

**PROSTATE CANCER, DIAGNOSIS
AND POTENTIAL PITFALLS**

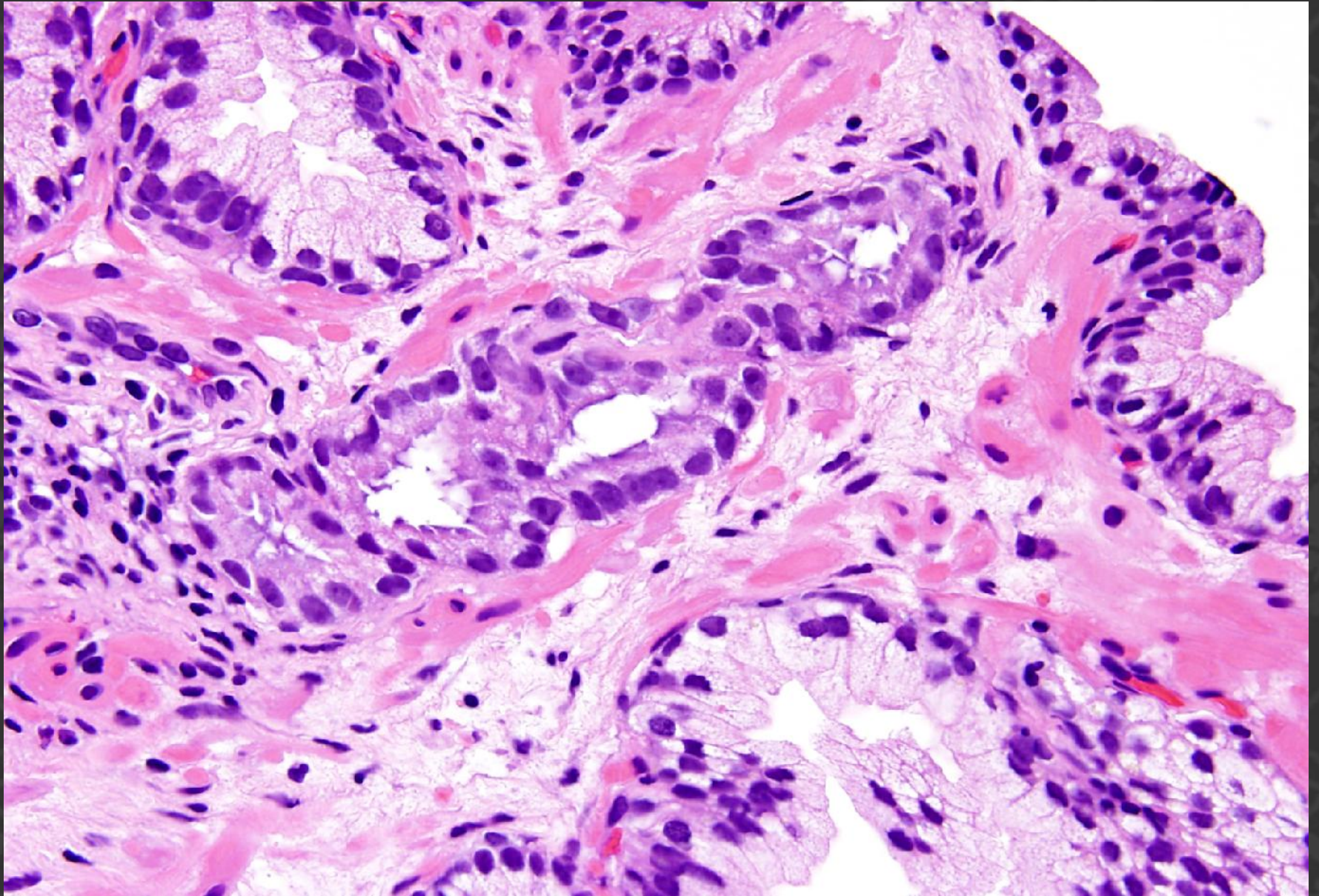
**Dr. Fatima Al-Hashimi, MD, FRCPath
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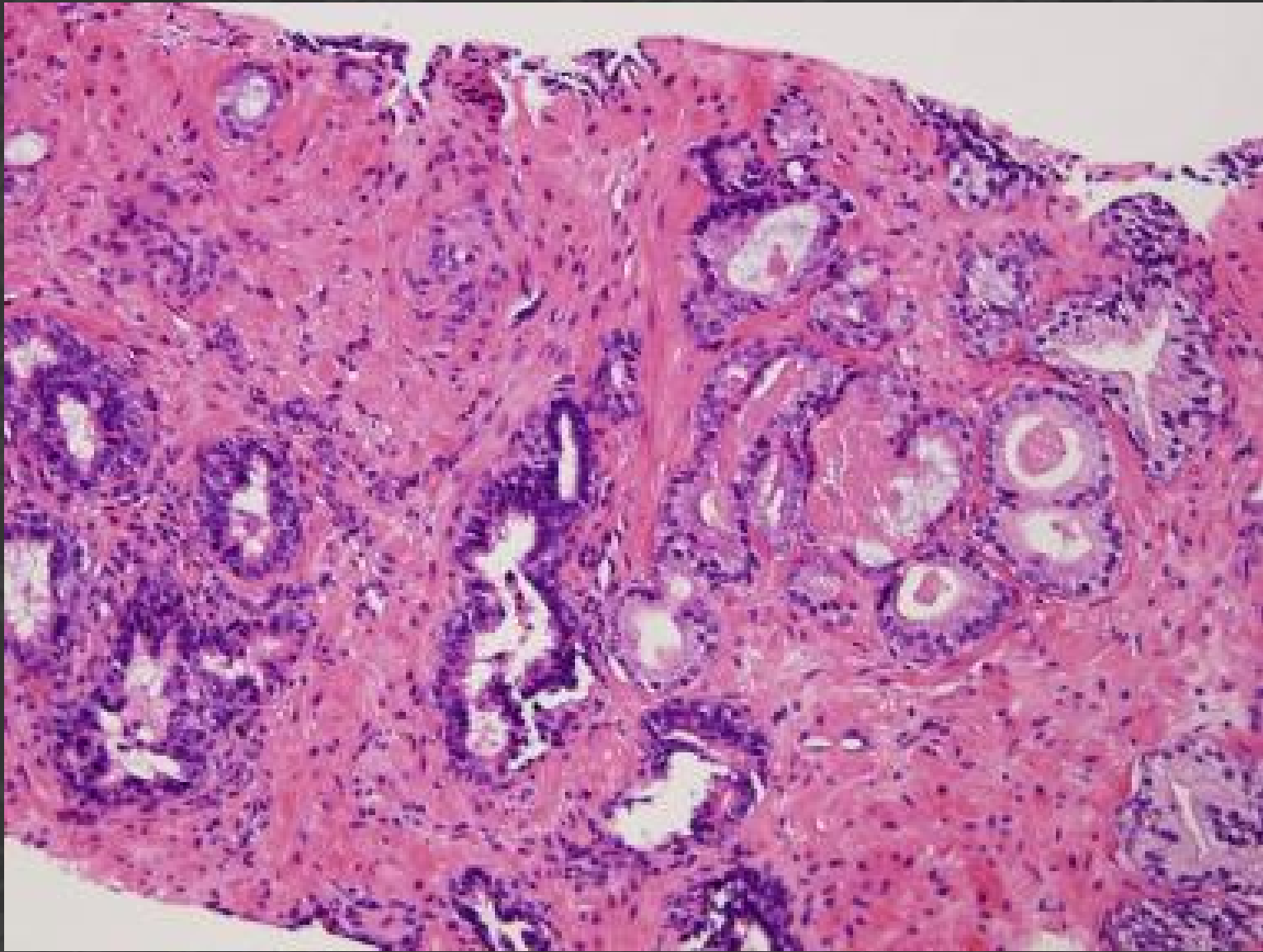


**THE DEFINITION OF PROSTATE
CARCINOMA**

FEATURES FAVOURING A DIAGNOSIS OF CARCINOMA

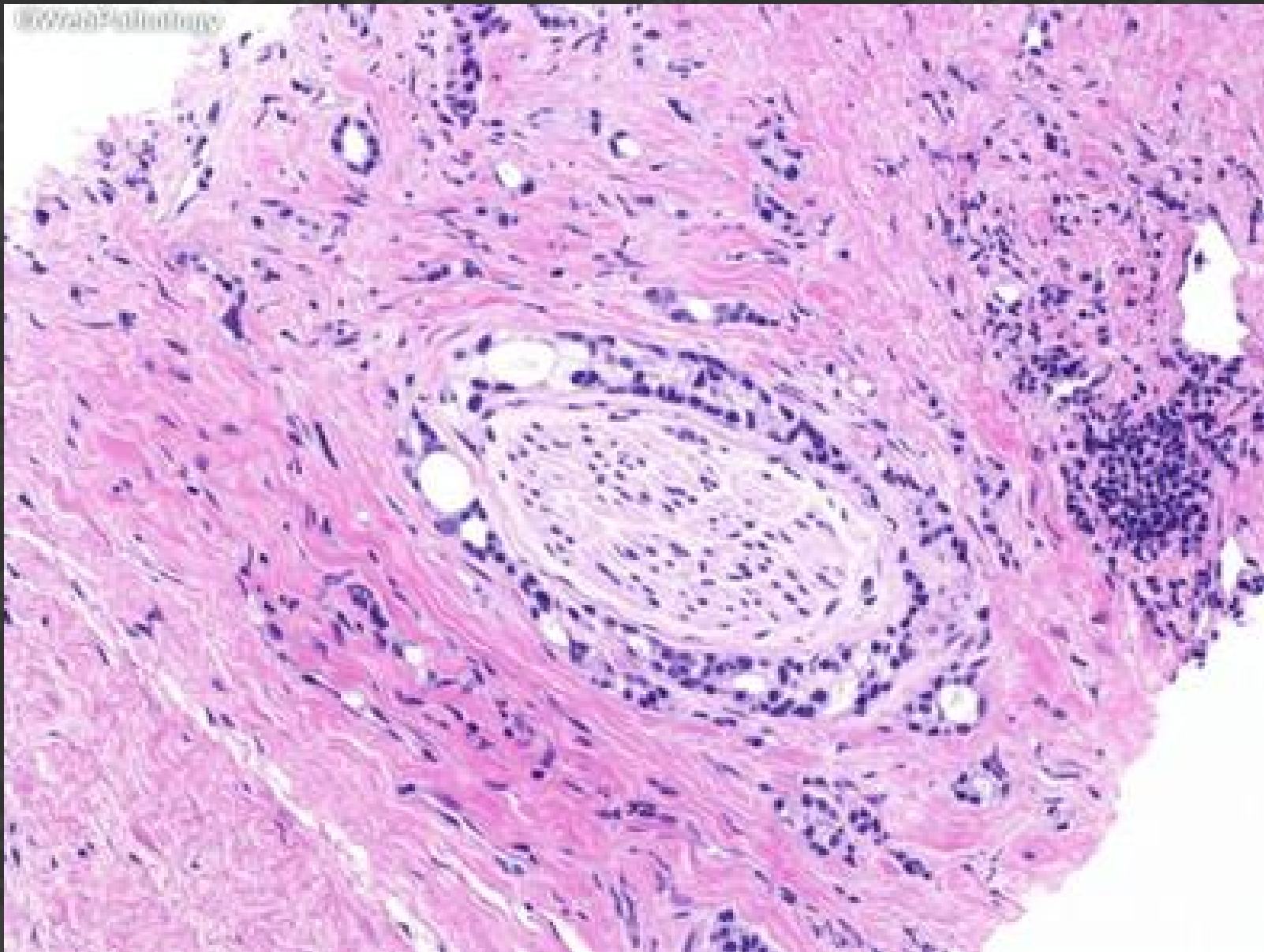
- Abnormal architectural pattern
- Nuclear enlargement
- Nuclear hyperchromasia
- Prominent nucleoli
- Mitotic/apoptotic figures
- Amphophilic cytoplasm
- Blue mucinous secretions
- Pink amorphous secretions
- Crystalloids

