Breast cancer pathology
Past, Present and Future

Professor Ibrahim Zardawi MD (2015)

Breast cancer

Oldest known form of cancer tumors in humans.

Described in ancient Egyptian Papyrus (1600 BC)

Egyptian treated breast cancer by cauterization

In 1654, Rembrandt van Rijn painted his famous Bathsheba, which depicts King David's wife naked at her bath. The painting has been regarded as an icon for breast cancer, apparently showing both primary breast cancer and metastatic disease in the axilla

Breast cancer

Pathologically, several different types of breast cancer have been identified for a very long time

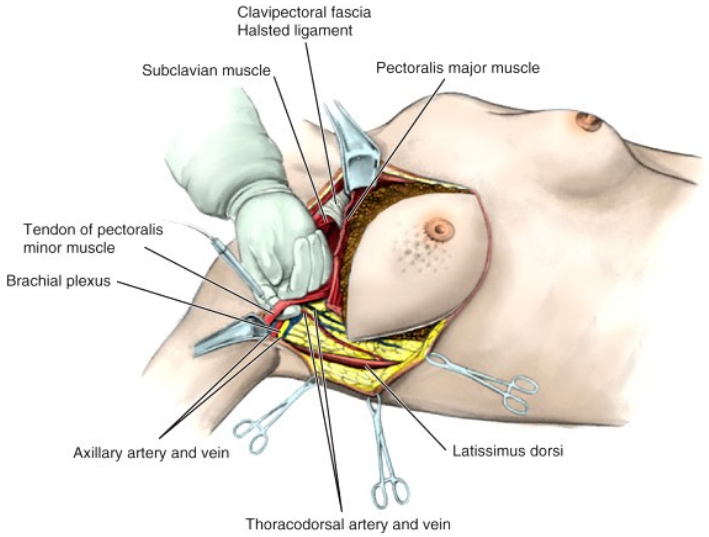
Clinically, until relatively recently, breast cancer was one disease

Breast cancer treatment

Radical surgery was the only treatment available in the beginning

In the 1950s, Radiotherapy and chemotherapy became available and were added.

A 3 pronged approach (surgery, radiotherapy and chemotherapy) became the standard of care in breast cancer management



ER receptor and Tamoxifen were discovered in the 1960s

Breast cancer became 2 diseases

- ER positive
- ER negative

In the 1980s, Her-2/neu was discovered in and Herceptin became available and was used in humans in 1990s

Breast cancer became 3 diseases

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letters to nature

Molecular portraits of human breast tumours

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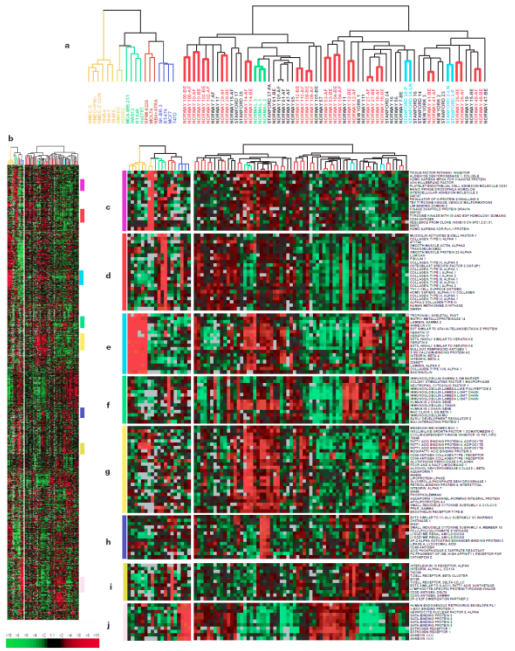
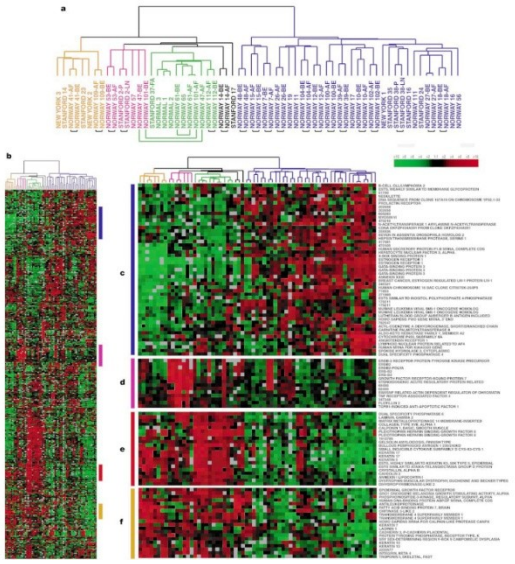




