIP** associated with **intermediate-risk PCa**

- **AIP:** ERG/PTEN status were similar to adjacent PCa in 97% and 88% of cases
- **IDCP:** ERG/PTEN status were similar to PCa in 96% and 91% of cases, respectively.

- **AIP represents a "lower-grade" spectrum of IDC-P**
- **IMMEDIATE** repeat biopsy

Atypical intraductal proliferation and intraductal carcinoma of the prostate on core needle biopsy: a comparative clinicopathological and molecular study with a proposal to expand the morphological spectrum of intraductal carcinoma
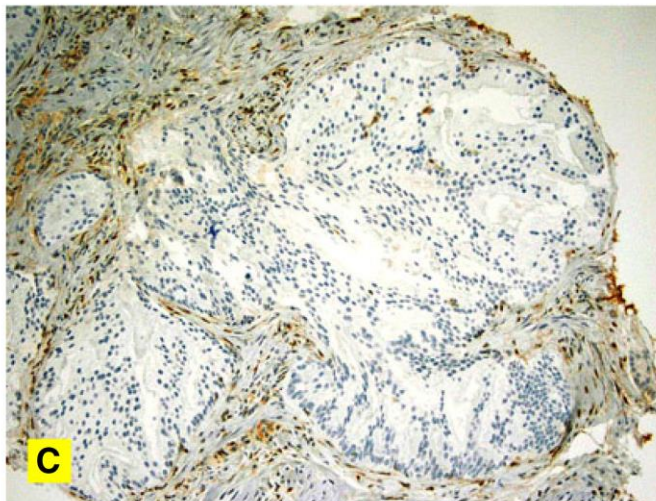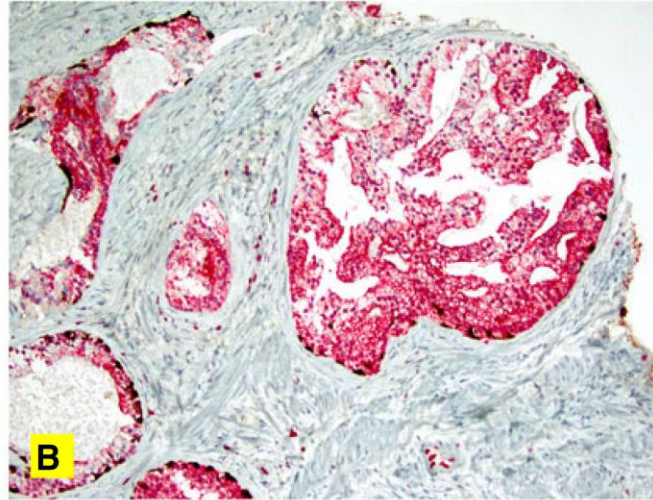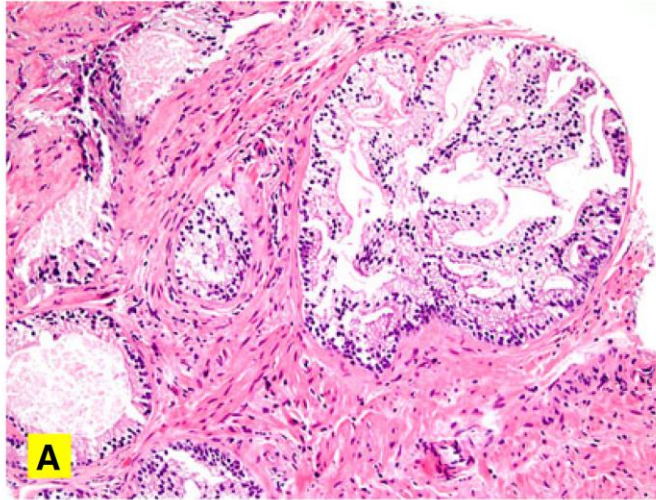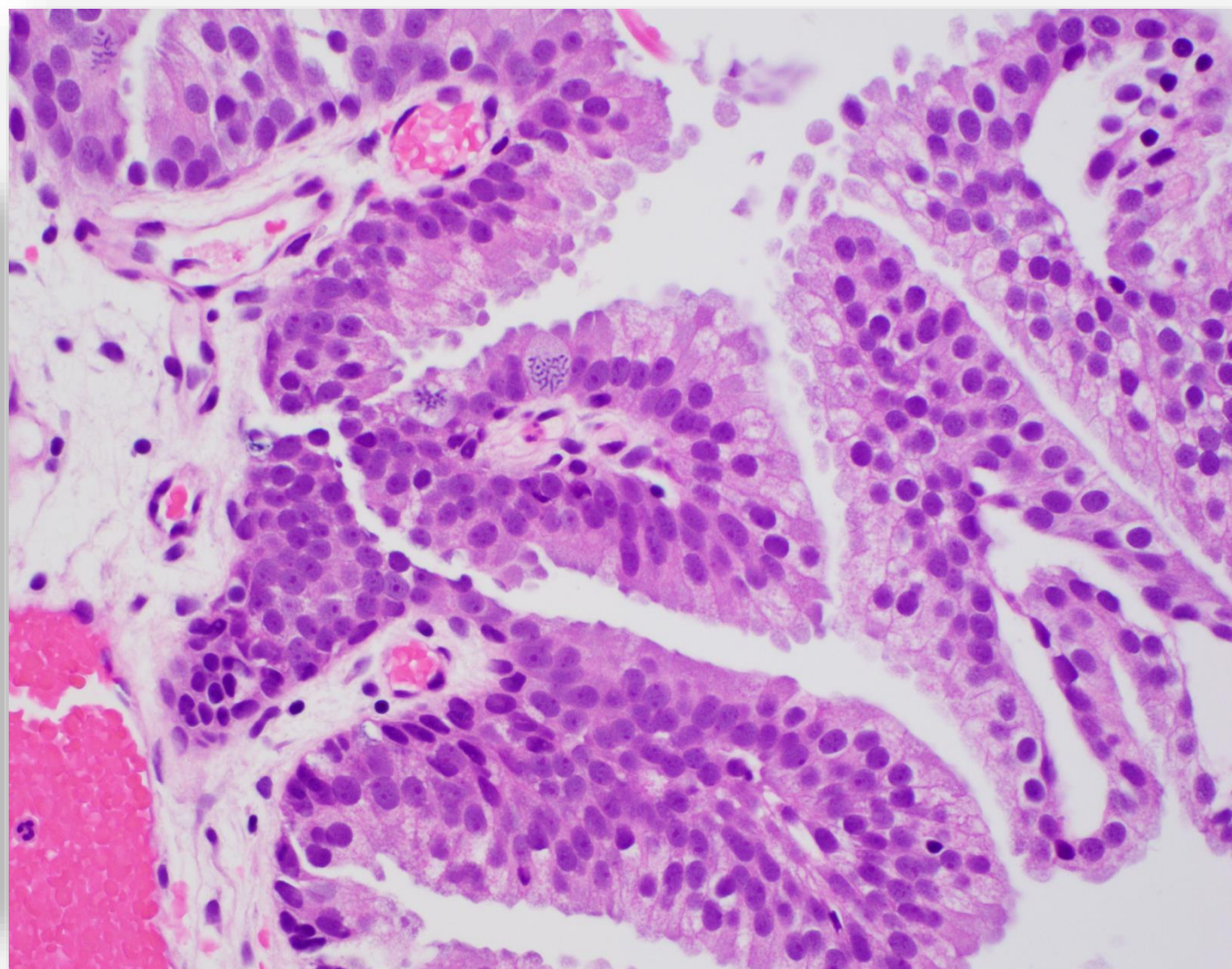
AIP

# Ductal IDC-P?
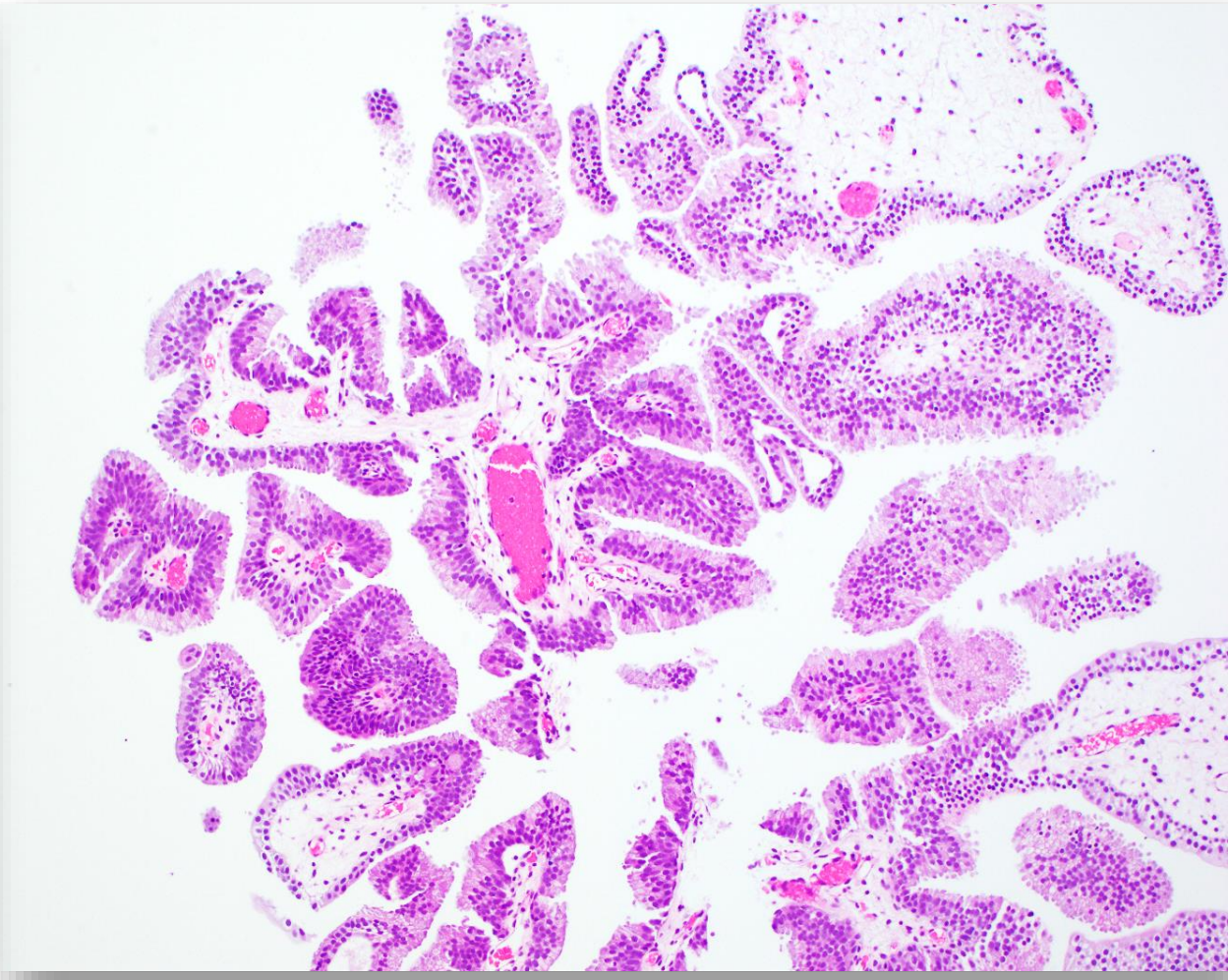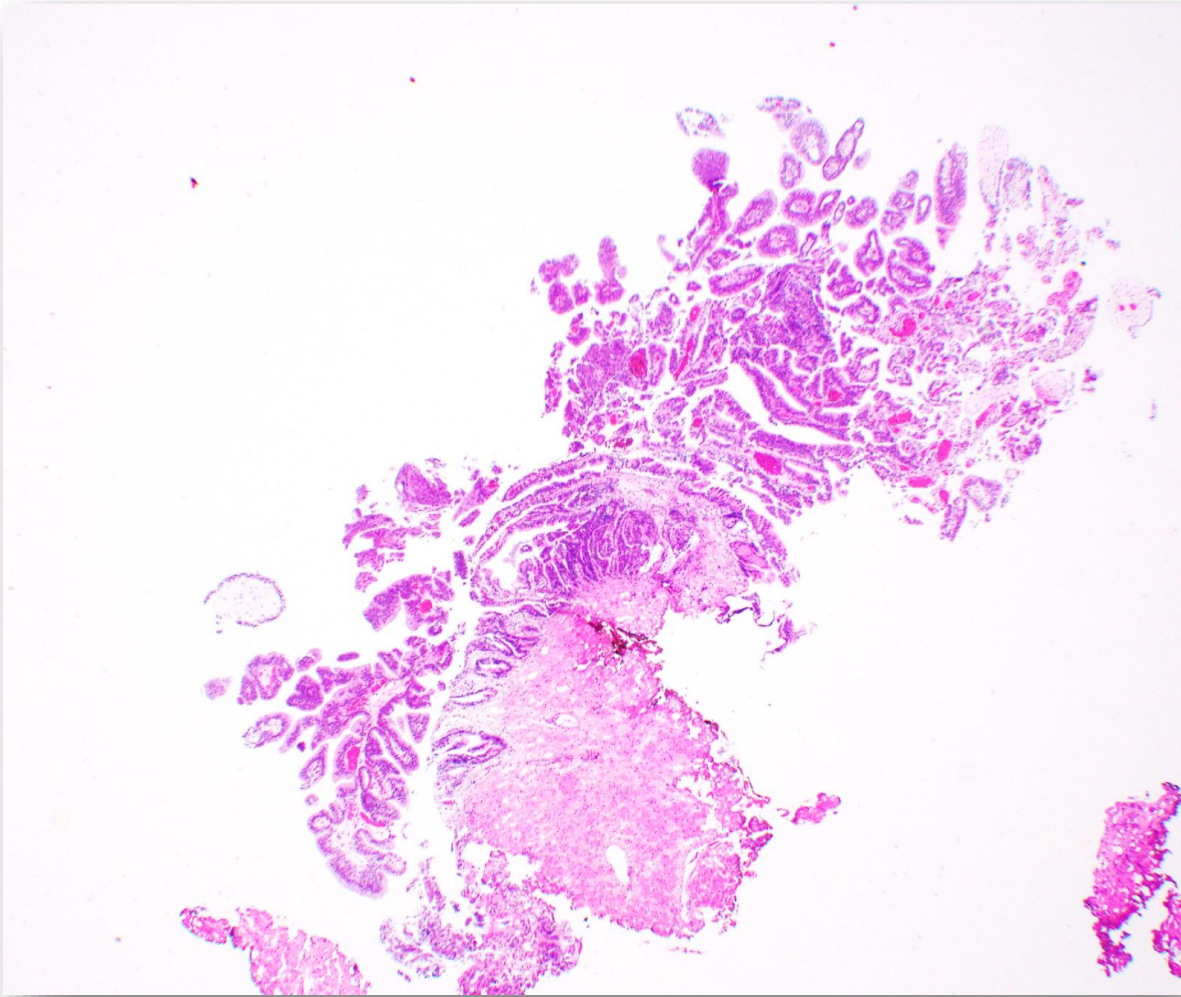
Ductal Carcinoma?
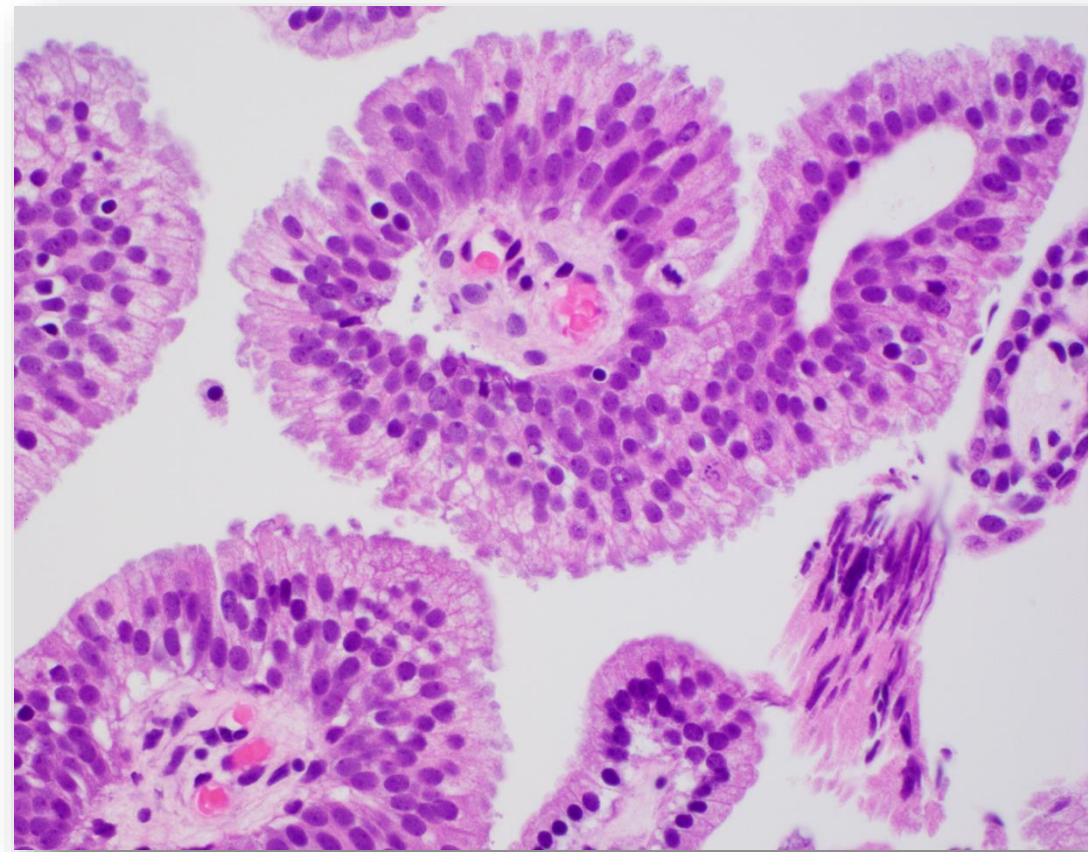
Ductal Carcinoma?
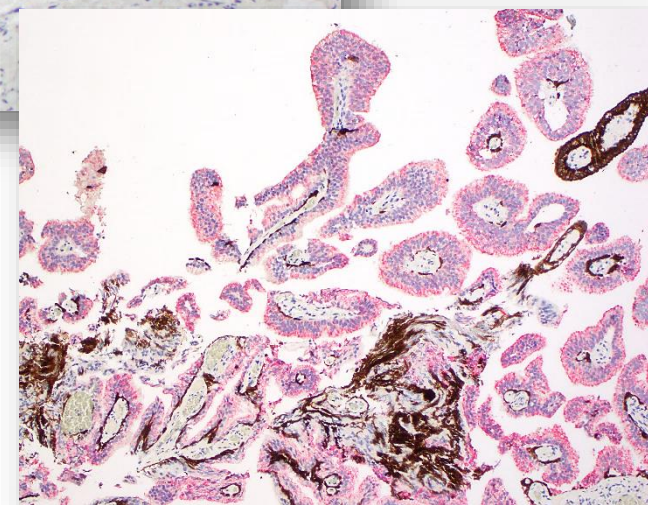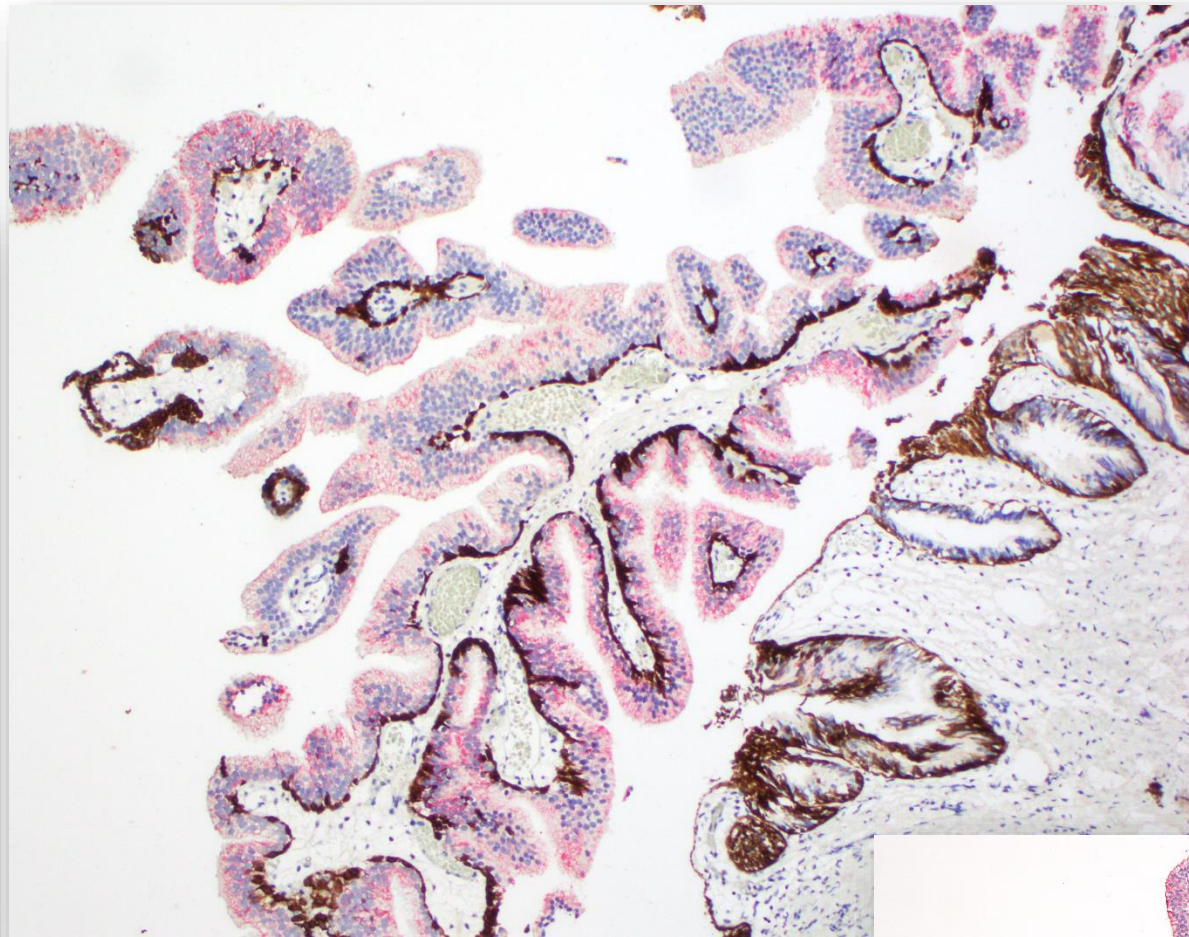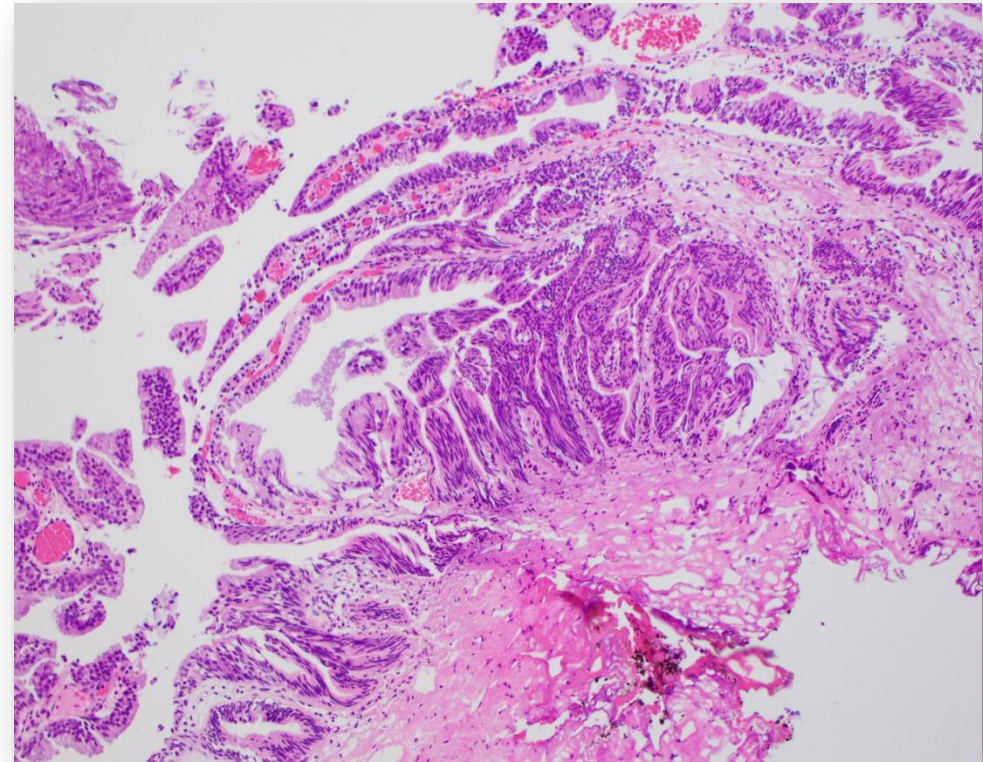
Non Invasive Ductal Ca
Ductal IDC-P?

# WHO Classification of the Urinary and Male Genital Tumours
## *5th edition series*

- WHO *5th edition series* **structural reorganization**

- Refinements of **terminology** and **classification**

- Precursor lesions **(HGPIN; IDC-P; IAP)**

- **Grading / computational pathology (AI)**

- Advances in **molecular pathways** (targets of therapy)

**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

- November 2014: 65 pathology experts & 17 clinicians (urologists, radiation oncologists, and oncologists) from 19 countries

- Grade Groups 1-5

# Prostate Adenocarcinoma Grading
# WHO *5th edition*

## The 2019 Genitourinary Pathology Society (GUPS) White Paper on Contemporary Grading of Prostate Cancer

Jonathan I. Epstein, MD; Mahul B. Amin, MD; Samson W. Fine, MD; Ferran Algaba, MD, PhD; Manju Aron, MD; Dilek E. Baydar, MD; Antonio Lopez Beltran, MD, PhD; Fadi Brimo, MD; John C. Cheville, MD; Maurizio Colecchia, MD; Eva Comperat, MD, PhD; Isabela Werneck da Cunha, MD, PhD; Warick Delprado, MD; Angelo M. DeMarzo, MD, PhD; Giovanna A. Giannico, MD; Jennifer B. Gordetsky, MD; Charles C. Guo, MD; Donna E. Hansel, MD, PhD; Michelle S. Hirsch, MD, PhD; Jiaoti Huang, MD, PhD; Peter A. Humphrey, MD, PhD; Rafael E. Jimenez, MD; Francesca Khani, MD; Qingnuan Kong, MD; Oleksandr N. Kryvenko, MD; L. Priya Kunju, MD; Priti Lal, MD; Mathieu Latour, MD; Tamara Lotan, MD; Fiona Maclean, MD; Cristina Magi-Galluzzi, MD, PhD; Rohit Mehra, MD; Santosh Menon, MD; Hiroshi Miyamoto, MD, PhD; Rodolfo Montironi, MD; George J. Netto, MD; Jane K. Nguyen, MD, PhD; Adeboye O. Osunkoya, MD; Anil Parwani, MD; Brian D. Robinson, MD; Mark A. Rubin, MD; Rajal B. Shah, MD; Jeffrey S. So, MD; Hiroyuki Takahashi, MD, PhD; Fabio Tavora, MD, PhD; Maria S. Tretiakova, MD, PhD; Lawrence True, MD; Sara E. Wobker, MD; Ximing J. Yang, MD, PhD; Ming Zhou MD, PhD; Debra L. Zynger, MD; Kiril Trpkov, MD

## The 2019 International Society of Urological Pathology (ISUP) Consensus Conference on Grading of Prostatic Carcinoma

Geert J.L.H. van Leenders, MD,* Theodorus H. van der Kwast, MD,† David J. Grignon, MD,‡ Andrew J. Evans, MD,§ Glen Kristiansen, MD,‖ Charlotte F. Kweldam, MD,* Geert Litjens, PhD,¶ Jesse K. McKenney, MD,# Jonathan Melamed, MD,** Nicholas Mottet, MD,††‡‡ Gladell P. Paner, MD,§§ Hemamali Samaratunga, FRCPA,‖‖ Ivo G. Schoots, MD,¶¶ Jeffry P. Simko, MD,## Toyonori Tsuzuki, MD,*** Murali Varma, MD,††† Anne Y. Warren, MD, FRCPath,‡‡‡ Thomas M. Wheeler, MD,§§§ Sean R. Williamson, MD,‖‖‖‖ ISUP Grading Workshop Panel Members, and Kenneth A. Iczkowski, MD¶¶

- 2019 grading changes proposed by ISUP and GUPS are **yet to be fully validated**

- **Specific differences** in recommendations **cannot be resolved on the basis of currently available evidence**

- Awaiting more definitive evidence, **pathologists should specify which variant of the Gleason grading system recommendations** is being used

# Prostate Adenocarcinoma Grading
## WHO *5th edition*

**Both societies advocate reporting**

- Estimate of the percentage of **pattern 4** with Gleason score 7 (GG2 or GG3)

- Presence of **invasive cribriform carcinoma** in Gleason score 7 and 8 cases (GG2-4)

- Acknowledged problems in **interobserver reproducibility** of pattern 4 (fused glands, poorly and formed glands more problematic than cribriform)

# Prostate Adenocarcinoma Grading
## **WHO** *5th edition*

**The 2019 Genitourinary Pathology Society (GUPS) White Paper on Contemporary Grading of Prostate Cancer**

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**Cribriform pattern 4 issues**

- Precise definition/reproducibility (*small vs large*)

- Distinction from IDC-P without IHC

- Exclusion of IDC-P from Gleason grading **may be problematic, and potentially unnecessary,** without more extensive utilization of IHC in routine practice
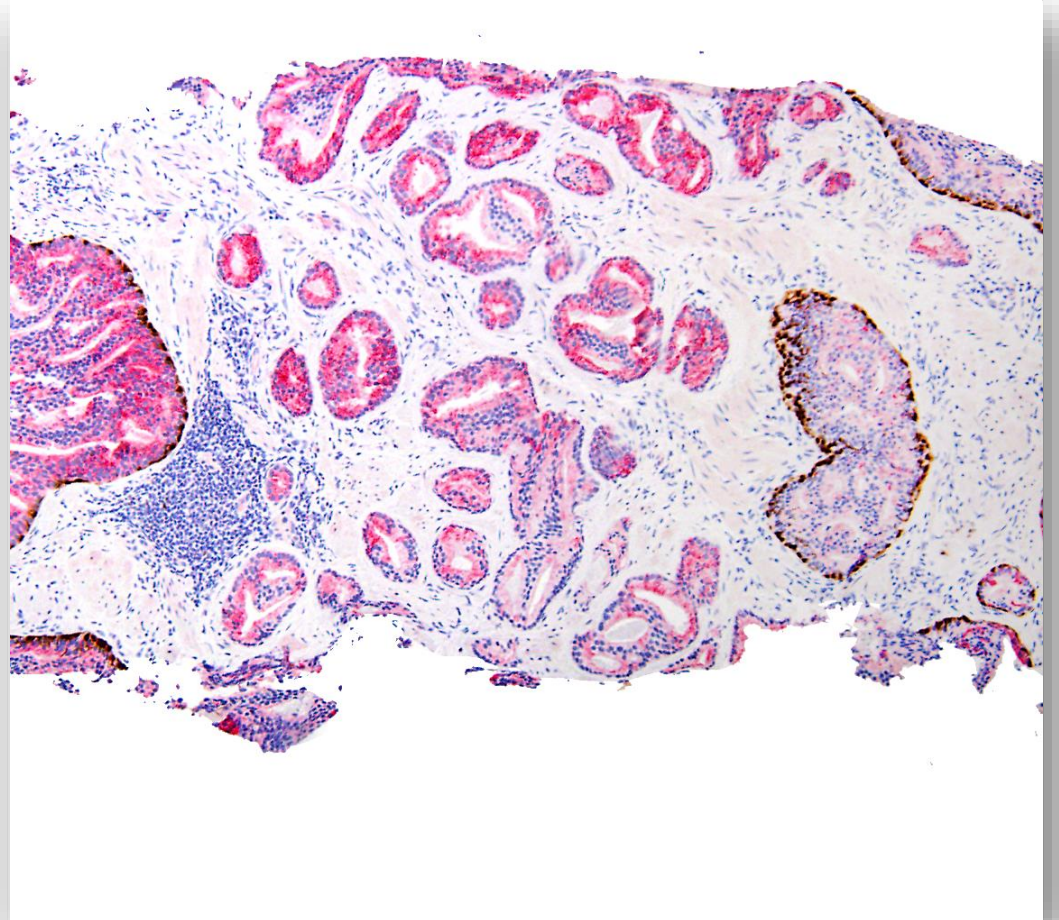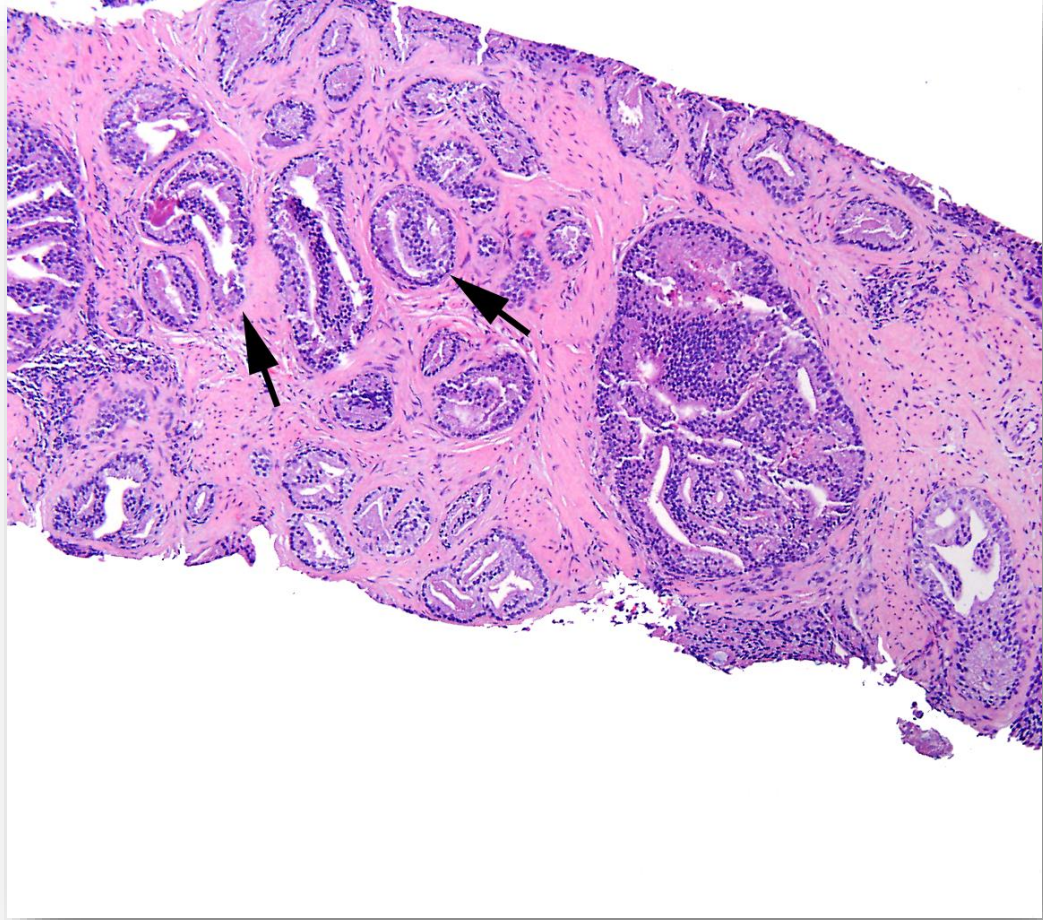
REVIEW

# Head to head: should the intraductal component of invasive prostate cancer be graded?

Murali Varma[1,2] iD & Jonathan I Epstein[3] iD
[1]*Cardiff University, Cardiff,* [2]*University Hospital of Wales, Cardiff, UK, and* [3]*The Johns Hopkins Medical Institutions, Baltimore, MD, USA*

# IDC-P Grading?

The 2019 International Society of Urological Pathology (ISUP) Consensus Conference on Grading of Prostatic Carcinoma

Geert J.L.H. van Leenders, MD,* Theodorus H. van der Kwast, MD,† David J. Grignon, MD,‡
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Anne Y. Warren, MD, FRCPath,‡‡‡ Thomas M. Wheeler, MD,§§§
Sean R. Williamson, MD,‖‖‖‖ ISUP Grading Workshop Panel Members,
and Kenneth A. Iczkowski, MD¶¶¶

*van Leenders, Geert J.L.H et al . AJSP 2020*

**TABLE 2.** Summary of ISUP 2019 Modifications to Prostate Cancer Grading

Report in biopsies the percentage Gleason pattern 4 for all GS 7 (ISUP GG 2 and 3)

For radical prostatectomies, include the presence of tertiary/minor Gleason patterns 4 and 5 in the GS, if constituting >5% of the tumor volume

Report in radical prostatectomies presence of tertiary/minor Gleason patterns 4 and 5

Do not grade IDC without invasive cancer

Incorporate the grade of IDC into the GS when invasive cancer is present

Comment on the presence and significance of IDC in biopsies and radical prostatectomy specimens

Comment on the presence and significance of invasive cribriform cancer in biopsies and radical prostatectomy specimens

Report in systematic biopsies a separate GS (ISUP GG) for each individual biopsy site

Report in mpMRI-targeted biopsies a global (aggregate) GS (ISUP GG) for each suspicious MRI lesion

Report specific benign histologic findings in suspicious (PIRADS 4-5) MRI-targeted biopsies without cancer

# The 2019 Genitourinary Pathology Society (GUPS) White Paper on Contemporary Grading of Prostate Cancer

Jonathan I. Epstein, MD; Mahul B. Amin, MD; Samson W. Fine, MD; Ferran Algaba, MD, PhD; Manju Aron, MD;
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Ming Zhou MD, PhD; Debra L. Zynger, MD; Kiril Trpkov, MD

## IDC-P Grading?

| | Table 8. Summary of Recommendations on Intraductal Carcinoma (IDC-P) |
|---|---|
| 1 | Report the presence of IDC-P in biopsy and radical prostatectomy specimens |
| 2 | Use criteria based on dense cribriform glands and/or solid nests and/or marked pleomorphism/necrosis. Dense cribriform glands are defined >50% of the gland composed of epithelium relative to luminal spaces; where the ratio is approximately equal, it is prudent to be conservative and diagnose the lesion as not meeting full criteria for IDC-P |
| 3 | When IDC-P is identified on prostate biopsy without concomitant invasive adenocarcinoma, add a comment stating that IDC-P is usually associated with high-grade prostate cancer |
| 4 | **Perform IHC for basal cell markers when the biopsy shows Gleason score 6 cancer and cribriform glands that include a differential diagnosis of IDC-P versus Gleason pattern 4 cancer** |
| 5 | **It is not necessary to perform basal cell IHC on needle biopsy and radical prostatectomy to identify IDC-P if the results of the stains would not change the overall highest Gleason score/Grade Group for the case** |
| 6 | **Do not include IDC-P in determining the final Gleason score on biopsy and/or radical prostatectomy** |

*Epstein JI et al . APLM 2020*

# Intraductal carcinoma has a minimal impact on Grade Group assignment in prostate cancer biopsy and radical prostatectomy specimens