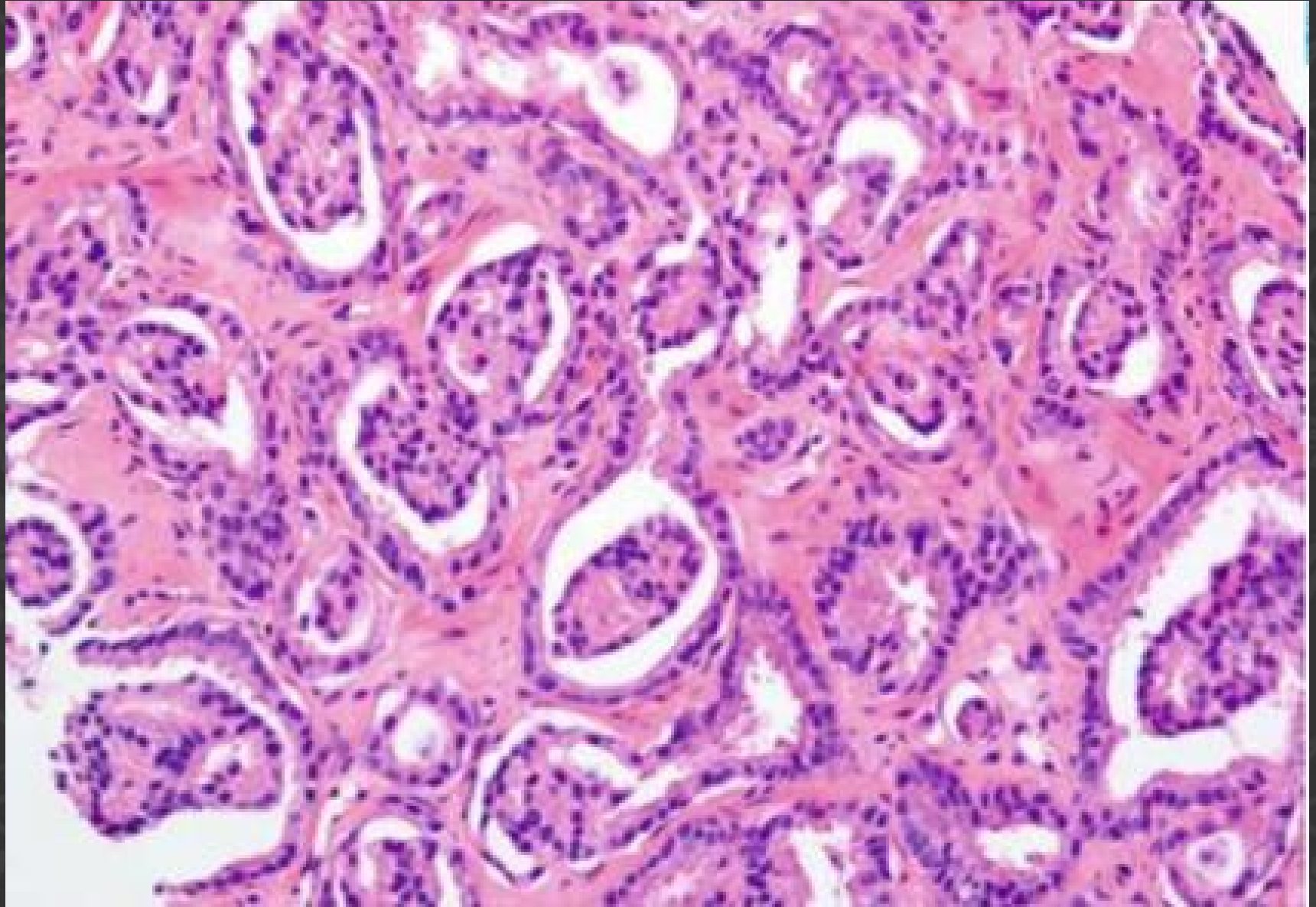


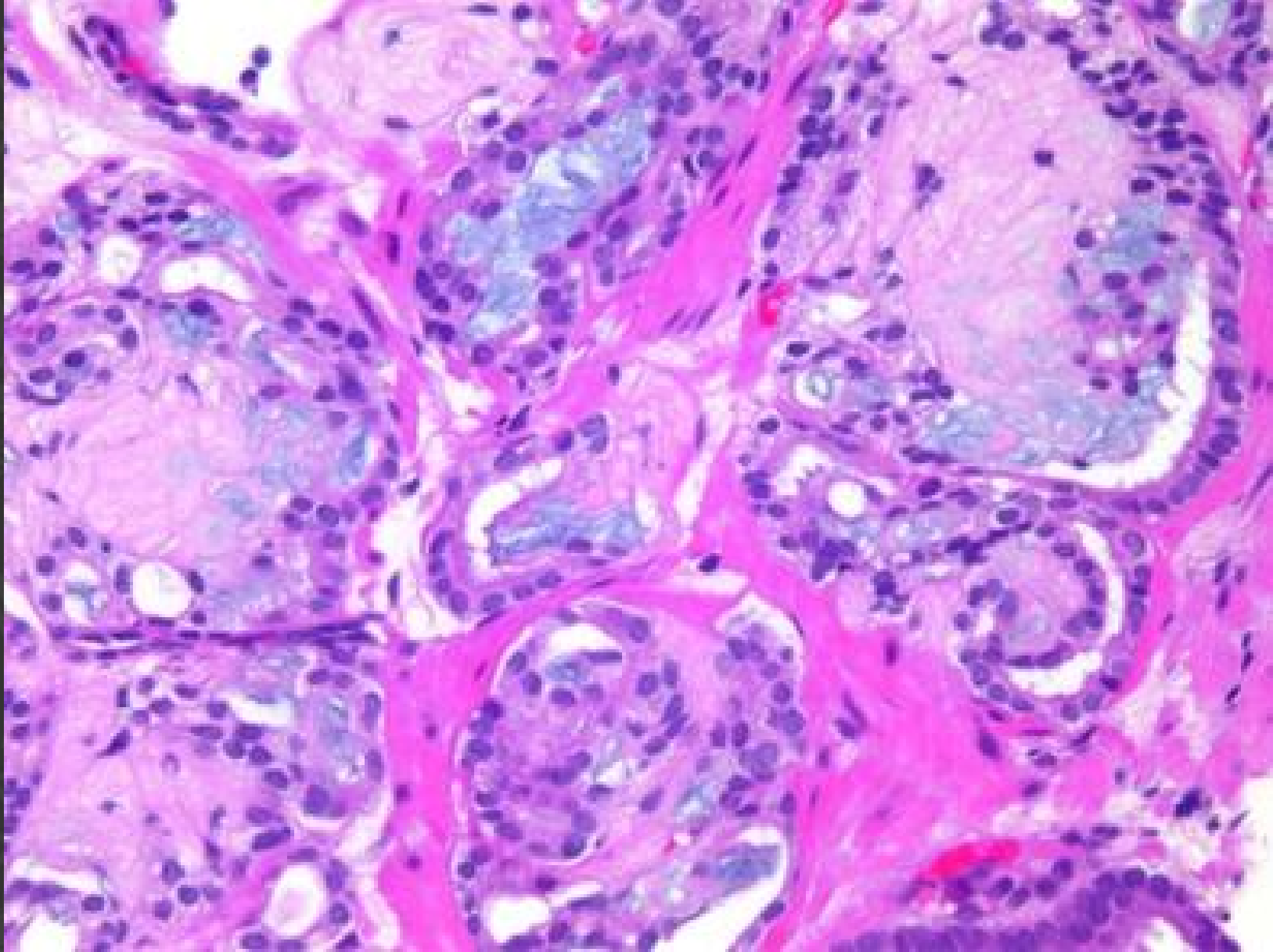


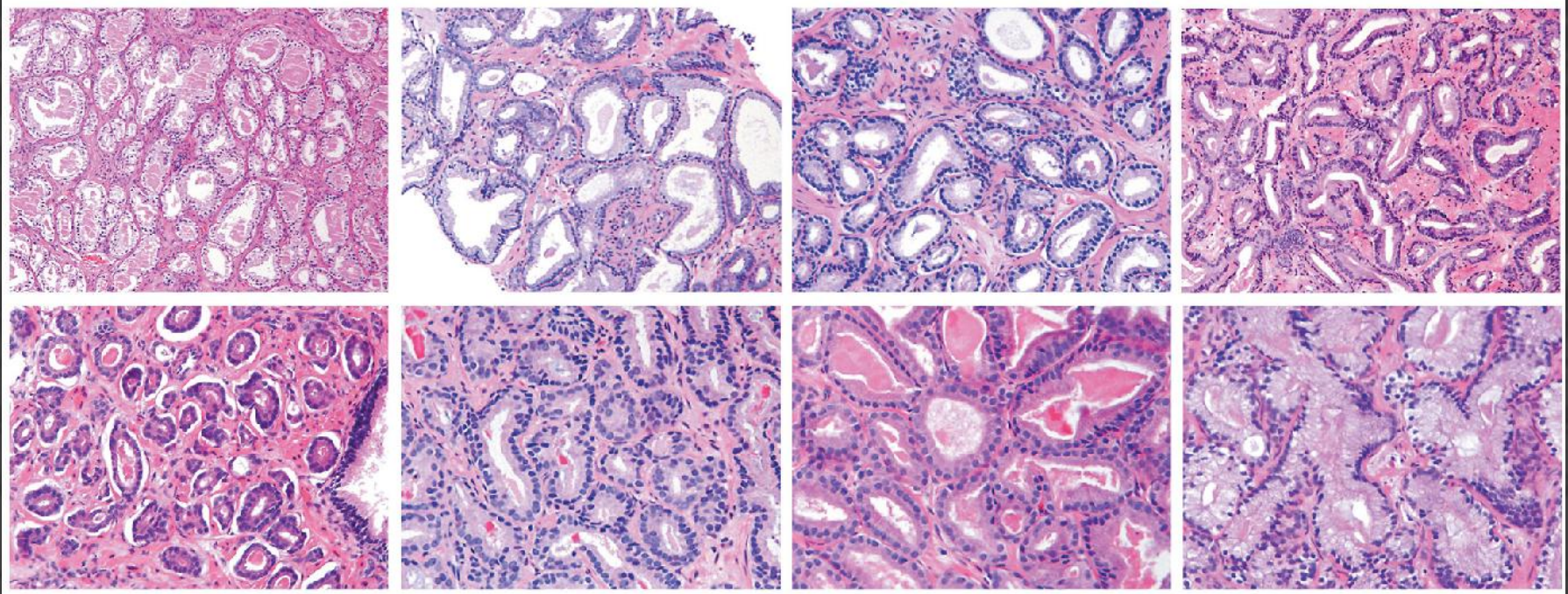
FEATURES DIAGNOSTIC OF PROSTATE ADENOCARCINOMA

- Perineural invasion
- Glomerulations
- Mucinous fibroplasia

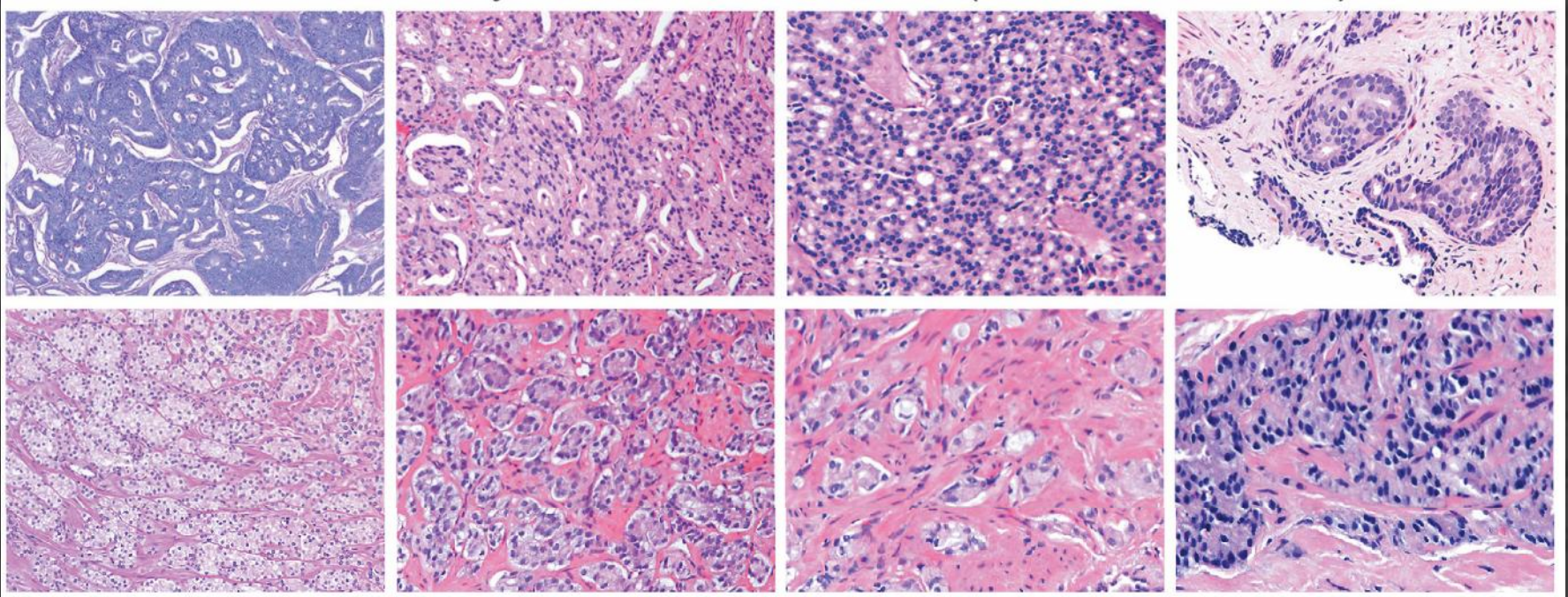




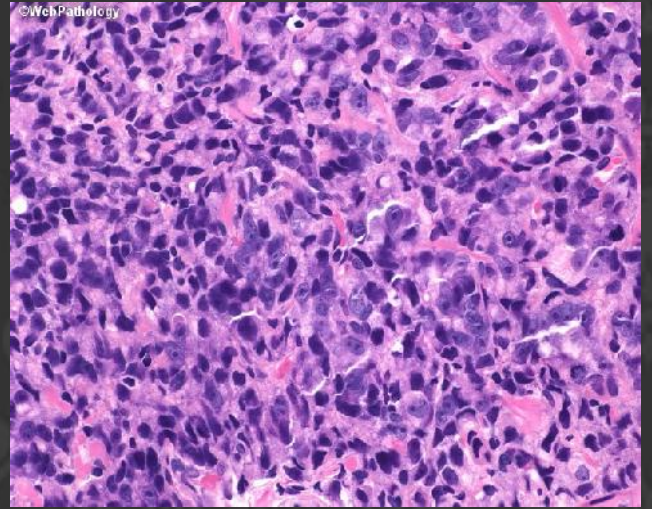
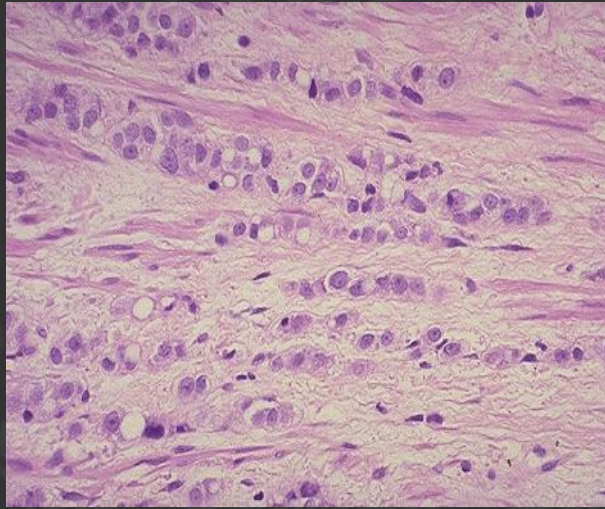
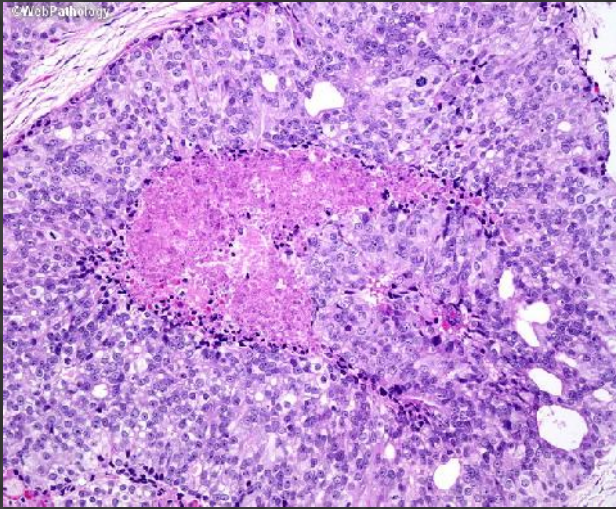




Gleason pattern 3. The tumour consists of small to medium-sized single glands of irregular shape and spacing, with elongated and angular forms.



Adenocarcinoma of the prostate Gleason pattern 4 with cribriform architecture, glomeruloid glands, fused glands and poorly-formed glands



Adenocarcinoma of the prostate Gleason pattern 5 solid nests with/out necrosis, single cells, cords and sheets

PROBLEMS WITH THE CURRENT GLEASON SYSTEM:

- 1) Scores 2-5 are currently no longer assigned and certain patterns that Gleason defined as a score of 6 are now graded as 7, thus leading to contemporary Gleason score 6 cancers having a better prognosis than historic score 6 cancers
- 2) The combination of Gleason scores into a 3-tier grouping (6,7,8-10) is used most frequently for prognostic and therapeutic purposes, despite $3+4=7$ vs. $4+3=7$ and 8 vs. 9-10 having very different prognoses
- 3) In practice the lowest score is now assigned a 6, although it is on a scale of 2-10. This leads to a logical yet incorrect assumption on the part of patients that their cancer is in the middle of the scale, compounding the fear of their cancer diagnosis with the belief that the cancer is serious, thus leading to an expectation that treatment is necessary.

WHY DO WE NEED A NEW GRADING SYSTEM?

To address the above deficiencies, a new 5 Grade Group system has been developed based on a study of >20,000 prostate cancer cases treated with radical prostatectomy and >5,000 cases treated by radiation therapy

- **Grade Group 1 (Gleason score ≤ 6)** – Only individual discrete well-formed glands
- **Grade Group 2 (Gleason score $3+4=7$)** – Predominantly well-formed glands with a lesser component of poorly-formed/fused/cribriform glands
- **Grade Group 3 (Gleason score $4+3=7$)** – Predominantly poorly-formed/fused/cribriform glands with a lesser component of well-formed glands
- **Grade Group 4 (Gleason score 8)**
 - Only poorly-formed/fused/cribriform glands or