The above publication identified 5 Molecular subtypes of breast cancer

- Basal-like
- ERBB2 (HER-2)
- Normal-like
- Luminal B
- Luminal A

Breast cancer for the Oncologist became 5 diseases

This initial molecular study almost 25 years using complementary DNA microarrays found that breast cancers could be classified into subtypes distinguished by pervasive differences in their gene expression profiling (GEP).

Five molecular types (luminal A, luminal B, $HER2^+$, basal-like and Normal-like) were suggested

Further refinement proposed a classification scheme that divided breast cancer into 4 intrinsic molecular subtypes: luminal A, luminal B, $HER2^+$ and basal-like.

The normal subtype was considered an artifact caused by a disproportionately high content of normal breast stromal cells in the frozen samples used for microarray analysis

Luminal carcinomas express estrogen receptor (ER) with variable cell proliferations

HER2 overexpression is the hallmark of $HER2^{+}$ tumors that lack estrogen (ER) and progesterone (PR) receptor expression

Basal-like carcinomas fail to express ER, PR or HER2 (triple-negative carcinoma), instead express basal cell markers cytokeratin (CK5/6) or Epidermal Growth Factor Receptor (EGFR)

Molecular subtypes of breast cancer	
Tumour subtype	**Tumour characteristics**
Luminal A	ER^+, PR^+, HER^- with low Ki-67 index of <14%
Luminal B	ER^+, PR+, $HER2^+$ or $HER2^-$ with high Ki-67 proliferative index of >14%
HER2 positive	ER^-, PR^- and $HER2^+$
Basal-like (triple negative)	ER^-, PR^-, $HER2^-$ but CK $5/6^+$ or EGFR+
This was adopted by scientific consensus meetings with minor modifications for better separations. The cutoff point for Ki-67 was raised from 14% to 20% and PR positivity was lowered to 20%	

Breast cancer for the Oncologist became at least 5 diseases

It was later shown that this was oversimplification because it did not reflect the molecular complexity of the breast cancer, nor cold it predict the true heterogeneity with the subgroups

Other approaches including 21-Gene Recurrence Score, Oncotype DX, Prosigna Gene Signature, MammaPrint to evaluate various aspect of breast cancer are currently in use