L. Lucia Rijstenberg,[1] Tim Hansum,[1] Eva Hollemans,[1] (iD) Charlotte F Kweldam,[1,2] Intan P Kümmerlin,[1] Chris H Bangma,[3] Theodorus H van der Kwast,[4] Monique J Roobol[3] & Geert J L H van Leenders[1] (iD)

- IDC-P grade assignment lead to GG change in **1.6%** of Bx & **0.6%** of RP

- Inclusion of IDC in GG **might affect decision-making** in individual patients

- **Minimal Impact on overall** prostate cancer management

# Computational Pathology
## Prostate Adenocarcinoma Grading

## Automated deep-learning system for Gleason grading of prostate cancer using biopsies: a diagnostic study

*Wouter Bulten, Hans Pinckaers, Hester van Boven, Robert Vink, Thomas de Bel, Bram van Ginneken, Jeroen van der Laak, Christina Hulsbergen-van de Kaa, Geert Litjens*

*Lancet Oncol* 2020

## Development and Validation of a Deep Learning Algorithm for Gleason Grading of Prostate Cancer From Biopsy Specimens

Kunal Nagpal, MS; Davis Foote, BS; Fraser Tan, PhD; Yun Liu, PhD; Po-Hsuan Cameron Chen, PhD; David F. Steiner, MD, PhD; Naren Manoj, BS; Niels Olson, MD; Jenny L. Smith, DO; Arash Mohtashamian, MD; Brandon Peterson, MD; Mahul B. Amin, MD; Andrew J. Evans, MD, PhD; Joan W. Sweet, MD; Carol Cheung, MD, PhD, JD; Theodorus van der Kwast, MD, PhD; Ankur R. Sangoi, MD; Ming Zhou, MD, PhD; Robert Allan, MD; Peter A. Humphrey, MD, PhD; Jason D. Hipp, MD, PhD; Krishna Gadepalli, MS; Greg S. Corrado, PhD; Lily H. Peng, MD, PhD; Martin C. Stumpe, PhD; Craig H. Mermel, MD, PhD

*JAMA Oncol.* 2020;

## Artificial intelligence for diagnosis and grading of prostate cancer in biopsies: a population-based, diagnostic study

*Peter Ström\*, Kimmo Kartasalo\*, Henrik Olsson, Leslie Solorzano, Brett Delahunt, Daniel M Berney, David G Bostwick, Andrew J Evans, David J Grignon, Peter A Humphrey, Kenneth A Iczkowski, James G Kench, Glen Kristiansen, Theodorus H van der Kwast, Katia R M Leite, Jesse K McKenney, Jon Oxley, Chin-Chen Pan, Hemamali Samaratunga, John R Srigley, Hiroyuki Takahashi, Toyonori Tsuzuki, Murali Varma, Ming Zhou, Johan Lindberg, Cecilia Lindskog, Pekka Ruusuvuori, Carolina Wählby, Henrik Grönberg, Mattias Rantalainen, Lars Egevad, Martin Eklund*

*Lancet Oncol* 2020

## Independent real-world application of a clinical-grade automated prostate cancer detection system

Leonard M da Silva[1], Emilio M Pereira[1], Paulo GO Salles[2], Ran Godrich[3], Rodrigo Ceballos[3], Jeremy D Kunz[3], Adam Casson[3], Julian Viret[3], Sarat Chandarlapaty[4], Carlos Gil Ferreira[1], Bruno Ferrari[1], Brandon Rothrock[3], Patricia Raciti[3], Victor Reuter[5], Belma Dogdas[3], George DeMuth[6], Jillian Sue[3], Christopher Kanan[3], Leo Grady[3], Thomas J Fuchs[3]\* and Jorge S Reis-Filho[5]\*

*J Pathol* June 2021;

# Prostate Adenocarcinoma Grading
## WHO *5th edition*

**Role of Computational Pathology & AI**

- AI-based algorithms can perform grading at the level of **experienced subspecialized uropathologists**
- Potential avenue for **improving inter- and intra-observer** variability
- AI-based algorithms could lead to **more accurate quantification of patterns**


- More **extensive prospective validation is needed**

# WHO Classification of the Urinary and Male Genital Tumours
## *5th edition series*

- WHO *5th edition series* **structural reorganization**

- Refinements of **terminology** and **classification**

- Precursor lesions **(HGPIN; IDC-P; IAP)**

- **Grading / computational pathology (AI)**

- Advances in **molecular pathways** (targets of therapy)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Inherited DNA-Repair Gene Mutations in Men with Metastatic Prostate Cancer

C.C. Pritchard, J. Mateo, M.F. Walsh, N. De Sarkar, W. Abida, H. Beltran, A. Garofalo, R. Gulati, S. Carreira, R. Eeles, O. Elemento, M.A. Rubin, D. Robinson, R. Lonigro, M. Hussain, A. Chinnaiyan, J. Vinson, J. Filipenko, L. Garraway, M.-E. Taplin, S. AlDubayan, G.C. Han, M. Beightol, C. Morrissey, B. Nghiem, H.H. Cheng, B. Montgomery, T. Walsh, S. Casadei, M. Berger, L. Zhang, A. Zehir, J. Vijai, H.I. Scher, C. Sawyers, N. Schultz, P.W. Kantoff, D. Solit, M. Robson, E.M. Van Allen, K. Offit, J. de Bono, and P.S. Nelson

July 2016

- 692 men with **metastatic prostate cancer** who were **unselected for family history** of cancer or **age** at diagnosis
- Multiplex sequencing assays to assess **GERMLINE** mutations **20 DNA-repair genes**
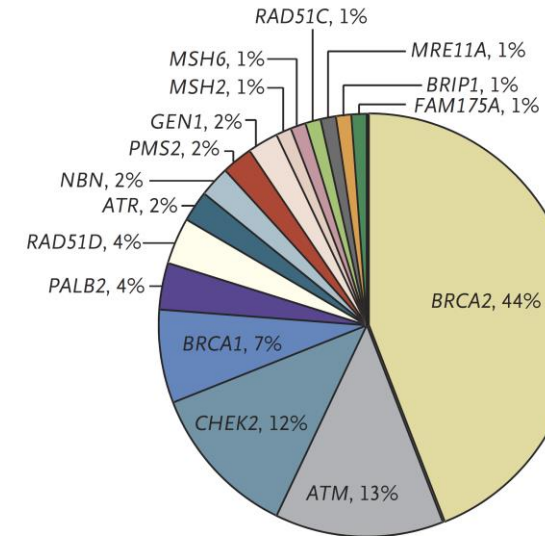
# Homologous Recombination Genes
## (DNA Repair Pathway Defect)
## Prostate NCCN 2018

- Prevalence of **inherited (germline)** homologous recombination gene mutations in men with **metastatic** or localized high risk was 11.8% and 6.0%, respectively

- Germline genetic testing and genetic counseling should be considered in all men with **high risk, very high risk, regional, or metastatic** prostate: BRCA1, BRCA2, ATM, PALB2, FANCA

*Pritchard CC, Mateo J, Walsh MF, et al. Inherited DNA-repair gene mutations in men with metastatic prostate cancer. N Engl J Med 2016;375:443-453*

## Homologous DNA Repair Pathway Defect
## Prostate NCCN 2018

- Consider testing (somatic): *BRCA1, BRCA2, ATM, PALB2, FANCA*:
  - early use of **platinum chemotherapy**
  - eligibility for clinical trials (e.g., **PARP inhibitors**)

*Mateo J, Carreira S, Sandhu S, et al. DNA-repair defects and olaparib in metastatic prostate cancer.*
*N Engl J Med 2015; 373: 1697-708.*

*Cheng HH, Pritchard CC, Boyd T, Nelson PS, Montgomery B. Biallelic inactivation of BRCA2 in platinum-sensitive metastatic castration-resistant prostate cancer.*
*Eur Urol 2016; 69: 992-5.*

ORIGINAL ARTICLE

WILEY  The Prostate

# Intraductal/ductal histology and lymphovascular invasion are associated with germline DNA-repair gene mutations in prostate cancer

Pedro Isaacsson Velho[1] | John L. Silberstein[2] | Mark C. Markowski[1] | Jun Luo[2] | Tamara L. Lotan[3] | William B. Isaacs[2] | Emmanuel S. Antonarakis[1,2]

| Patient characteristics | | | |
|---|---|---|---|
| | Germline mutation positive | Germline mutation negative | |
| Total no. of patients | N = 21 | N = 129 | P value |
| Median age (in years), and range | | | |
|   At initial diagnosis | 61 (49-75) | 63 (41-88) | 0.56 |
|   At time of germline testing | 65 (58-79) | 68 (44-88) | 0.22 |
| Race, % (N) | | | |
|   White | 80.9% (17) | 89.1% (115) | 0.48 |
|   Non-white | 19.1% (4) | 10.9% (14) | |
| 1st or 2nd degree relative, % (N) | | | |
|   With prostate cancer | 38.1% (8) | 40.3% (52) | 1.00 |
|   With breast, ovarian, uterine, colon, gastric, or pancreatic cancer | 52.3% (11) | 51.9% (67) | 1.00 |
| Patients who fulfill NCCN criteria for genetic screening (see Table 4) | | | |
|   Evaluable patients (N) | 18 | 90 | 0.06 |
|   Positive criteria, % (N) | 55.6% (10) | 20.0% (18) | |
|   Negative criteria, % (N) | 44.4% (8) | 80.0% (72) | |
| Type of tissue used for histological analysis | | | |
|   Radical prostatectomy, % (N) | 71.4% (15) | 63.6% (82) | 0.62 |
|   Prostate biopsies, % (N) | 28.6% (6) | 36.4% (47) | |
| Clinical state at the time of germline testing | | | |
|   Biochemical recurrence after local therapy, % (N) | 38.1% (8) | 48.1% (62) | 0.61 |
|   Metastatic hormone-sensitive PCa, % (N) | 19.0% (4) | 19.4% (25) | |
|   Metastatic castration-resistant PCa, % (N) | 42.9% (9) | 32.5% (42) | |
| Tumor stage at diagnosis*, % (N) | | | |
|   T1/T2 | 33.3% (7) | 34.8% (45) | 0.81 |
|   T3/T4 | 61.9% (13) | 52.7% (68) | |
|   Not reported | 4.7% (1) | 12.4% (16) | |
| M1 disease at diagnosis, % (N) | 14.2% (3) | 23.2% (30) | 0.40 |
| Gleason sum at diagnosis, % (N) | | | |
|   ≤7 | 23.8% (5) | 40.3% (52) | 0.15 |
|   ≥8 | 76.1% (16) | 58.1% (75) | |
|   Not reported | 0% (0) | 1.6% (2) | |
| Presence of intraductal or ductal histology, % (N) | 47.6% (10) | 11.6% (15) | 0.003 |
| Presence of lymphovascular invasion, % (N) | 52.3% (11) | 13.9% (18) | <0.001 |
| Presence of perineural invasion, % (N) | 52.3% (11) | 51.9% (67) | 1.00 |
| PSA level at diagnosis (ng/mL) | | | |
|   Median (range) | 5.5 (1.3-22.0) | 8.6 (0.9-1540) | 0.01 |

# MMR/ MSI
## Prostate NCCN 2018

- Positive MSI-H or dMMR (IHC):
  - Eligibility for **pembrolizumab** in later lines of treatment for CRPC (M1 Castration Resistant)

  - The prevalence of **MMR deficiency in metastatic CPRC 2%-5%**

# Clinical Features and Therapeutic Outcomes in Men with Advanced Prostate Cancer and DNA Mismatch Repair Gene Mutations

Emmanuel S. Antonarakis [a,b,*], Farah Shaukat [a], Pedro Isaacsson Velho [a], Harsimar Kaur [c], Eugene Shenderov [a,b], Drew M. Pardoll [a,b], Tamara L. Lotan [a,c]
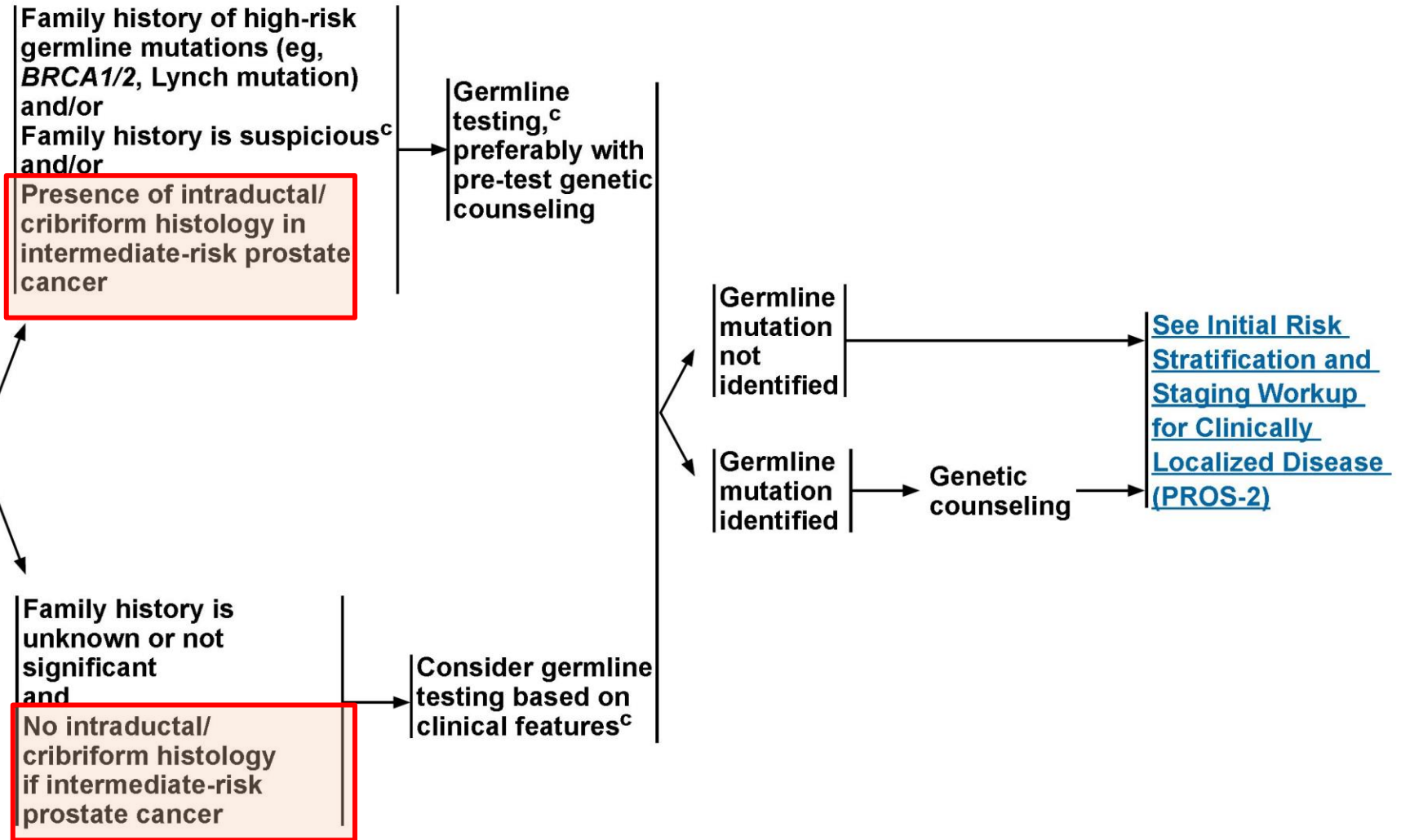
[a] Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine, Baltimore, MD, USA; [b] Bloomberg-Kimmel Institute for Cancer Immunotherapy, Johns Hopkins University School of Medicine, Baltimore, MD, USA; [c] Department of Pathology, Johns Hopkins University School of Medicine, Baltimore, MD, USA

| Patient ID | Gleason score, tumor stage | Specimen type tested | Variant histology | MMR gene mutation | Protein IHC status | MSI markers shifted [a] | MSI status [a] | Mutation load | Other mutations of interest |
|---|---|---|---|---|---|---|---|---|---|
| #1 | 4 + 5 = 9 T3a N0 | RP | None noted | MSH2 (C778X*) | MSH2 and MSH6 loss [b] MLH1 and PMS2 intact | 0/5 | MSS | 11 muts/Mb [c] | AKT1 (E17K) CTNNB1 (D32G) TMPRSS2–ERG fusion |
| #2 | 3 + 4 = 7 T3bN1 | RP | None noted | PMS2 (L729Qfs*6) | MSH2, MSH6, MLH1, PMS2 all intact | 0/5 | MSS | 3 muts/Mb | TP53 (R273H) PMS2 (T728A) |
| #3 | 3 + 4 = 7 T3b N0 | RP | None noted | gMSH6 (A1320Sfs*5) | Adequate tissue not available | No somatic (tumor) DNA analysis was performed | | | |
| #4 | 5 + 5 = 10 | Bx | None noted | MSH6 (F1088Sfs*2) | MSH6 loss only MSH2, MLH1, PMS2 intact | 3/5 | MSI-high | 18 muts/Mb | PMS2 (D414Tfs*34) JAK1 (N339Ifs*3) RET (L1048Sfs*61) RNF43 (G659Vfs*41) |
| #5 | 4 + 5 = 9 | Bx | None noted | MSH6 (F1088Lfs*5) | MSH2 and MSH6 loss MLH1 and PMS2 intact | 3/5 | MSI-high | 35 muts/Mb | BRCA2 (N1784Kfs*3) HRAS (P167Rfs*51) JAK2 (N457Mfs*22) TP53 (D281N) |
| #6 | 4 + 5 = 9 | Bx | Intraductal carcinoma | gMSH6 (V1192Lfs*3) | Adequate tissue not available | No somatic (tumor) DNA analysis was performed | | | |
| #7 | 4 + 5 = 9 T3b N0 | RP | None noted | PMS2 (M622Efs*5) | MSH2, MSH6, MLH1, PMS2 all intact | 0/5 | MSS | 6 muts/Mb | KMT2A (S774Vfs*12) TP53 (H179Q) |
| #8 | 4 + 5 = 9 T3a N0 | RP | None noted | MLH1 (heterozygous gene deletion) | MLH1 and PMS2 loss MSH2 and MSH6 intact | 2/5 | MSI-high | 13 muts/Mb | PTEN (K267Efs*9) RNF43 (G659Vfs*41) TP53 (T155I) TMPRSS2–ERG fusion |
| #9 | Unknown (no primary tumor biopsy) | Lymph node | None noted | MSH2 (L376Ffs*13) | MSH2 and MSH6 loss MLH1 and PMS2 intact | 4/5 | MSI-high | 42 muts/Mb | PMS1 (T256Hfs*2) TP53 (Q167X*) TP53 (S240G) PIK3CA (H1047R) |
| #10 | 4 + 5 = 9 | Bx | Intraductal carcinoma | MSH6 (E192X*) | Adequate tissue not available | 1/5 | MSI-low | 8 muts/Mb | TP53 (E271V) BRCA2 (P3189H) |
| #11 | 4 + 5 = 9 | Bx | None noted | MLH1 (T206Mfs*23) | PMS2 loss only MLH1, MSH2, MSH6 intact | 2/5 | MSI-high | 20 muts/Mb | BRCA1 (Q1111Efs*5) PTEN (T319Ifs*1) RNF43 (G659Vfs*41) CTNNB1 (T41A) TMPRSS2–ERG fusion |
| #12 | 4 + 4 = 8 | Bx | None noted | gMSH6 (E230Sfs*4) | MSH6 loss only MSH2, MLH1, and PMS2 all intact | 2/5 | MSI-high | 22 muts/Mb | TP53 (A76Vfs*55) TMPRSS2–ERG fusion |
| #13 | 4 + 5 = 9 T3a N0 | RP | Intraductal carcinoma | MSH2 (E809X*) + LOH of 2nd allele | MSH2 and MSH6 loss MLH1 and PMS2 intact | 4/5 | MSI-high | 165 muts/Mb | MSH6 (F1104Lfs*11) ATM (L663Ffs*2) ERCC4 (M361Nfs*4) ERCC5 (E474Nfs*15) FANCM (V1336Lfs*2) |

**INITIAL PROSTATE CANCER DIAGNOSIS[a,b,c]**

- Perform digital rectal exam (DRE) to confirm clinical stage
- Perform and/or collect prostate specific antigen (PSA) and calculate PSA density and PSA doubling time (PSADT)
- Obtain and review diagnostic prostate biopsies
- Estimate life expectancy (See Principles of Life Expectancy Estimation [PROS-A])
- Inquire about known high-risk germline mutations[c]
- Obtain family history[c]

Family history of high-risk germline mutations (eg, *BRCA1/2*, Lynch mutation) and/or
Family history is suspicious[c] and/or
Presence of intraductal/ cribriform histology in intermediate-risk prostate cancer

→ Germline testing,[c] preferably with pre-test genetic counseling

Family history is unknown or not significant
and
No intraductal/ cribriform histology if intermediate-risk prostate cancer

→ Consider germline testing based on clinical features[c]

Germline mutation not identified → See Initial Risk Stratification and Staging Workup for Clinically Localized Disease (PROS-2)

Germline mutation identified → Genetic counseling → See Initial Risk Stratification and Staging Workup for Clinically Localized Disease (PROS-2)

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## PRINCIPLES OF GENETICS AND MOLECULAR/BIOMARKER ANALYSIS

| |
|---|
| **Germline testing is recommended _in patients with a personal history of prostate cancer_ in the following scenarios:** |

**• By Prostate Cancer Stage or Risk Group (diagnosed at any age)**
  ‣ Metastatic, regional (node positive), very-high risk localized, high-risk localized prostate cancer

**• By Family History[a] and/or Ancestry**
  ‣ ≥1 first-, second-, or third-degree relative with:
    ◊ breast cancer at age ≤50 y
    ◊ colorectal or endometrial cancer at age ≤50 y
    ◊ male breast cancer at any age
    ◊ ovarian cancer at any age
    ◊ exocrine pancreatic cancer at any age
    ◊ metastatic, regional, very-high-risk, high-risk prostate cancer at any age
  ‣ ≥1 first-degree relative (father or brother) with:
    ◊ prostate cancer[b] at age ≤60 y
  ‣ ≥2 first-, second-, or third-degree relatives with:
    ◊ breast cancer at any age
    ◊ prostate cancer[b] at any age
  ‣ ≥3 first- or second-degree relatives with:
    ◊ Lynch syndrome-related cancers, especially if diagnosed <50 y: colorectal, endometrial, gastric, ovarian, exocrine pancreas, upper
      tract urothelial, glioblastoma, biliary tract, and small intestinal cancer
  ‣ A known family history of familial cancer risk mutation (pathogenic/likely pathogenic variants), especially in: *BRCA1, BRCA2, ATM,*
    *PALB2, CHEK2, MLH1, MSH2, MSH6, PMS2, EPCAM*
  ‣ Ashkenazi Jewish ancestry
**• Personal history of breast cancer**

| |
|---|
| **Germline testing may be considered _in patients with a personal history of prostate cancer_ in the following scenarios:** |

**• By Prostate Cancer Tumor Characteristics (diagnosed at any age)**
    ◊ intermediate-risk prostate cancer with intraductal/cribriform histology[c]
**• By prostate cancer[b] AND a prior personal history of any of the following cancers:**
    ◊ exocrine pancreatic, colorectal, gastric, melanoma, pancreatic, upper tract urothelial, glioblastoma, biliary tract, and small intestinal

[a] Close blood relatives include first-, second-, and third-degree relatives on the same side of the family. See Pedigree: First-, Second-, and Third-Degree Relatives of
  Proband (EVAL-B) in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic.
[b] Family history of prostate cancer should not include relatives with clinically localized Grade Group 1 disease.
[c] Acinar prostate adenocarcinoma with invasive cribriform pattern, intraductal carcinoma of prostate (IDC-P) or ductal adenocarcinoma component have increased
  genomic instability, and germline testing may be considered.

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**PRINCIPLES OF GENETICS AND MOLECULAR/BIOMARKER ANALYSIS**

**SOMATIC TUMOR TESTING**

- Tumor testing for HRD (BRCA1, BRCA2, ATM, PALB2, FANCA, RAD51D, CHEK2, and CDK12) **recommended** in metastatic PCa and **considered** in regional PCa

- Tumor testing for MSI or dMMR **recommended** in metastatic CRPCa and **considered** in regional or castration-naïve metastatic PCa

- TMB testing. **considered** in metastatic CRPCa

# PCA Commercial Gene Expression Assays

| Assay | Company | Sample | Platform | Clinical Application |
|-------|---------|--------|----------|---------------------|
| **Prolaris®,** | Myriad Genetics | FFPE Needle Biopsy or Prostatectomy Tissue | **Cell-Cycle Progression (CCP) Score**: Expression of 31 cell cycle genes; quantitative RT-PCR | • Calculate risk of BCR or metastasis post RP<br>• Predict death of disease in conservatively treated on needle biopsy |
| **Oncotype DX®** | Genomic Health | FFPE Needle Biopsy Tissue | **Genomic Predictor Score (GPS):** Expression of 12 genes; (androgen pathway, cellular organization, cell proliferation and stromal response) ;quantitative RT-PCR | • Risk assessment prior to treatment intervention<br>• Predict adverse pathologic features |
| **Decipher™** | GenomeDx | FFPE Needle Biopsy or Prostatectomy Tissue | **Genomic Classifier (GC):** Expression of 22 genes; Gene Expression Profiling Arrays | • Calculate risk for metastasis post RP<br>• Guide clinical decision for radiotherapy in adjuvant or salvage setting<br>• Predict metastasis post RP on needle biopsy |

**PRINCIPLES OF GENETICS AND MOLECULAR/BIOMARKER ANALYSIS**

| Table 1. Initial Risk Stratification for Clinically Localized Disease | | | | |
|---|---|---|---|---|
| **Category** | **Tool** | **Predictive** | **Prognostic** | **Endpoint Trained For** |
| **Clinical** | NCCN | No | Yes | BCR* |
| | STAR-CAP[1] | No | Yes | PCSM |
| | CAPRA[3] | No | Yes | BCR |
| | MSKCC[4] | No | Yes | BCR and PCSM |
| **Imaging** | MRI | No | Yes | - |
| | PET | No | Yes | - |
| **Gene Expression Testing** | Decipher | No | Yes | Metastasis |
| | Prolaris | No | Yes | Time to BCR and time to death from prostate cancer |
| | Oncotype DX Prostate | No | Yes | Adverse pathology |
| **Germline Testing** | BRCA2 | No | Yes | - |
| *Very-low, low, favorable-intermediate, unfavorable-intermediate, high, very-high, and regional prostate cancer. | | | | |

| Table 2. Tumor-Based Molecular Assays Can be Considered in Patients with Life Expectancy ≥10y as follows: | | | | | | |
|---|---|---|---|---|---|---|
| | **Very low risk** | **Low risk** | **Favorable intermediate risk** | **Unfavorable intermediate risk** | **High risk** | **Very high risk** |
| **Decipher** | No | Yes | Yes | Yes | Yes | No |
| **Prolaris** | No | Yes | Yes | Yes | Yes | No |
| **Oncotype DX Prostate** | No | Yes | Yes | No | No | No |

# Conclusions

5th edition of WHO Classification of the Urinary and Male Genital Tumours is bringing some refinements to Prostate tumours classification

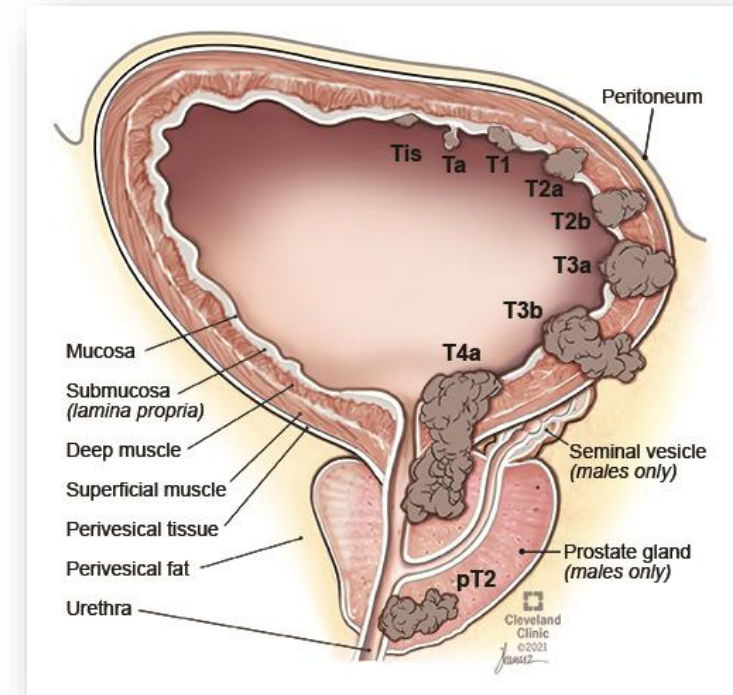URO 5 acknowledges that several issues in PCA classification remain controversial

**WHO Classification of the Urinary and Male Genital Tumours**
5th edition series
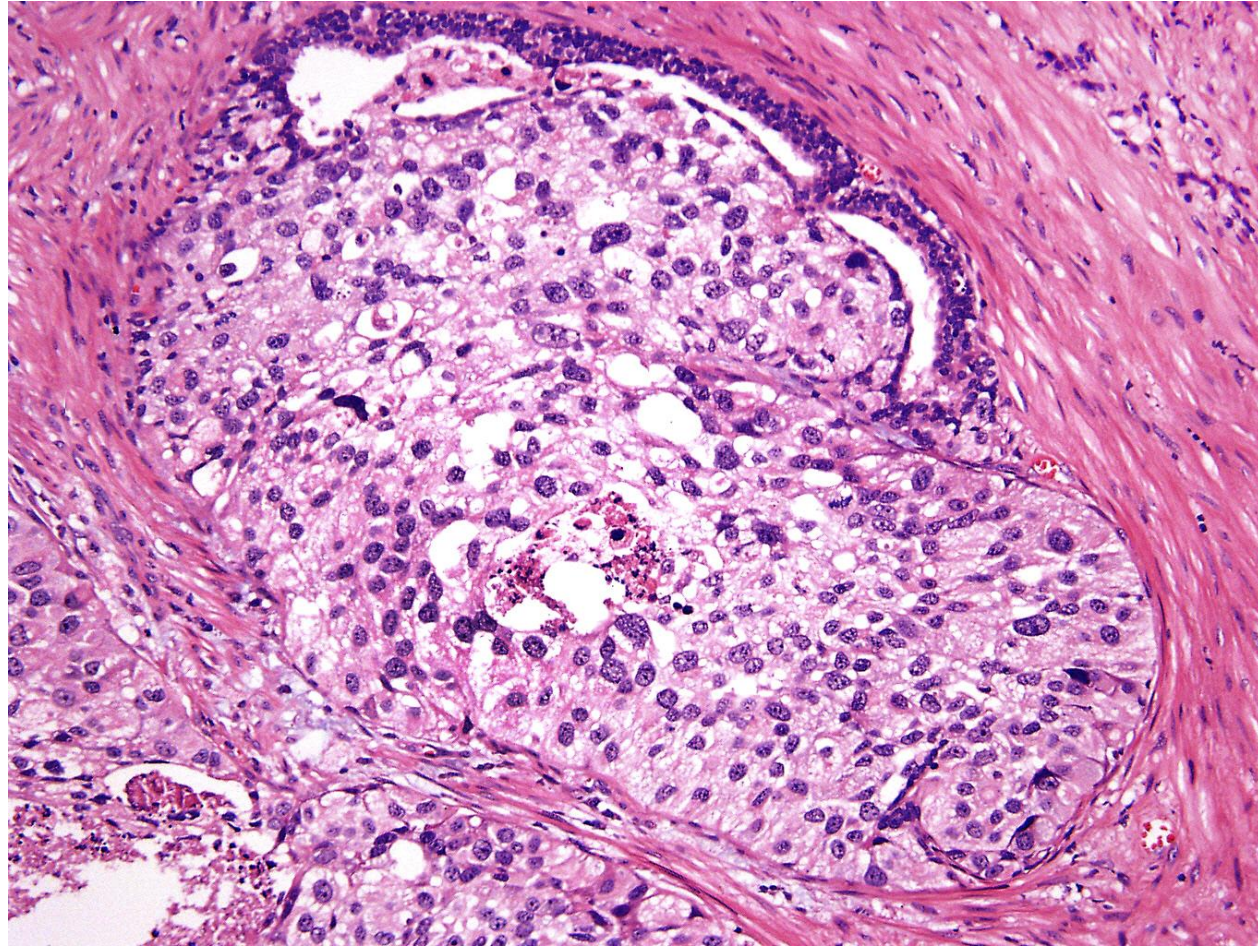
**Staging urothelial carcinoma invading prostate stroma**

- Originated in urethra **(pT2)**

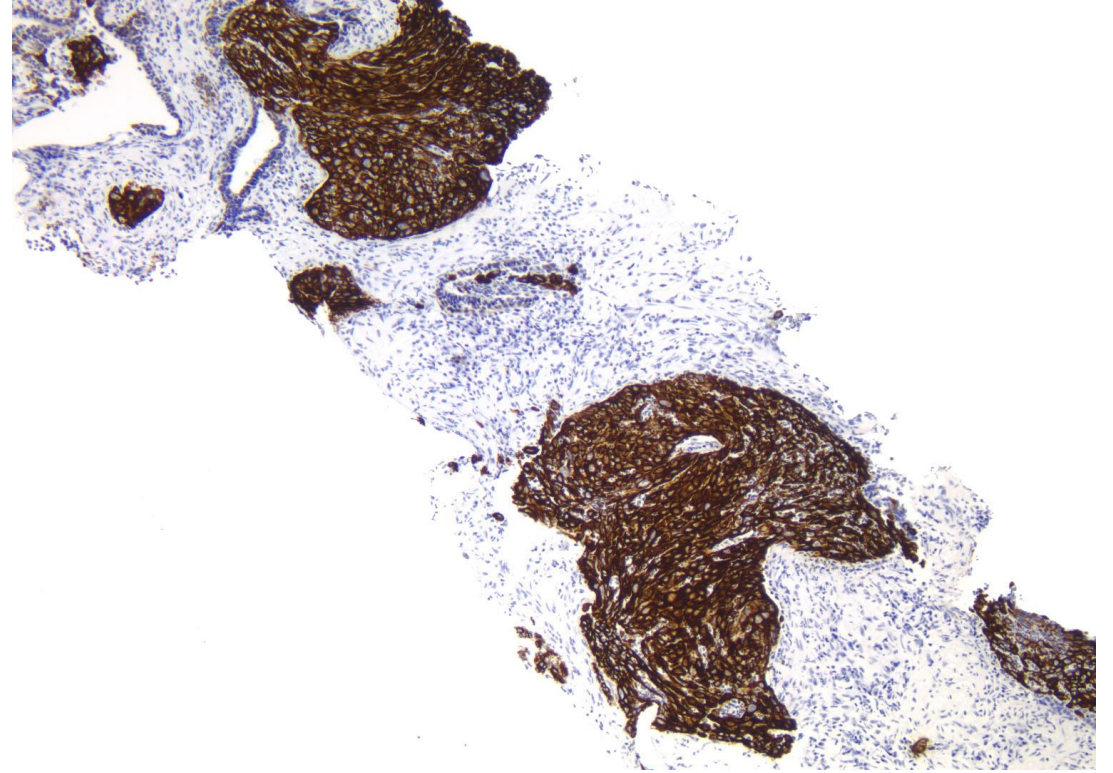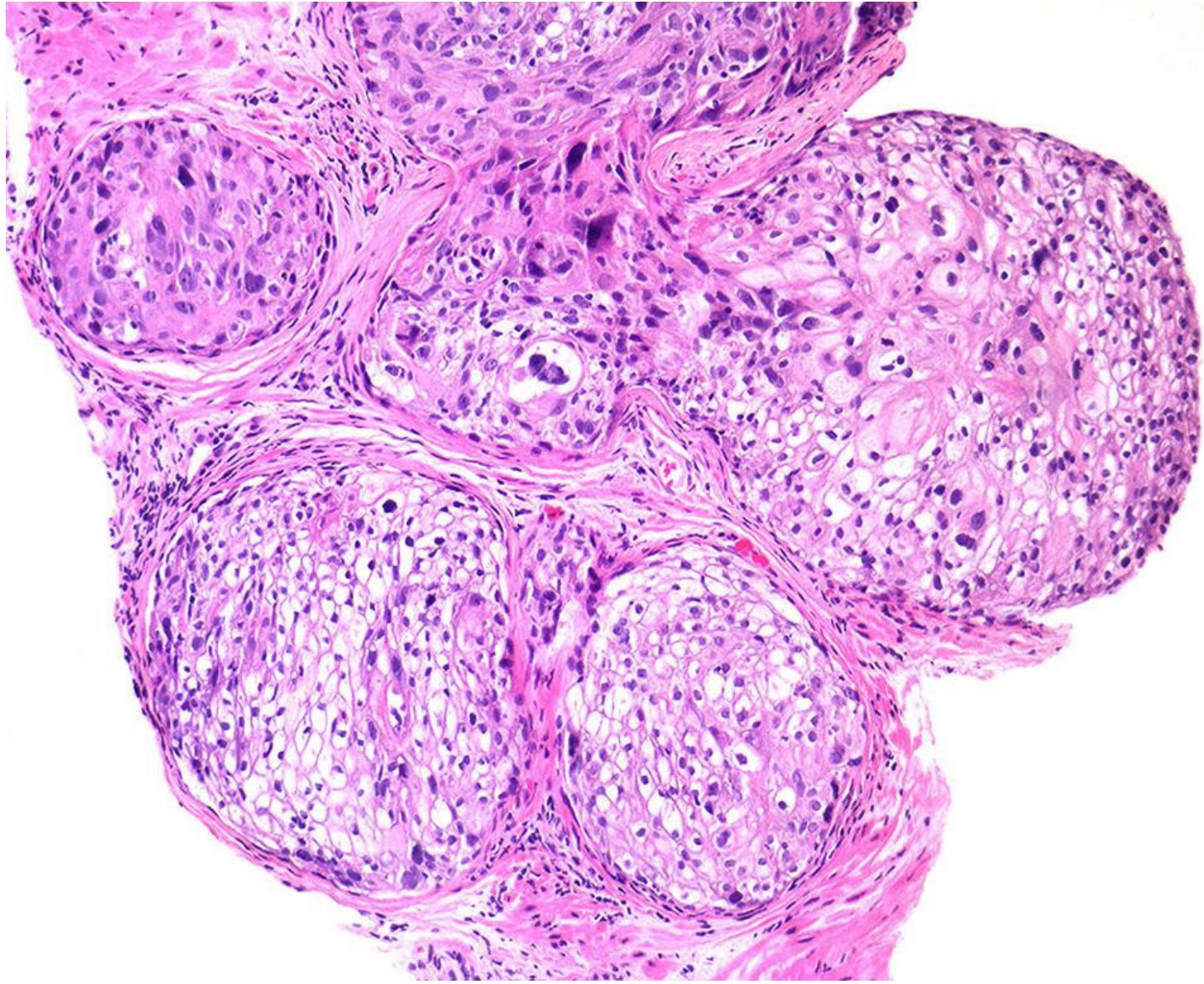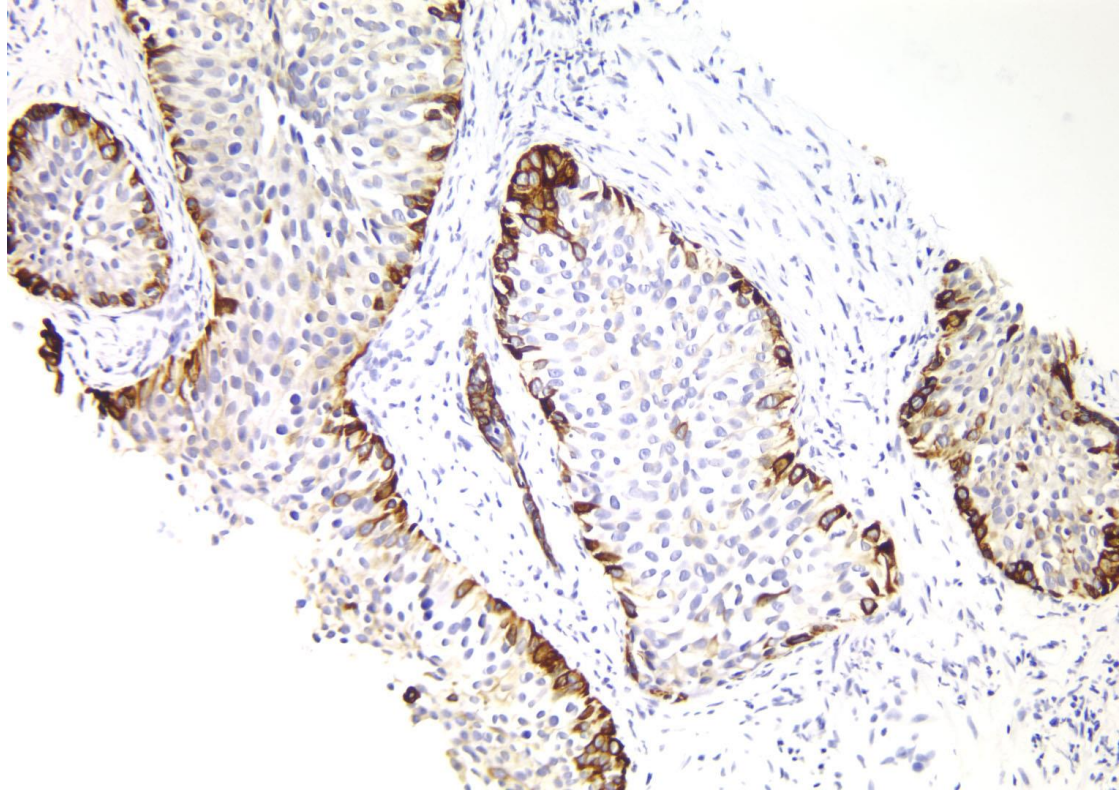- Contiguous **direct invasion** from transmural bladder primary **(pT4a)**