 - Predominantly well-formed glands with a lesser component lacking glands or
 - Predominantly lacking glands or with a lesser component of well-formed glands
- **Grade Group 5 (Gleason scores 9-10)** – Lacks gland formation (or with necrosis) with or w/o poorly-formed/fused/cribriform glands

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DO ADENOCARCINOMAS OF THE PROSTATE WITH GLEASON SCORE (GS) ≤ 6 HAVE THE POTENTIAL TO METASTASIZE TO LYMPH NODES?

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totally embedded RPs from multiple institutions, there was not a single case of a GS ≤ 6 tumor with LN metastases. In contrast to prevailing assumptions, Gleason score ≤ 6 tumors do not appear to

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ORIGINAL REPORT

Gleason Score and Lethal Prostate Cancer: Does $3 + 4 = 4 + 3$?

From the Departments of Epidemiology, Biostatistics, and Nutrition, Harvard School of Public Health; Channing Laboratory and Division of

Jennifer R. Stark, Sven Perner, Meir J. Stampfer, Jennifer A. Sinnott, Stephen Finn, Anna S. Eisenstein, Jing Ma, Michelangelo Fiorentino, Tobias Kurth, Massimo Loda, Edward L. Giovannucci, Mark A. Rubin, and Lorelei A. Mucci

Results

For prostatectomy specimens, $4 + 3$ cancers were associated with a three-fold increase in lethal PCa compared with $3 + 4$ cancers (95% CI, 1.1 to 8.6). The discrimination of models of standardized scores from prostatectomy (C-statistic, 0.86) and biopsy (C-statistic, 0.85) were improved compared to models of original scores (prostatectomy C-statistic, 0.82; biopsy C-statistic, 0.72).



**MIMICKERS OF PROSTATE
CANCER**

Benign mimickers in relation to major growth patterns of prostatic adenocarcinoma

Small gland pattern

Seminal vesicle ***

Cowper's gland

Atrophy***

Partial atrophy***

Post-atrophic hyperplasia

Reactive atypia

Mucinous metaplasia

Nephrogenic metaplasia (adenoma)

Basal cell hyperplasia***

Benign nodular hyperplasia

Sclerosing adenosis**

Verumontanum mucosal gland hyperplasia

Mesonephric gland hyperplasia

Atypical adenomatous hyperplasia

Large gland pattern

Clear cell cribriform hyperplasia

Adenoid cystic-like basal cell hyperplasia

Reactive atypia

Fused gland pattern

Paraganglioma

Xanthoma

Malakoplakia

Solid and single-cell pattern

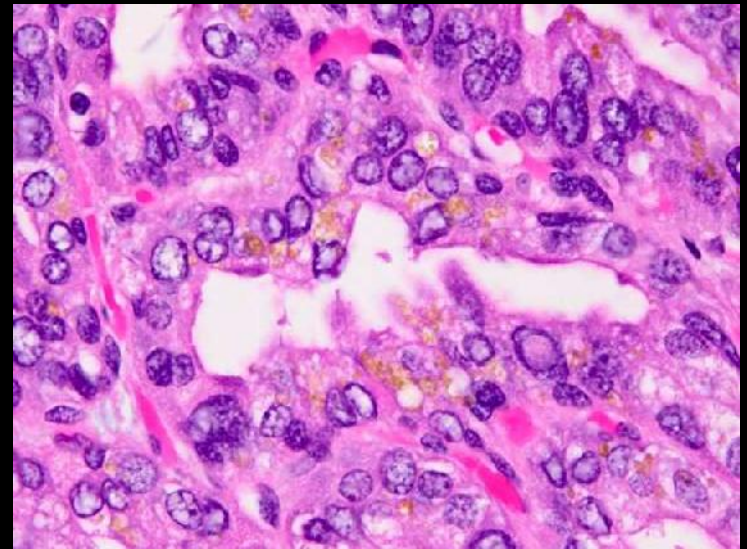
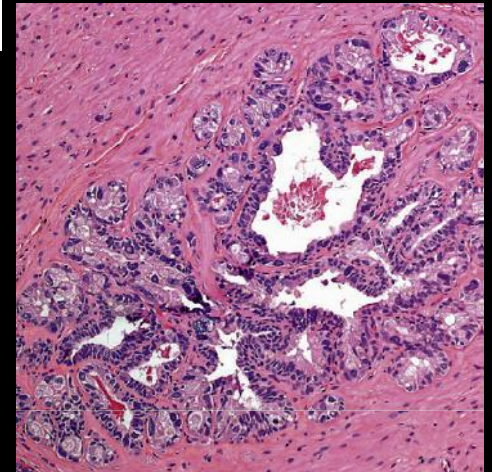
Usual prostatitis with crush artifacts