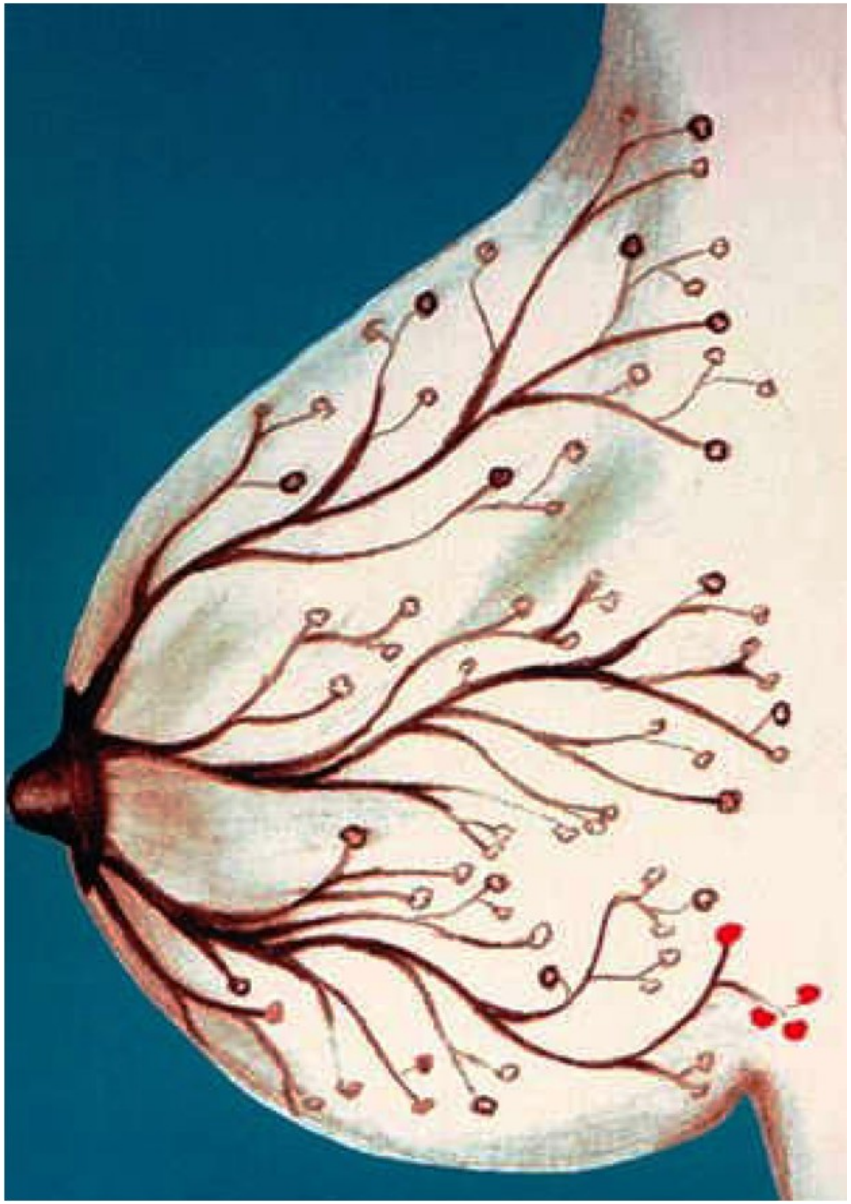
Next-generation sequencing (NGS) approach generates large numbers of genetic alterations, most of which is currently not clinically actionable and have not guaranteed effective targeted therapeutic responses