Courtesy of Dr. Oleksandr Kryvenko

# Should we grade IDC-P ?

# Intraductal Spread of Urothelial Carcinoma

ORIGINAL ARTICLE

# Inherited DNA-Repair Gene Mutations in Men with Metastatic Prostate Cancer

**Legend (left figure):**
- BRCA2 repeat region
- DNA-binding domain
- Tower domain
- Oligosaccharide-binding domain
- Telomere length maintenance and DNA-repair domain
- FAT domain
- PIK3 domain
- FATC domain
- UME domain
- HATPase domain
- DNA-repair domain
- MutL C-terminal
- Mutator SI domain
- Mutator SII domain
- Mutator SIII domain
- Mutator SIV domain
- Mutator SV domain
- Forkhead-associated domain
- NIBRIN BRCT domain
- NBS1 domain
- RAD51 domain
- Protein kinase domain
- RING domain
- BRCT serine-rich region
- Ethylene insensitive 3
- BRCA1 C-terminal
- DEAD2 domain
- Helicase C-terminal
- XPG N-terminal
- XPG I region
- Metalloprotease
- PWWP domain
- PALB2 WD40 domain
- Frameshift deletion
- Frameshift insertion
- Splice site
- Nonsense substitution
- Missense substitution

Left panel gene plots (No. of Mutations vs Amino Acids):
- BRCA2 (0–3418)
- ATM (0–3056)
- ATR (0–2644) — Long del exon 45-47+UTR
- FAM175A (0–409)
- PMS2 (0–863)
- MSH2 (0–934) — Long del exon 1–8
- NBN (0–754)
- RAD51C (0–376)
- CHEK2 (0–543)
- BRCA1 (0–1663)
- BRIP1 (0–1249)
- GEN1 (0–908)
- MRE11A (0–708)
- MSH6 (0–1360)
- PALB2 (0–1186)
- RAD51D (0–300)

Right panel pie chart:
- BRCA2, 44%
- ATM, 13%
- CHEK2, 12%
- BRCA1, 7%
- PALB2, 4%
- RAD51D, 4%
- ATR, 2%
- NBN, 2%
- PMS2, 2%
- GEN1, 2%
- MSH2, 1%
- MSH6, 1%
- RAD51C, 1%
- MRE11A, 1%
- BRIP1, 1%
- FAM175A, 1%

## INITIAL RISK STRATIFICATION AND STAGING WORKUP FOR CLINICALLY LOCALIZED DISEASE

| Risk Group | Clinical/Pathologic Features | | | Imaging[f,g] | Germline Testing[c] | Molecular/ Biomarker Analysis of Tumor[c] | Initial Therapy |
|---|---|---|---|---|---|---|---|
| Very low[d] | Has all of the following:<br>• T1c<br>• Grade Group 1<br>• PSA <10 ng/mL<br>• Fewer than 3 prostate biopsy fragments/cores positive, ≤50% cancer in each fragment/core[e]<br>• PSA density <0.15 ng/mL/g | | | • Consider confirmatory prostate biopsy ± mpMRI to establish candidacy for active surveillance | Recommended if family history positive<br>See PROS-1 | Not indicated | See PROS-3 |
| Low[d] | Has all of the following but does not qualify for very low risk:<br>• T1–T2a<br>• Grade Group 1<br>• PSA <10 ng/mL | | | • Consider confirmatory prostate biopsy ± mpMRI to establish candidacy for active surveillance | Recommended if family history positive<br>See PROS-1 | Consider if life expectancy ≥10 y[j] | See PROS-4 |
| Intermediate[d] | Has all of the following:<br>• No high-risk group features<br>• No very-high-risk group features<br>• Has one or more intermediate risk factors (IRF):<br>‣ T2b–T2c<br>‣ Grade Group 2 or 3<br>‣ PSA 10–20 ng/mL | Favorable intermediate | Has all of the following:<br>• 1 IRF<br>• Grade Group 1 or 2<br>• <50% biopsy cores positive[e] | • Consider confirmatory prostate biopsy ± mpMRI to establish candidacy for active surveillance<br>• Bone imaging[h]: not recommended for staging<br>• Pelvic ± abdominal imaging[i]: recommended if nomogram predicts >10% probability of pelvic lymph node involvement<br>• If regional or distant metastases are found, see PROS-8 | Recommended if family history positive or intraductal/cribriform histology<br>See PROS-1 | Consider if life expectancy ≥10 y[j] | See PROS-5 |
| | | Unfavorable intermediate | Has one or more of the following:<br>• 2 or 3 IRFs<br>• Grade Group 3<br>• ≥ 50% biopsy cores positive[e] | • Bone imaging[h]: recommended if T2 and PSA >10 ng/mL<br>• Pelvic ± abdominal imaging[i]: recommended if nomogram predicts >10% probability of pelvic lymph node involvement<br>• If regional or distant metastases are found, see PROS-8 | Recommended if family history positive or intraductal/cribriform histology<br>See PROS-1 | Consider if life expectancy ≥10 y[j] | See PROS-6 |
| High | Has no very-high-risk features and has exactly one high-risk feature:<br>• T3a OR<br>• Grade Group 4 or Grade Group 5 OR<br>• PSA >20 ng/mL | | | • Bone imaging[h]: recommended<br>• Pelvic ± abdominal imaging[i]: recommended<br>• If regional or distant metastases are found, see PROS-8 | Recommended | Consider if life expectancy ≥10 y[j] | See PROS-7 |
| Very high | Has at least one of the following:<br>• T3b–T4<br>• Primary Gleason pattern 5<br>• 2 or 3 high-risk features<br>• >4 cores with Grade Group 4 or 5 | | | • Bone imaging[h]: recommended<br>• Pelvic ± abdominal imaging[i]: recommended<br>• If regional or distant metastases are found, see PROS-8 | Recommended | Not routinely recommended | See PROS-7 |

## GENETIC AND MOLECULAR BIOMARKER ANALYSIS FOR ADVANCED PROSTATE CANCER[c]

| Risk Group | Clinical/Pathologic Features | Germline Testing[c] | Molecular and Biomarker Analysis of Tumor[c] | Initial Therapy |
|---|---|---|---|---|
| Regional | Any T, N1, M0 | Recommended | Consider tumor testing for homologous recombination gene mutations (HRRm) and for microsatellite instability (MSI) or mismatch repair deficiency (dMMR) | See PROS-9 |
| Metastatic | Any T, Any N, M1 | Recommended | Recommend tumor testing for HRRm and consider tumor testing for MSI or dMMR | See PROS-13 |

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## INITIAL RISK STRATIFICATION AND STAGING WORKUP FOR CLINICALLY LOCALIZED DISEASE

| Risk Group | Clinical/Pathologic Features | | | Imaging[f,g] | Germline Testing[c] | Molecular/ Biomarker Analysis of Tumor[c] | Initial Therapy |
|---|---|---|---|---|---|---|---|
| Very low[d] | Has all of the following: <br>• T1c <br>• Grade Group 1 <br>• PSA <10 ng/mL <br>• Fewer than 3 prostate biopsy fragments/cores positive, ≤50% cancer in each fragment/core[e] <br>• PSA density <0.15 ng/mL/g | | | • Consider confirmatory prostate biopsy ± mpMRI to establish candidacy for active surveillance | Recommended if family history positive <br>See PROS-1 | Not indicated | See PROS-3 |
| Low[d] | Has all of the following but does not qualify for very low risk: <br>• T1–T2a <br>• Grade Group 1 <br>• PSA <10 ng/mL | | | • Consider confirmatory prostate biopsy ± mpMRI to establish candidacy for active surveillance | Recommended if family history positive <br>See PROS-1 | Consider if life expectancy ≥10 y[j] | See PROS-4 |
| Intermediate[d] | Has all of the following: <br>• No high-risk group features <br>• No very-high-risk group features <br>• Has one or more intermediate risk factors (IRF): <br>▸ T2b–T2c <br>▸ Grade Group 2 or 3 <br>▸ PSA 10–20 ng/mL | Favorable intermediate | Has all of the following: <br>• 1 IRF <br>• Grade Group 1 or 2 <br>• <50% biopsy cores positive[e] | • Consider confirmatory prostate biopsy ± mpMRI to establish candidacy for active surveillance <br>• Bone imaging[h]: not recommended for staging <br>• Pelvic ± abdominal imaging[i]: recommended if nomogram predicts >10% probability of pelvic lymph node involvement <br>• If regional or distant metastases are found, see PROS-8 | Recommended if family history positive or intraductal/cribriform histology <br>See PROS-1 | Consider if life expectancy ≥10 y[j] | See PROS-5 |
| | | Unfavorable intermediate | Has one or more of the following: <br>• 2 or 3 IRFs <br>• Grade Group 3 <br>• ≥ 50% biopsy cores positive[e] | • Bone imaging[h]: recommended if T2 and PSA >10 ng/mL <br>• Pelvic ± abdominal imaging[i]: recommended if nomogram predicts >10% probability of pelvic lymph node involvement <br>• If regional or distant metastases are found, see PROS-8 | Recommended if family history positive or intraductal/cribriform histology <br>See PROS-1 | Consider if life expectancy ≥10 y[j] | See PROS-6 |
| High | Has no very-high-risk features and has exactly one high-risk feature: <br>• T3a OR <br>• Grade Group 4 or Grade Group 5 OR <br>• PSA >20 ng/mL | | | • Bone imaging[h]: recommended <br>• Pelvic ± abdominal imaging[i]: recommended <br>• If regional or distant metastases are found, see PROS-8 | Recommended | Consider if life expectancy ≥10 y[j] | See PROS-7 |
| Very high | Has at least one of the following: <br>• T3b–T4 <br>• Primary Gleason pattern 5 <br>• 2 or 3 high-risk features <br>• >4 cores with Grade Group 4 or 5 | | | • Bone imaging[h]: recommended <br>• Pelvic ± abdominal imaging[i]: recommended <br>• If regional or distant metastases are found, see PROS-8 | Recommended | Not routinely recommended | See PROS-7 |

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## INITIAL RISK STRATIFICATION AND STAGING WORKUP FOR CLINICALLY LOCALIZED DISEASE

| Risk Group | Clinical/Pathologic Features | | | Imaging[f,g] | Germline Testing[c] | Molecular/ Biomarker Analysis of Tumor[c] | Initial Therapy |
|---|---|---|---|---|---|---|---|
| Very low[d] | Has all of the following:<br>• T1c<br>• Grade Group 1<br>• PSA <10 ng/mL<br>• Fewer than 3 prostate biopsy fragments/cores positive, ≤50% cancer in each fragment/core[e]<br>• PSA density <0.15 ng/mL/g | | | • Consider confirmatory prostate biopsy ± mpMRI to establish candidacy for active surveillance | Recommended if family history positive See PROS-1 | Not indicated | See PROS-3 |
| Low[d] | Has all of the following but does not qualify for very low risk:<br>• T1–T2a<br>• Grade Group 1<br>• PSA <10 ng/mL | | | • Consider confirmatory prostate biopsy ± mpMRI to establish candidacy for active surveillance | Recommended if family history positive See PROS-1 | Consider if life expectancy ≥10 y[j] | See PROS-4 |
| Intermediate[d] | Has all of the following:<br>• No high-risk group features<br>• No very-high-risk group features<br>• Has one or more intermediate risk factors (IRF):<br>▸ T2b–T2c<br>▸ Grade Group 2 or 3<br>▸ PSA 10–20 ng/mL | Favorable intermediate | Has all of the following:<br>• 1 IRF<br>• Grade Group 1 or 2<br>• <50% biopsy cores positive[e] | • Consider confirmatory prostate biopsy ± mpMRI to establish candidacy for active surveillance<br>• Bone imaging[h]: not recommended for staging<br>• Pelvic ± abdominal imaging[i]: recommended if nomogram predicts >10% probability of pelvic lymph node involvement<br>• If regional or distant metastases are found, see PROS-8 | Recommended if family history positive or intraductal/cribriform histology See PROS-1 | Consider if life expectancy ≥10 y[j] | See PROS-5 |
| | | Unfavorable intermediate | Has one or more of the following:<br>• 2 or 3 IRFs<br>• Grade Group 3<br>• ≥ 50% biopsy cores positive[e] | • Bone imaging[h]: recommended if T2 and PSA >10 ng/mL<br>• Pelvic ± abdominal imaging[i]: recommended if nomogram predicts >10% probability of pelvic lymph node involvement<br>• If regional or distant metastases are found, see PROS-8 | Recommended if family history positive or intraductal/cribriform histology See PROS-1 | Consider if life expectancy ≥10 y[j] | See PROS-6 |
| High | Has no very-high-risk features and has exactly one high-risk feature:<br>• T3a OR<br>• Grade Group 4 or Grade Group 5 OR<br>• PSA >20 ng/mL | | | • Bone imaging[h]: recommended<br>• Pelvic ± abdominal imaging[i]: recommended<br>• If regional or distant metastases are found, see PROS-8 | Recommended | Consider if life expectancy ≥10 y[j] | See PROS-7 |
| Very high | Has at least one of the following:<br>• T3b–T4<br>• Primary Gleason pattern 5<br>• 2 or 3 high-risk features<br>• >4 cores with Grade Group 4 or 5 | | | • Bone imaging[h]: recommended<br>• Pelvic ± abdominal imaging[i]: recommended<br>• If regional or distant metastases are found, see PROS-8 | Recommended | Not routinely recommended | See PROS-7 |

# Conclusions

Stratifying PCA management based on **integrated clinical, radiologic, pathologic and molecular** based risk groups will assure **avoidance of overtreatment** and **proper management of lethal disease**

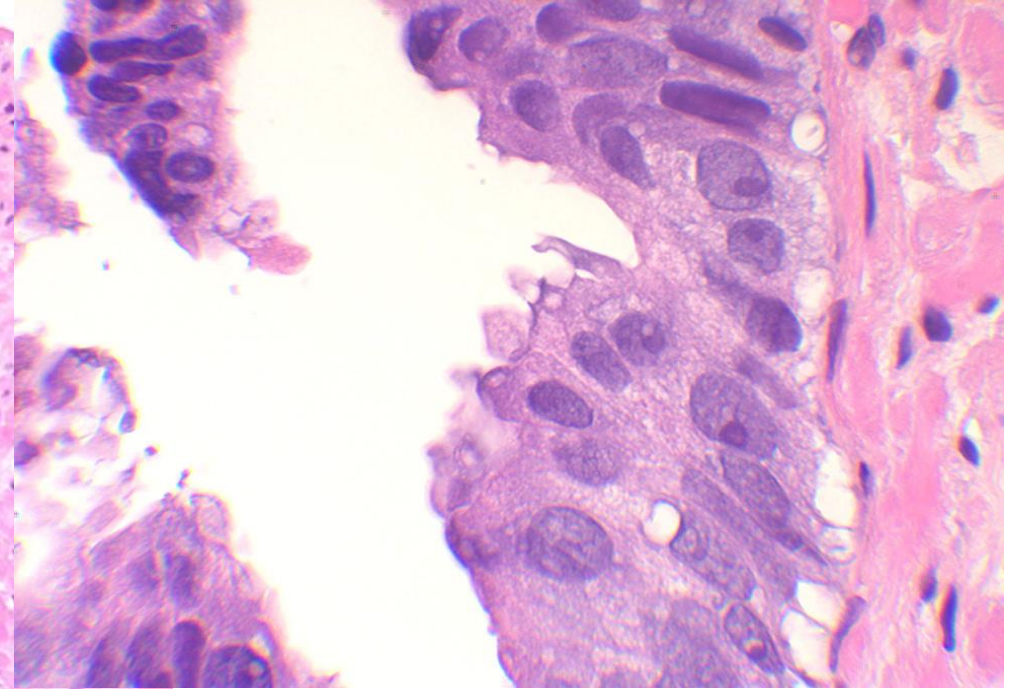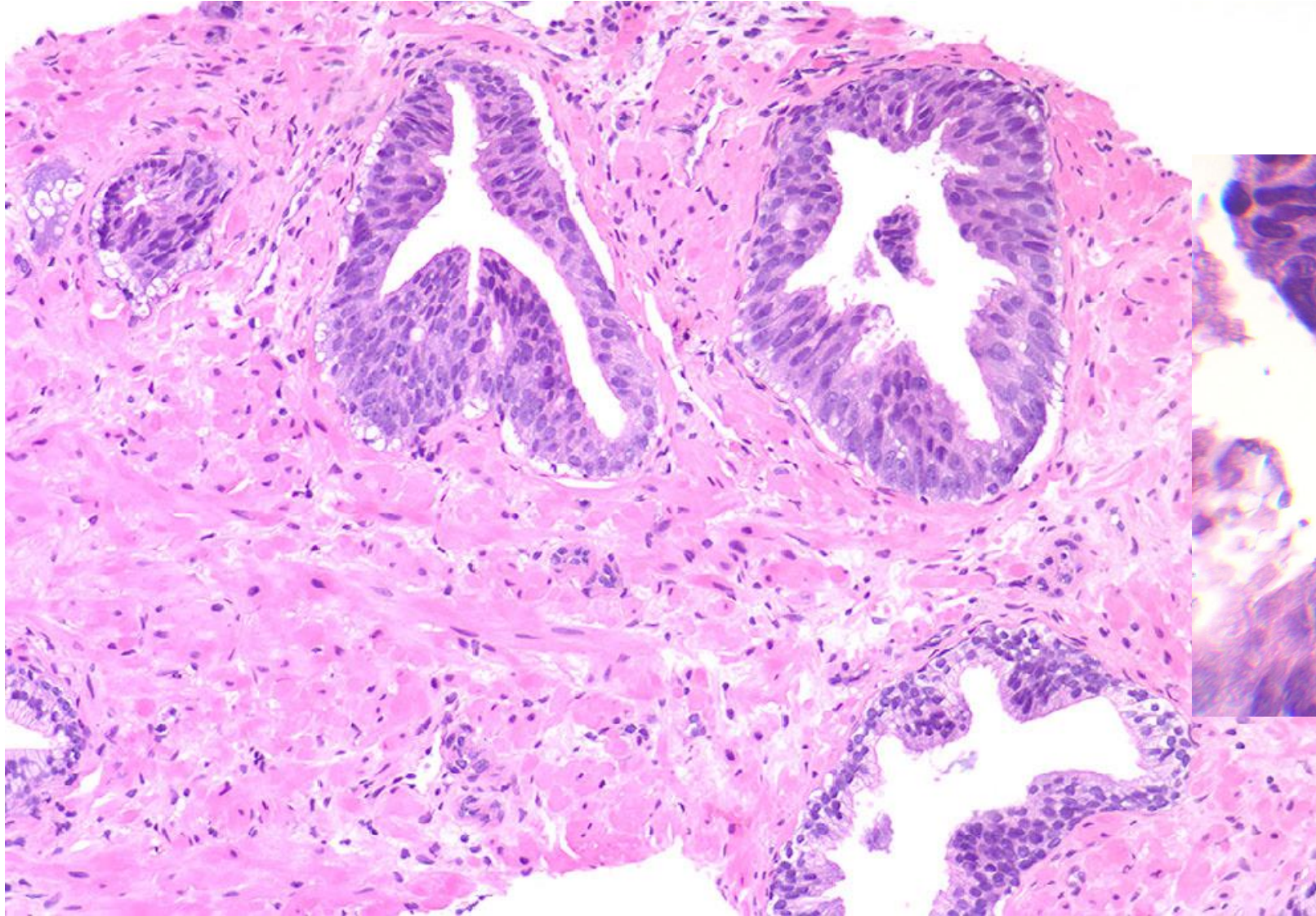**PTEN/ERG (Active Surveillance)**

Presence of **IDC-P** on needle biopsy could trigger **Germline Molecular Testing for DNA-Repair Defect and dMMR**

New targets of Rx and **predictive molecular markers:** *Genomics* and **Immune Checkpoint Pathway**

**Genomic Classifiers** are to be considered in the <u>appropriate setting</u>
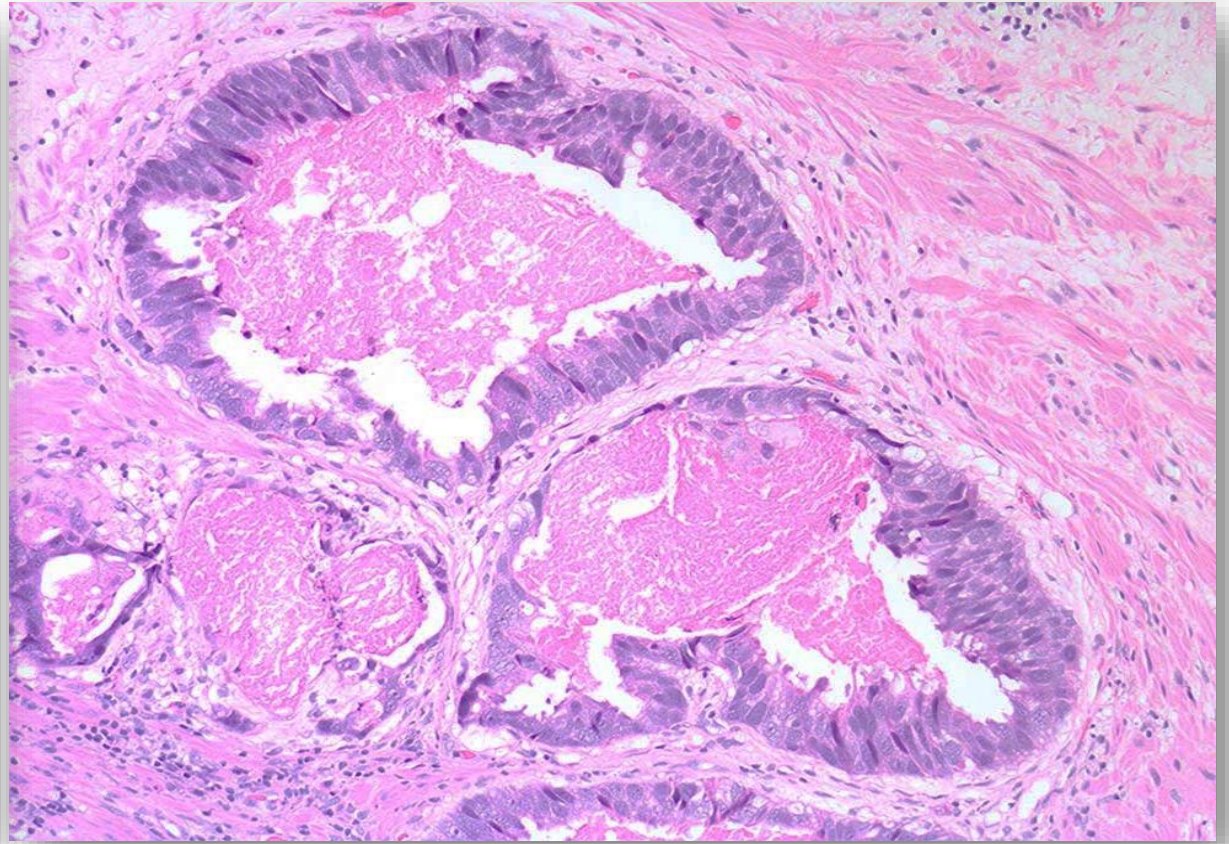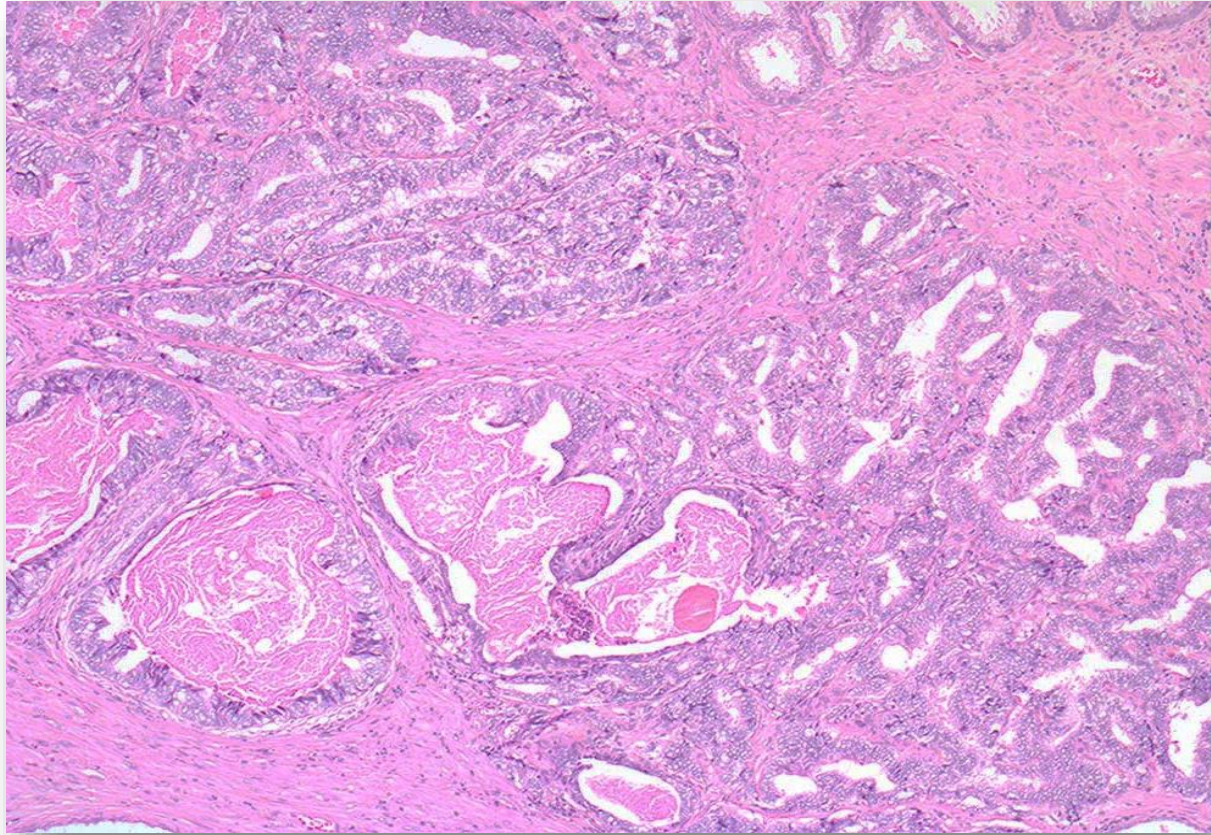
HGPIN
Tufted

HGPIN
flat
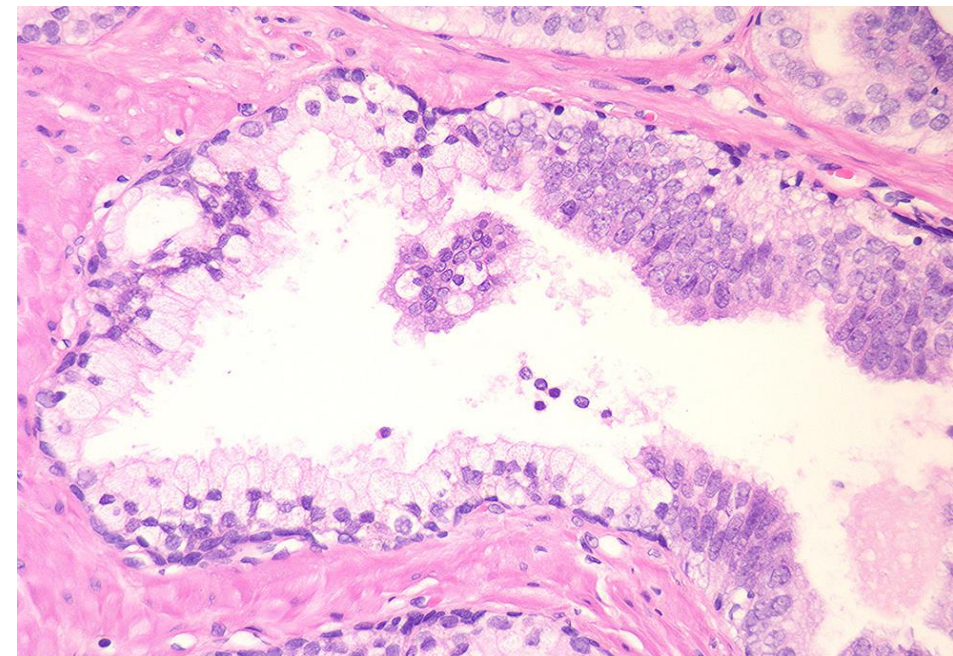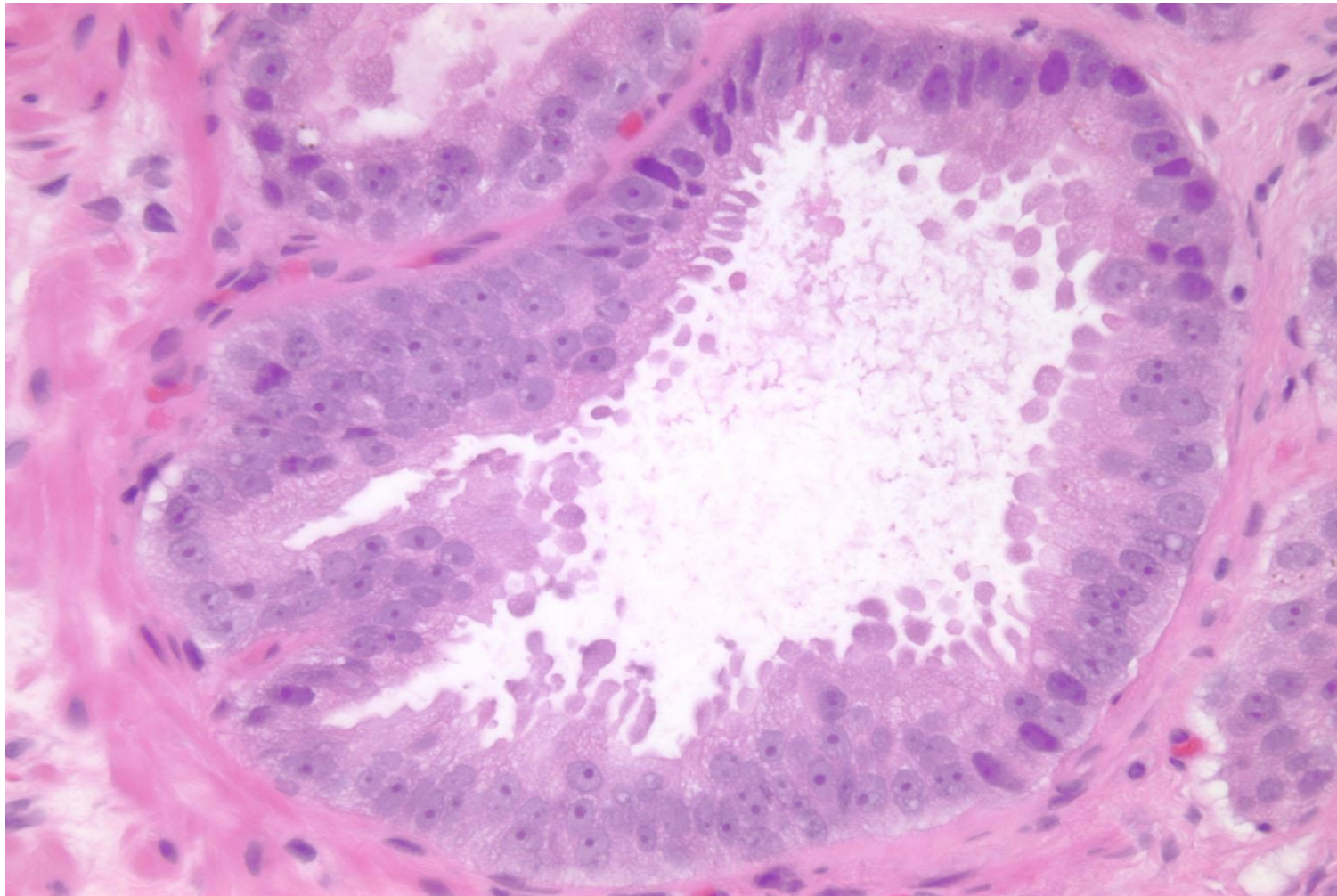
# Gleason Score 3 + 4 = 7 Prostate Cancer With Minimal Quantity of Gleason Pattern 4 on Needle Biopsy Is Associated With Low-risk Tumor in Radical Prostatectomy Specimen

Cheng Cheng Huang, MD,* Max Xiangtian Kong, MD,* Ming Zhou, MD, PhD,*†
Andrew B. Rosenkrantz, MD,‡ Samir S. Taneja, MD,†‡ Jonathan Melamed, MD,*
and Fang-Ming Deng, MD, PhD*

- 10/22 (45%) cases with G7 (5% Pattern 4) on Bx have **pathologically insignificant tumor** in the RP

- GS, pTstage, total tumor volume, and rate of insignificant tumor in RP **were not significantly different** between GS 3+3=6 and GS7 (5% Pattern 4)

# Differential Diagnosis of IDC-P

- **HGPIN**
- **Cribriform acinar adenocarcinoma**
- **Ductal adenocarcinoma**
- **Intraductal spread of HGTCC**
- Cribriform Hyperplasia (Central zone)
- Basal Cell Hyperplasia

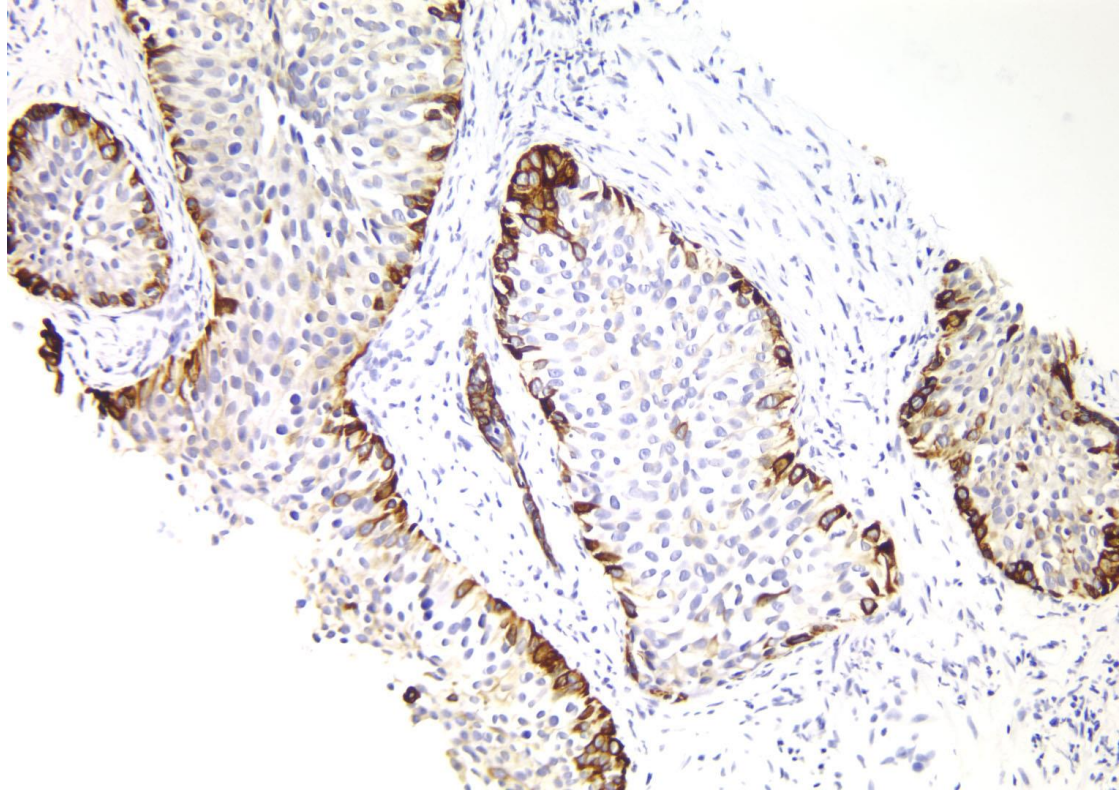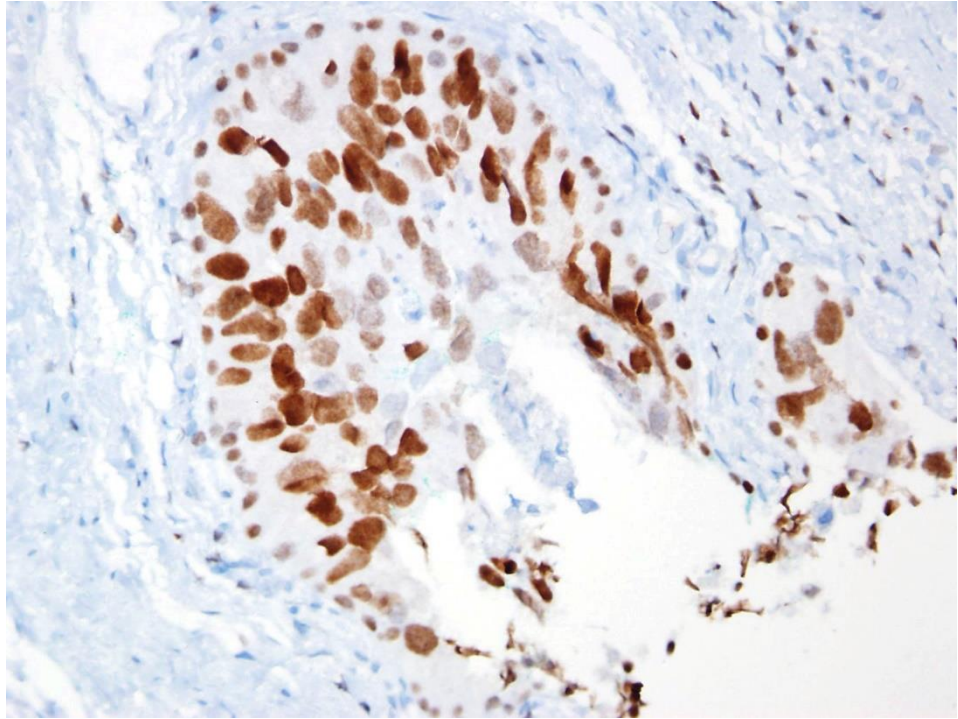# Differential Diagnosis of Intraductal Lesions of the Prostate
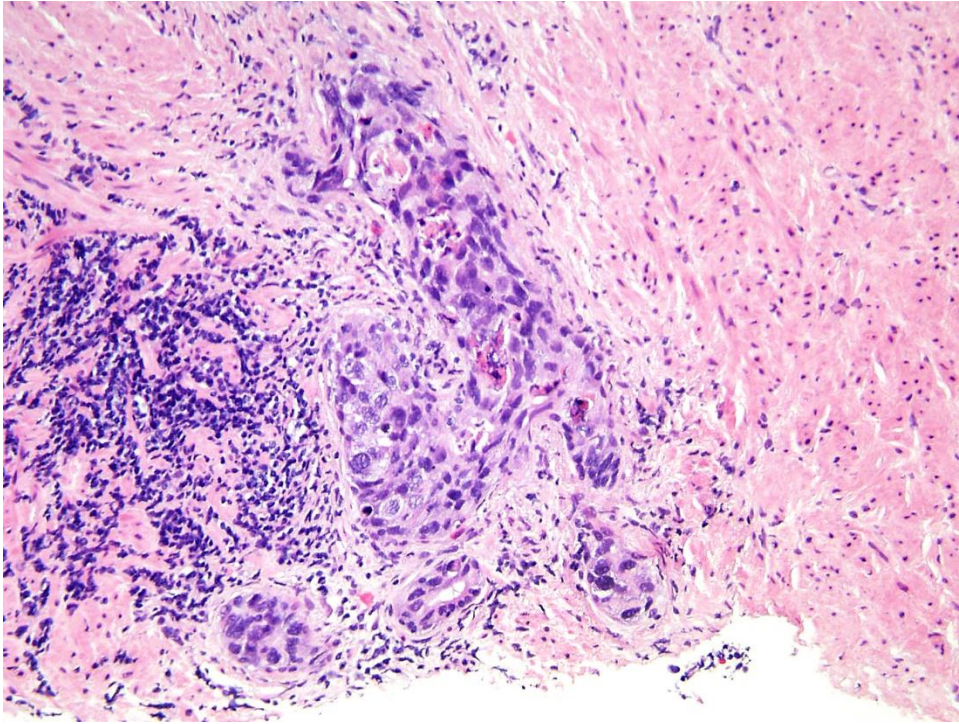
*Sara E. Wobker, MD, MPH\* and Jonathan I. Epstein, MD\*†‡*