Non-specific granulomatous prostatitis

Signet-ring-like change in lymphocytes and stromal cells

SEMINAL VESICLE

- SV consists of a central lumen with branching glands that give rise to numerous small glands
- Scattered or random nuclear atypia is often present in the luminal cells but mitoses are not identified. Small nuclear pseudoinclusions are often seen.
- Cytoplasmic golden-brown lipofuscin pigment is a constant feature although the amount varies from case to case
- SV epithelium stains positively for PAX-2, PAX-8 and MUC6 and negatively/focal weak for prostatic-specific antigen (PSA) and prostatic acid phosphatase (PAP). 34bE12 stains the basal layer of SV glands



BASAL CELL HYPERPLASIA

BCH is typically seen as part of benign prostatic hyperplasia in the transition zone, but may also affect the peripheral zone and encountered in needle biopsies. BCH may also occur in association with atrophy, often in the setting of antiandrogen and radiation therapy

BCH manifests as nodular expansion of uniform round glands with stratified nuclei

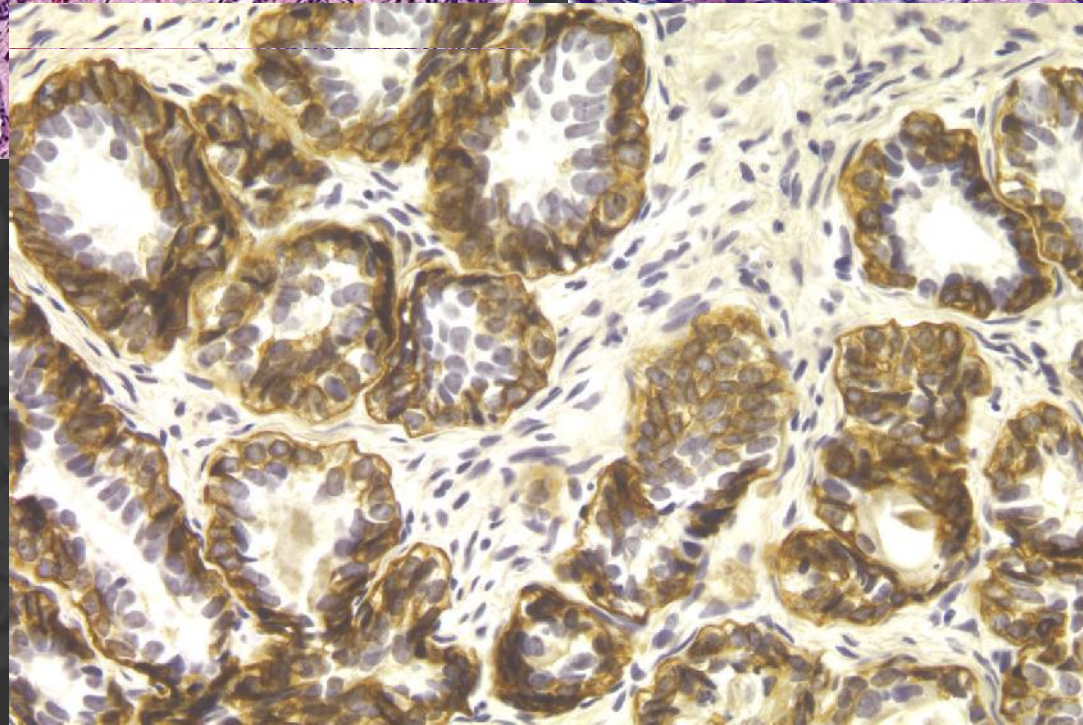
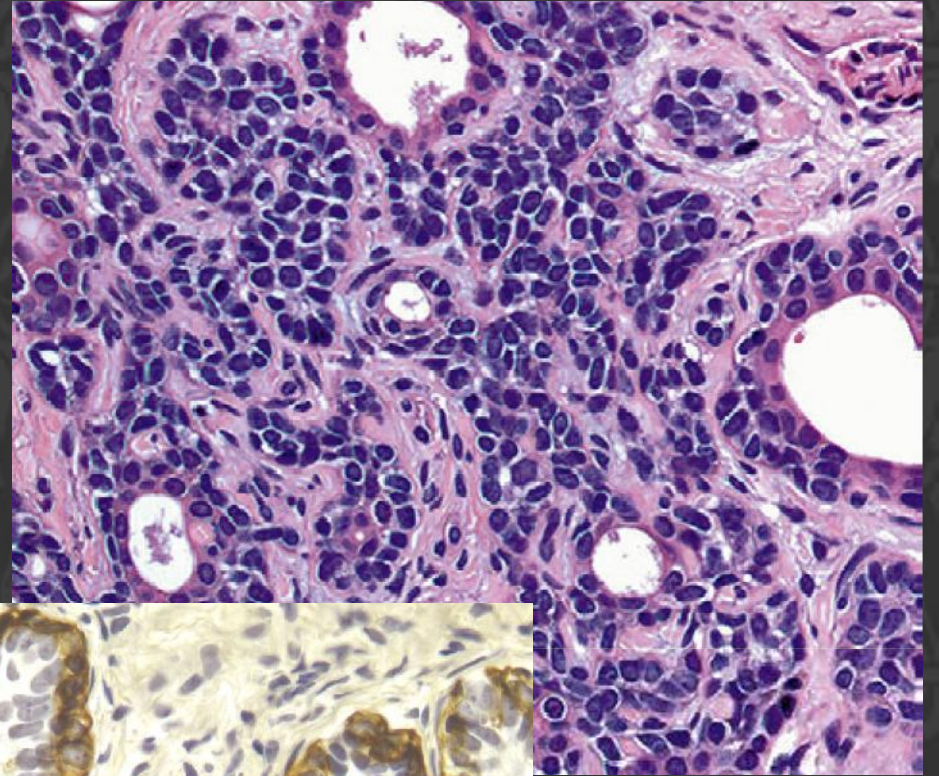
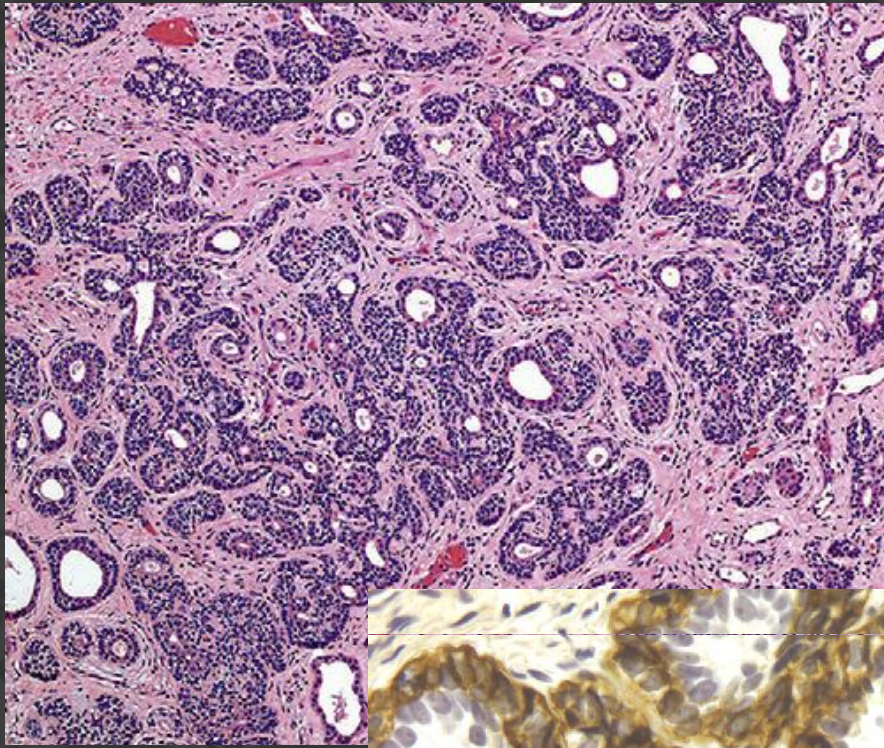
Cells have scant cytoplasm and oval or somewhat elongated nuclei with homogeneous vesicular chromatin and indistinct nucleoli

In complete BCH, basal cells form solid nests without luminal formation

In incomplete BCH, residual small lumina are lined by secretory cells with clear or eosinophilic cytoplasm that are surrounded by multiple layers of basal cells

The basal cells are positive for basal cell markers 34bE12 and p63, negative for AMACR, but may be weakly and focally positive for PSA and PSAP

BCH may be confused with PCa, but the presence of dense cellular stroma, multiple layers of oval and vesicular nuclei, microcalcifications and cytoplasmic hyaline globules are features that distinguish BCH from PCa



ADENOSIS

Adenosis

Lobular

Small glands share cytoplasmic and nuclear features with admixed larger benign glands

Pale-clear cytoplasm

Medium sized nucleoli

Blue mucinous secretions rare

Corpora amylacea common

Basal cells present

Cancer

Haphazard growth pattern

Small glands differ in either nuclear or cytoplasmic features from adjacent benign glands