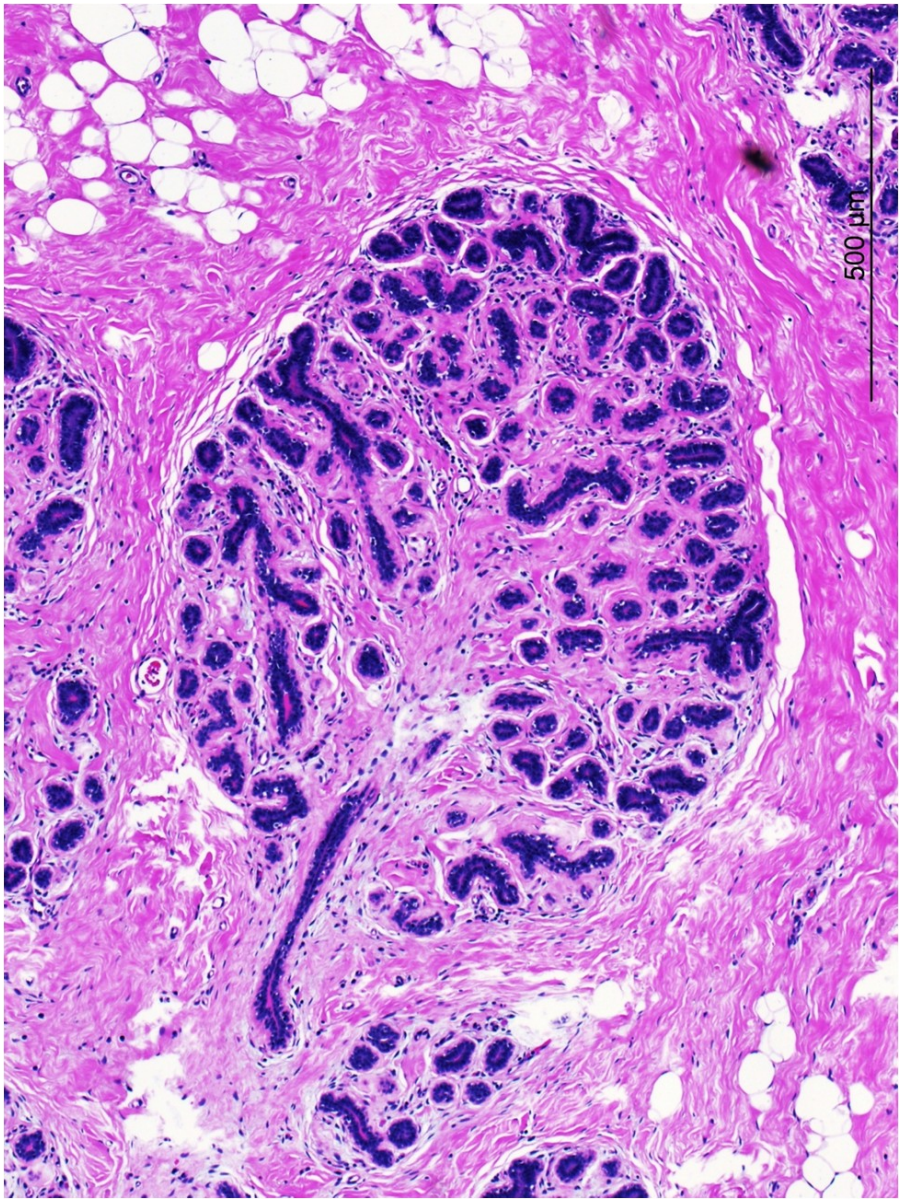
Other molecular studies evaluating the clinical significance of the mutational frequency of oncogenes, tumour suppressor genes and other biological pathways and tumor microenvironment with the aim of finding actionable