# Intraductal Spread of Urothelial Carcinoma
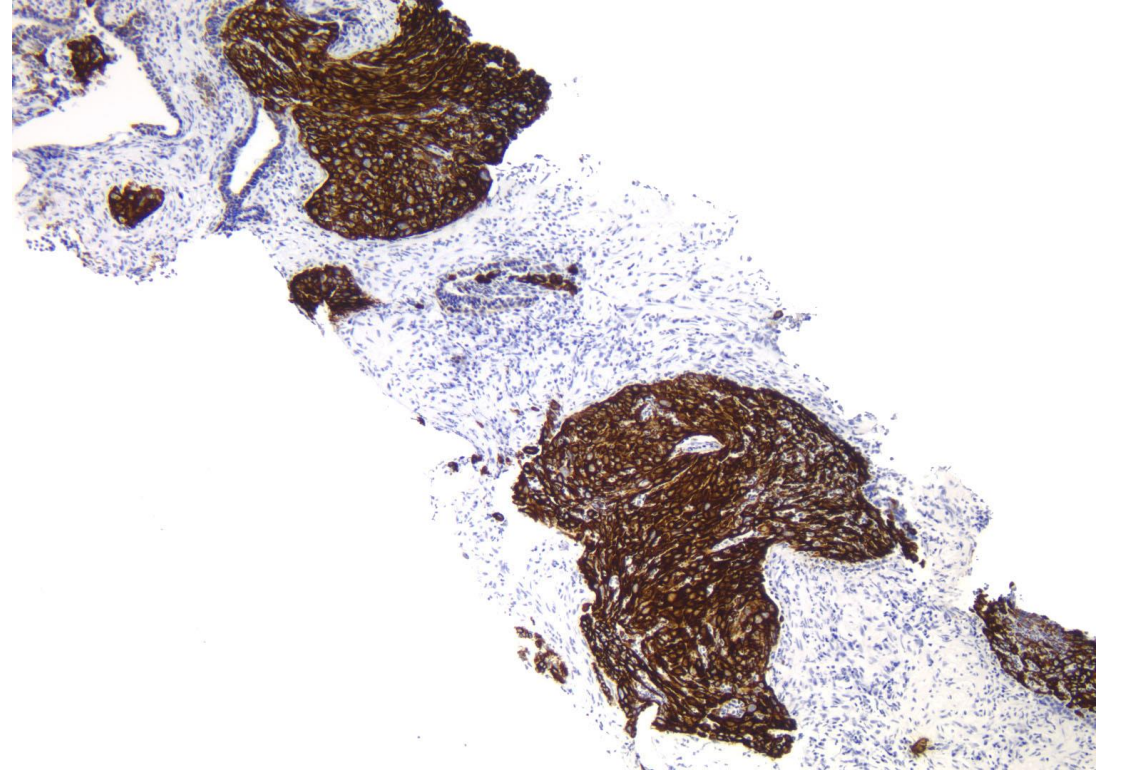
# Grading

• However, in some radical prostatectomy specimens the prostate cancer may consist of more than two Gleason patterns with the highest grade(pattern 5) representing the smallest volume, referred to as a tertiary high grade pattern. In this situation, if the tertiary grade pattern comprises >5% of the tumour volume it becomes the secondary pattern in Gleason scoring [[ISBN 978-92-832-2437-2, WHO Classification of Tumours of the Urinary System and Male Genital Organs, Humphrey PA et al, Acinar adenocarcinoma, 138-162, 2016, Lyon, IARC]] {28177964; 32589068; 32459716; 32589068}. Although the 5% cut-off is somewhat arbitrary, higher tertiary pattern volumes are associated with a worse prognosis {18718699; 27810358; 27993581; 28117112; 30181565}. If there is a higher grade component comprising ≤5% of the tumour, depending on the grading scenario, it may be dealt with differently in the 2019 ISUP and GUPS systems (see Tables 2 and 3). Some authors have advocated for more quantitative grading recognizing that the amount of high grade (patterns 4/5) tumour strongly correlates with outcome {10737486;12131299;26542947}.

•

• At the 2014 ISUP conference the concept of Grade Groups (GG) — alternatively referred to as ISUP Grade/Grade Groups or simply WHO Grade, in part to distinguish it from the various grade grouping systems used in various studies prior to 2013—was endorsed. These correspond to Gleason scores but have some advantages with respect to the communication of results to patients, clinicians and researchers, for instance Gleason score 3 + 3 = 6 cancers are assigned GG1 to highlight their generally favourable prognosis, while 3 + 4 = 7 cancers are placed in a separate GG to 4 + 3 = 7 to emphasize the higher risk of recurrence associated with the latter {23464824; 26492179}.

•

• The 2019 grading changes proposed by ISUP and GUPS are yet to be fully validated and there are also some specific differences between the recommendations from the two bodies which cannot be resolved on the basis of currently available published evidence (Table 3) {32459716; 32589068; 33027069}. Both organisations advocate reporting an estimate of the percentage of pattern 4 cancer present in prostate biopsies with Gleason score 7 (GG2 or GG3), as well as the presence of invasive cribriform carcinoma in Gleason score 7 and 8 cases (GG2-4), since several studies have shown that these features have prognostic and clinical significance {26920466; 27457260; 26542947; 25189638; 21685037; 26939875}. However, there are acknowledged problems relating to interobserver reproducibility in the assessment of pattern 4 carcinoma, especially for poorly formed or fused gland patterns, with kappa coefficients for the former ranging from ranging from 0.27 to 0.34 (fair agreement only) {21679996; 26099009; 27028587}. Although pathologists are more consistent in recognizing invasive cribriform carcinoma than the other morphological patterns included within Gleason grade pattern 4, there are still issues surrounding its precise definition (especially small versus large cribriform glands), reproducibility, and consistent distinction from intraductal carcinoma of prostate (IDCP) without using immunohistochemistry (IHC) {21685037; 27028587; 30349027; 32815034}. Furthermore given the latter point, the exclusion of IDCP from Gleason grading may be problematic, and potentially unnecessary, without more extensive utilisation of IHC in routine practice {29878934; 30720899; 32542746}. In the interim, while awaiting more definitive evidence to resolve the differences between the 2019 ISUP and GUPS proposals, pathologists should specify which variant of the Gleason grading system recommendations is being used in routine reporting and publications to allow meaningful analyses and comparisons of cohorts.

•

• A recent development is the introduction of computer-assisted prostate cancer grading using artificial intelligence. A series of studies has shown that AI-based algorithms can perform prostate cancer grading at the level of experienced, subspecialized uropathologists {31304394; 31926806, 31926805; 32701148}. Although more extensive, and prospective, validation of these algorithms in clinical practice is needed, they offer a potential avenue for improving prostate cancer grading. Specifically, by supporting inexperienced or non-specialized pathologists, inter- and intra-observer variability in grading can be reduced, as has been shown in preliminary studies {32759979; 33180129}. Furthermore, AI-based algorithms could play an important role in more accurate quantification of patterns due to their ability to individually count of every cell and gland belonging to a specific pattern. The first commercial offerings have received CE certification in 2020.
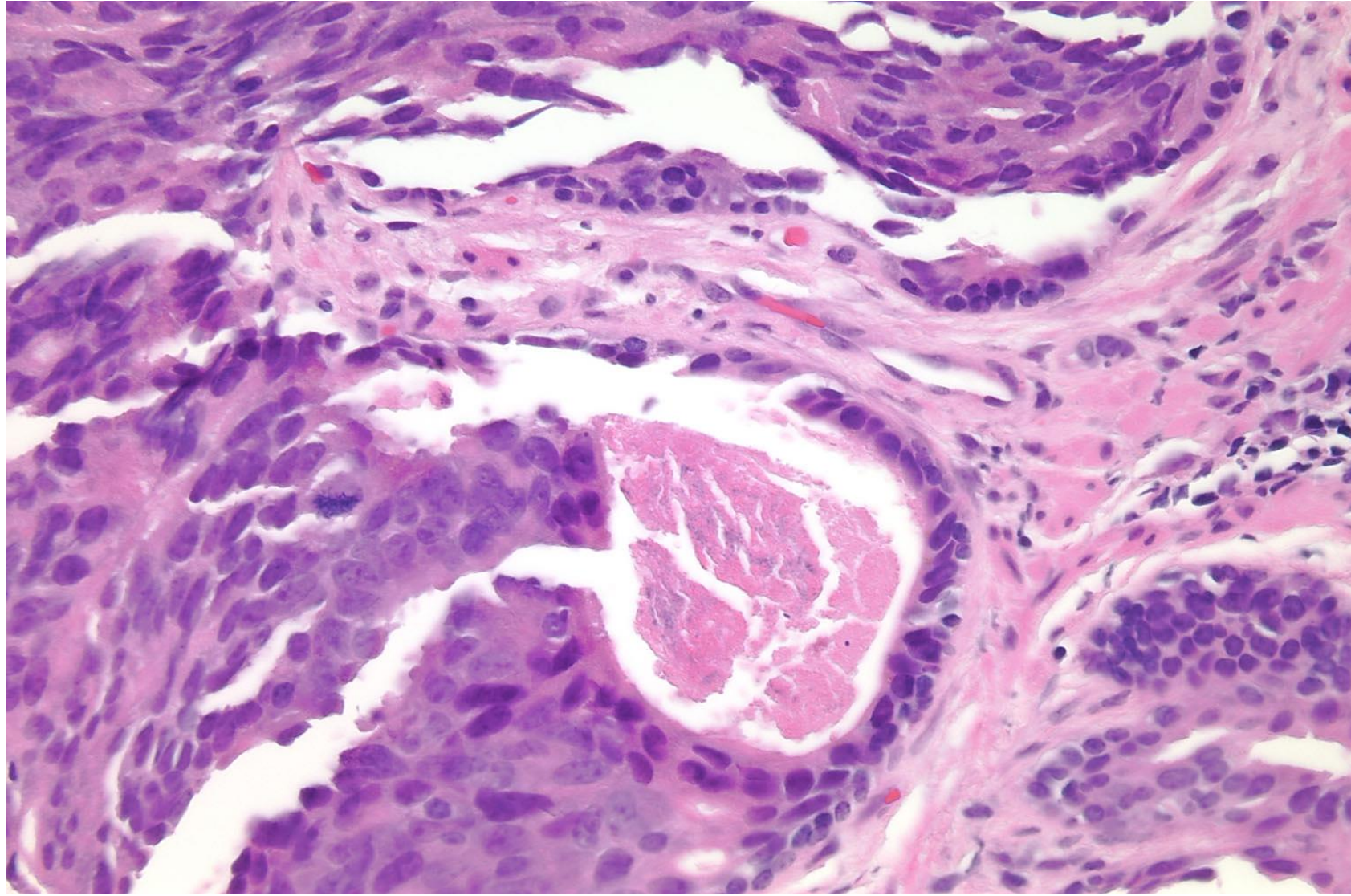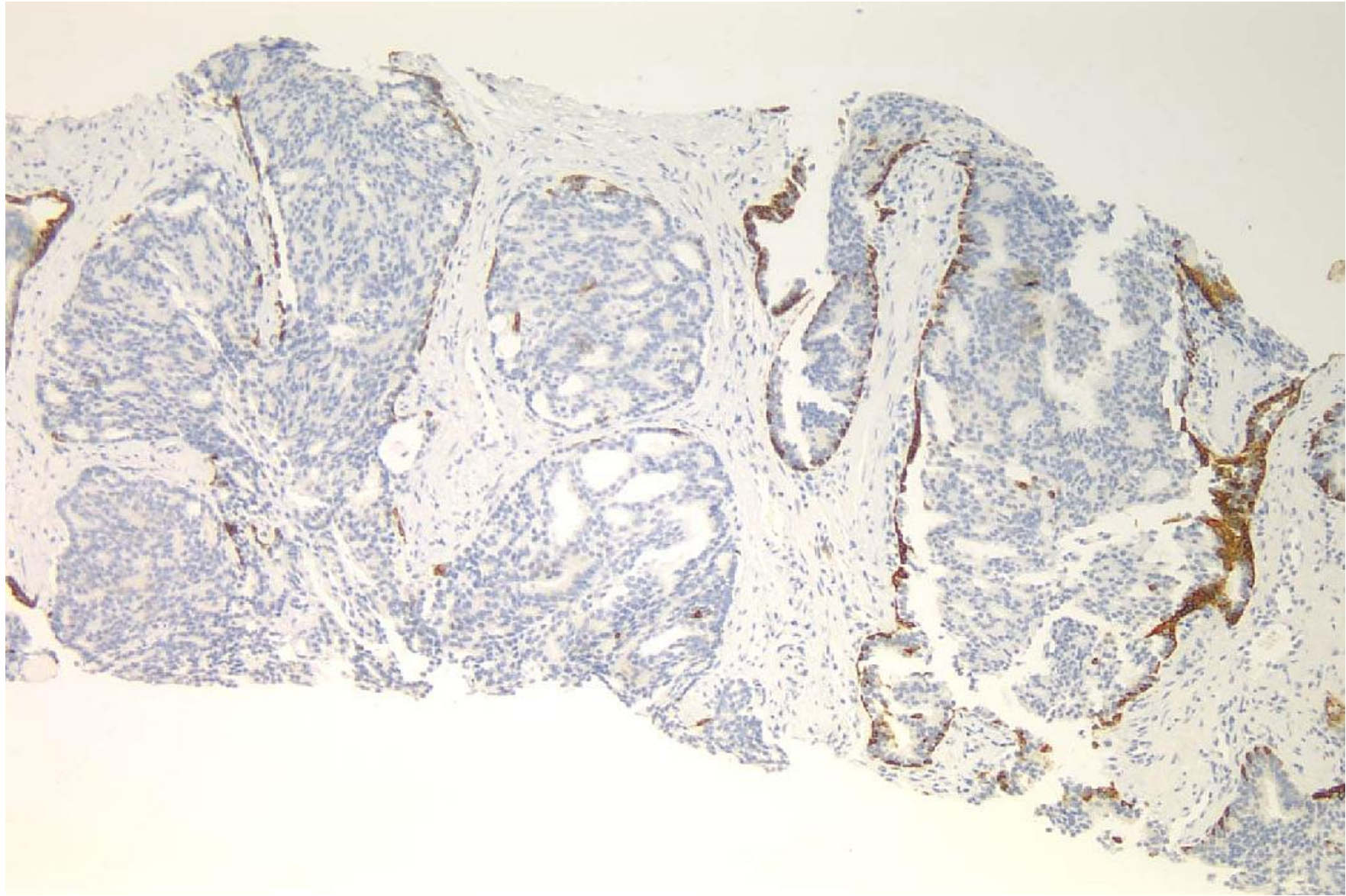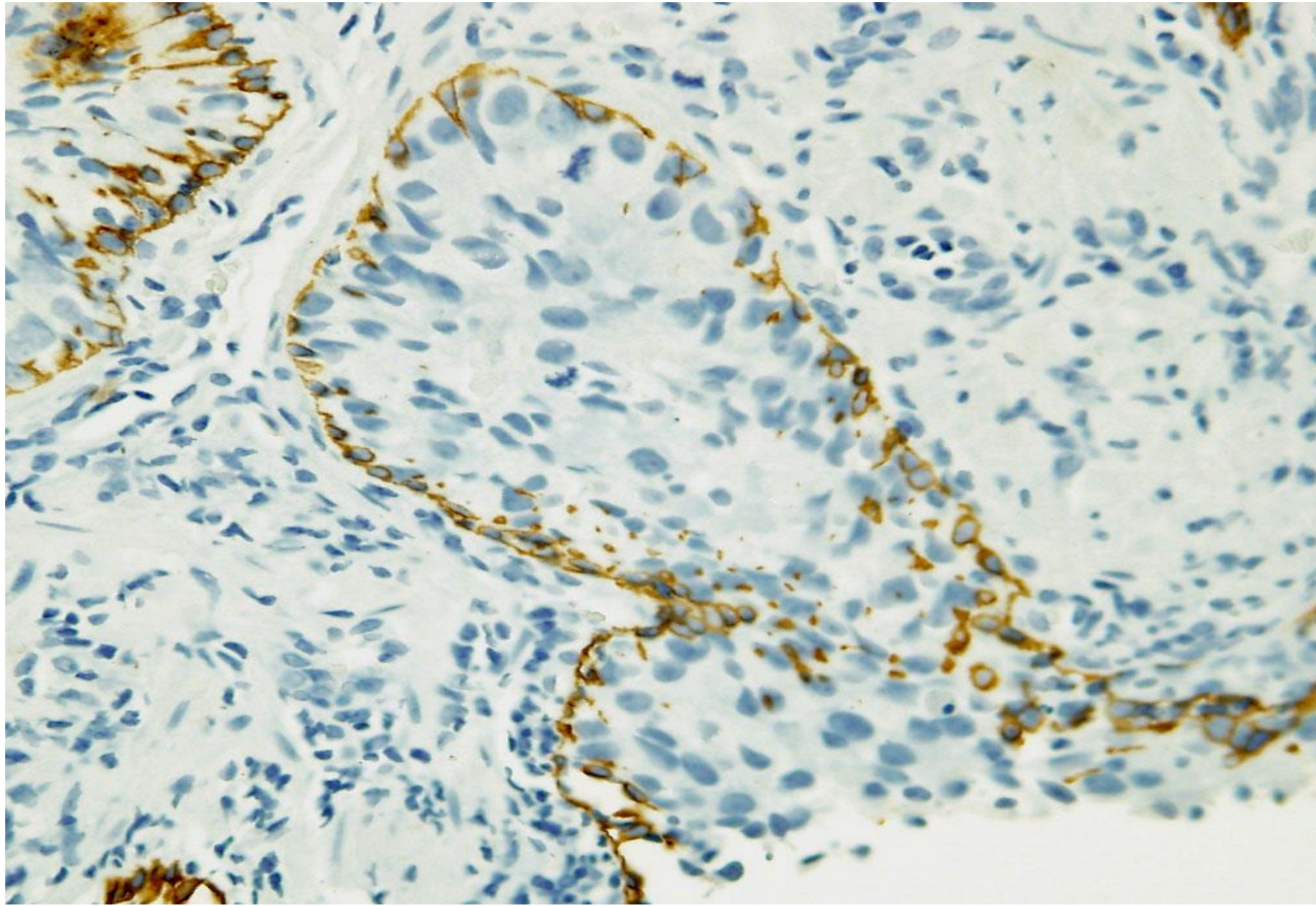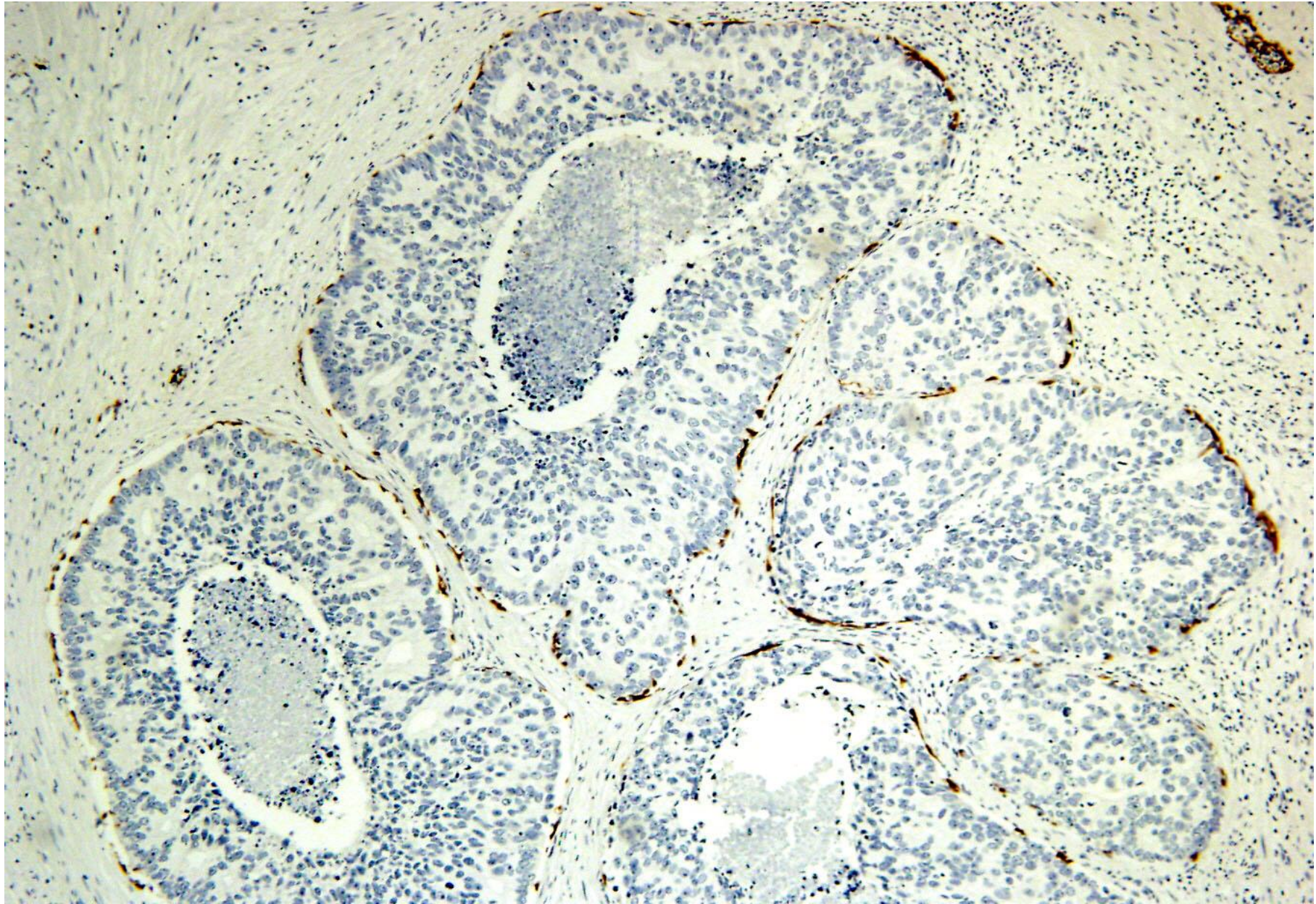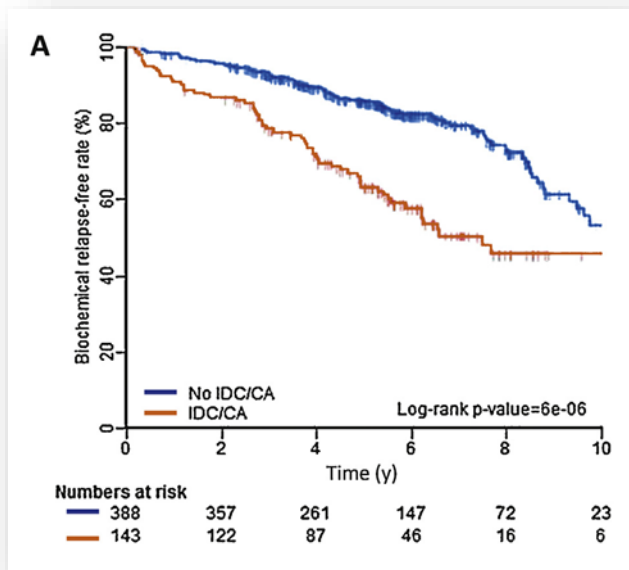
# Prostatic Intraductal Carcinoma (IDC-P)

- Distinctive morphology from HGPIN

- **Associated with high grade invasive cancer** and **poor pathology** at RP & relatively poor prognosis with other therapies

- An **advanced stage of tumor progression** with intraductal spread of tumor **(mostly)**

- **Justified to treat patients** with intraductal carcinoma on biopsy even in the absence of documented infiltrating cancer
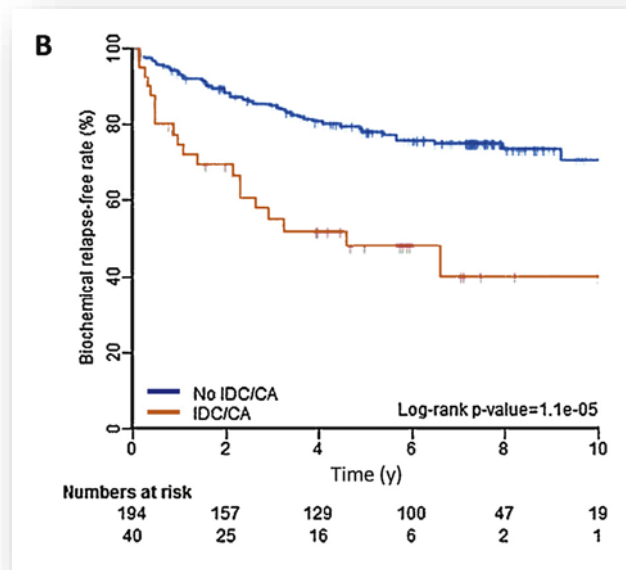
# A Prostate Cancer "*Nimbosus*": Genomic Instability and *SChLAP1* Dysregulation Underpin Aggression of Intraductal and Cribriform Subpathologies

*Melvin L.K. Chua [a,†], Winnie Lo [a], Melania Pintilie [a], Jure Murgic [a,‡], Emilie Lalonde [b,c], Vinayak Bhandari [b,c], Osman Mahamud [c], Anuradha Gopalan [d], Charlotte F. Kweldam [e], Geert J.L.H. van Leenders [e], Esther I. Verhoef [e], Agnes Marije Hoogland [e], Julie Livingstone [b], Alejandro Berlin [a], Alan Dal Pra [a,§], Alice Meng [a], Junyan Zhang [a], Michèle Orain [f], Valérie Picard [f], Hélène Hovington [f], Alain Bergeron [f], Louis Lacombe [f], Yves Fradet [f], Bernard Têtu [f], Victor E. Reuter [d], Neil Fleshner [g], Michael Fraser [a], Paul C. Boutros [b,c,h], Theodorus H. van der Kwast [e,i,∥,*], Robert G. Bristow [a,c,∥,**]*

CANADIAN        MSKCC        Pooled

# WHO Classification of the Urinary and Male Genital Tumours
## 5th edition series

**Epithelial tumours**
*Glandular neoplasms*

| | |
|---|---|
| Acinar adenocarcinoma | 8140/3 |
|    Atrophic | |
|    Pseudohyperplastic | |
|    Microcystic | |
|    Foamy gland | |
|    Mucinous (colloid) | 8480/3 |
|    Signet ring–like cell | 8490/3 |
|    Pleomorphic giant cell | |
|    Sarcomatoid | 8572/3 |
| Prostatic intraepithelial neoplasia, | |
|    high-grade | 8148/2 |
| Intraductal carcinoma | 8500/2 |
| Ductal adenocarcinoma | 8500/3 |
|    Cribriform | 8201/3 |
|    Papillary | 8260/3 |
|    Solid | 8230/3 |
| Urothelial carcinoma | 8120/3 |

*Squamous neoplasms*

| | |
|---|---|
|    Adenosquamous carcinoma | 8560/3 |
|    Squamous cell carcinoma | 8070/3 |
| Basal cell carcinoma | 8147/3 |

| | |
|---|---|
| Leiomyosarcoma | 8890/3 |
| Rhabdomyosarcoma | 8900/3 |
| Leiomyoma | 8890/0 |
| Angiosarcoma | 9120/3 |
| Synovial sarcoma | 9040/3 |
| Inflammatory myofibroblastic tumour | 8825/1 |
| Osteosarcoma | 9180/3 |
| Undifferentiated pleomorphic sarcoma | 8802/3 |
| Solitary fibrous tumour | 8815/1 |
| Solitary fibrous tumour, malignant | 8815/3 |
| Haemangioma | 9120/0 |
| Granular cell tumour | 9580/0 |

**Haematolymphoid tumours**

| | |
|---|---|
| Diffuse large B-cell lymphoma | 9680/3 |
| Chronic lymphocytic leukaemia / | |
|    small lymphocytic lymphoma | 9823/3 |
| Follicular lymphoma | 9690/3 |
| Mantle cell lymphoma | 9673/3 |
| Acute myeloid leukaemia | 9861/3 |
| B lymphoblastic leukaemia/lymphoma | 9811/3 |

**Miscellaneous tumours**

| | |
|---|---|
| Cystadenoma | 8440/0 |
| Nephroblastoma | 8960/3 |
| Rhabdoid tumour | 8963/3 |
| Germ cell tumours | |
| Clear cell adenocarcinoma | 8310/3 |
| Melanoma | 8720/3 |
| Paraganglioma | 8693/1 |
| Neuroblastoma | 9500/3 |

**Metastatic tumours**

*Tumours of the seminal vesicles*

**Epithelial tumours**

| | |
|---|---|
| Adenocarcinoma | 8140/3 |
| Squamous cell carcinoma | 8070/3 |

**Mixed epithelial and stromal tumours**

| | |
|---|---|
| Cystadenoma | 8440/0 |

**Mesenchymal tumours**

| | |
|---|---|
| Leiomyoma | 8890/0 |
| Schwannoma | 9560/0 |
| Mammary-type myofibroblastoma | 8825/0 |
| Gastrointestinal stromal tumour, NOS | 8936/1 |
| Leiomyosarcoma | 8890/3 |
| Angiosarcoma | 9120/3 |
| Liposarcoma | 8850/3 |
| Solitary fibrous tumour | 8815/1 |
| Haemangiopericytoma | 9150/1 |

**Miscellaneous tumours**

| | |
|---|---|
| Choriocarcinoma | 9100/3 |
| Seminoma | 9061/3 |
| Well-differentiated neuroendocrine tumour / | |
|    carcinoid tumour | 8240/3 |
| Lymphomas | |
| Ewing sarcoma | 9364/3 |

**Metastatic tumours**

The morphology codes are from the International Classification of Diseases for Oncology (ICD-O) {917A}. Behaviour is coded /0 for benign tumours; /1 for unspecified, borderline, or uncertain behaviour; /2 for carcinoma in situ and grade III intraepithelial neoplasia; and /3 for malignant tumours. The classification is modified from the previous WHO classification {756A}, taking into account changes in our understanding of these lesions.

| WHO Uro 4 | WHO Uro 5 |
|---|---|

Epithelial tumours
*Glandular neoplasms*
Acinar adenocarcinoma
    Atrophic
    Pseudohyperplastic
    Microcystic
    Foamy gland
    Mucinous (colloid)
    Signet ring–like cell
    Pleomorphic giant cell
    Sarcomatoid
Prostatic intraepithelial neoplasia,
    high-grade
Intraductal carcinoma
Ductal adenocarcinoma
    Cribriform
    Papillary
    Solid
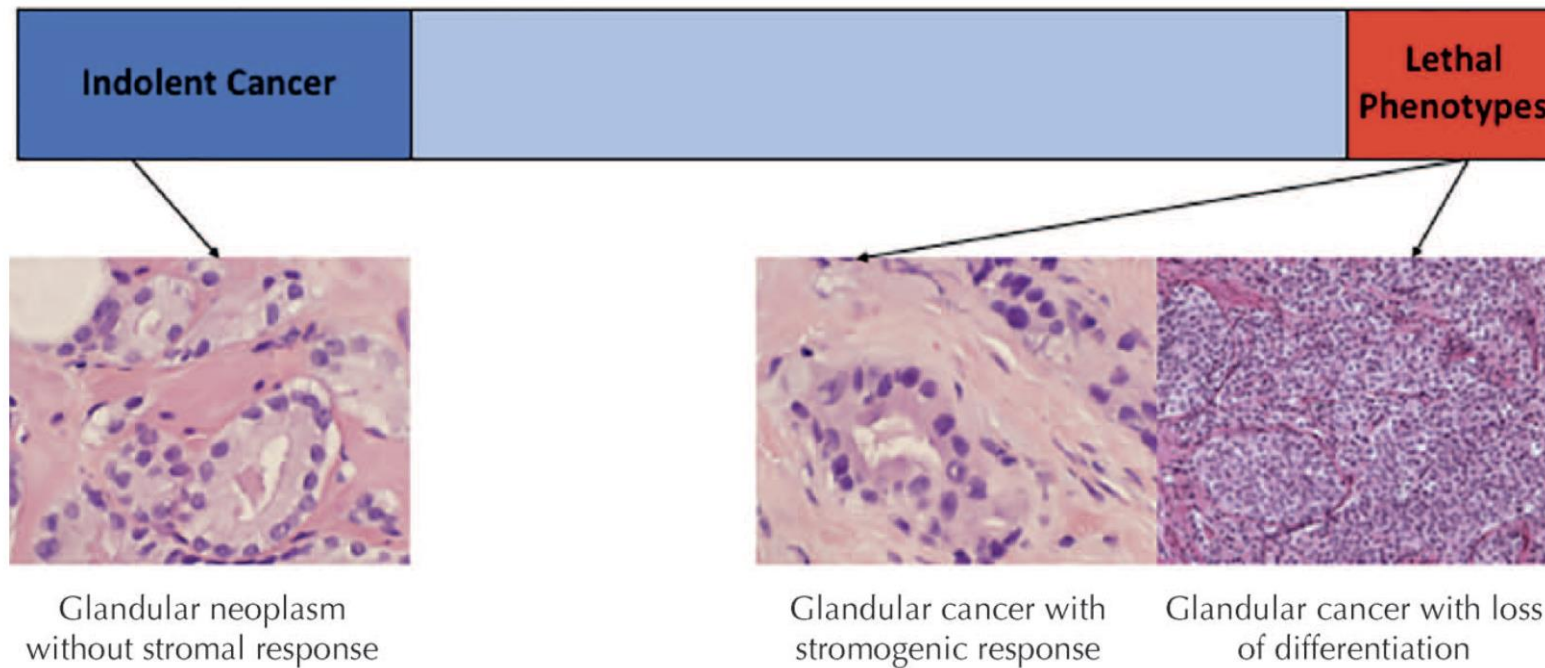Urothelial carcinoma
*Squamous neoplasms*
    Adenosquamous carcinoma
    Squamous cell carcinoma
Basal cell carcinoma

**Epithelial tumours**
*Glandular neoplasms*
Acinar adenocarcinoma
  Atrophic
  Pseudohyperplastic
  Microcystic
  Foamy gland
  Mucinous (colloid)
  Signet ring-like cell
  Pleomorphic giant cell
  Sarcomatoid
Prostatic intraepithelial neoplasia,
  high-grade
Intraductal carcinoma
Ductal adenocarcinoma
  Cribriform
  Papillary
  Solid
*Urothelial carcinoma*
*Squamous neoplasms*
  *Adenosquamous carcinoma*
  *Squamous cell carcinoma*
*Basal cell carcinoma*

# Moving Beyond Gleason Scoring

Brian Miles, MD; Michael Ittmann, MD, PhD; Thomas Wheeler, MD; Mohammad Sayeeduddin, BS; Antonio Cubilla, MD; David Rowley, PhD; Ping Bu, MD; Yi Ding, PhD; Yan Gao, MD; MinJae Lee, PhD; Gustavo E. Ayala, MD

Glandular neoplasm without stromal response

Glandular cancer with stromogenic response

Glandular cancer with loss of differentiation

# Prostatic Intraepithelial Neoplasia (HGPIN)

- Architecturally benign glands with malignant appearing cells containing **prominent nucleoli**

- **No uniform** definition as to **how prominen**t nucleoli or how many nucleoli per gland

- Architecturally most common is **tufting** and then **micropapillary** with **flat** and **cribriform** least common.
  - No need to comment on pattern as no difference in risk of subsequent cancer, **except maybe for cribriform**