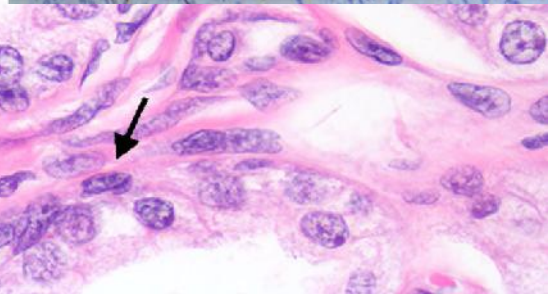
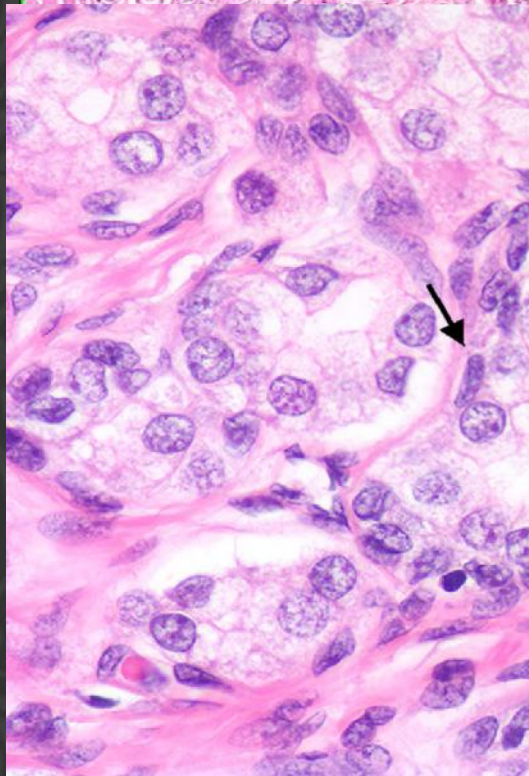
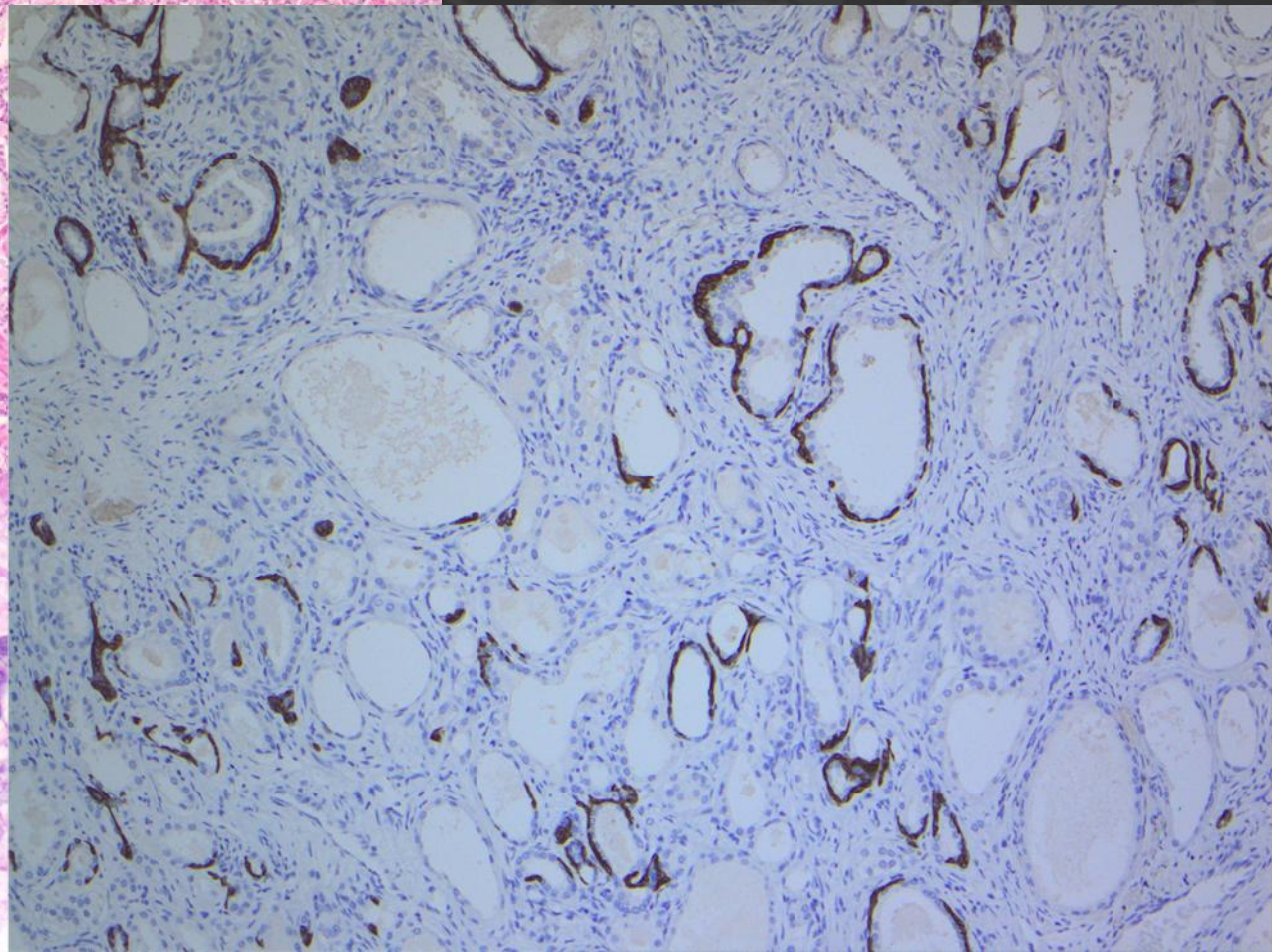
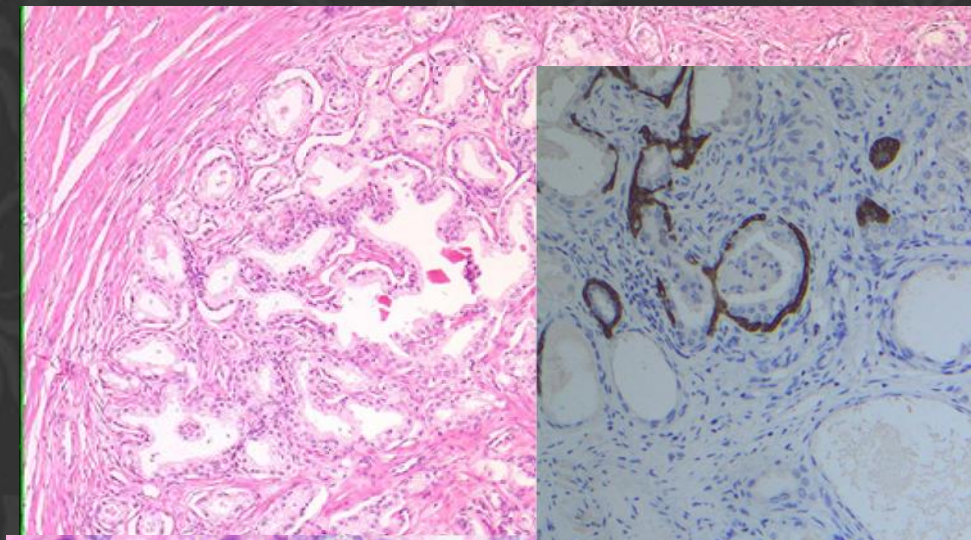
Occasionally amphophilic cytoplasm

Occasionally large nucleoli

Blue mucinous secretions common

Corpora amylacea rare

Basal cells absent



“Adenosis is a mimicker of prostate cancer which is not associated with an increased risk of cancer”

NEPHROGENIC ADENOMA

- Small poorly formed glands, small tubules resembling renal tubules and dilated cysts resembling ectatic vessels are seen
- The tubules are frequently surrounded by thick basement membrane. The lining epithelial cells are flat, cuboidal and hobnail with uniform nuclei. Clear and signet-ring cells may be seen
- Nuclear atypia, if present, appears degenerative. Mitoses are rare or absent
- Most NA express PAX-2 and PAX-8 and AMACR. Cytoplasmic 34bE12 staining is found in >50% of cases.
- A panel using PAX-2 or PAX-8, PSA, PAP, and 34bE12 is useful in separating NA from PCa.

**FEATURES MIMICKING PROSTATE
CANCER**

Presence of tubules, cords, and signet ring-like tubules

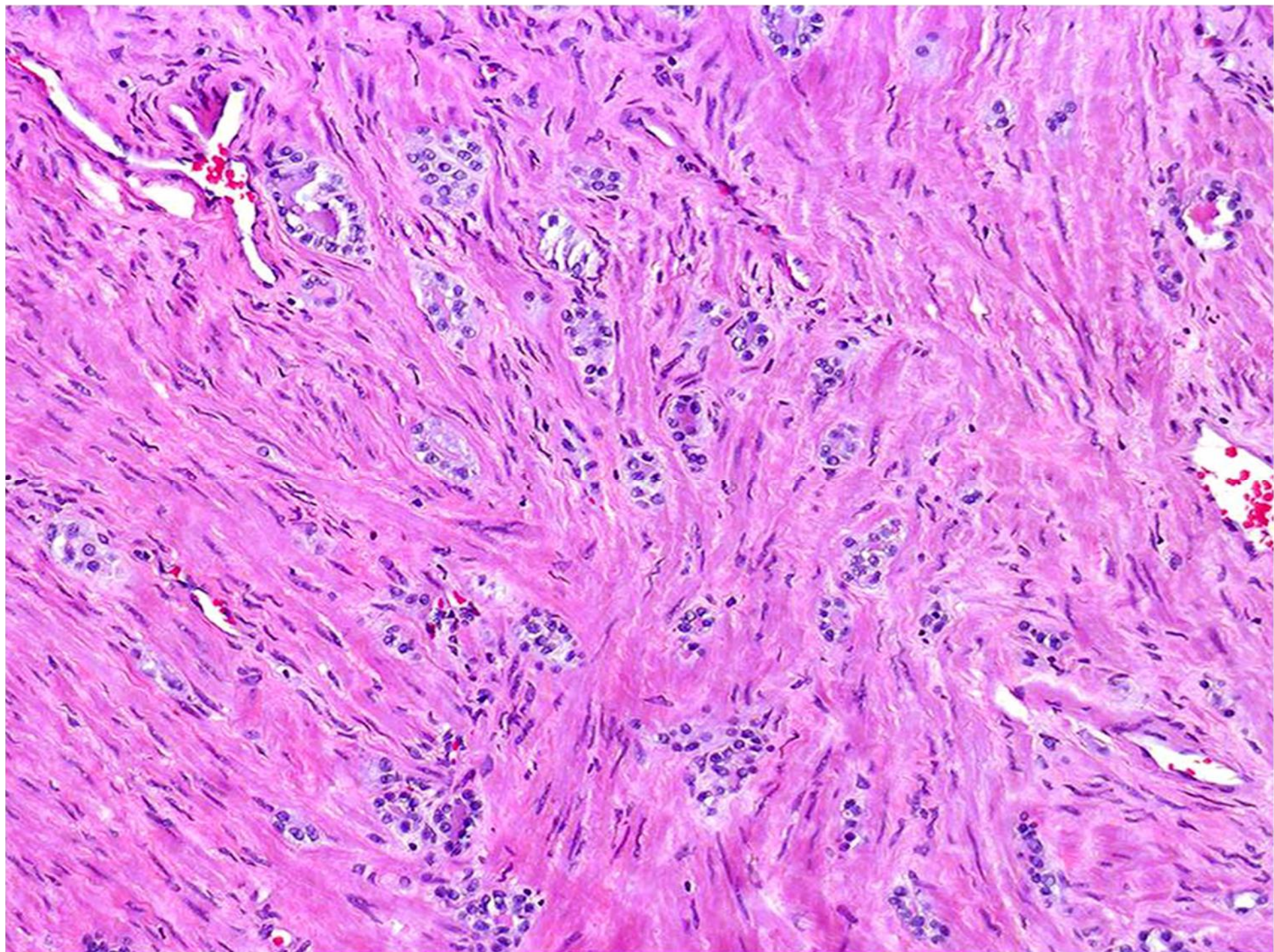
Prominent nucleoli

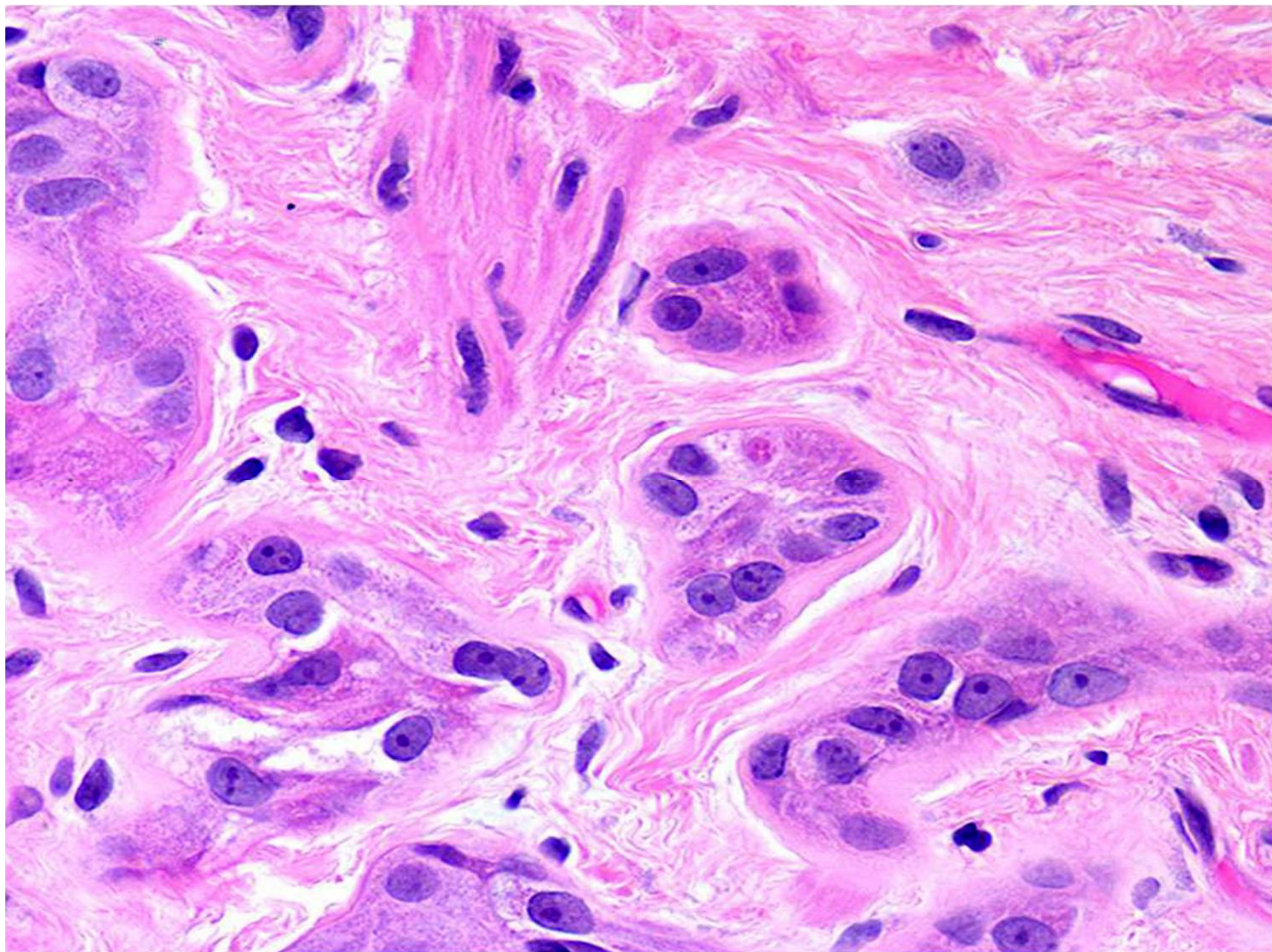
Muscle involvement

Blue-tinged mucinous secretions (32%)