marker are being extensively investigated

Treatment of breast cancer
“Shotgun medicine”
Treatment was based on average results from randomised clinical trials

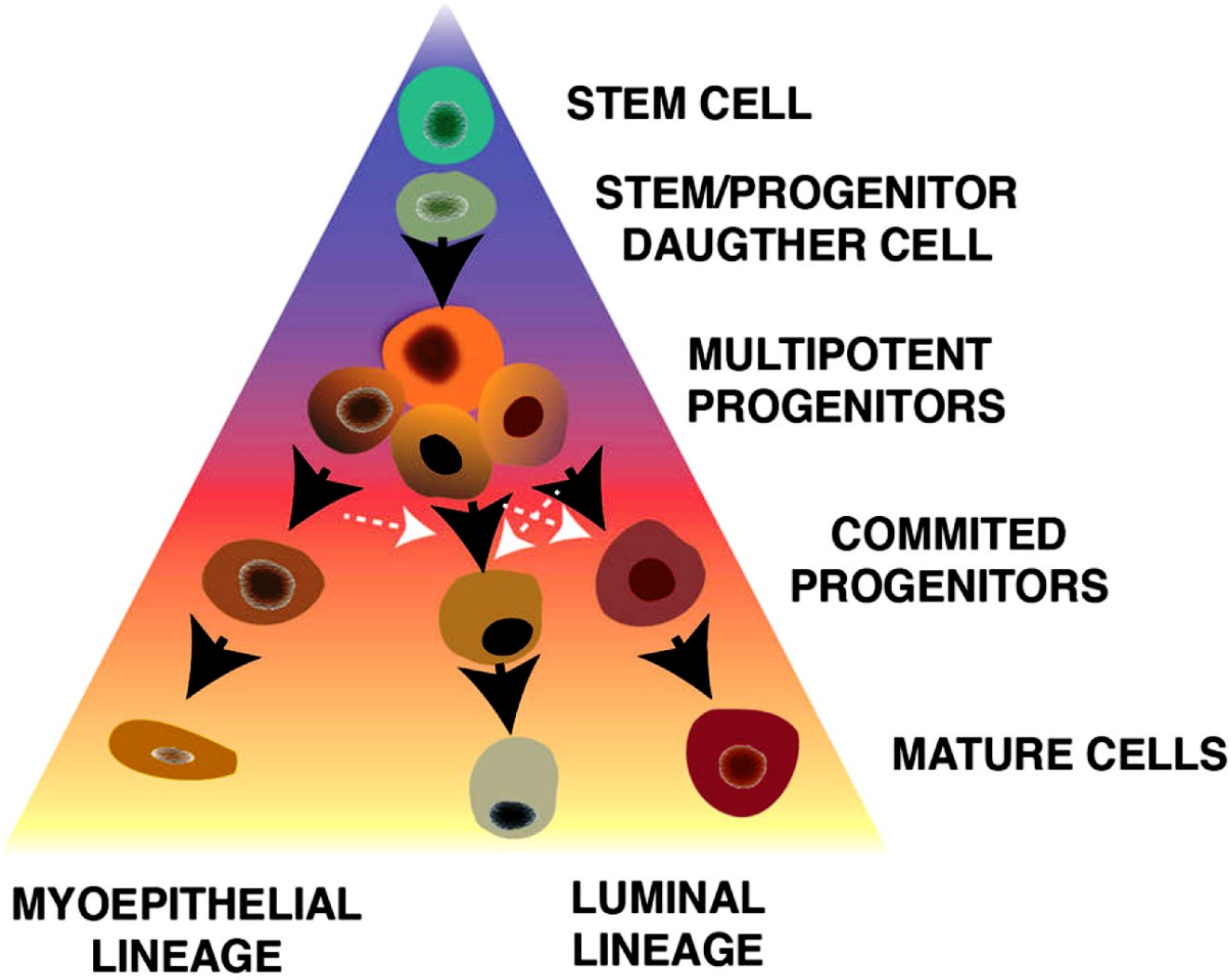
“Precision Medicine”
Treatment is based on refined information