## INITIAL RISK STRATIFICATION AND STAGING WORKUP FOR CLINICALLY LOCALIZED DISEASE

| Risk Group | Clinical/Pathologic Features | | | Imaging[f,g] | Germline Testing[c] | Molecular/ Biomarker Analysis of Tumor[c] | Initial Therapy |
|---|---|---|---|---|---|---|---|
| Very low[d] | Has all of the following:<br>• T1c<br>• Grade Group 1<br>• PSA <10 ng/mL<br>• Fewer than 3 prostate biopsy fragments/cores positive, ≤50% cancer in each fragment/core[e]<br>• PSA density <0.15 ng/mL/g | | | Not indicated | Recommended if family history positive or intraductal/cribriform histology<br>See PROS-1 | Not indicated | See PROS-3 |
| Low[d] | Has all of the following but does not qualify for very low risk:<br>• T1–T2a<br>• Grade Group 1<br>• PSA <10 ng/mL | | | Not indicated | Recommended if family history positive or intraductal/cribriform histology<br>See PROS-1 | Consider if life expectancy ≥10 y[j] | See PROS-4 |
| Intermediate[d] | Has all of the following:<br>• No high-risk group features<br>• No very-high-risk group features<br>• Has one or more intermediate risk factors (IRF):<br>‣ T2b–T2c<br>‣ Grade Group 2 or 3<br>‣ PSA 10–20 ng/mL | Favorable intermediate | Has all of the following:<br>• 1 IRF<br>• Grade Group 1 or 2<br>• <50% biopsy cores positive[e] | • Bone imaging[h]: not recommended for staging<br>• Pelvic ± abdominal imaging[i]: recommended if nomogram predicts >10% probability of pelvic lymph node involvement<br>• If regional or distant metastases are found, see PROS-8 | Recommended if family history positive or intraductal/cribriform histology<br>See PROS-1 | Consider if life expectancy ≥10 y[j] | See PROS-5 |
| | | Unfavorable intermediate | Has one or more of the following:<br>• 2 or 3 IRFs<br>• Grade Group 3<br>• ≥50% biopsy cores positive[e] | • Bone imaging[h]: recommended if T2 and PSA >10 ng/mL<br>• Pelvic ± abdominal imaging[i]: recommended if nomogram predicts >10% probability of pelvic lymph node involvement<br>• If regional or distant metastases are found, see PROS-8 | Recommended if family history positive or intraductal/cribriform histology<br>See PROS-1 | Consider if life expectancy ≥10 y[j] | See PROS-6 |
| High | Has no very-high-risk features and has at least one high-risk feature:<br>• T3a OR<br>• Grade Group 4 or Grade Group 5 OR<br>• PSA >20 ng/mL | | | • Bone imaging[h]: recommended<br>• Pelvic ± abdominal imaging[i]: recommended if nomogram predicts >10% probability of pelvic lymph node involvement<br>• If regional or distant metastases are found, see PROS-8 | Recommended | Consider if life expectancy ≥10 y[j] | See PROS-7 |
| Very high | Has at least one of the following:<br>• T3b–T4<br>• Primary Gleason pattern 5<br>• 2 or 3 high-risk features<br>• >4 cores with Grade Group 4 or 5 | | | • Bone imaging[h]: recommended<br>• Pelvic ± abdominal imaging[i]: recommended if nomogram predicts >10% probability of pelvic lymph node involvement<br>• If regional or distant metastases are found, see PROS-8 | Recommended | Not routinely recommended | See PROS-7 |

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## INITIAL RISK STRATIFICATION AND STAGING WORKUP FOR CLINICALLY LOCALIZED DISEASE

| Risk group | Clinical/pathologic features | | | Imaging[h,i] | Germline testing | Molecular and biomarker analysis of tumor[l] | Initial therapy |
|---|---|---|---|---|---|---|---|
| Very low[f] | • T1c AND<br>• Grade Group 1 AND<br>• PSA <10 ng/mL AND<br>• Fewer than 3 prostate biopsy fragments/cores positive, ≤50% cancer in each fragment/core[g] AND<br>• PSA density <0.15 ng/mL/g | | | Not indicated | Recommended if family history positive or intraductal histology See PROS-1 | Not indicated | See PROS-4 |
| Low[f] | • T1-T2a AND<br>• Grade Group 1 AND<br>• PSA <10 ng/mL | | | Not indicated | Recommended if family history positive or intraductal histology See PROS-1 | Consider if life expectancy ≥10y[m] | See PROS-5 |
| Intermediate[f] | Has no high- or very-high-risk features and has one or more intermediate risk factors (IRF):<br>• T2b-T2c<br>• Grade Group 2 or 3<br>• PSA 10–20 ng/mL | Favorable intermediate | • 1 IRF and<br>• Grade Group 1 or 2 and<br>• <50% biopsy cores positive[g] | • Bone imaging[j]: not recommended for staging<br>• Pelvic ± abdominal imaging: recommended if nomogram predicts >10% probability of pelvic lymph node involvement<br><br>• If regional or distant metastases are found, see PROS-9 | Recommended if family history positive or intraductal histology See PROS-1 | Consider if life expectancy ≥10y[m] | See PROS-6 |
| | | Unfavorable intermediate | • 2 or 3 IRFs and/or<br>• Grade Group 3 and/or<br>• ≥50% biopsy cores positive[g] | • Bone imaging[j]: recommended if T2 and PSA >10 ng/mL<br>• Pelvic ± abdominal imaging: recommended if nomogram predicts >10% probability of pelvic lymph node involvement<br><br>• If regional or distant metastases are found, see PROS-9 | Recommended if family history positive or intraductal histology See PROS-1 | Not routinely recommended | See PROS-7 |
| High | • T3a OR<br>• Grade Group 4 or Grade Group 5 OR<br>• PSA >20 ng/mL | | | • Bone imaging[j]: recommended<br>• Pelvic ± abdominal imaging: recommended if nomogram predicts >10% probability of pelvic lymph node involvement<br><br>• If regional or distant metastases are found, see PROS-9 | Recommended[c,k] | Not routinely recommended | See PROS-8 |
| Very high | • T3b-T4 OR<br>• Primary Gleason pattern 5 OR<br>• >4 cores with Grade Group 4 or 5 | | | • Bone imaging[j]: recommended<br>• Pelvic ± abdominal imaging: recommended if nomogram predicts >10% probability of pelvic lymph node involvement<br><br>• If regional or distant metastases are found, see PROS-9 | Recommended[c,k] | Not routinely recommended | See PROS-8 |

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## INITIAL RISK STRATIFICATION AND STAGING WORKUP FOR CLINICALLY LOCALIZED DISEASE

| Risk group | Clinical/pathologic features | | | Imaging[h,i] | Germline testing | Molecular and biomarker analysis of tumor[l] | Initial therapy |
|---|---|---|---|---|---|---|---|
| Very low[f] | • T1c AND<br>• Grade Group 1 AND<br>• PSA <10 ng/mL AND<br>• Fewer than 3 prostate biopsy fragments/cores positive, ≤50% cancer in each fragment/core[g] AND<br>• PSA density <0.15 ng/mL/g | | | Not indicated | Recommended if family history positive or intraductal histology<br>See PROS-1 | Not indicated | See PROS-4 |
| Low[f] | • T1-T2a AND<br>• Grade Group 1 AND<br>• PSA <10 ng/mL | | | Not indicated | Recommended if family history positive or intraductal histology<br>See PROS-1 | Consider if life expectancy ≥10y[m] | See PROS-5 |
| Intermediate[f] | Has no high- or very-high-risk features and has one or more intermediate risk factors (IRF):<br>• T2b-T2c<br>• Grade Group 2 or 3<br>• PSA 10–20 ng/mL | Favorable intermediate | • 1 IRF and<br>• Grade Group 1 or 2 and<br>• <50% biopsy cores positive[g] | • Bone imaging[j]: not recommended for staging<br>• Pelvic ± abdominal imaging: recommended if nomogram predicts >10% probability of pelvic lymph node involvement<br><br>• If regional or distant metastases are found, see PROS-9 | Recommended if family history positive or intraductal histology<br>See PROS-1 | Consider if life expectancy ≥10y[m] | See PROS-6 |
| | | Unfavorable intermediate | • 2 or 3 IRFs and/or<br>• Grade Group 3 and/or<br>• ≥50% biopsy cores positive[g] | • Bone imaging[j]: recommended if T2 and PSA >10 ng/mL<br>• Pelvic ± abdominal imaging: recommended if nomogram predicts >10% probability of pelvic lymph node involvement<br><br>• If regional or distant metastases are found, see PROS-9 | Recommended if family history positive or intraductal histology<br>See PROS-1 | Not routinely recommended | See PROS-7 |
| High | • T3a OR<br>• Grade Group 4 or Grade Group 5 OR<br>• PSA >20 ng/mL | | | • Bone imaging[j]: recommended<br>• Pelvic ± abdominal imaging: recommended if nomogram predicts >10% probability of pelvic lymph node involvement<br><br>• If regional or distant metastases are found, see PROS-9 | Recommended[c,k] | Not routinely recommended | See PROS-8 |
| Very high | • T3b-T4 OR<br>• Primary Gleason pattern 5 OR<br>• >4 cores with Grade Group 4 or 5 | | | • Bone imaging[j]: recommended<br>• Pelvic ± abdominal imaging: recommended if nomogram predicts >10% probability of pelvic lymph node involvement<br><br>• If regional or distant metastases are found, see PROS-9 | Recommended[c,k] | Not routinely recommended | See PROS-8 |

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## INITIAL RISK STRATIFICATION AND STAGING WORKUP FOR CLINICALLY LOCALIZED DISEASE

| Risk group | Clinical/pathologic features | | | Imaging[h,i] | Germline testing | Molecular and biomarker analysis of tumor[l] | Initial therapy |
|---|---|---|---|---|---|---|---|
| Very low[f] | • T1c AND<br>• Grade Group 1 AND<br>• PSA <10 ng/mL AND<br>• Fewer than 3 prostate biopsy fragments/cores positive, ≤50% cancer in each fragment/core[g] AND<br>• PSA density <0.15 ng/mL/g | | | Not indicated | Recommended if family history positive or intraductal histology<br>See PROS-1 | Not indicated | See PROS-4 |
| Low[f] | • T1-T2a AND<br>• Grade Group 1 AND<br>• PSA <10 ng/mL | | | Not indicated | Recommended if family history positive or intraductal histology<br>See PROS-1 | Consider if life expectancy ≥10y[m] | See PROS-5 |
| Intermediate[f] | Has no high- or very-high-risk features and has one or more intermediate risk factors (IRF):<br>• T2b-T2c<br>• Grade Group 2 or 3<br>• PSA 10–20 ng/mL | Favorable intermediate | • 1 IRF and<br>• Grade Group 1 or 2 and<br>• <50% biopsy cores positive[g] | • Bone imaging[j]: not recommended for staging<br>• Pelvic ± abdominal imaging: recommended if nomogram predicts >10% probability of pelvic lymph node involvement<br><br>If regional or distant metastases are found, see PROS-9 | Recommended if family history positive or intraductal histology<br>See PROS-1 | Consider if life expectancy ≥10y[m] | See PROS-6 |
| | | Unfavorable intermediate | • 2 or 3 IRFs and/or<br>• Grade Group 3 and/or<br>• ≥50% biopsy cores positive[g] | • Bone imaging[j]: recommended if T2 and PSA >10 ng/mL<br>• Pelvic ± abdominal imaging: recommended if nomogram predicts >10% probability of pelvic lymph node involvement<br><br>If regional or distant metastases are found, see PROS-9 | Recommended if family history positive or intraductal histology<br>See PROS-1 | Not routinely recommended | See PROS-7 |
| High | • T3a OR<br>• Grade Group 4 or Grade Group 5 OR<br>• PSA >20 ng/mL | | | • Bone imaging[j]: recommended<br>• Pelvic ± abdominal imaging: recommended if nomogram predicts >10% probability of pelvic lymph node involvement<br><br>If regional or distant metastases are found, see PROS-9 | Recommended[c,k] | Not routinely recommended | See PROS-8 |
| Very high | • T3b-T4 OR<br>• Primary Gleason pattern 5 OR<br>• >4 cores with Grade Group 4 or 5 | | | • Bone imaging[j]: recommended<br>• Pelvic ± abdominal imaging: recommended if nomogram predicts >10% probability of pelvic lymph node involvement<br><br>If regional or distant metastases are found, see PROS-9 | Recommended[c,k] | Not routinely recommended | See PROS-8 |

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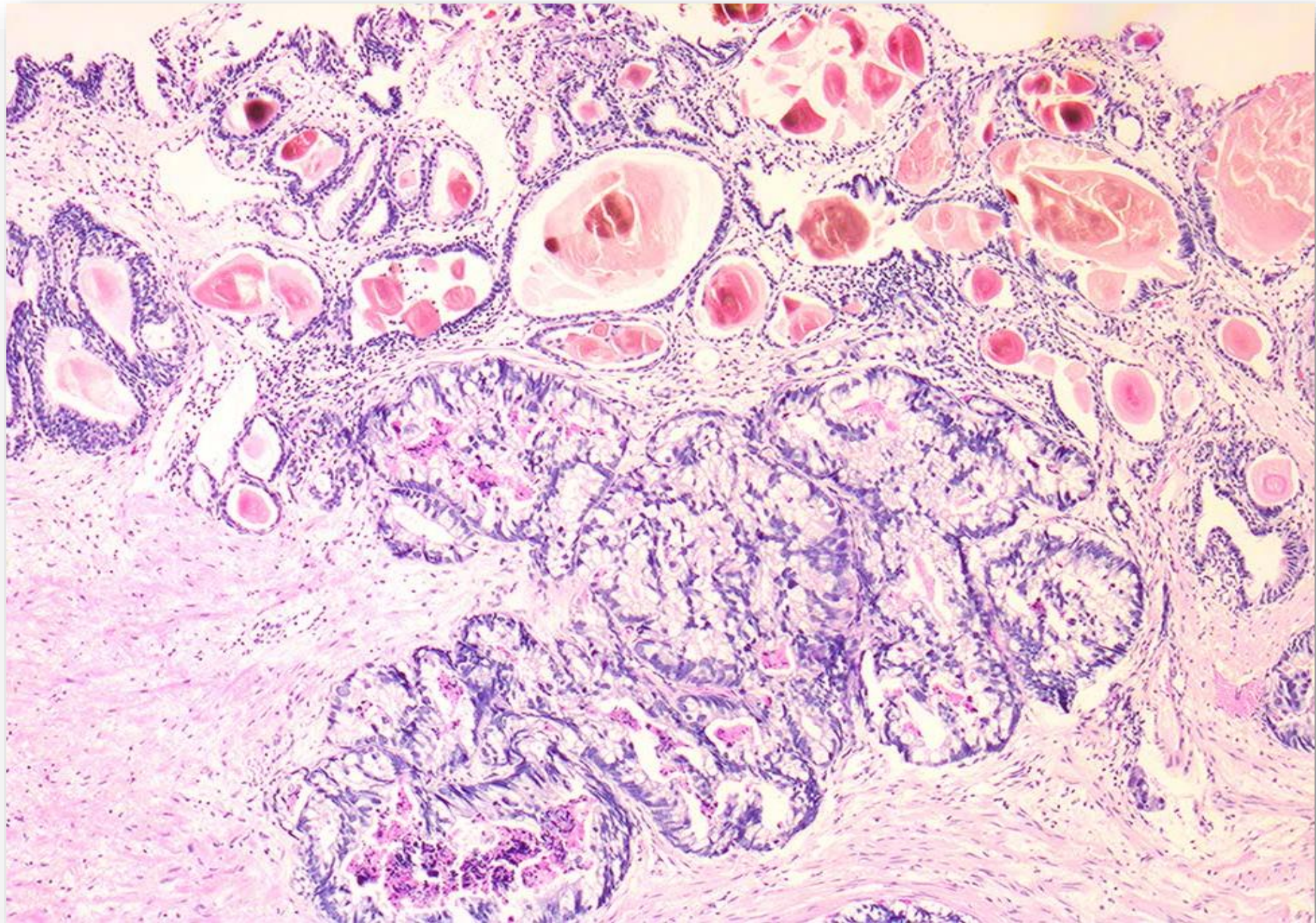
## INITIAL RISK STRATIFICATION AND STAGING WORKUP FOR CLINICALLY LOCALIZED DISEASE

| Risk group | Clinical/pathologic features | | | Imaging[h,i] | Germline testing | Molecular and biomarker analysis of tumor[l] | Initial therapy |
|---|---|---|---|---|---|---|---|
| Very low[f] | • T1c AND<br>• Grade Group 1 AND<br>• PSA <10 ng/mL AND<br>• Fewer than 3 prostate biopsy fragments/cores positive, ≤50% cancer in each fragment/core[g] AND<br>• PSA density <0.15 ng/mL/g | | | Not indicated | Recommended if family history positive or intraductal histology<br>See PROS-1 | Not indicated | See PROS-4 |
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## INITIAL RISK STRATIFICATION AND STAGING WORKUP FOR CLINICALLY LOCALIZED DISEASE

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## GENETIC AND MOLECULAR BIOMARKER ANALYSIS FOR ADVANCED PROSTATE CANCER

| Risk group | Clinical/pathologic features | Germline testing | Molecular and biomarker analysis of tumor[l] | Initial therapy |
|---|---|---|---|---|
| Regional | Any T, N1, M0 | Recommended[c,k] | Consider tumor testing for homologous recombination gene mutations and for microsatellite instability (MSI) or mismatch repair deficiency (dMMR)[dd,ee] | See PROS-10 |
| Metastatic[ff] | Any T, Any N, M1 | Recommended[c,k] | Consider tumor testing for homologous recombination gene mutations and for MSI or dMMR [dd,ee] | See PROS-14 |

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## National Comprehensive Cancer Network®

### GENETIC AND MOLECULAR BIOMARKER ANALYSIS FOR ADVANCED PROSTATE CANCER

| Risk group | Clinical/pathologic features | Germline testing | Molecular and biomarker analysis of tumor[l] | Initial therapy |
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Non Invasive Ductal Ca
Ductal DCIS?
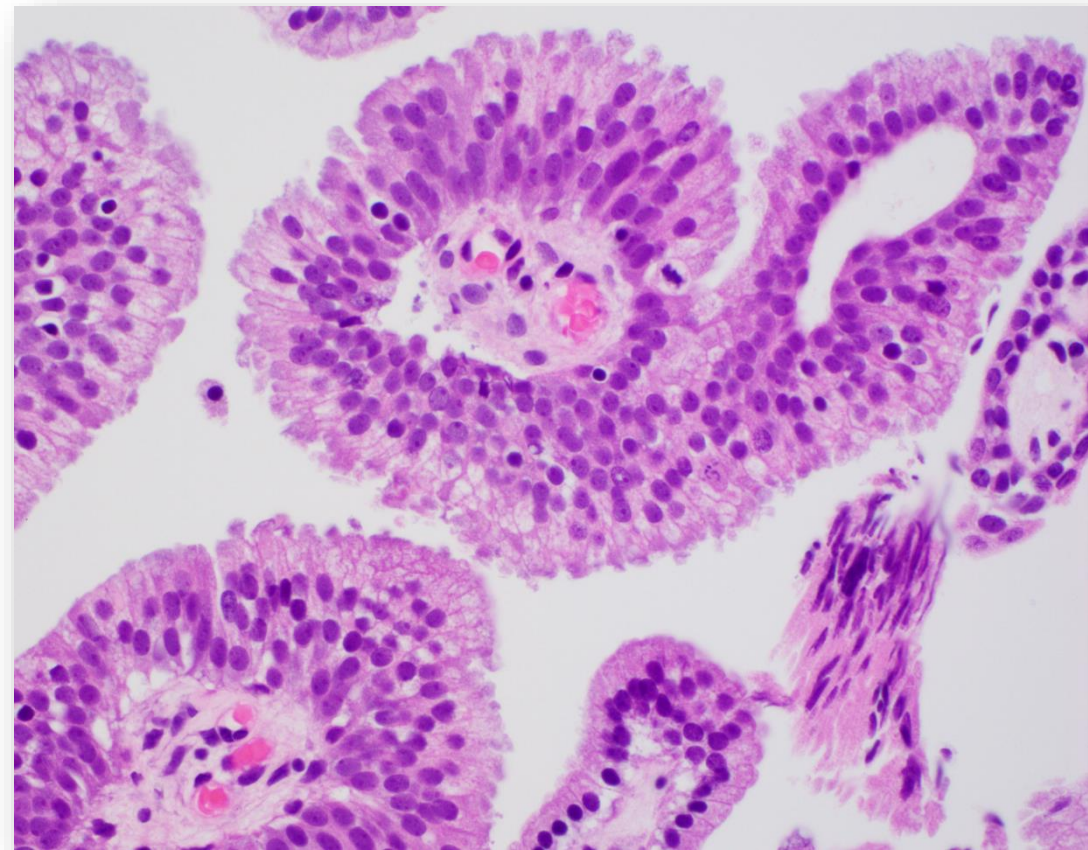
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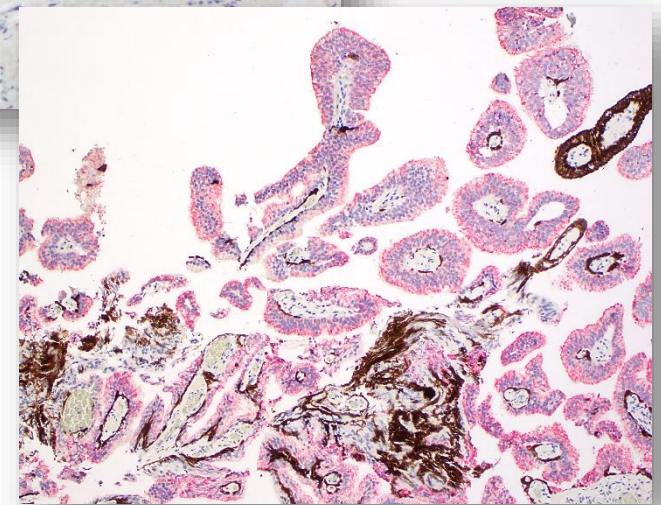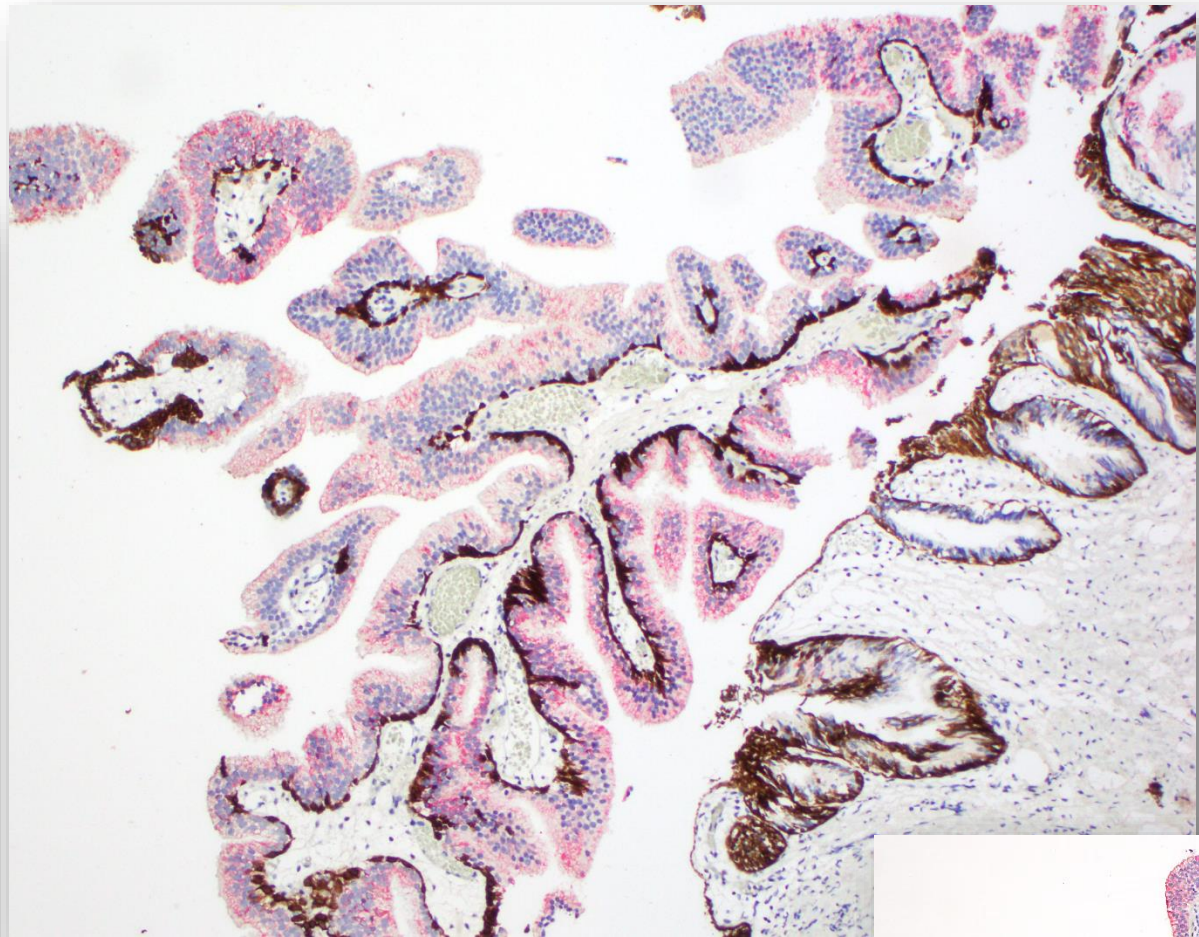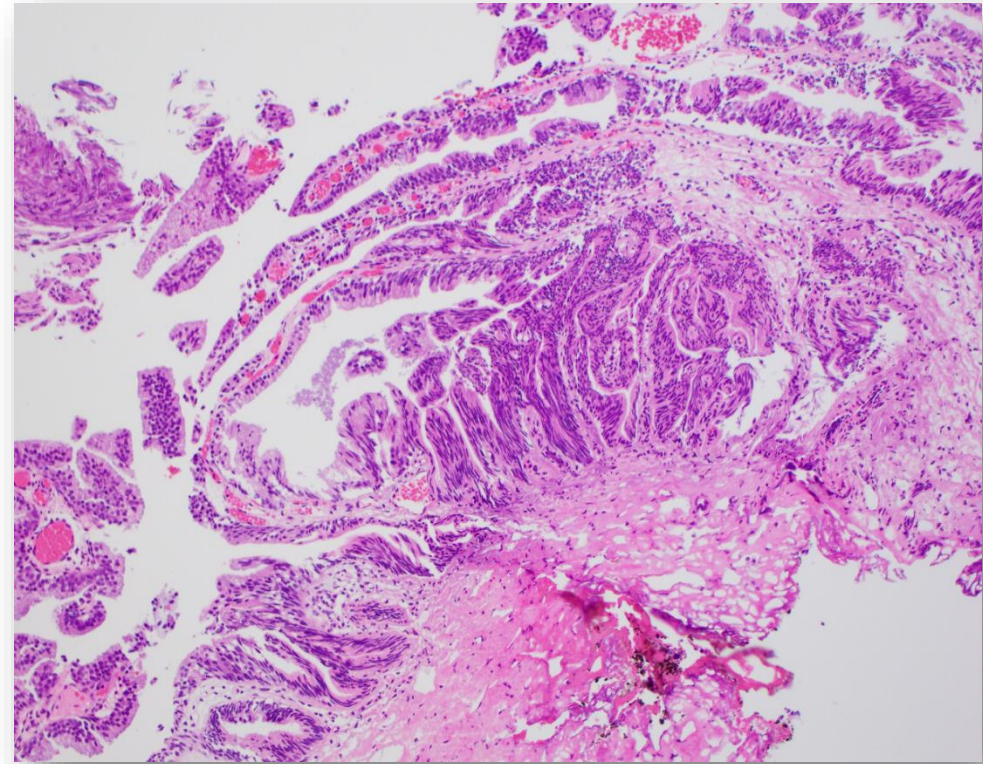
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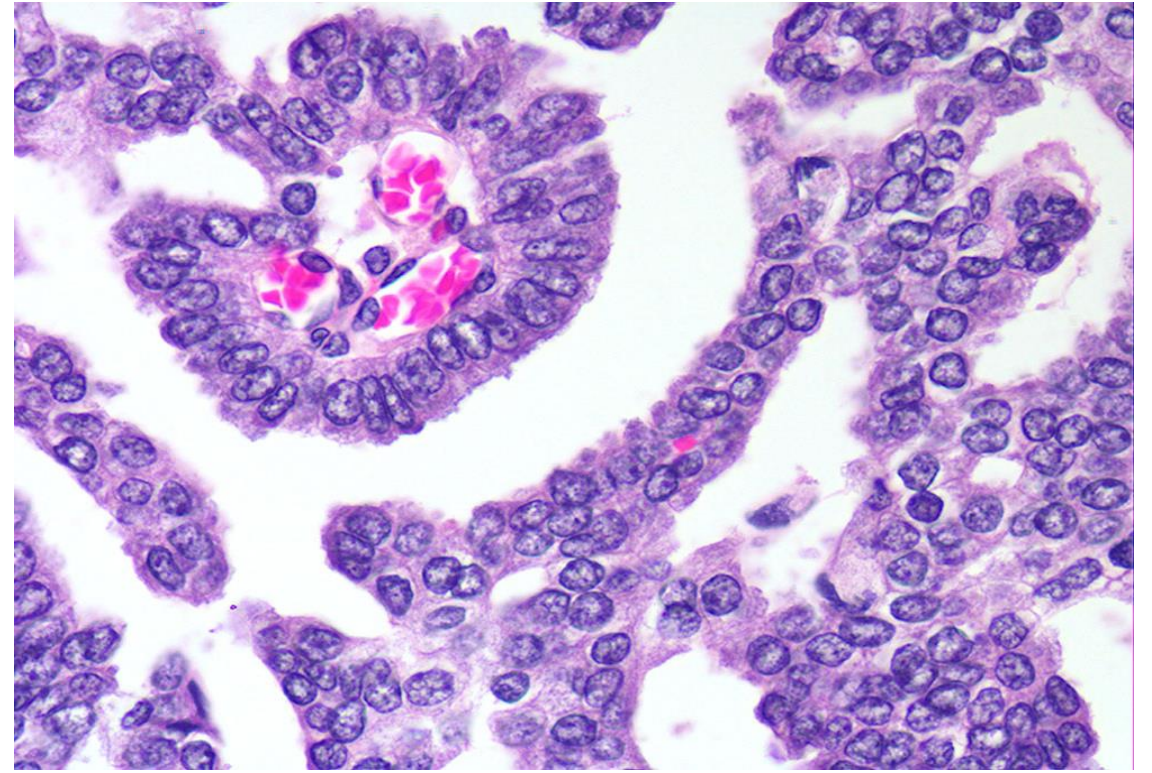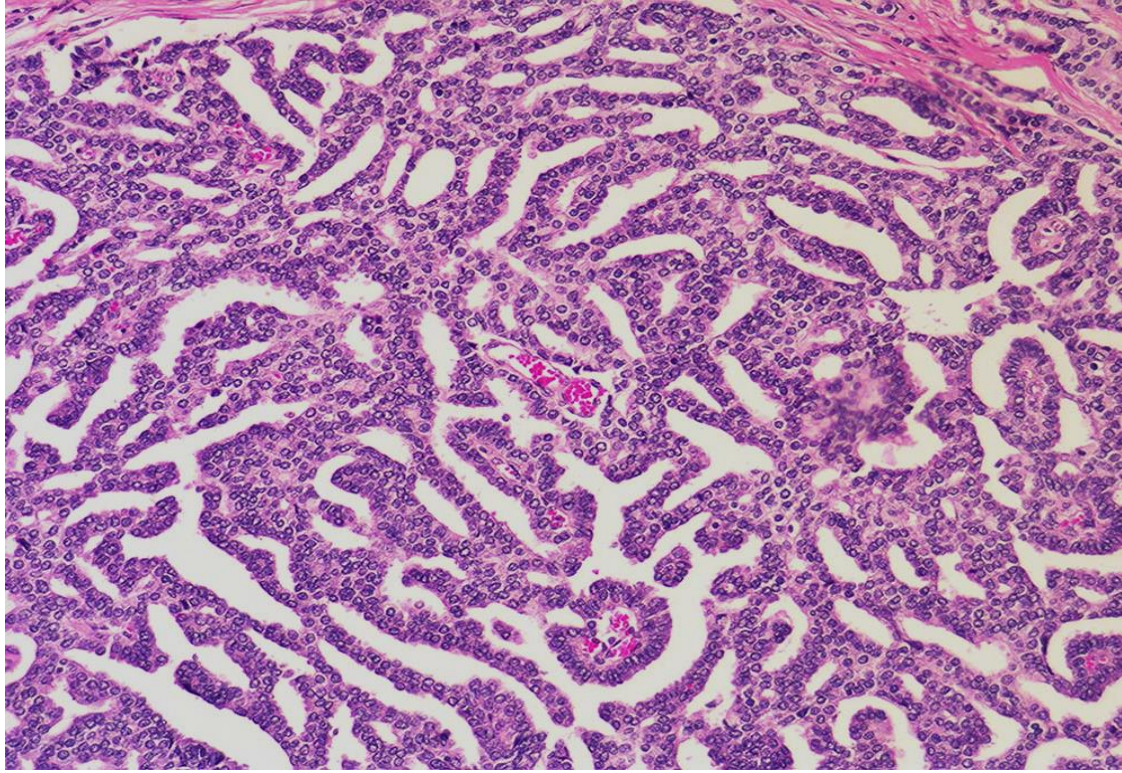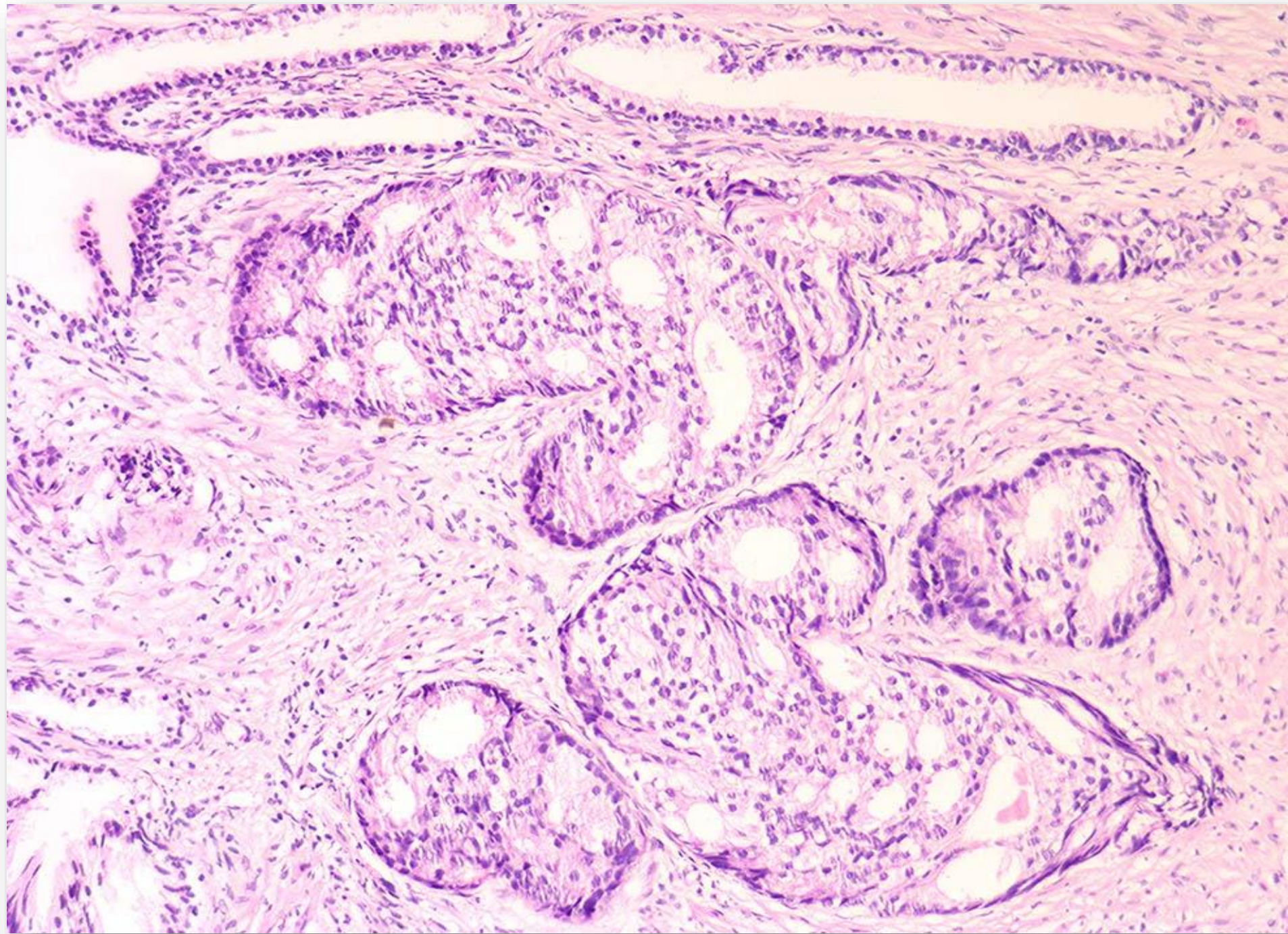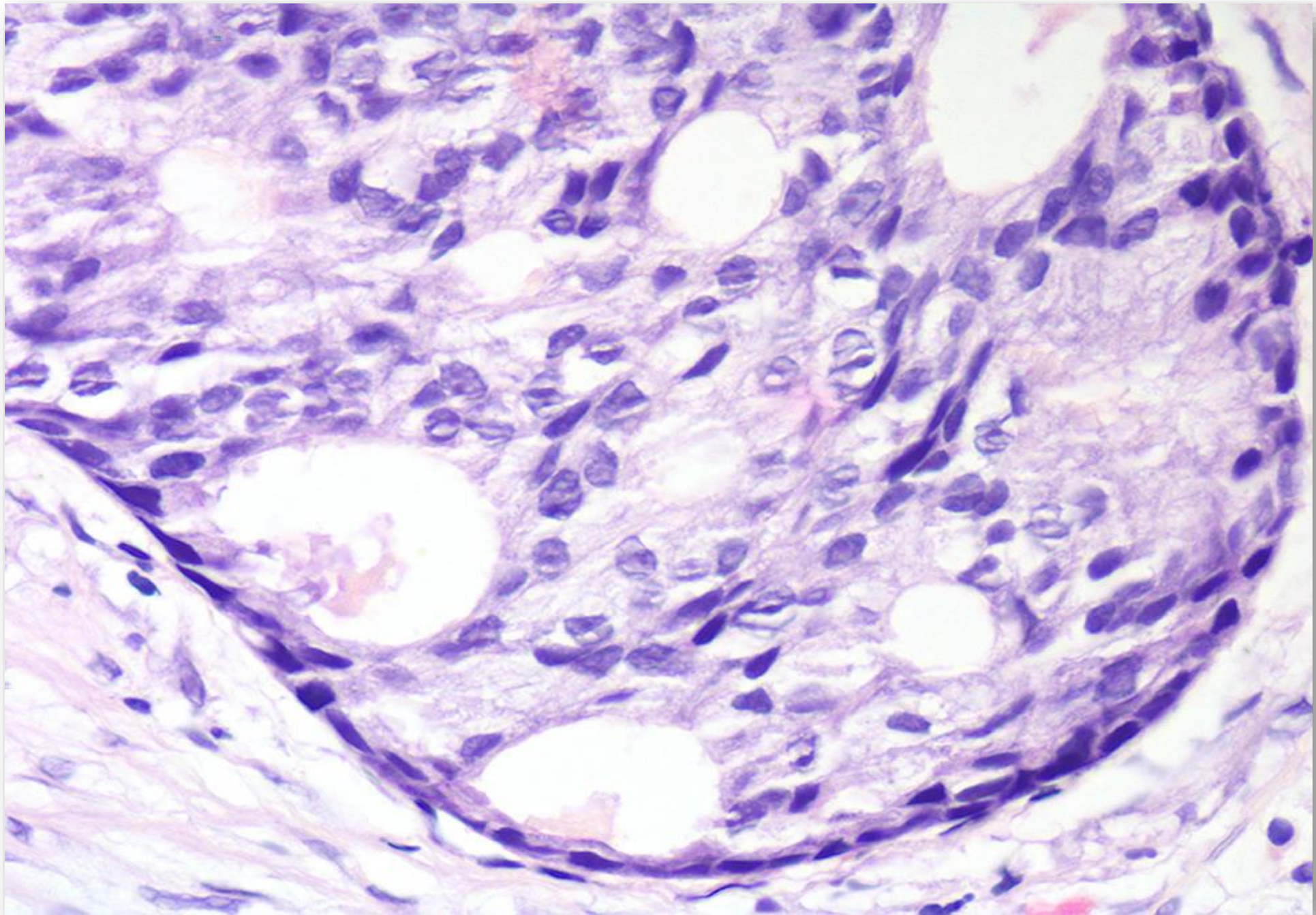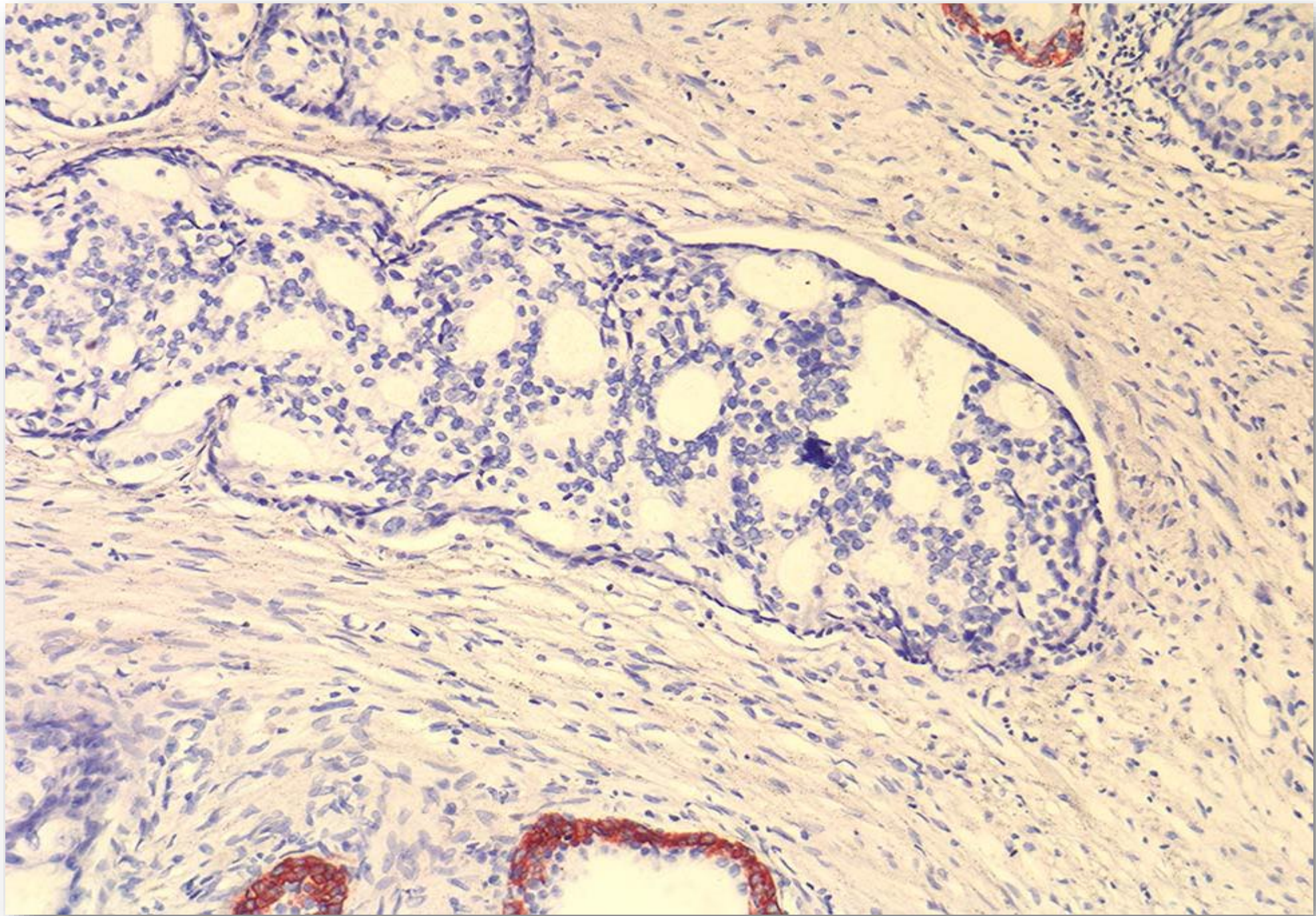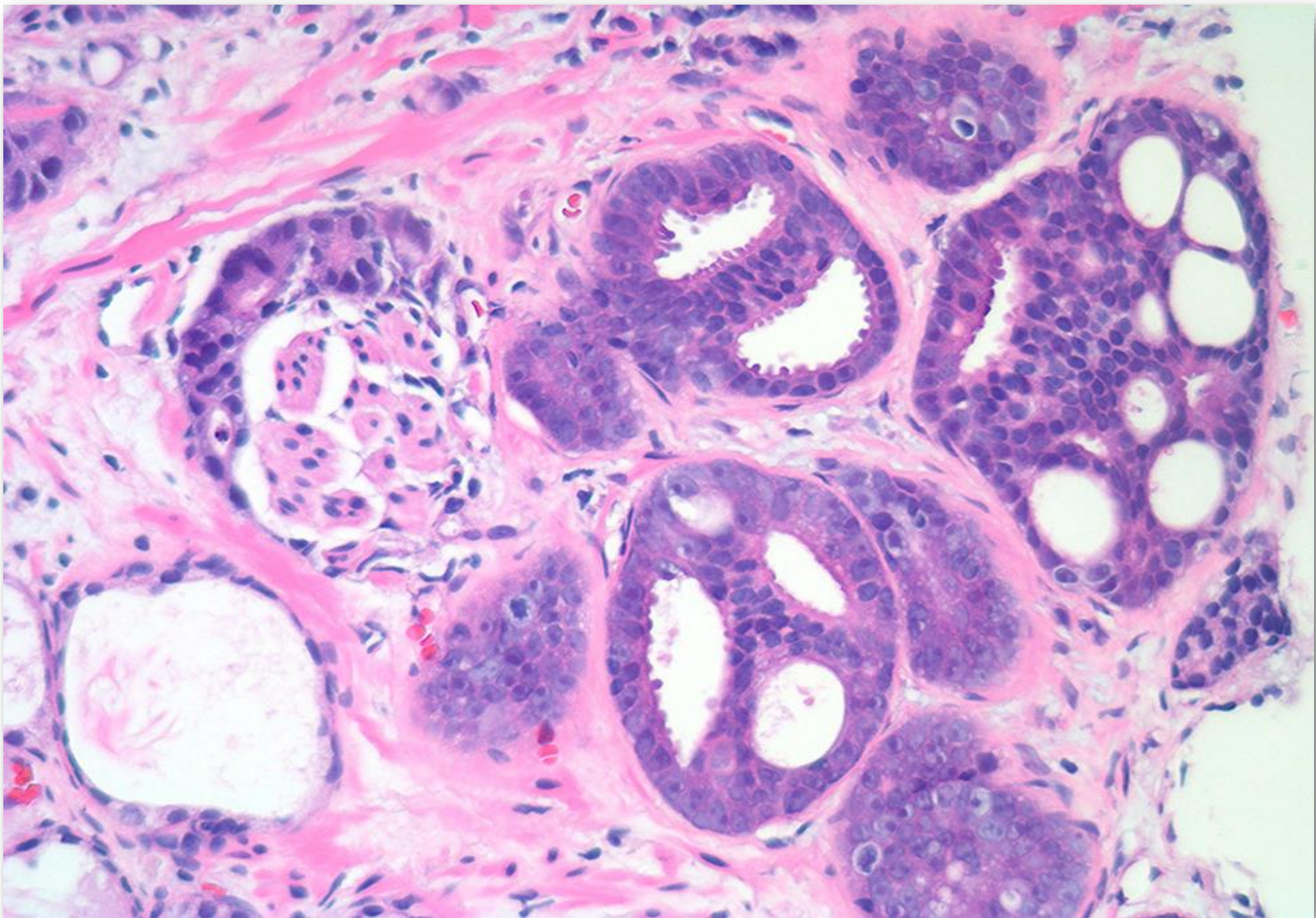
# IDCP