Focal PSA (36%) and PSAP (50%)

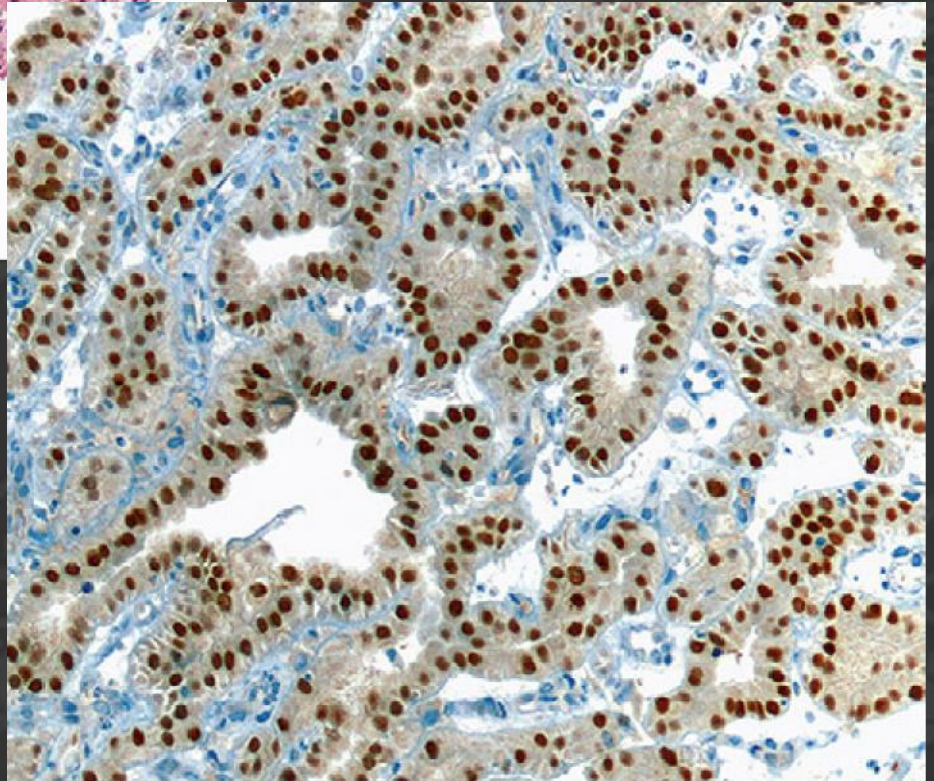
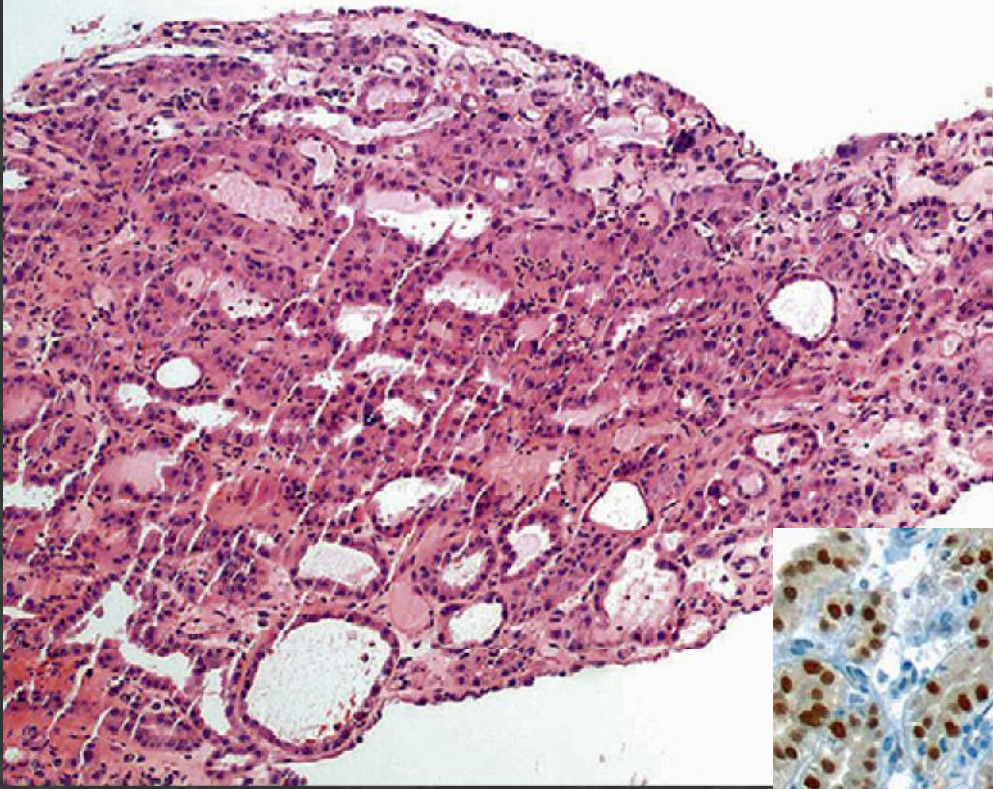
Negative staining for HMWCK in some cases





NEPHROGENIC ADENOMA VS. PROSTATE CA.

- Focal PSA and PSAP positivity in 1/3 of cases, tends to not be diffusely strong
- Negative staining for HMWCK in 62%-75% of cases
- Cases with positive HMWCK rules out prostate cancer
- Positive AMACR (racemase) in 35%-58% of cases
- Positive PAX2 in NA and not in prostate cancer





ATROPHY

DEFINITION AND CAUSATIVE FACTORS

- Atrophy is a common process typically found in older patients, but also present in young adult prostates
- Idiopathic in many cases
- Atrophy is commonly associated with chronic inflammation and may be a manifestation of local chronic ischaemia
- Atrophy can also be the result of radiation and antiandrogen therapy

ATROPHY

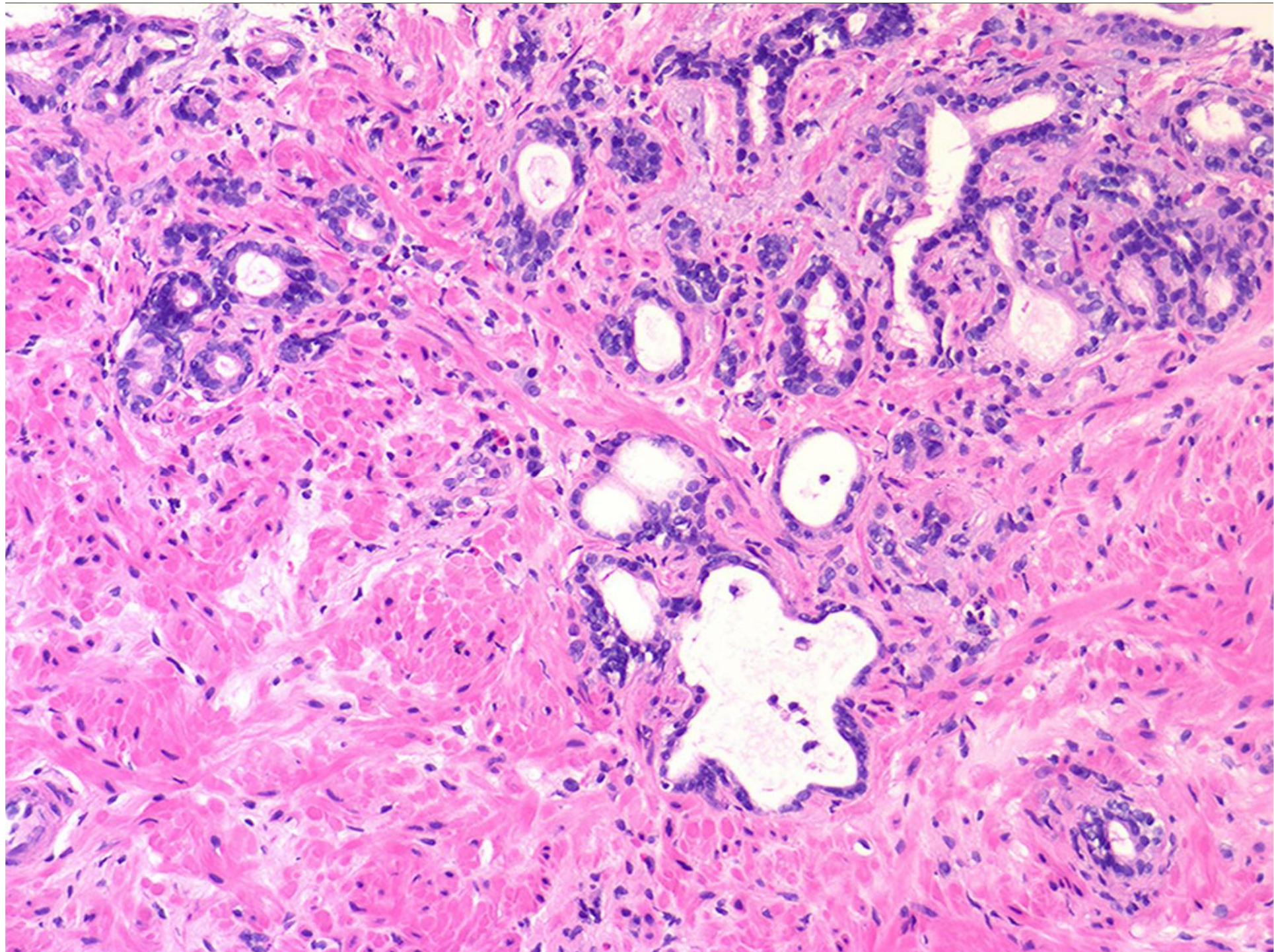
- Simple atrophy
- Cystic atrophy,
- Post-atrophic hyperplasia
- Partial atrophy