Normal breast (terminal duct-lobular unit)

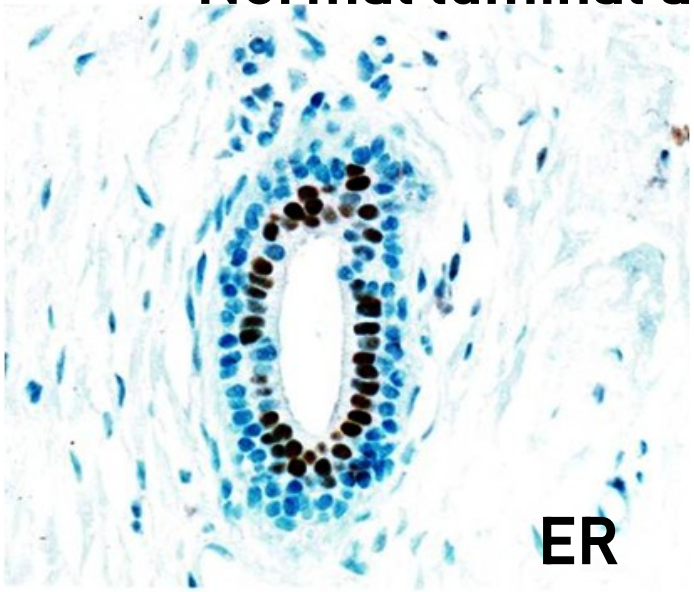




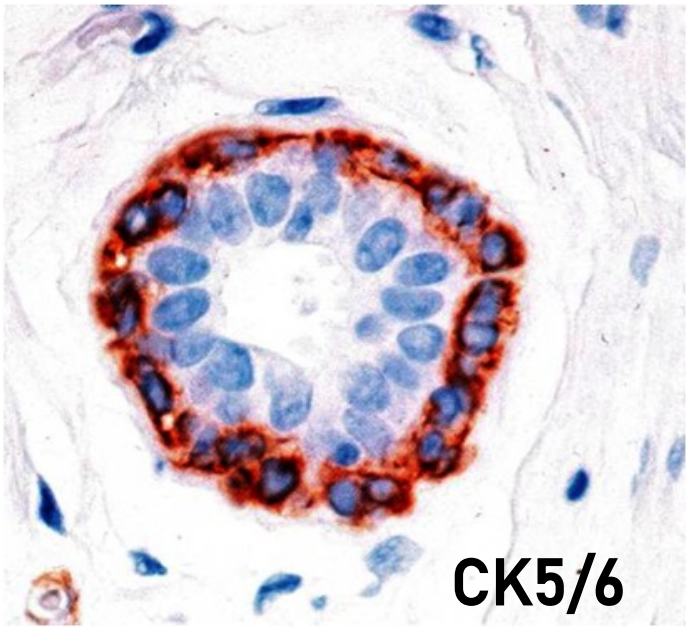
Normal breast epithelium
Stem cell to mature cells (luminal and myoepithelial)