- **6.1.1.2: Intraductal carcinoma**

- **Definition**
- Intraductal carcinoma of the prostate (IDC-P) is a neoplastic epithelial proliferation involving pre-existing, generally expanded, duct-acinar structures and characterized by architectural and cytologic atypia beyond what is acceptable for HGPIN. It is typically associated with high-grade and high-stage prostate carcinoma but in rare cases may represent a precursor lesion.
-
Intraductal carcinoma of the prostate (IDC-P) is a neoplastic epithelial proliferation that is located within and significantly expands the native prostatic ducts and acini. Morphological IDC-P may represent two biologically distinct entities. In a vast majority of cases it is associated with invasive high grade carcinoma and considered a late 'colonization'-type event in the evolution of prostatic acinar carcinoma {16980940; 8669528; 9523662}. In a small subset of cases, IDC-P is seen in the absence of invasive prostate cancer, and may represent an in-situ carcinoma that exhibits much greater architectural and/or cytological atypia than high grade prostatic intraepithelial neoplasia (HGPIN).
- Current evidence suggests IDC-P may represent two biologically distinct entities. In a vast majority of cases, IDC-P is currently thought to be a late event in the setting of high grade invasive prostate cancer, with propensity for intraductal/acinar spread. Studies support IDC-P being distinct from HGPIN and showing overlap with profiles of high grade invasive prostate cancer. Early studies found that IDC-P and Gleason pattern 4/5 prostate cancer show a similar frequency of genomic instability as determined by loss of heterozygosity and comparative genomic hybridization, more common than that in Gleason pattern 3 prostate cancer and HGPIN {18383208, 10951489}. Several recent studies have shown that prostate cancer with IDC-P and/or invasive cribriform cancer is associated with higher percent genomic alteration than prostate cancer without these patterns {29295717, 28511883}. Specific somatic copy number gene alterations known to be associated with aggressive prostate cancer that have been observed in IDC-P studies include loss of *PTEN*, *CDH1*, and *BCAR1* and gain of *MYC* {29295717}. Expression of *SchLAP1*, a long noncoding RNA associated with poor prognosis in prostate cancer, has been observed with >3X the frequency in prostate cancer with an IDC-P/invasive cribriform pattern {28511883}. Mutations in *SPOP* and *TP53* as well as the transcription factor *FOXA1* are more frequent in cases with IDC-P/invasive cribriform cancer when compared to cases without these findings {29295717} - NOT VALIDATED . *ERG* rearrangement is present in the majority of IDC-P {20220513}, loss of *PTEN* expression may be identified in up to ~85% of IDC-P, with the latter very uncommonly seen in HGPIN {23222491}.
- Rarely, IDC-P is found without a concomitant invasive prostate cancer or adjacent to only microinvasive prostate cancer, raising the possibility that IDC-P may represent an in situ-type lesion preceding development of invasive prostate cancer {20723921, 17617002, 30993692}. A single study of IDC-P cases without invasive prostate cancer or with concurrent Gleason score 6 prostate cancer identified activating oncogenic driver mutations in genes within the MAPK and PI3K pathways, extraordinarily rare findings in prostate cancer; discordance in either ERG or PTEN expression detected by immunohistochemistry between IDC-P and the concomitant Gleason score 6 prostate cancer was also noted {30993692} - NOT VALIDATED. These findings suggest that IDC-P seen in these contexts are unlikely to be a precursor to associated low-grade invasive prostate cancer but may represent a molecularly unique in-situ tumor. Others dispute the existence of a true in situ IDC-P {31843189}, as there are no reliable morphological features to distinguish between IDC-P with or without associated invasive prostate cancer. In prostate biopsies, lack of concomitant invasive prostate cancer generally represents under-sampling; follow-up radical prostatectomy specimens – when completely sampled – have virtually never displayed IDC-P alone.
- ERG gene fusion and PTEN genomic alterations and loss of protein expression may be helpful in selected patients (REF).
-
- REFS to consider (from Mark Rubin):
- PMID: 28515055 WES of 105 AA PCA from the US
PMID: 25056375. AA vs White molecular differences SPINK1 overexpression was evaluated by immunohistochemistry, ERG rearrangement and PTEN deletion by FISH, and SPOP mutation by Sanger sequencing.

PMID: 24563616 SPOP mutation frequency from 720 prostate cancer samples from six international cohorts spanning Caucasian, African American, and Asian patients,
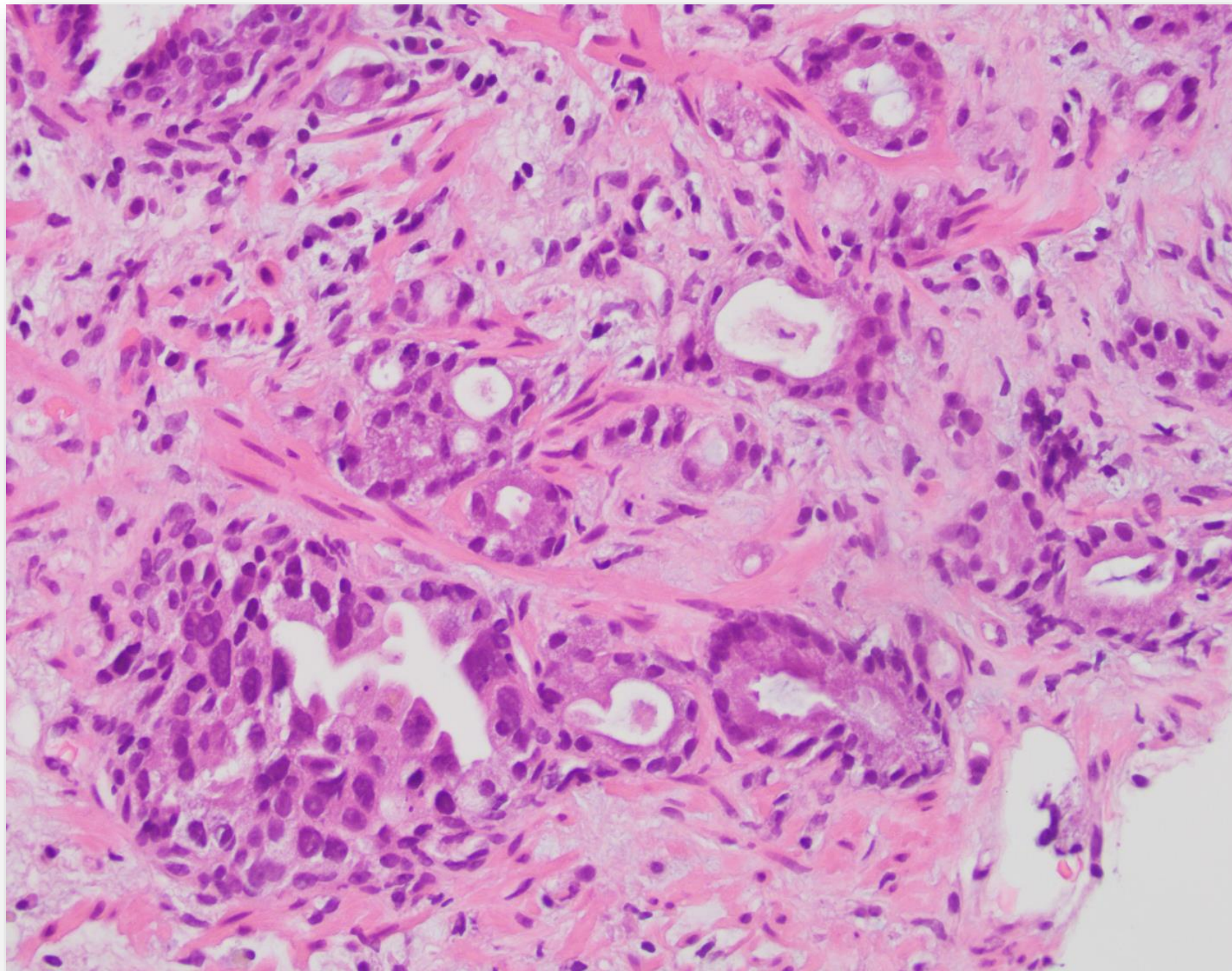
-
From a differential diagnosis standpoint, it is most crucial, particularly in biopsies, to distinguish IDC-P from HGPIN, as their clinical associations are drastically different.  For atypical lesions that do not meet the criteria for IDC-P, the term "atypical intraductal proliferation (AIP)" is preferred.
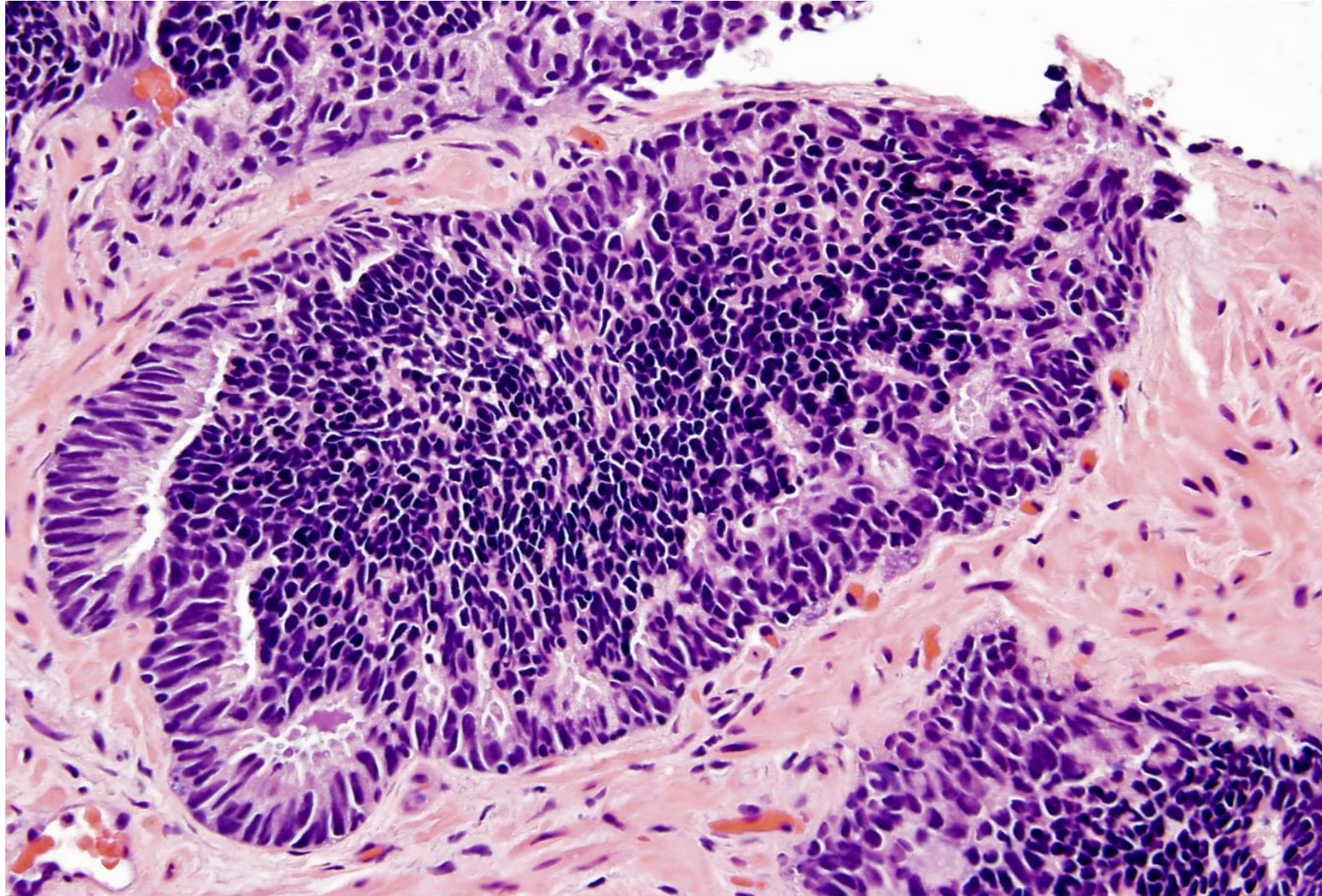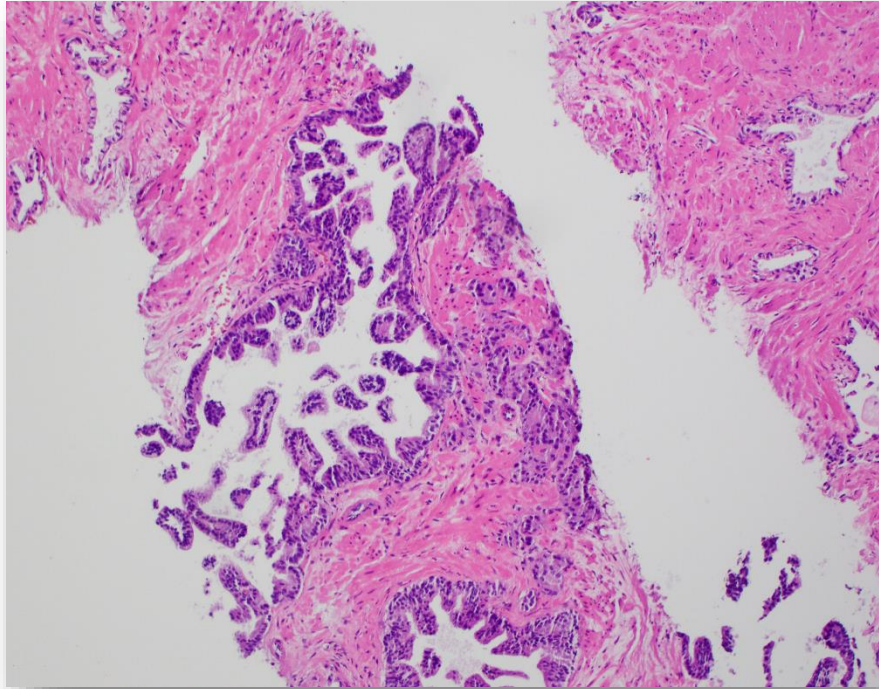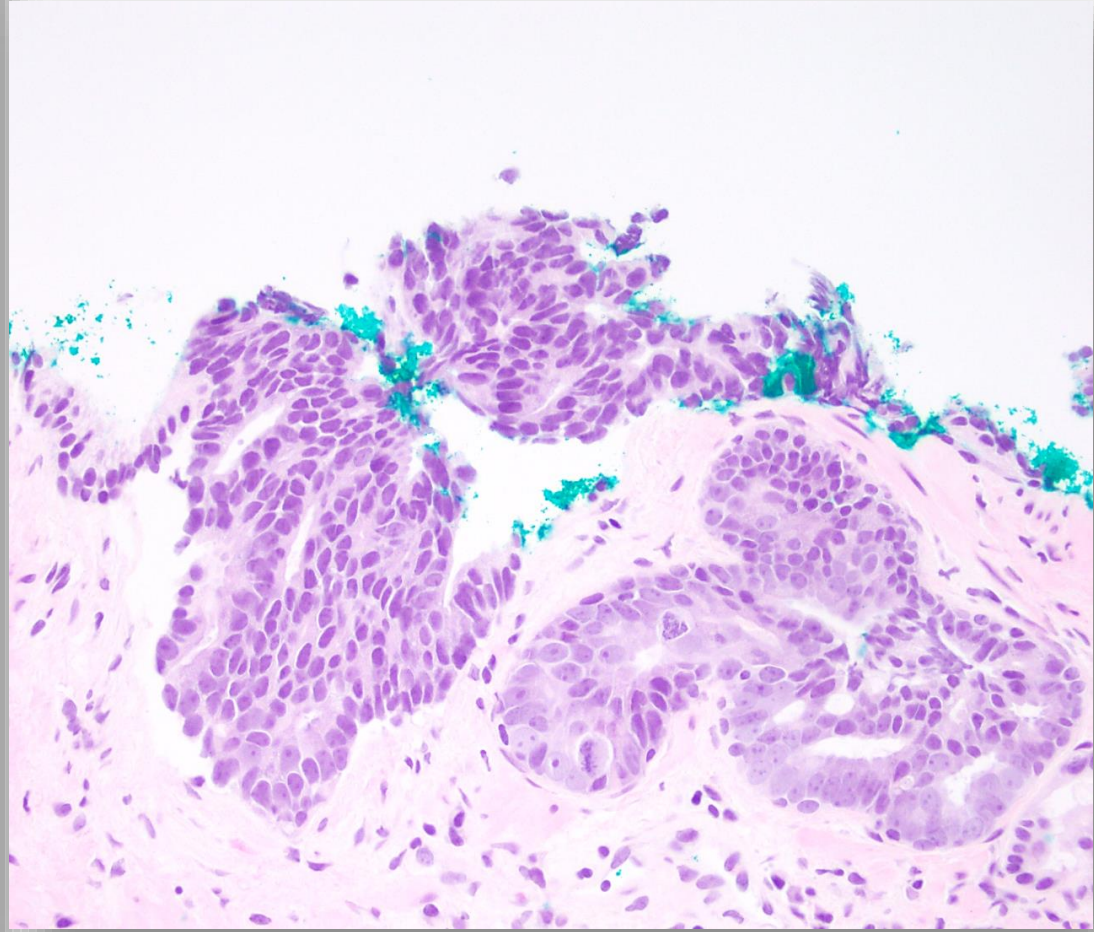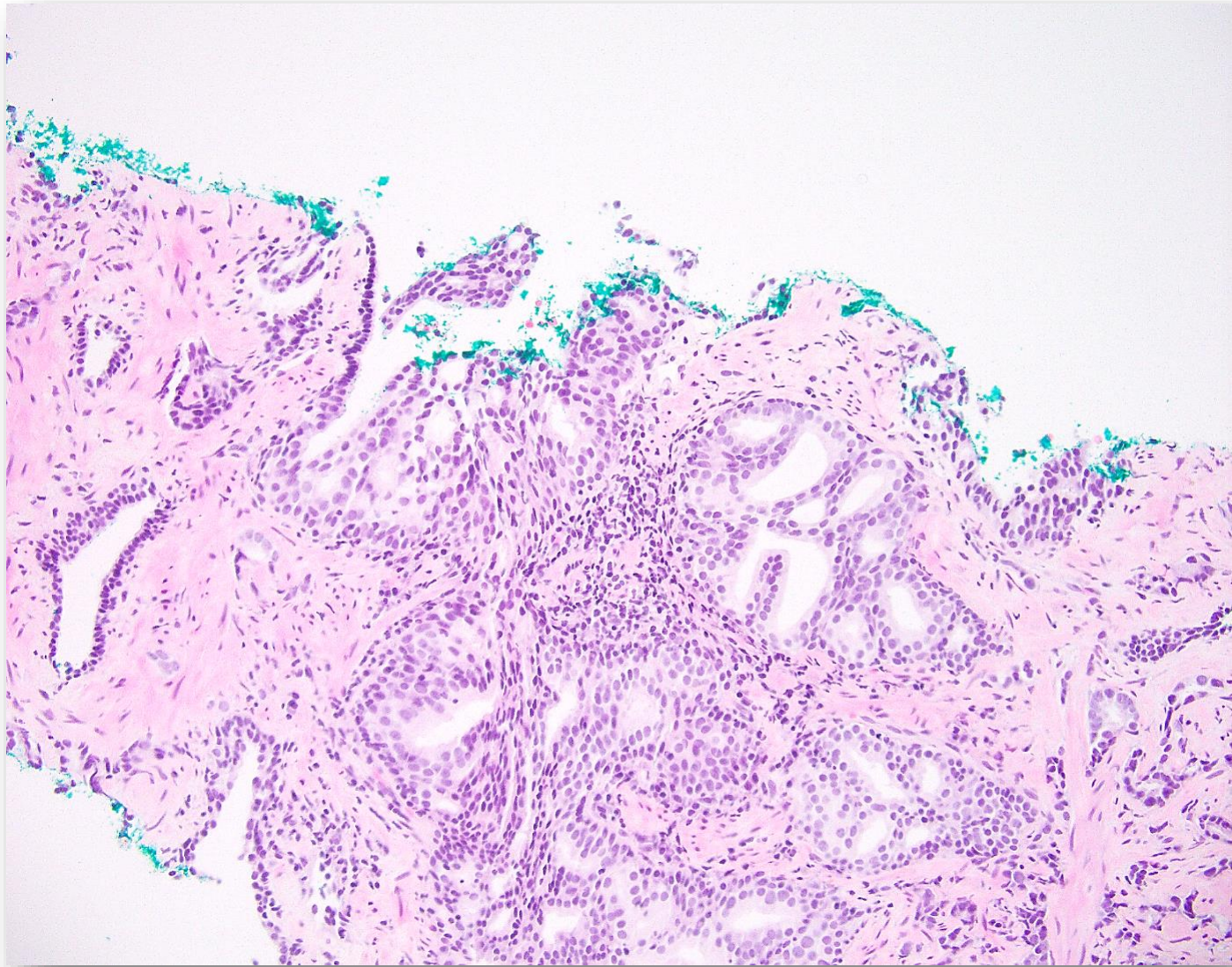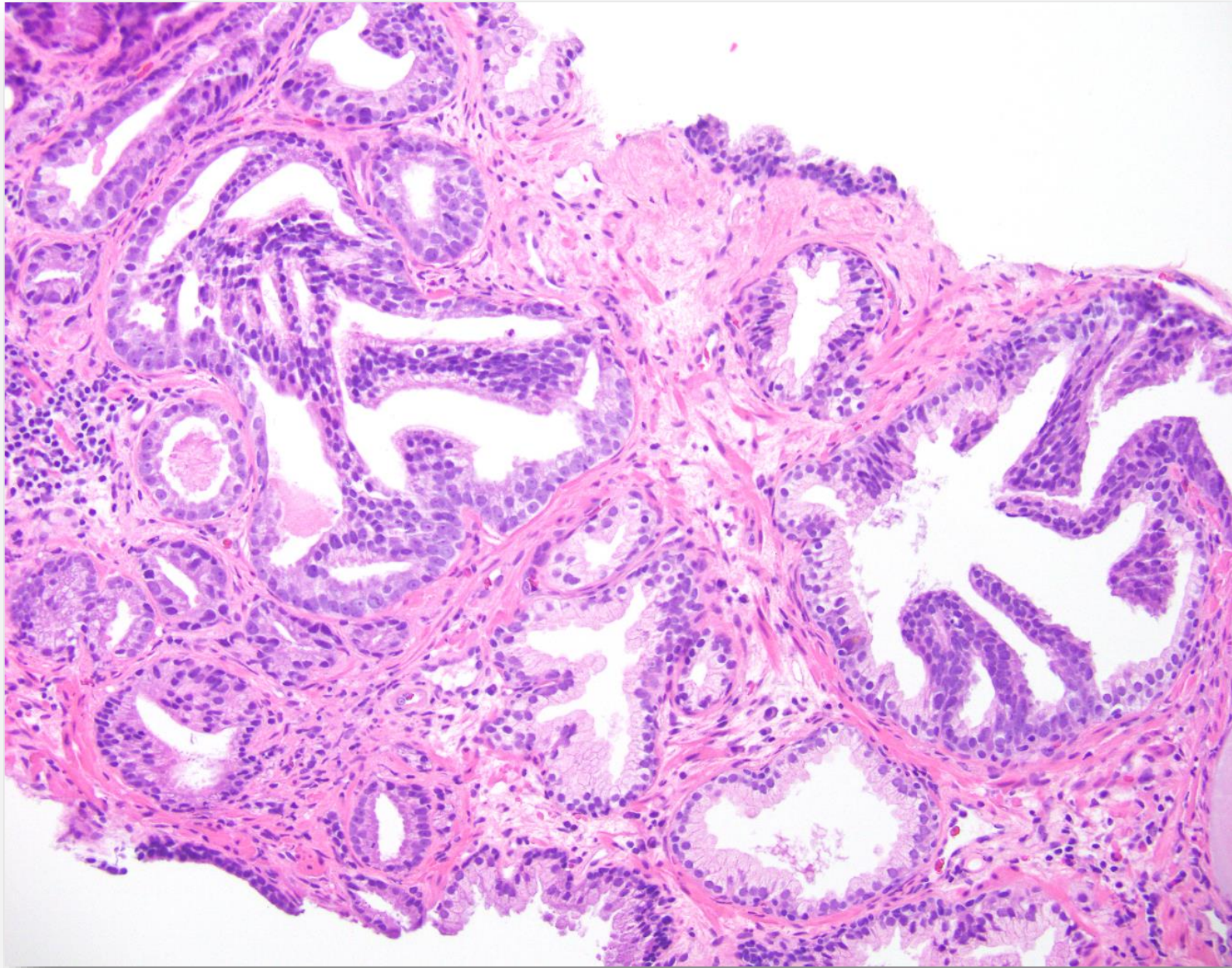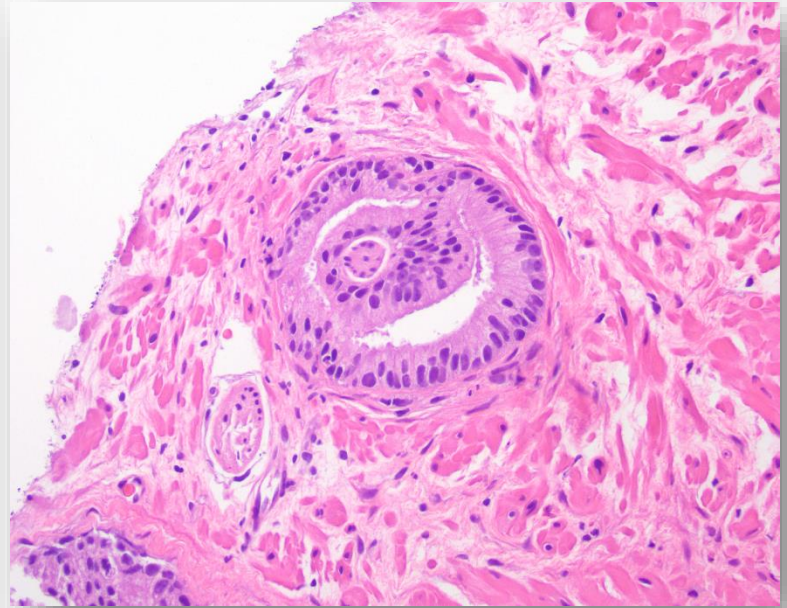
PIN with adjacent Invasive Ca.
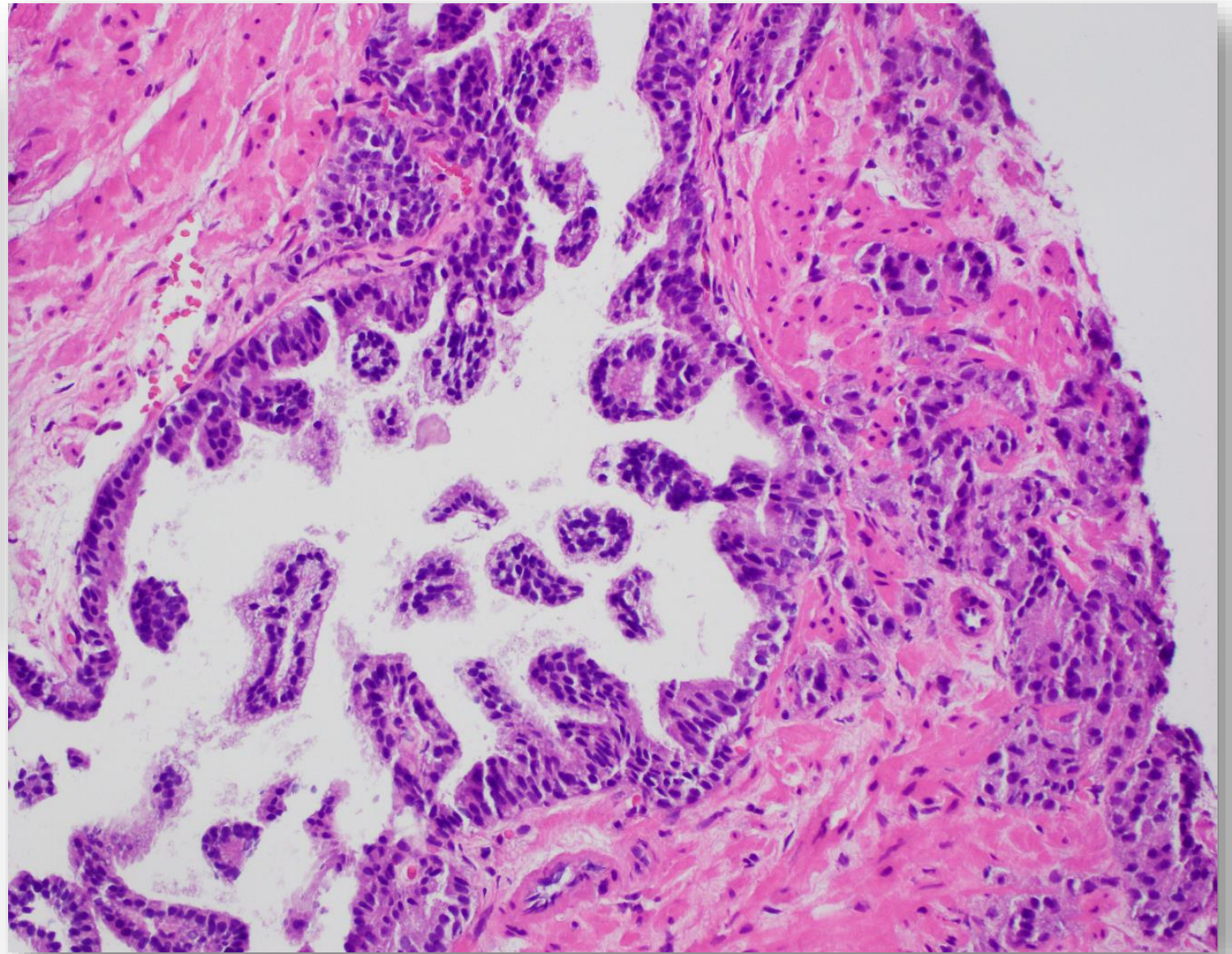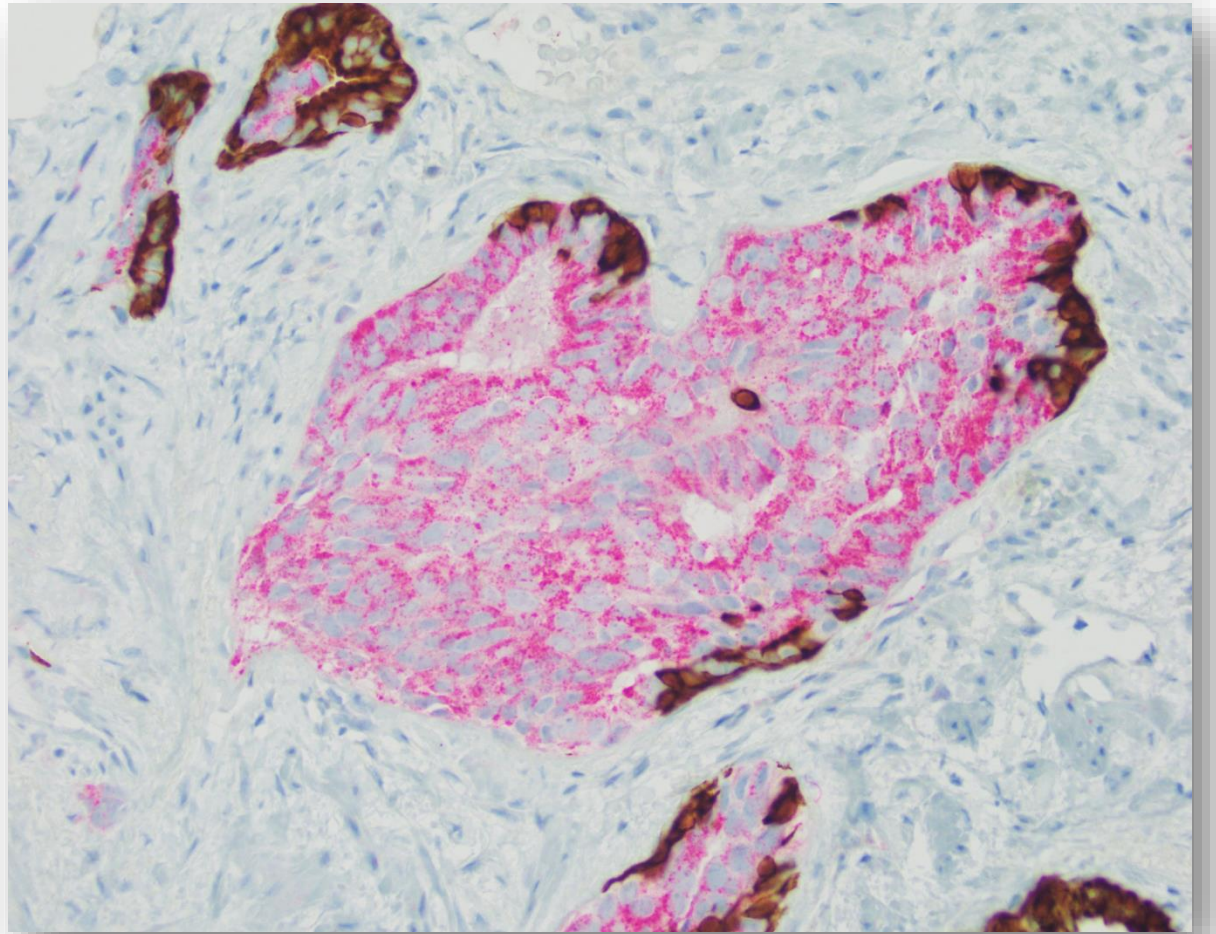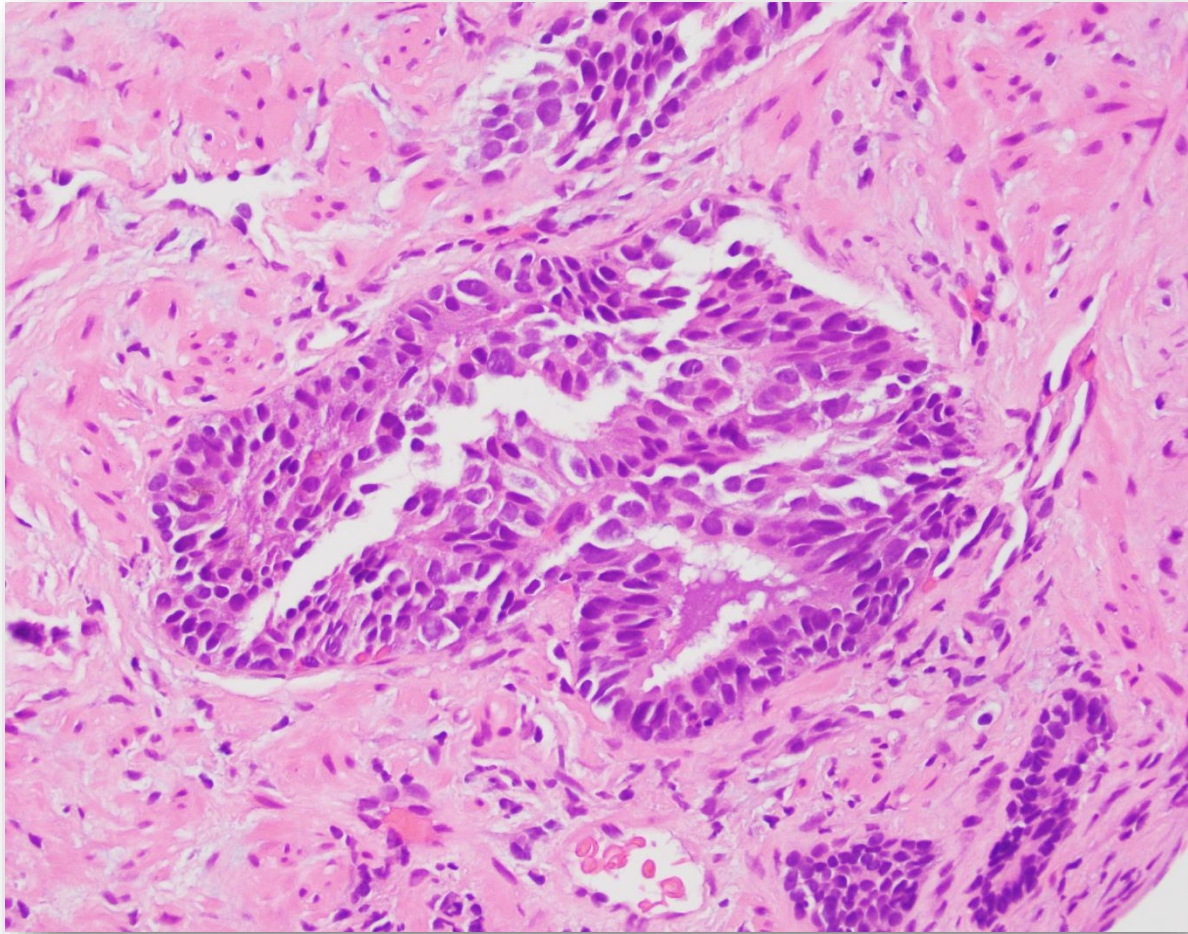
IDC-P
With adjacent 3+4=7