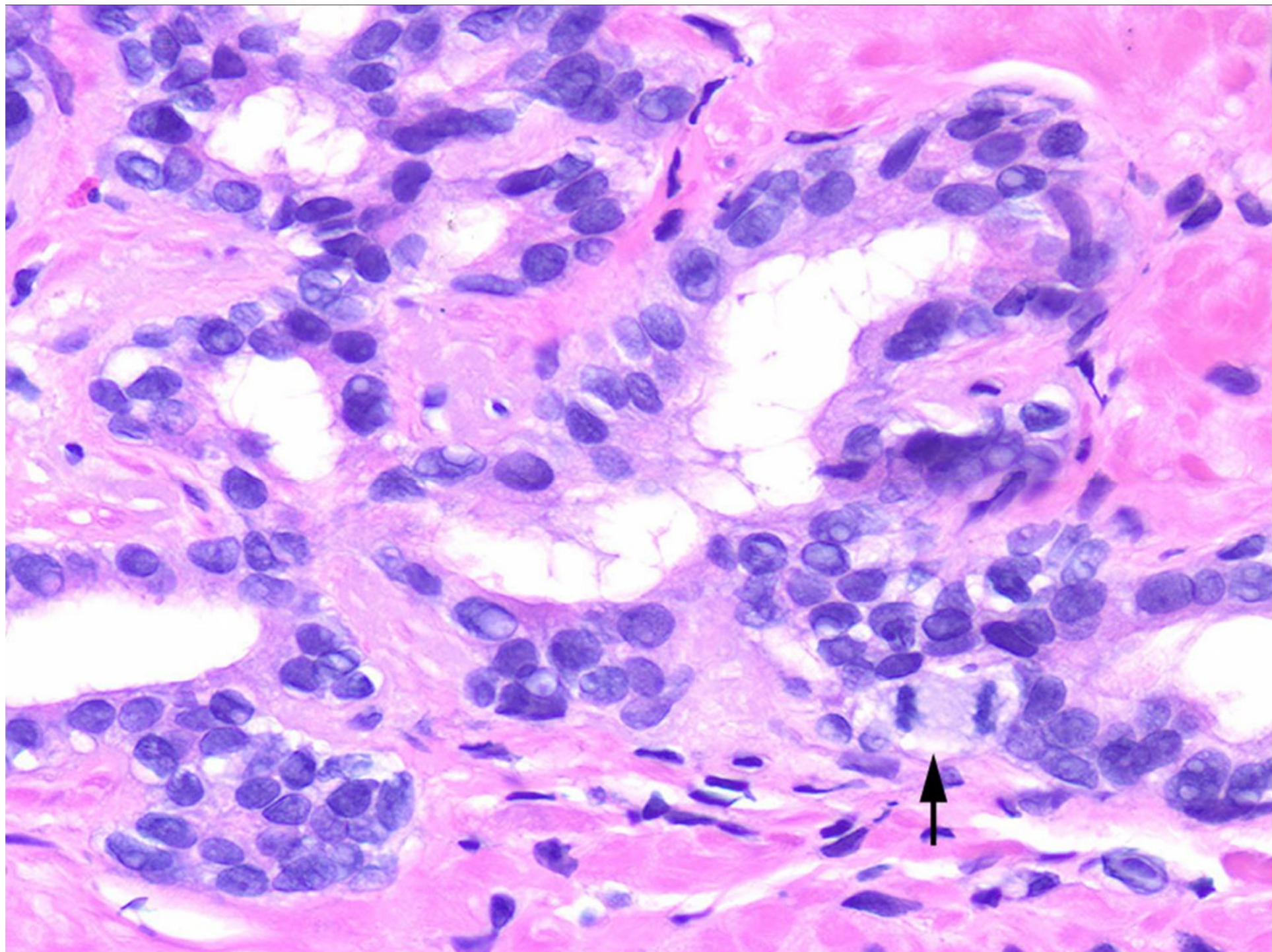
These patterns often co-exist

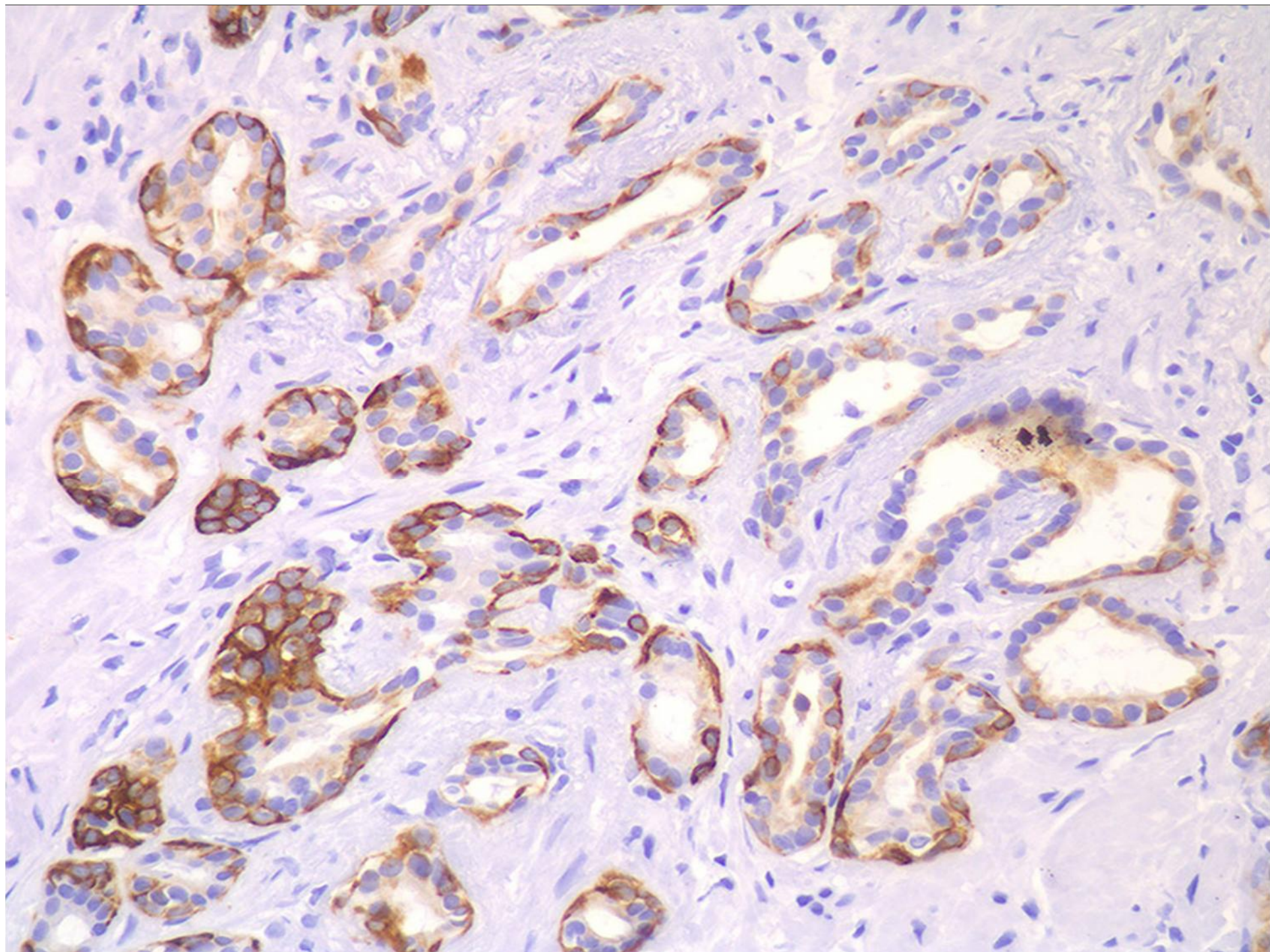
SIMPLE ATROPHY

- The overall glandular architecture is preserved but the glands appear shrunken
- The stroma is frequently sclerotic and contains inflammation
- Cystic changes are often present
- The term cystic atrophy is applied when the atrophic glands are significantly dilated and rounded and cyst-like

Simple and cystic atrophy does not pose diagnostic challenges.

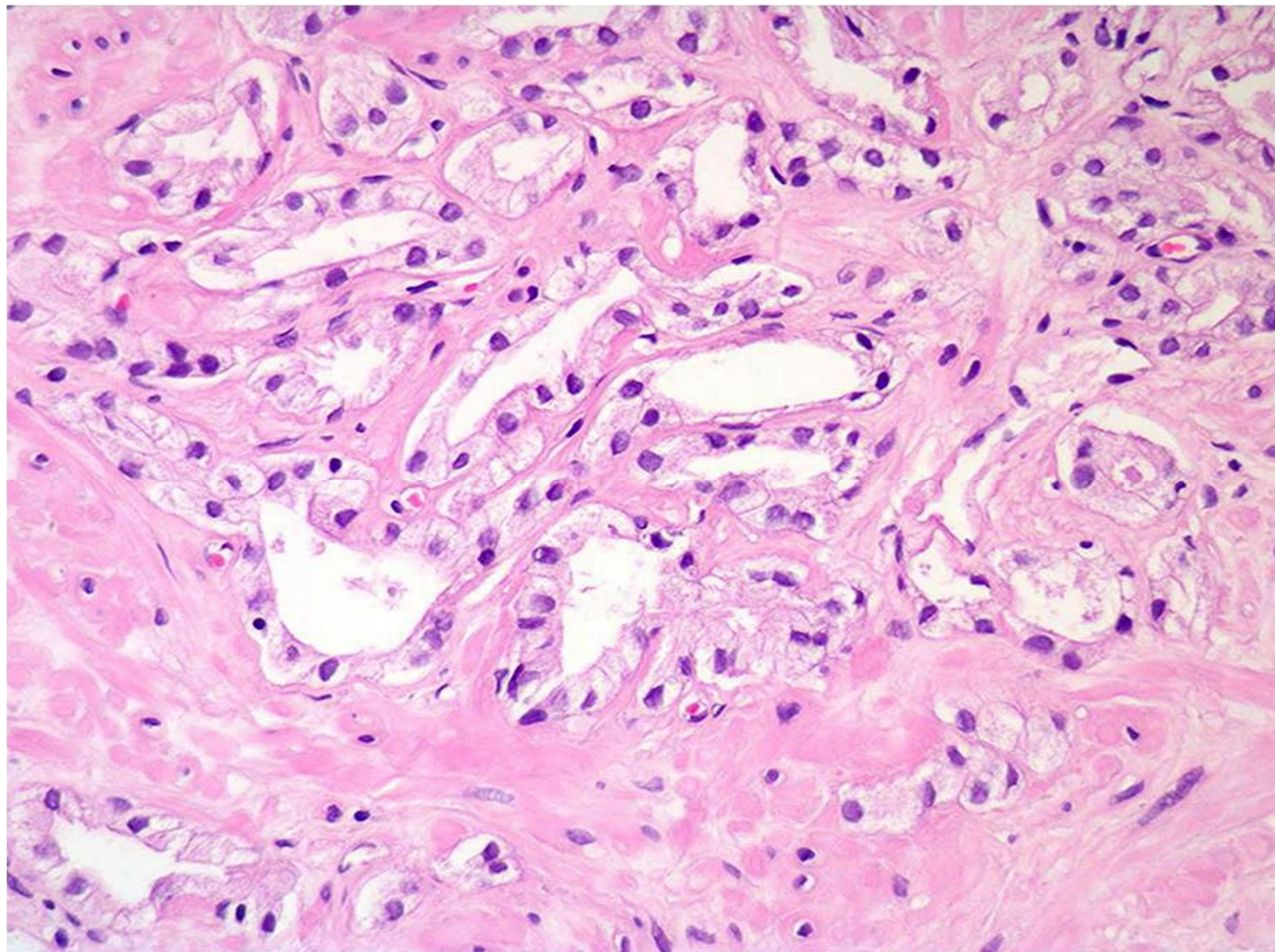


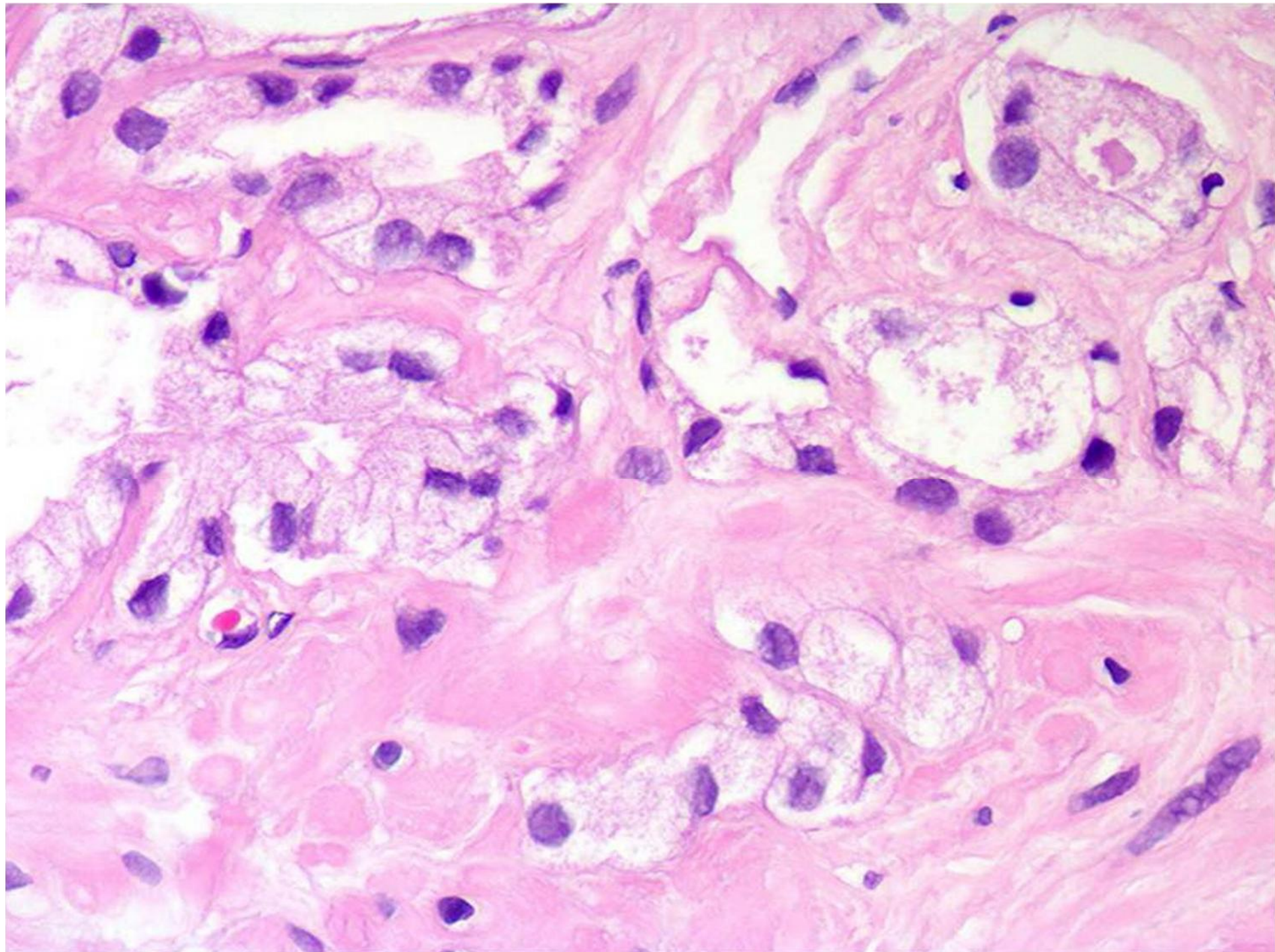


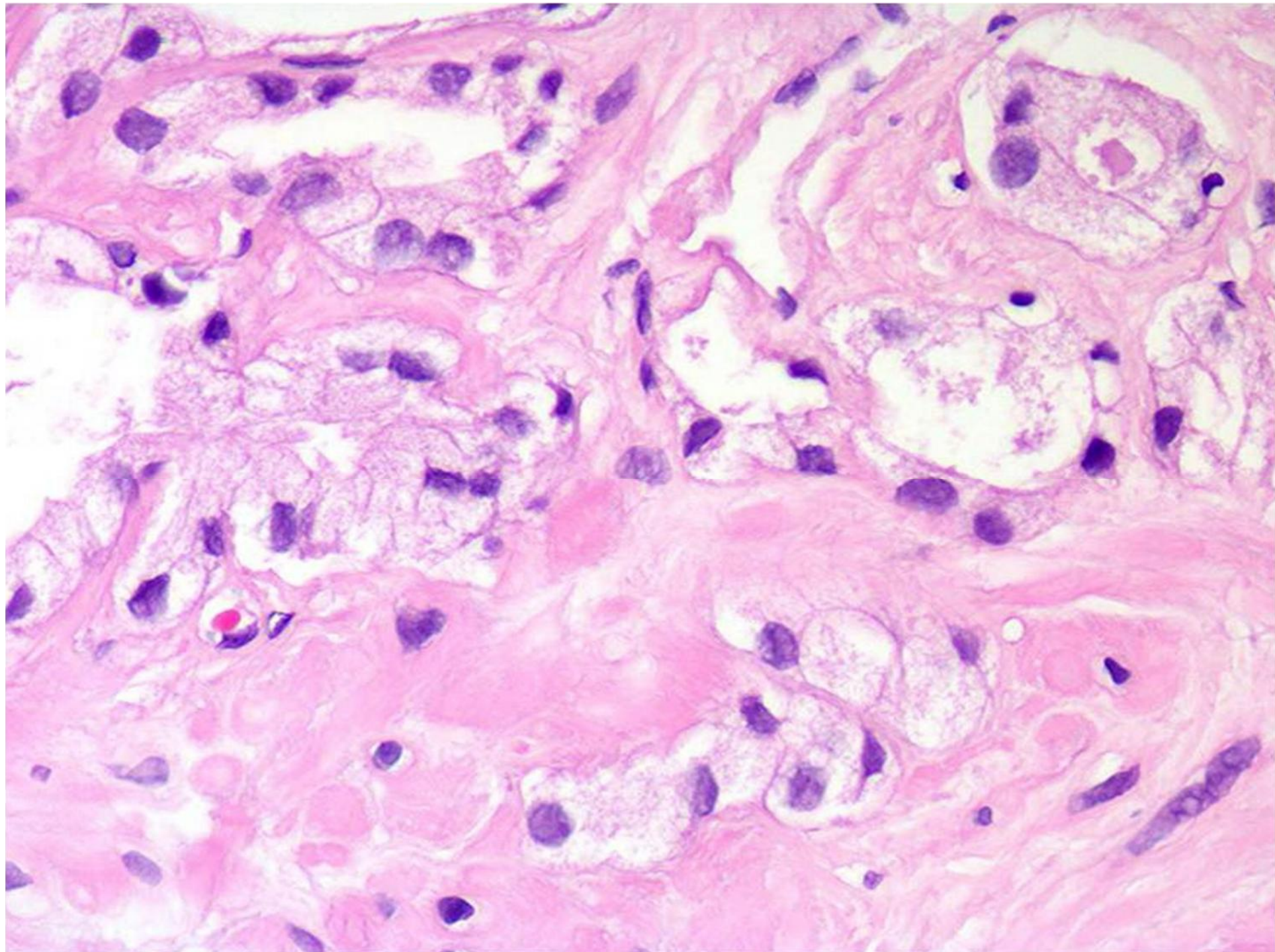


PARTIAL ATROPHY

- Partial atrophy usually has a lobular, or sometimes more diffuse and disorganized architecture, at low magnification
- The glands vary in size and the large glands typically have highly irregular contour
- The glands appear pale rather than basophilic due to abundant cytoplasm lateral to the nuclei
- Nuclei may be slightly enlarged with small or inconspicuous nuclei
- Granular eosinophilic luminal secretions and occasionally mucin may be seen
- Immunostains for basal cell markers are often patchy in most glands, and may be entirely negative in some glands
- The stain for AMACR is positive in many examples of PA although the staining intensity is generally less than that seen in PCa.

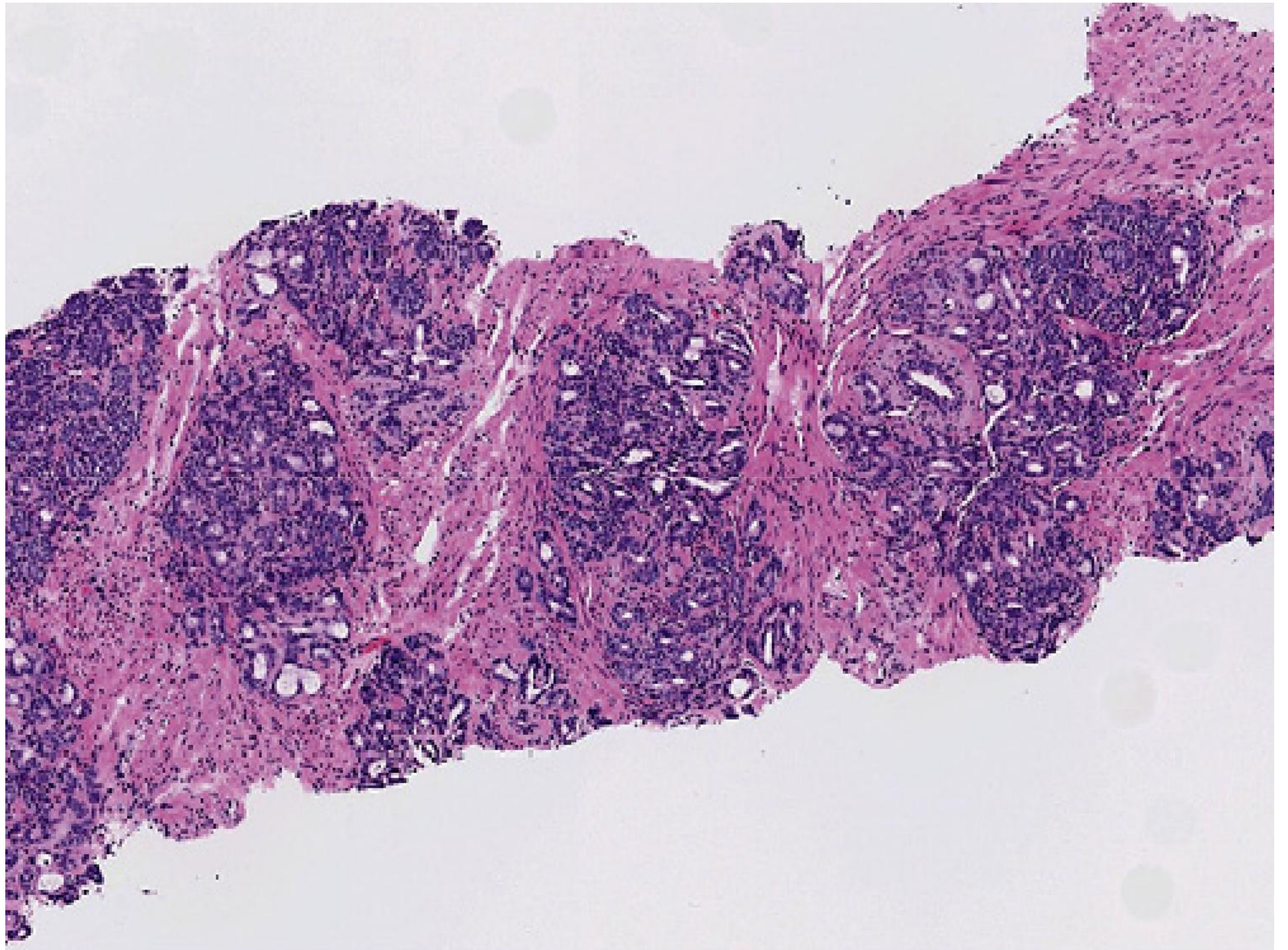






POST ATROPHIC HYPERPLASIA

- PAH consists of lobular collection of small, round and basophilic acini frequently arranged around central dilated “feeder” ducts
- The stroma is sclerotic and contains inflammation
- Secretory cells are low cuboidal with scant cytoplasm
- Basal cells may proliferate and show mild to moderate nucleolar enlargement
- Basal cell markers usually demonstrate continuous but sometime patchy positivity
- PAH generally lacks AMACR expression





TAKE HOME MESSAGE

Prostate biopsies and TURs are some of the most difficult specimens to evaluate, in part due to the wide range of mimickers of both moderately and poorly differentiated adenocarcinoma of the prostate.

Recognition of these mimickers' unique histologic features can prevent an overdiagnosis of prostate cancer.