IDC-P
Intraductal Spread

IDCP-P
Intraductal Spread

IDC-P?

# Intraductal carcinoma of the prostate on needle biopsy: histologic features and clinical significance

Charles C Guo[1] and Jonathan I Epstein[1,2,3]

| *Cribriform acinar adenocarcinoma* | *Cribriform IDC-P* |
|---|---|
| Absence of contour or branching architecture of prostatic ducts | Contour or branching architectures of prostatic ducts |
| Irregular, infiltrating borders | Rounded, circumscribed borders |
| Absence of basal cells | Basal cells present |

| *Ductal adenocarcinoma* | *IDC-P* |
|---|---|
| Cribriform with large slit-like lumina | Cribriform with small rounded lumens |
| Tall columnar cells | Cuboidal cells |
| Papillary fronds with fibrovascular cores | Micropapillary tufts lacking fibrovascular cores |
| Basal cells usually absent | Basal cells always present |

| *Intraductal spread of UC* | *IDC-P* |
|---|---|
| Rarely associated with glandular features or cribriform pattern | Often associated with focal glandular features and cribriform pattern |
| Immunohistochemically negative for PSA or PSAP | Immunohistochemically positive for PSA or PSAP |
| Positive for HMWCK or thrombomodulin | Negative for HMWCK or thrombomodulin |
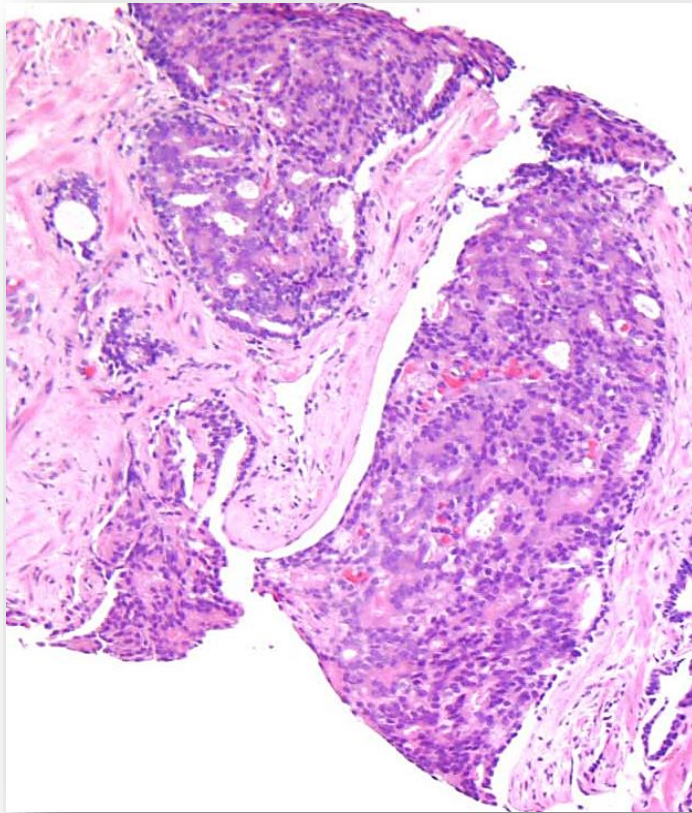
IDC-P
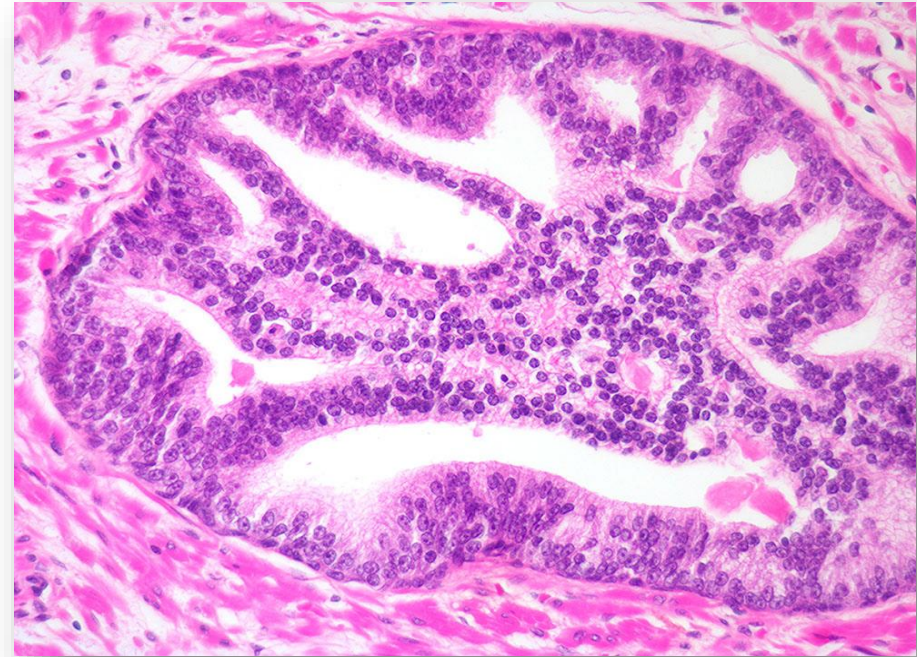
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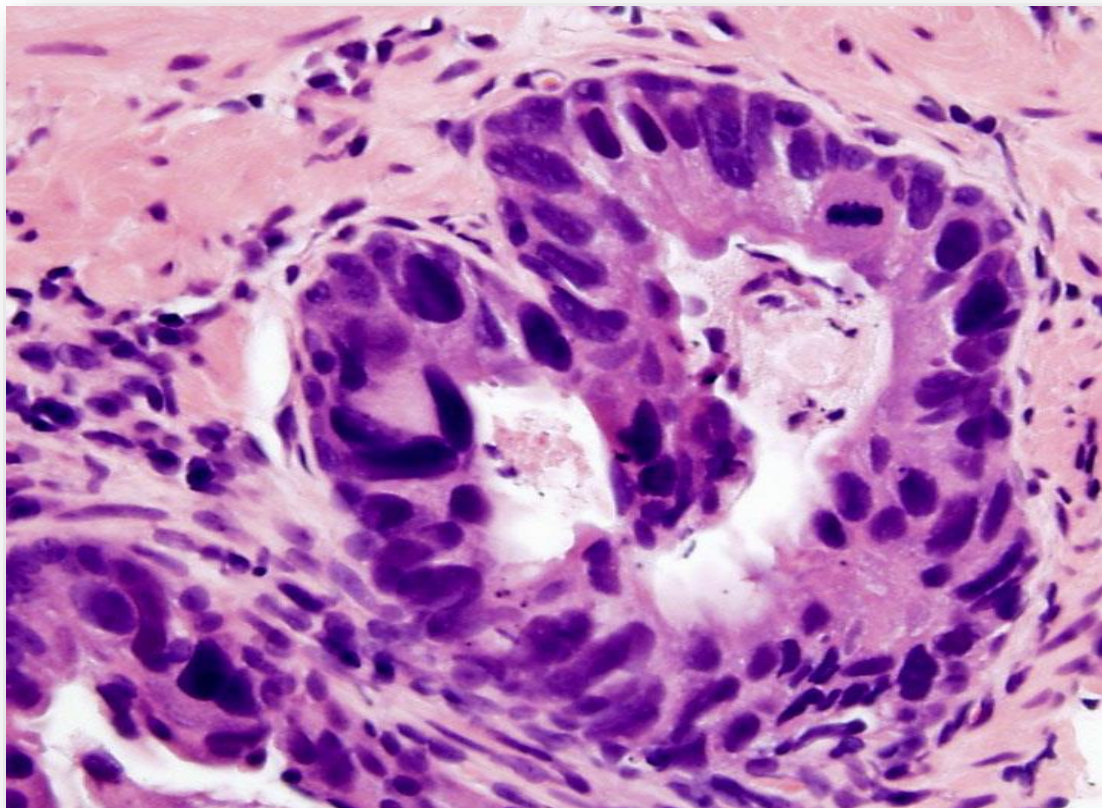
IDC-P

HGPIN

# Ductal Adenocarcinoma
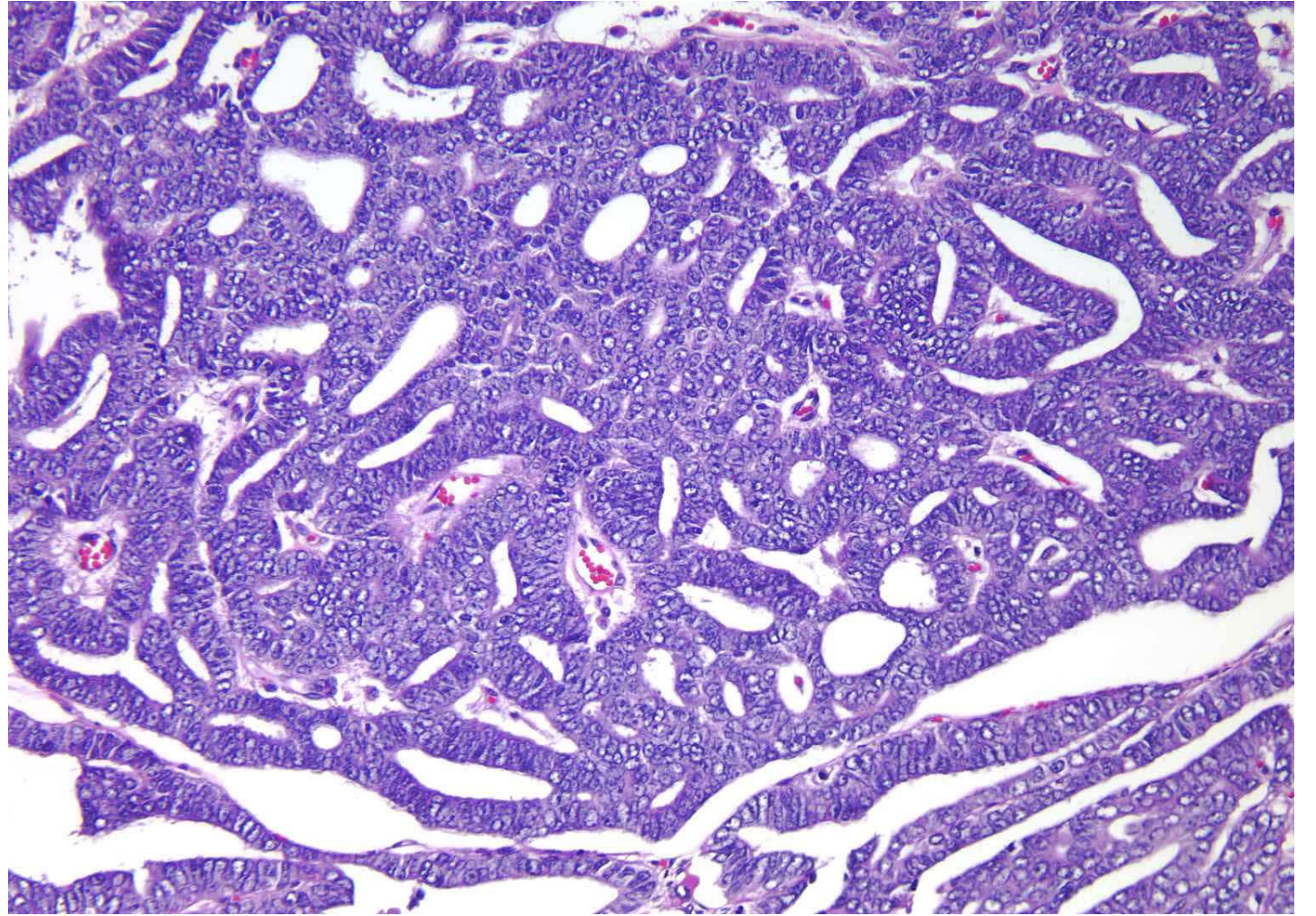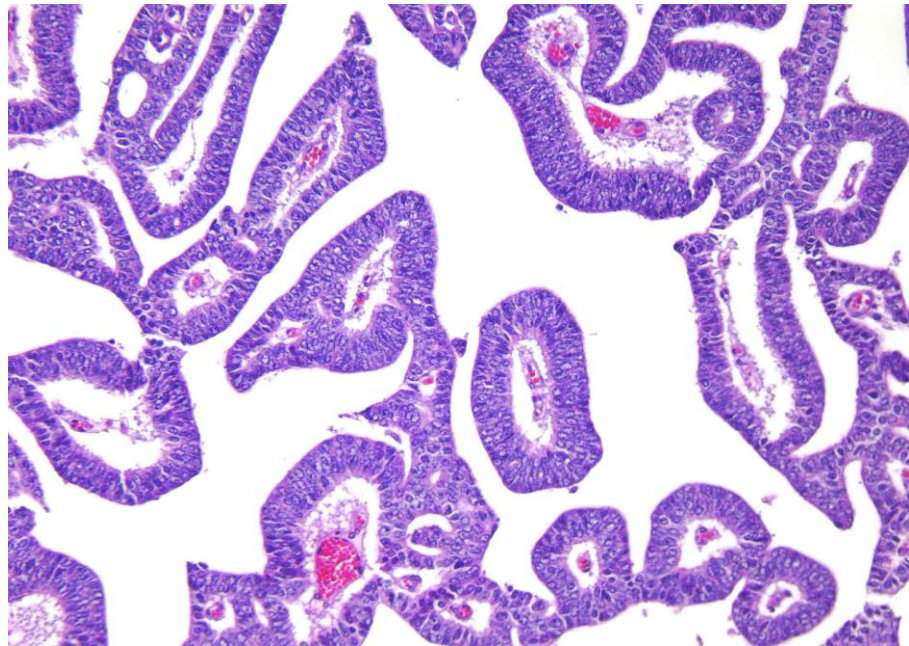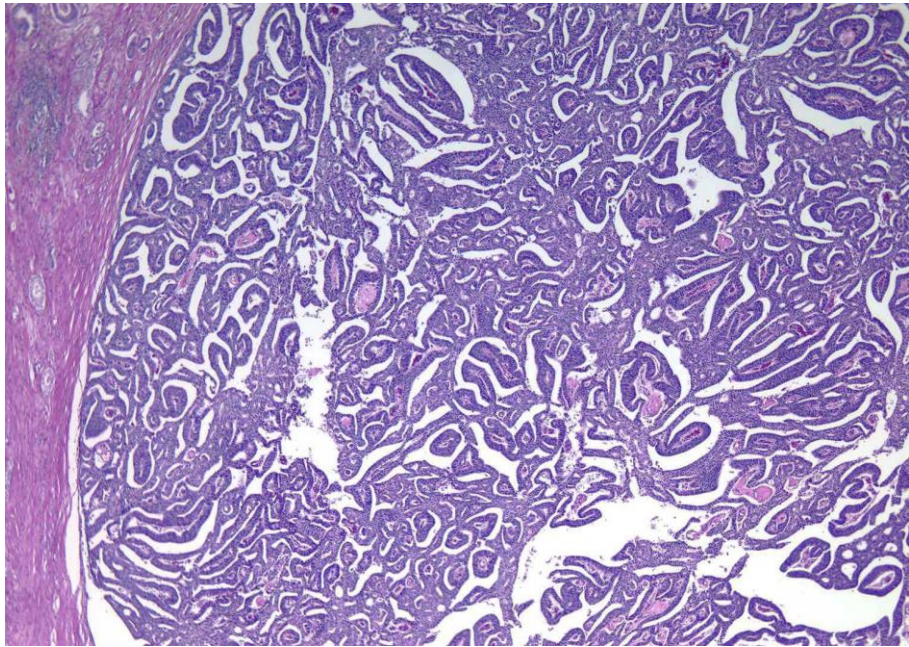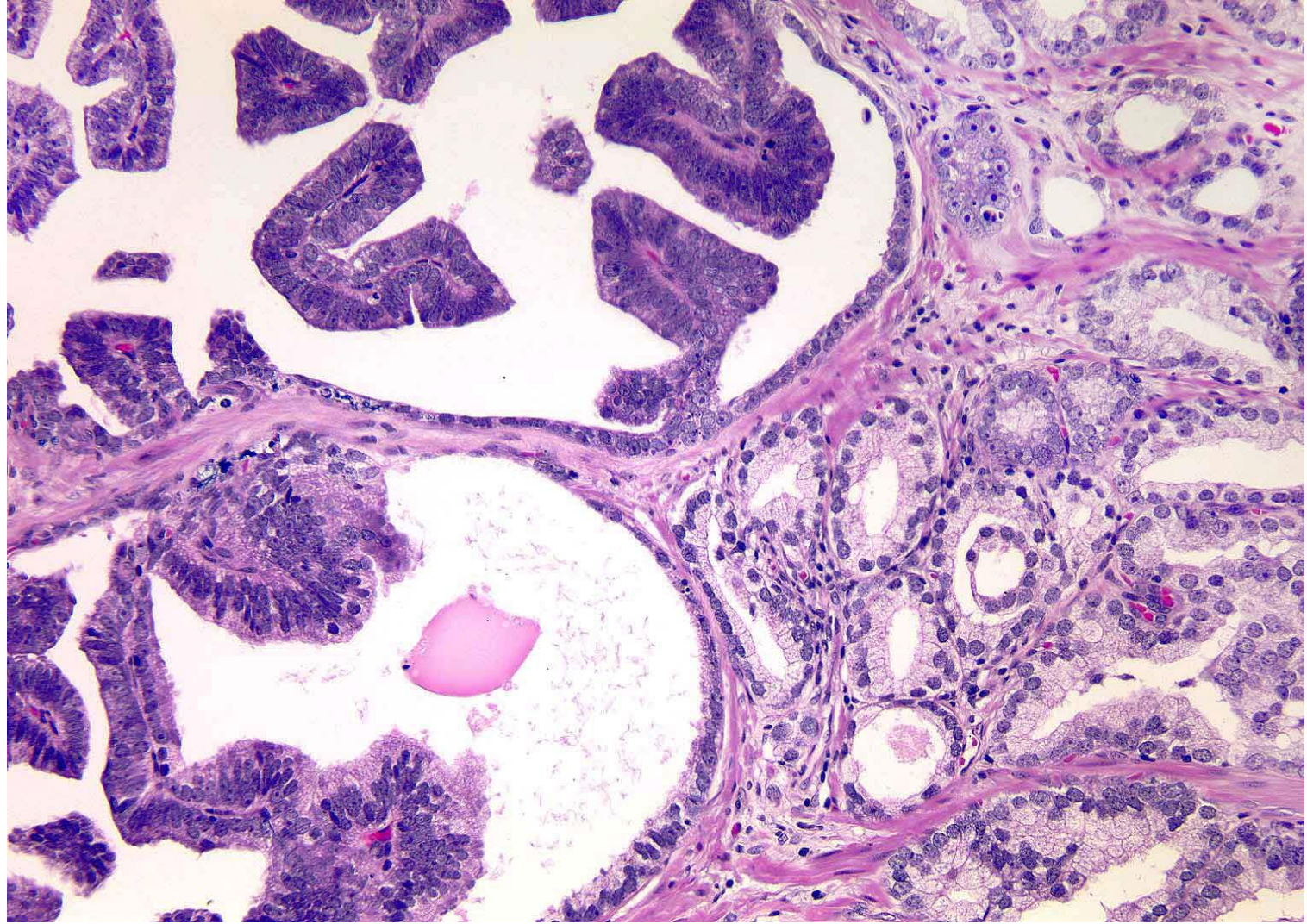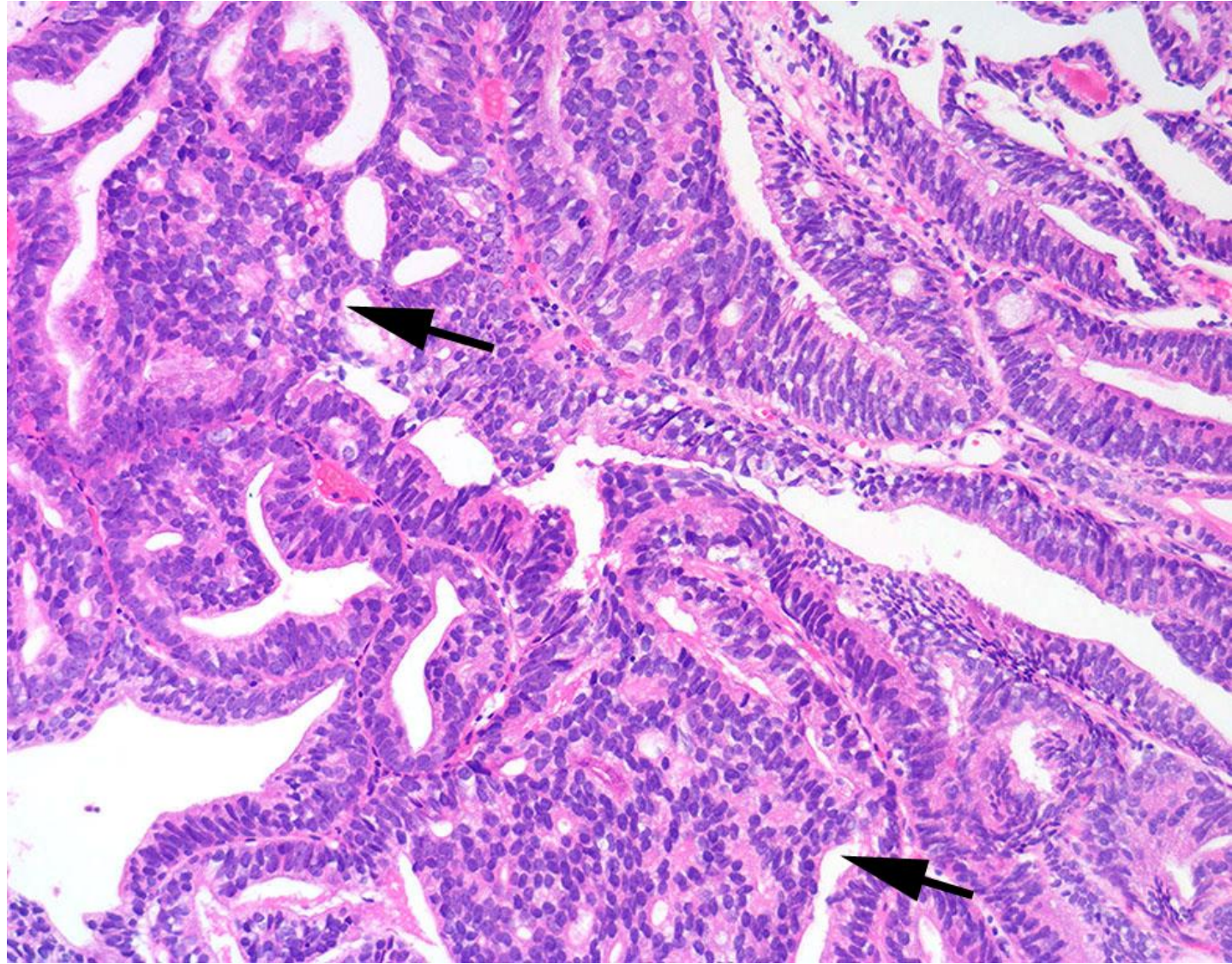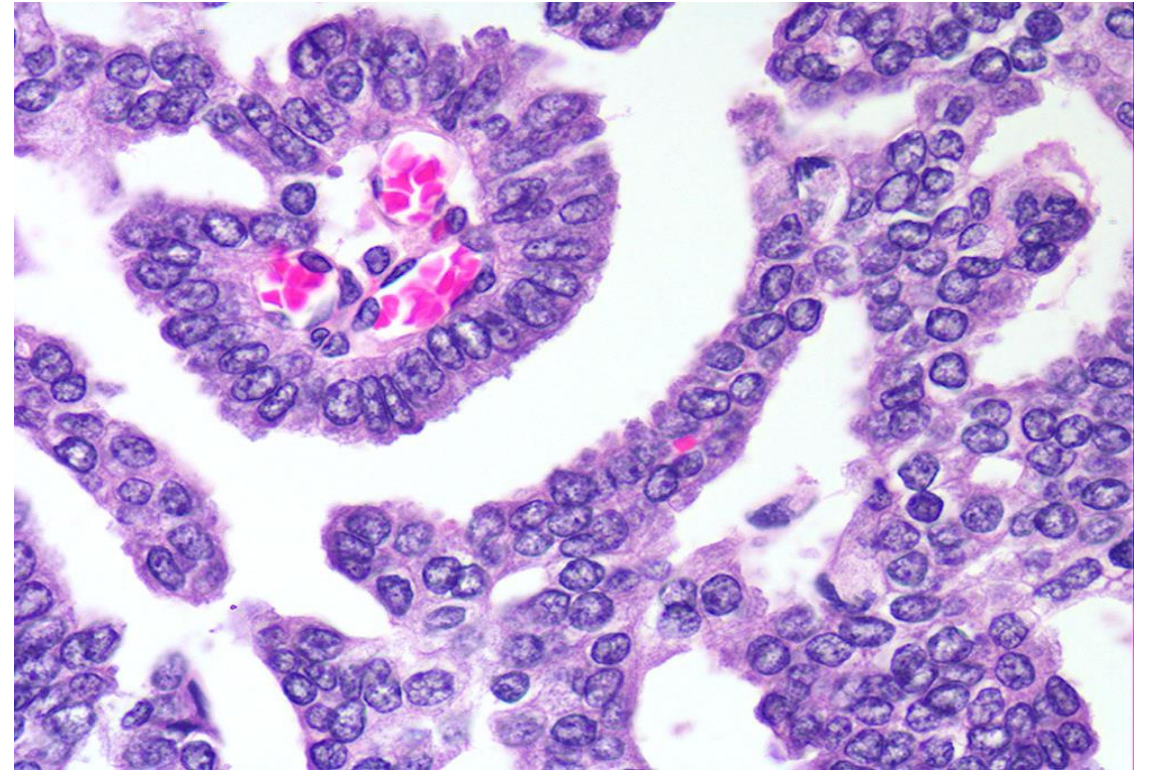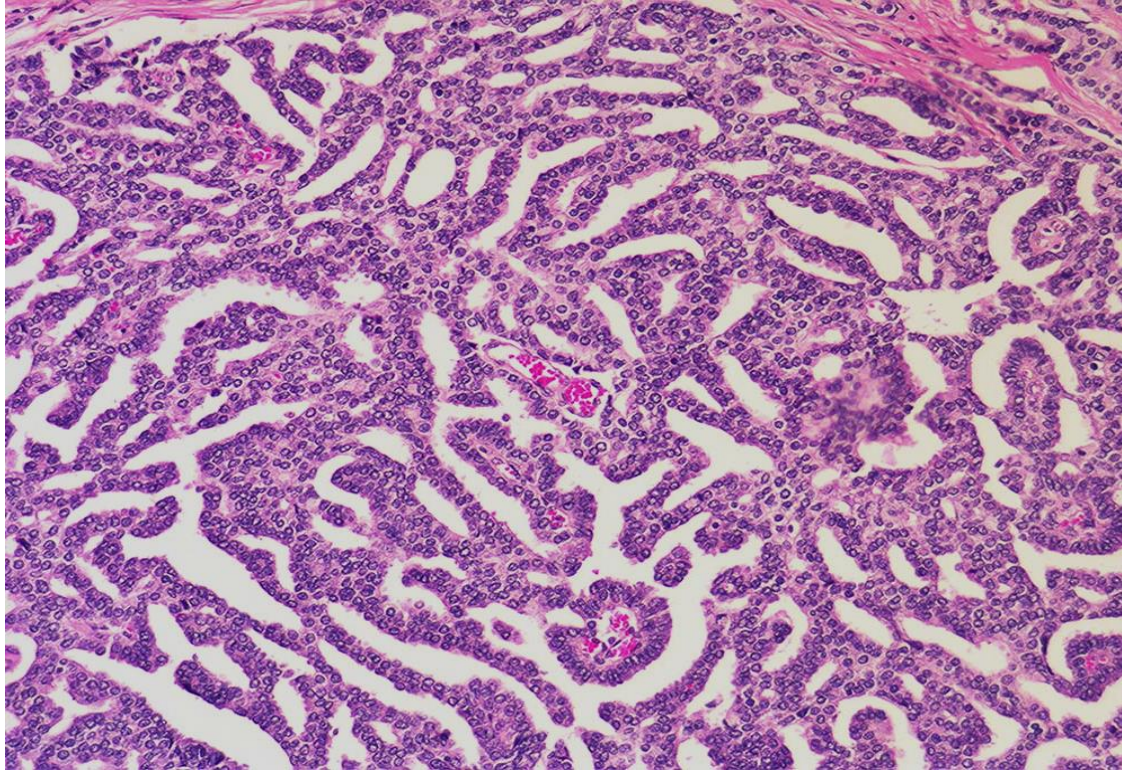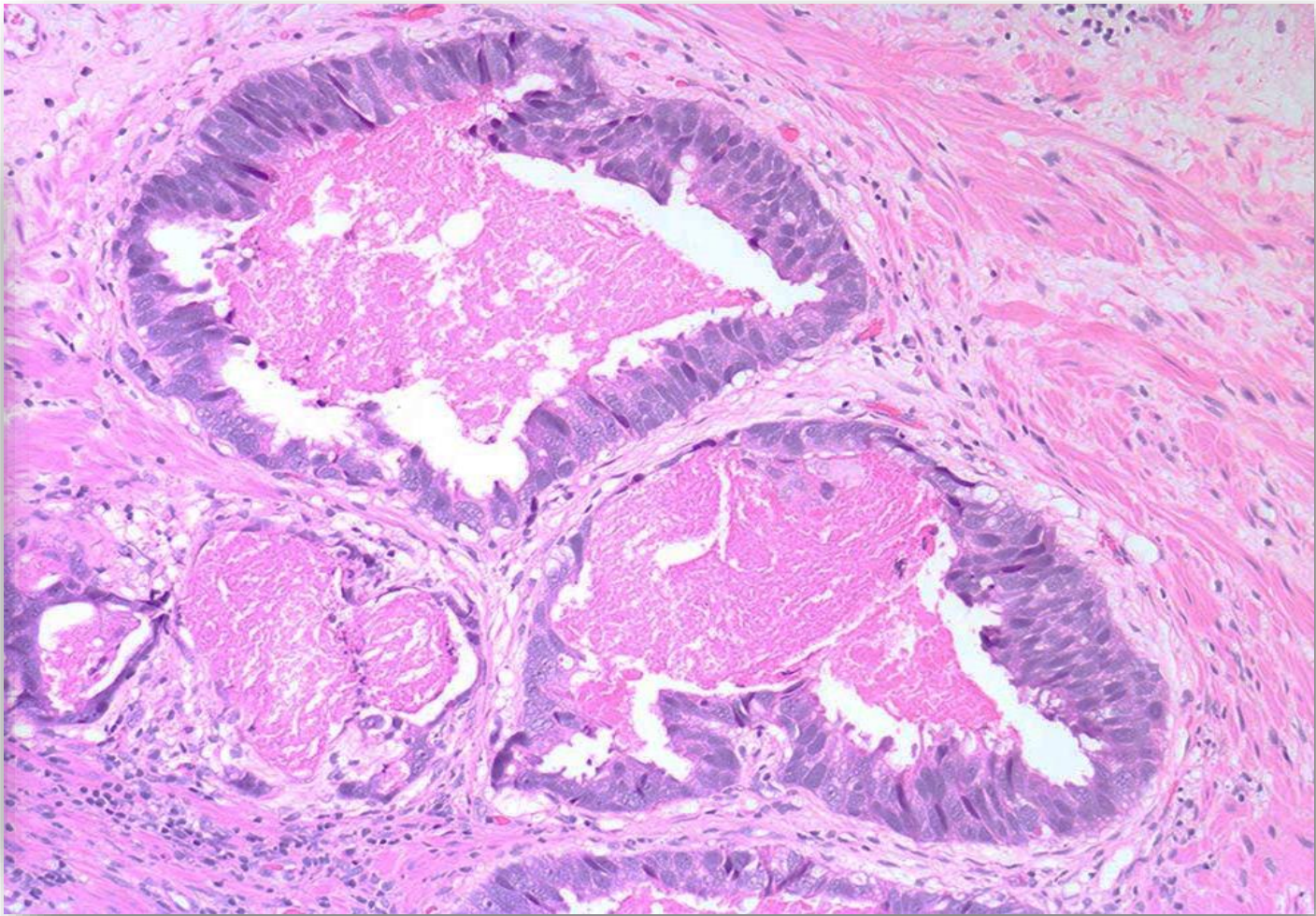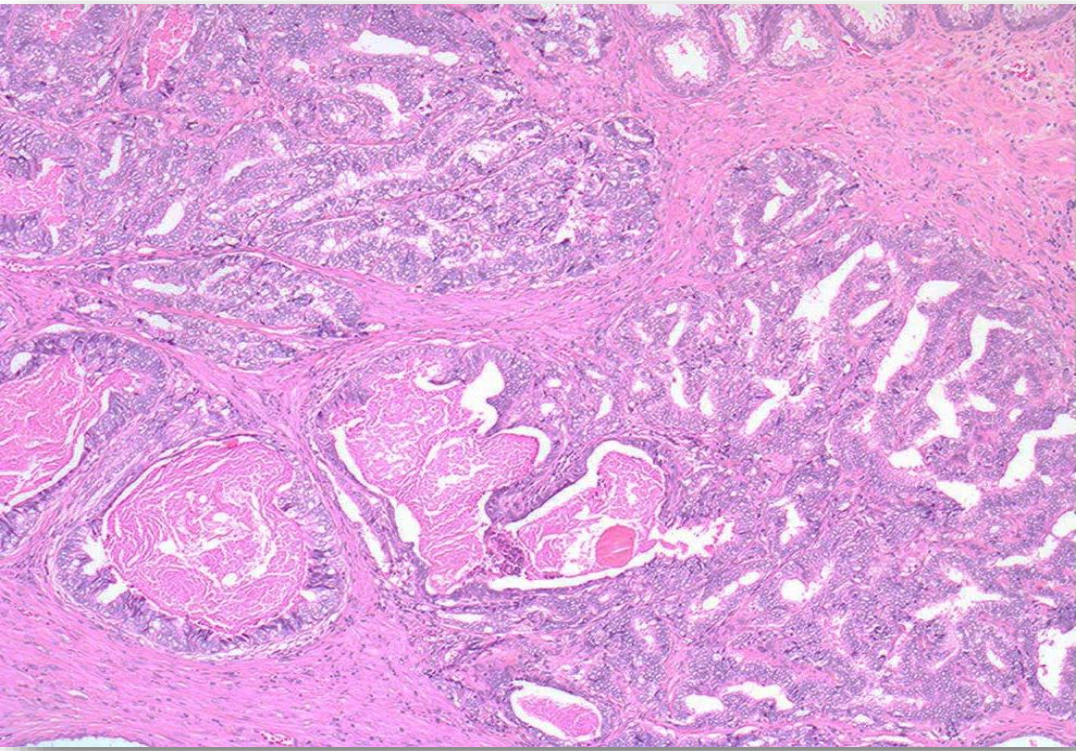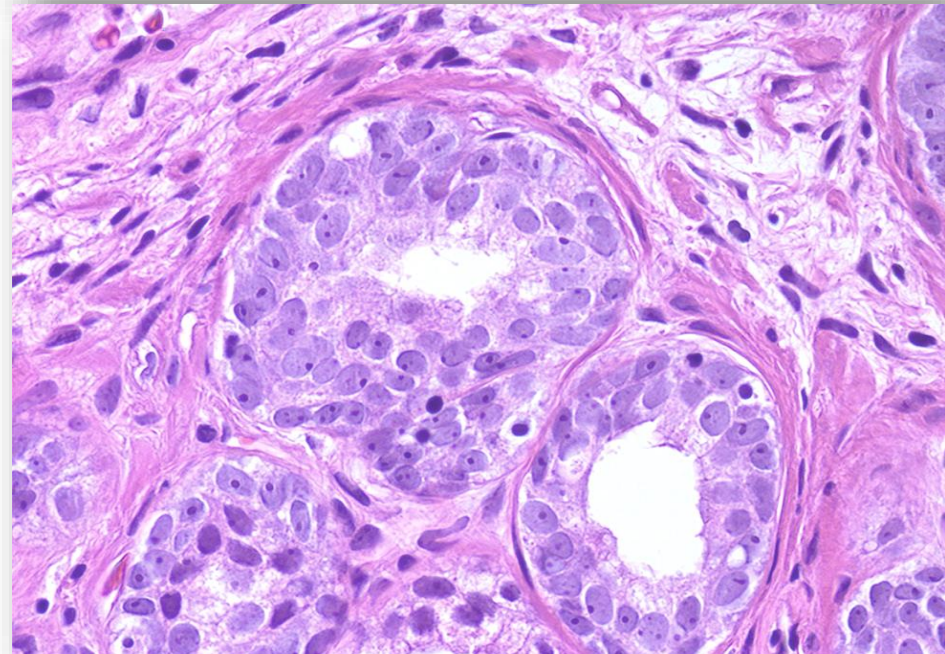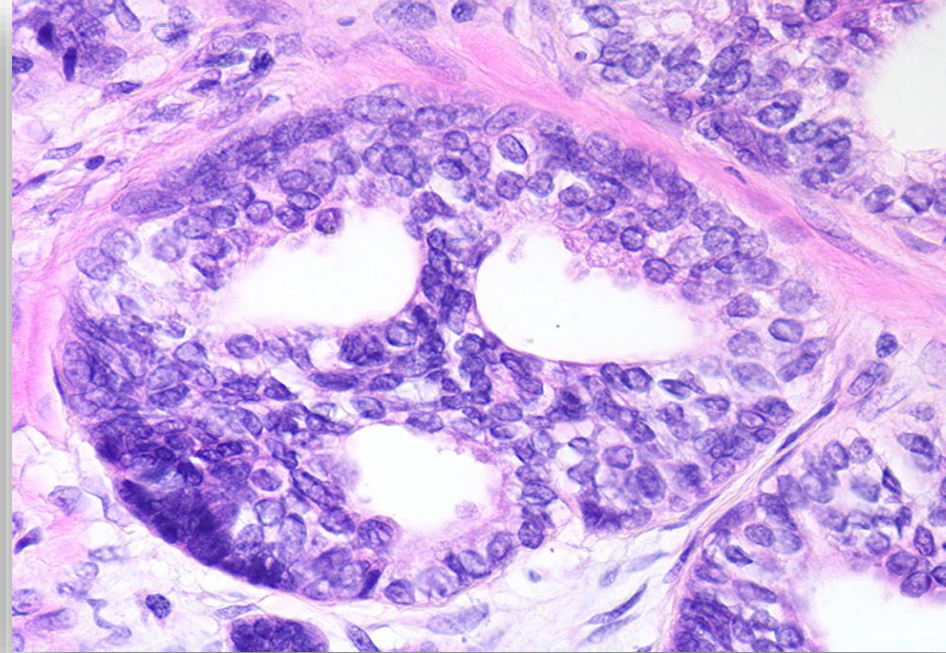
# Clear Cribriform Hyperplasia
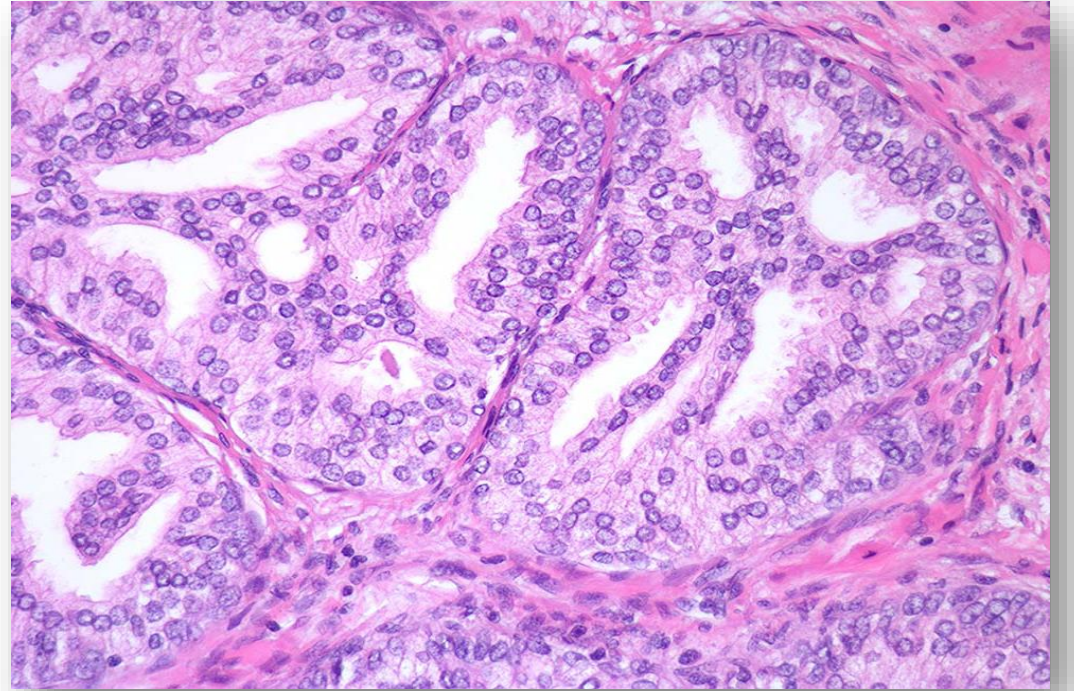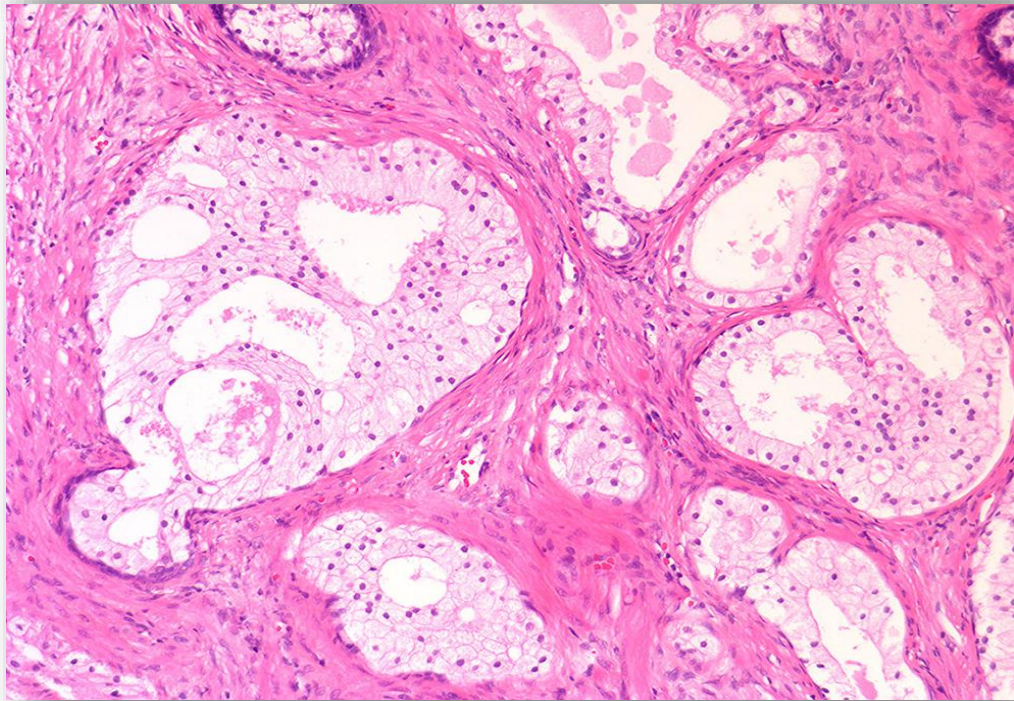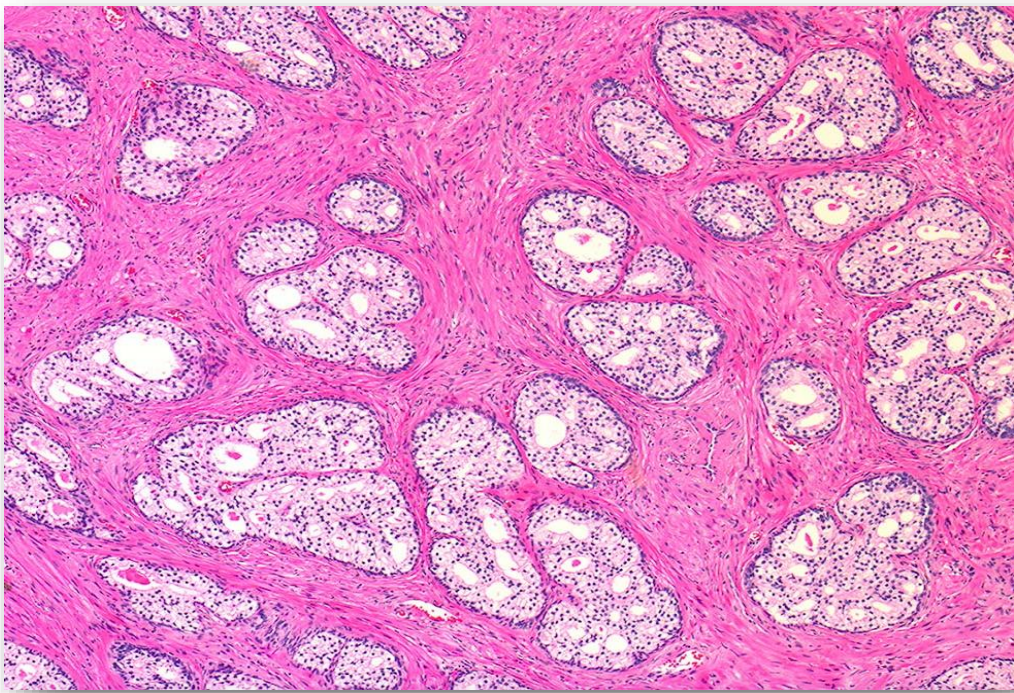
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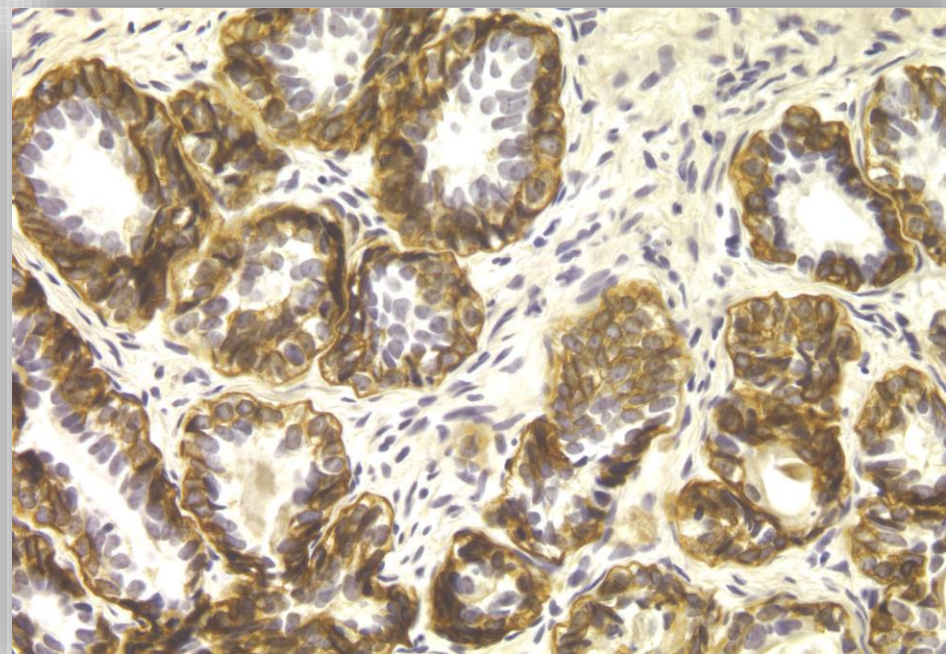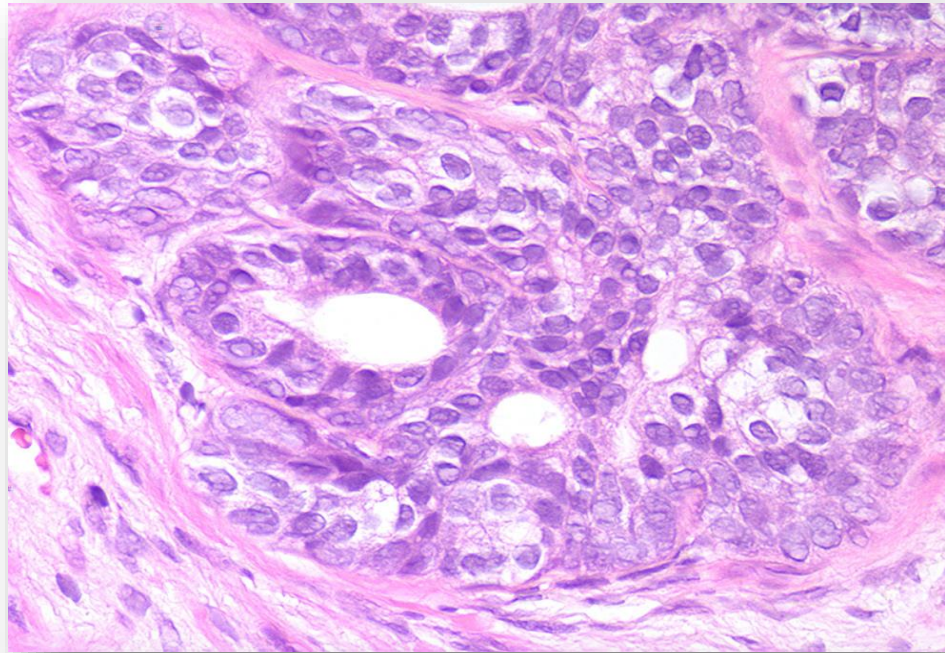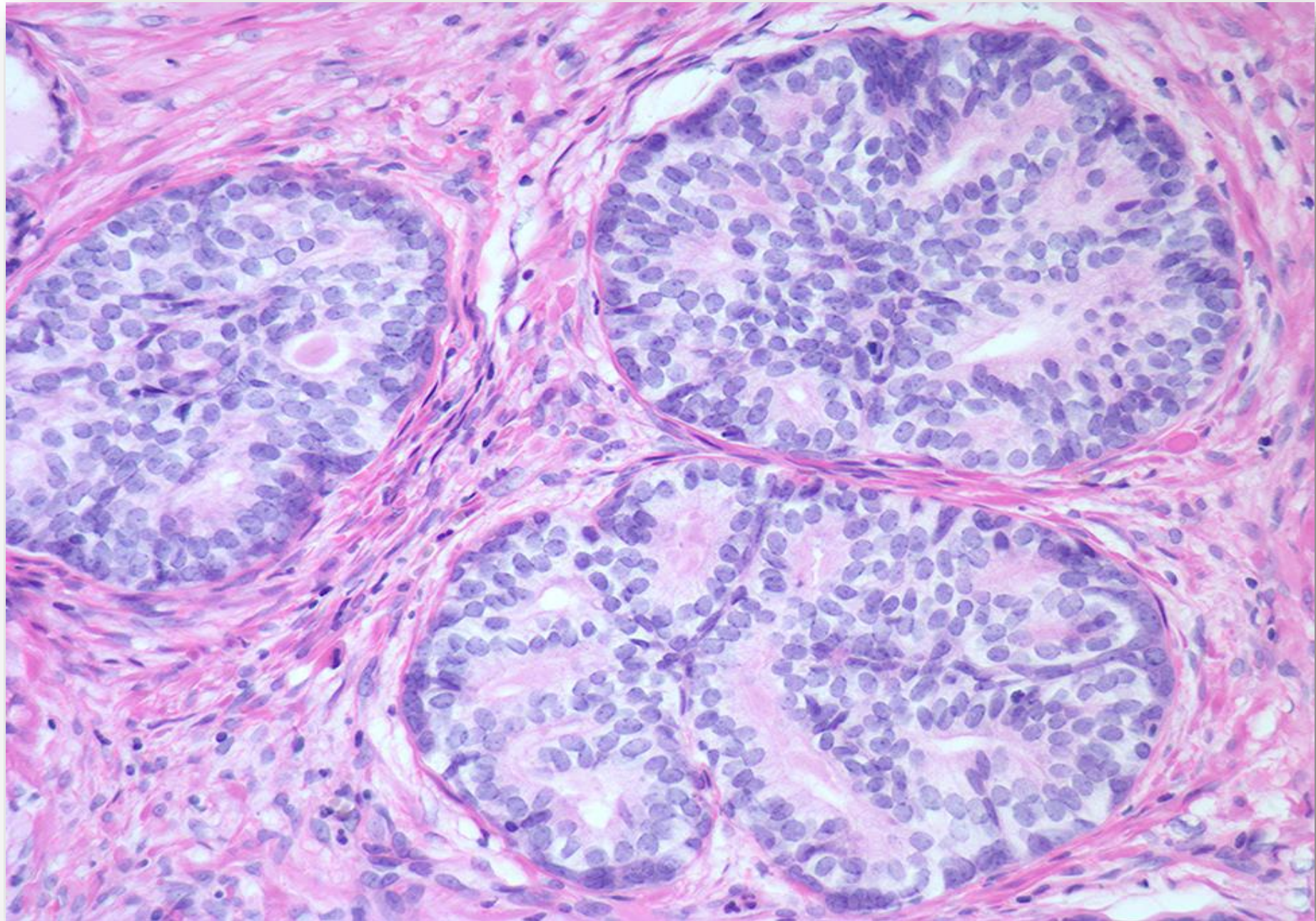
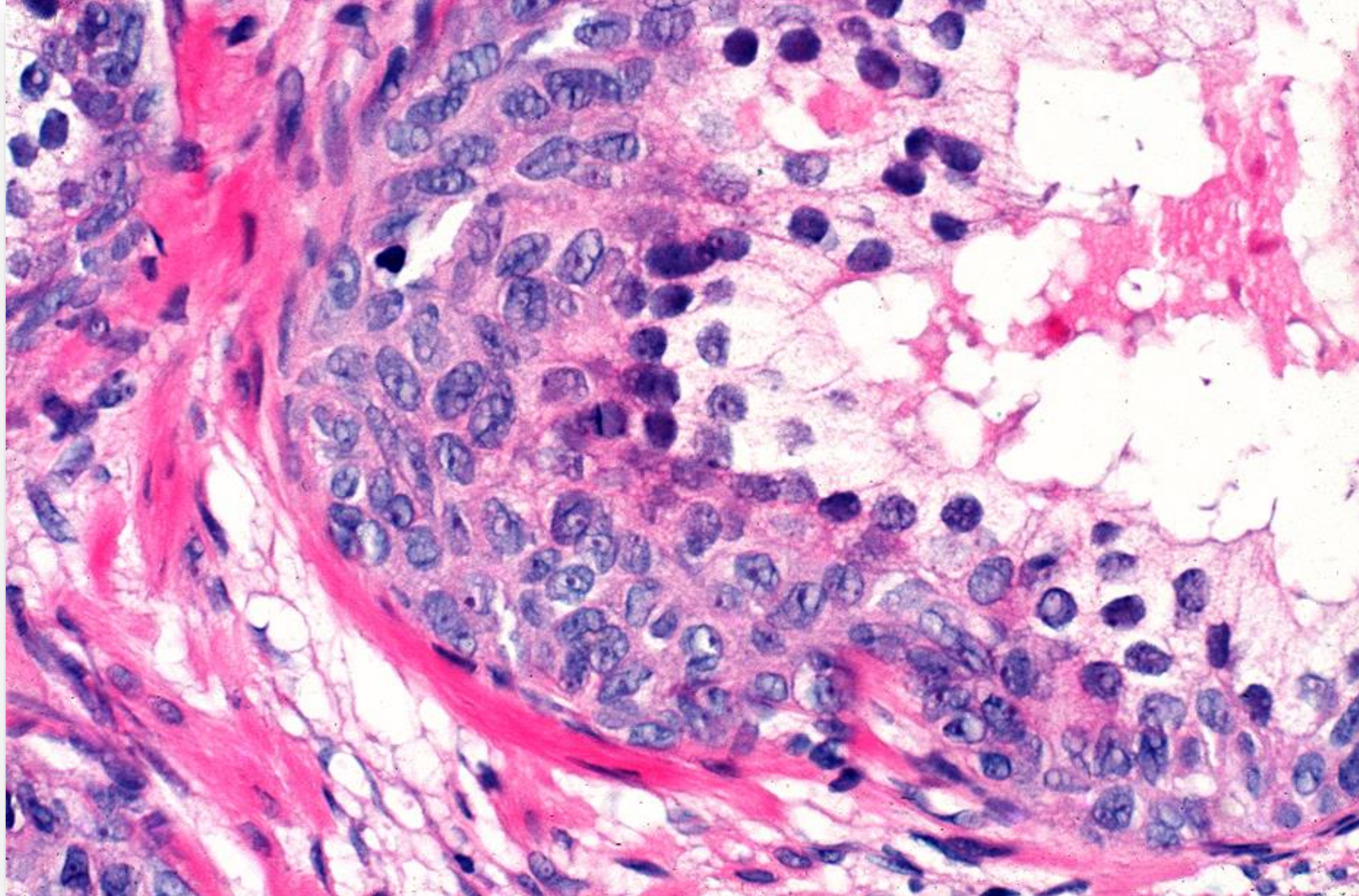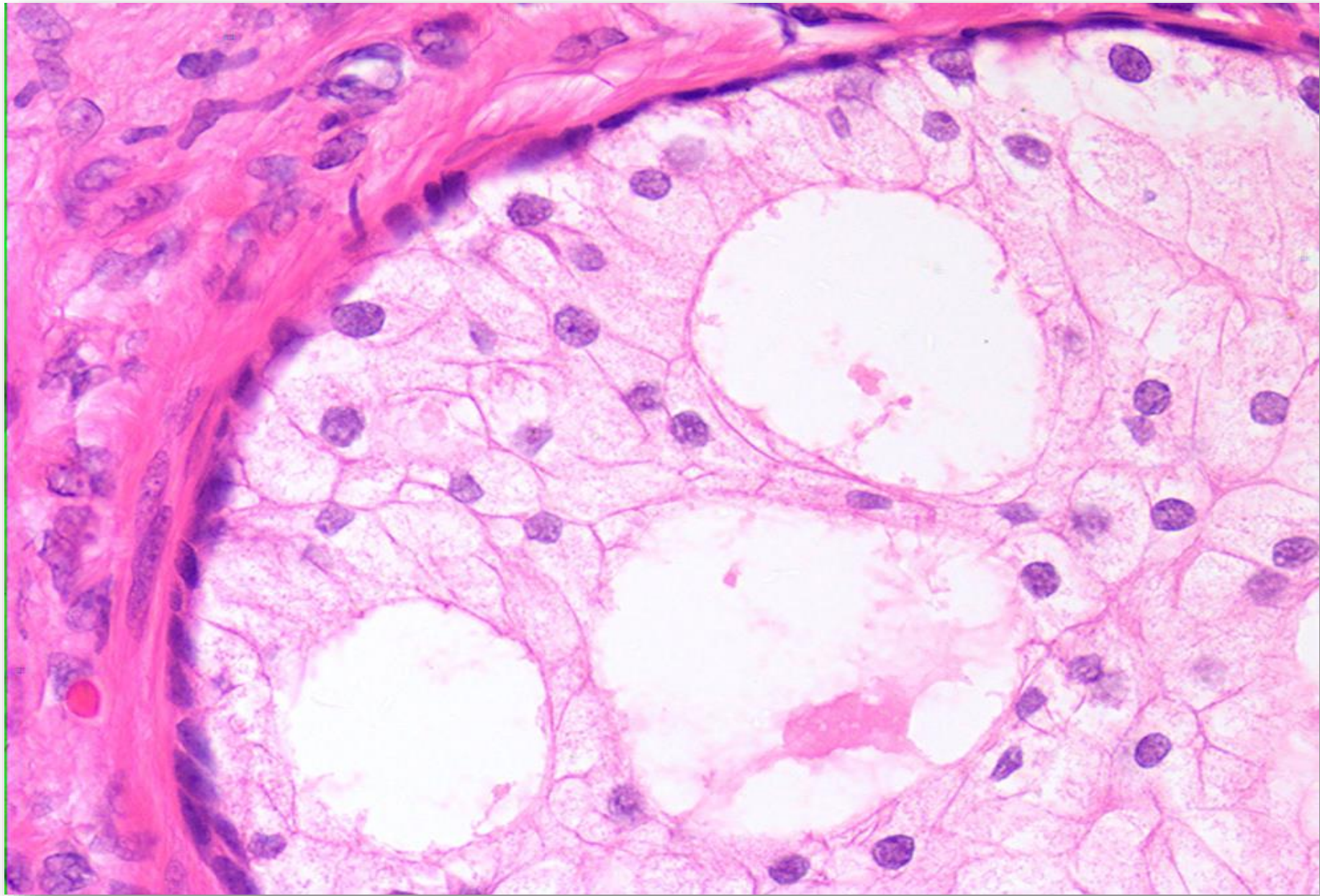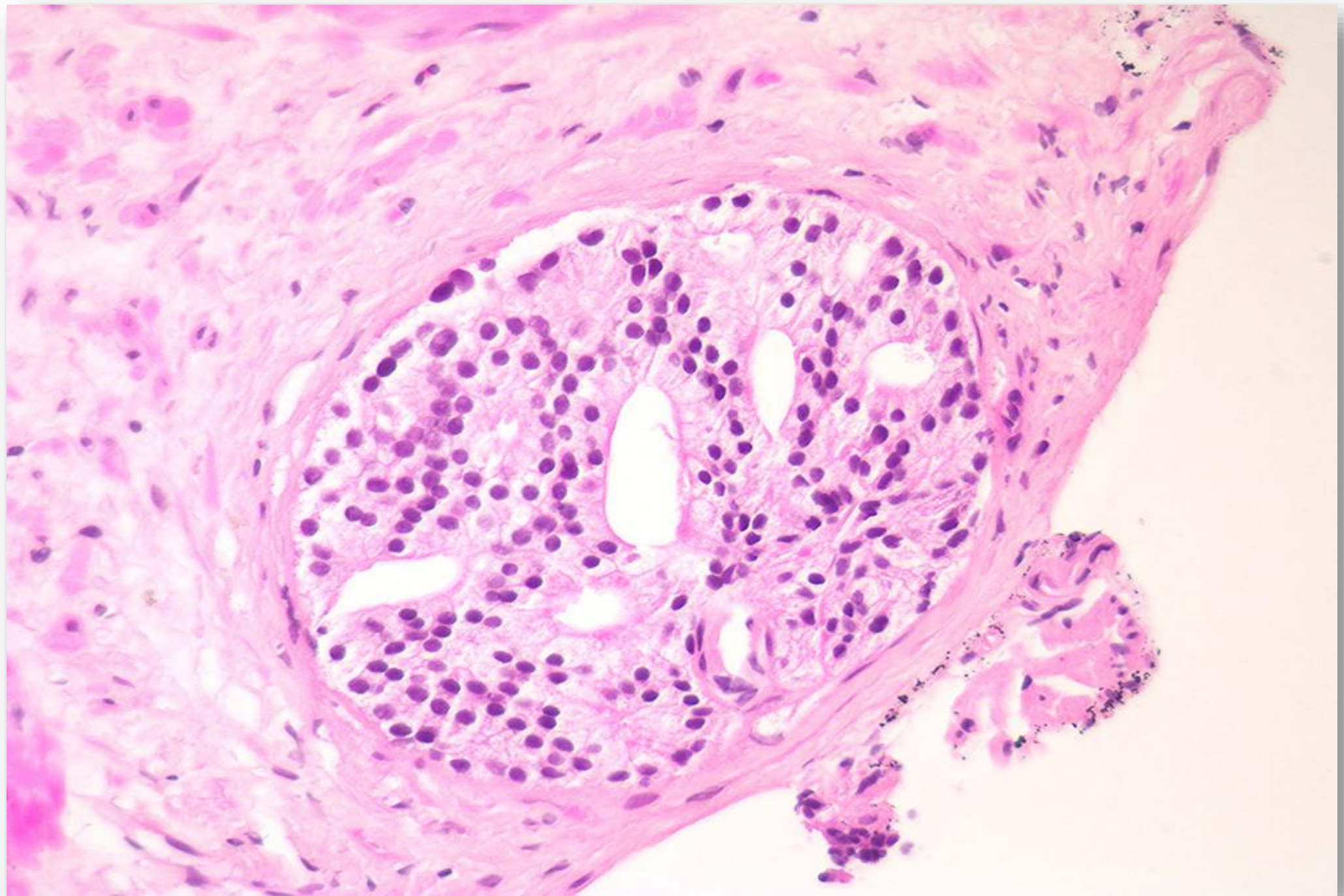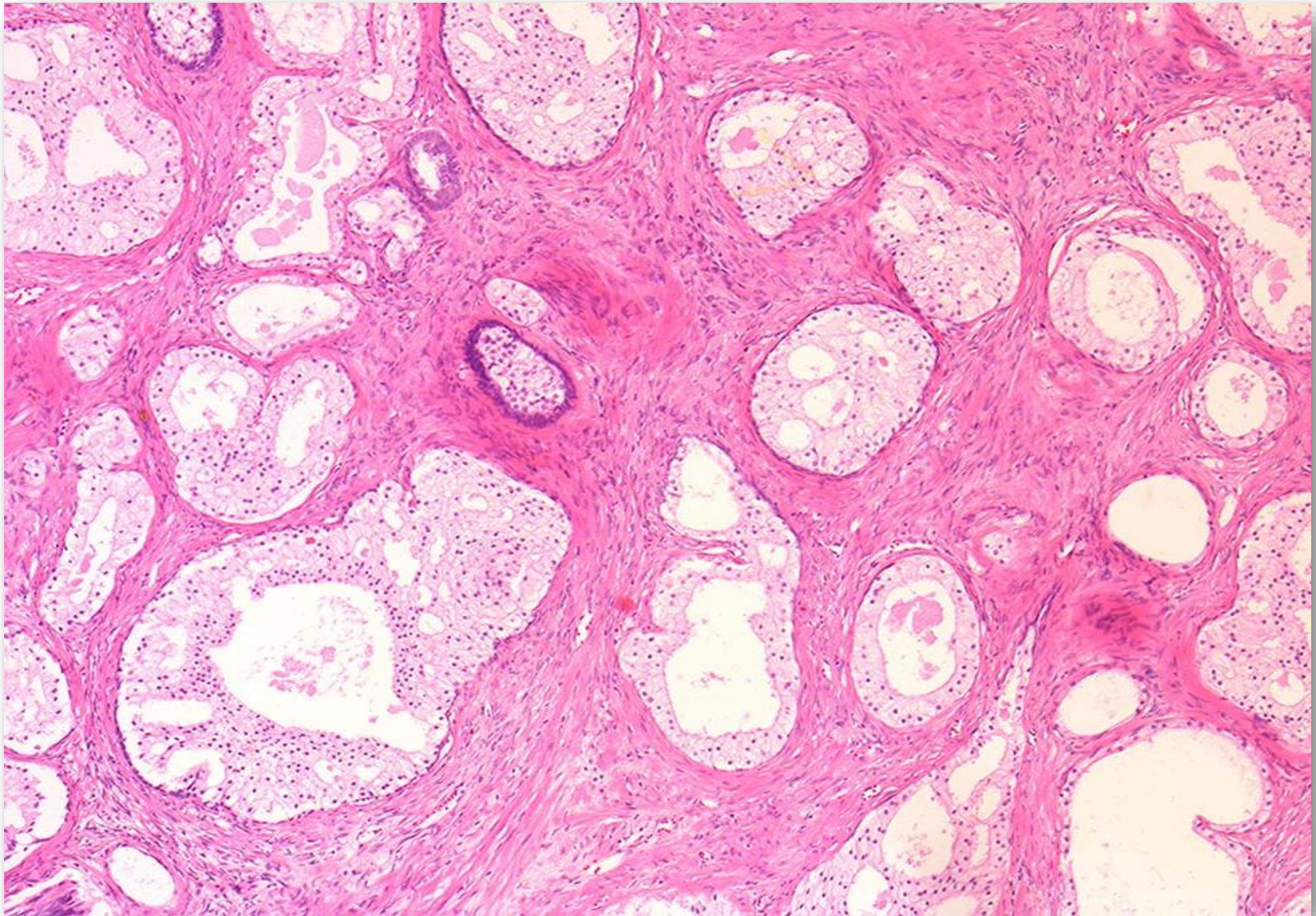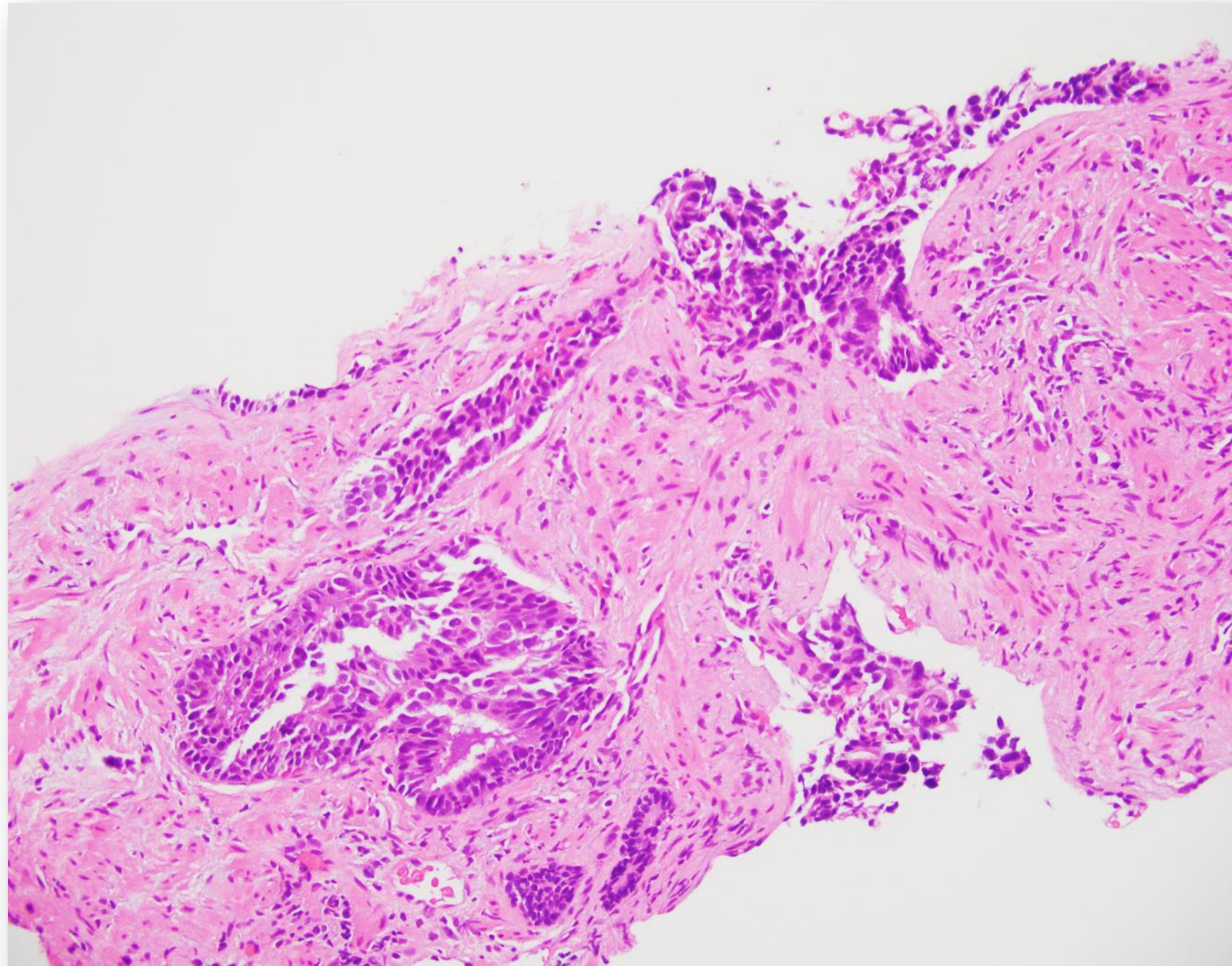# Central Zone Histology

IDC-P?

Basal cell marker immunohistochemistry is recommended for prostate biopsies displaying isolated IDC-P without concomitant invasive prostate cancer {32459716; 32589068}

Immunohistochemistry is not considered necessary in cases when the distinction between IDC-P and invasive prostate cancer will not change the assigned prostate cancer grade {32459716; 32589068}.
There is wide agreement that when IDC-P is identified on prostate biopsy without concomitant invasive cancer it should not be graded, but rather, a comment should detail IDC-Ps usual association with aggressive prostate cancer. There is also agreement that when IDC-P is observed in setting of invasive prostate cancer, its presence should be noted. However, whether IDC-P should additionally be incorporated, based on its architectural pattern, into prostate cancer grading remains controversial at this time, due insufficient data {32692448}.