Normal luminal and basal (myoepithelial) cells

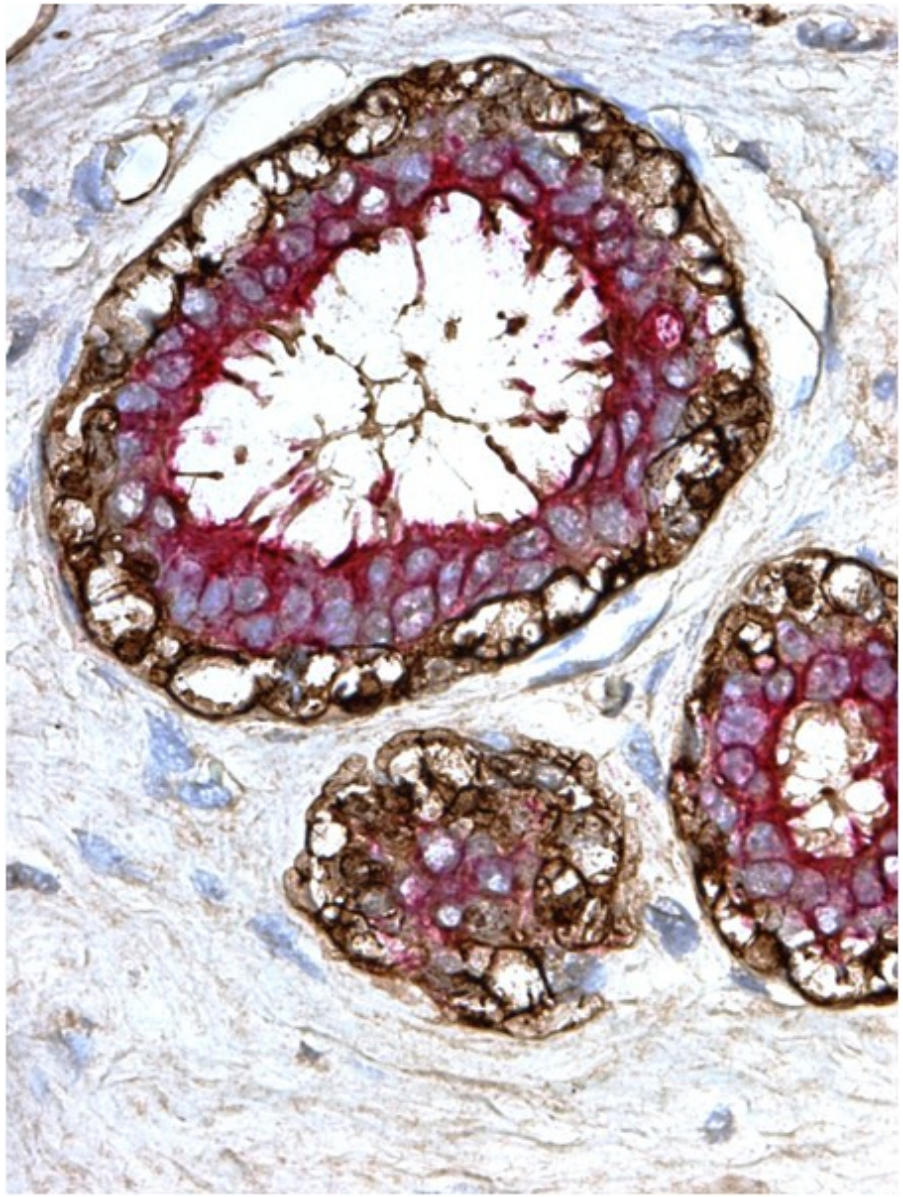


Luminal cells



Basal (myoepithelial) cells

Normal breast
Luminal and basal (myoepithelial) cells

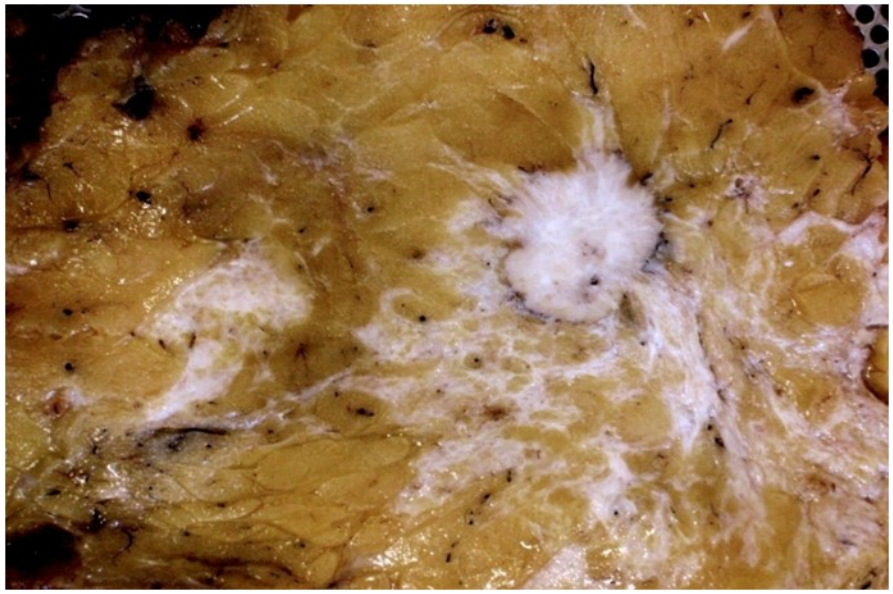


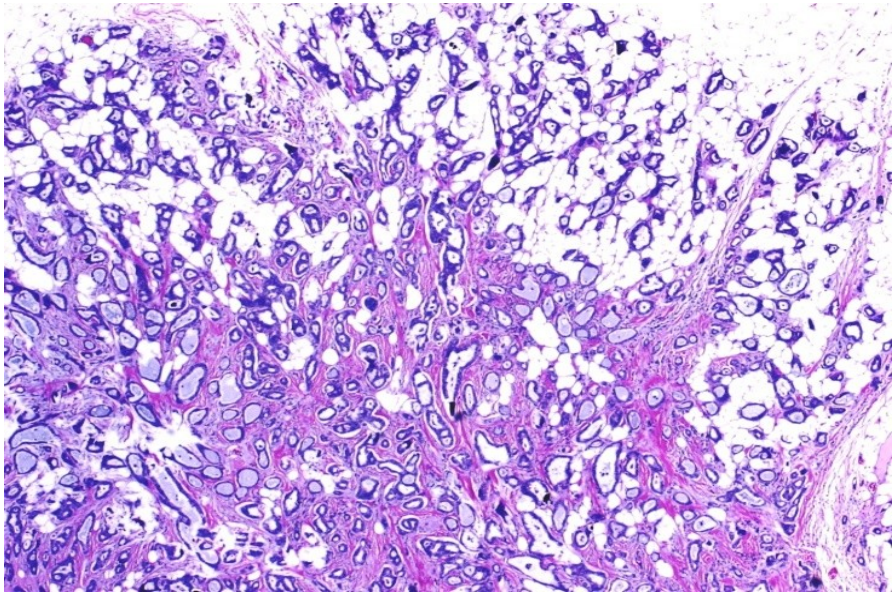
Double staining with different cytokeratins

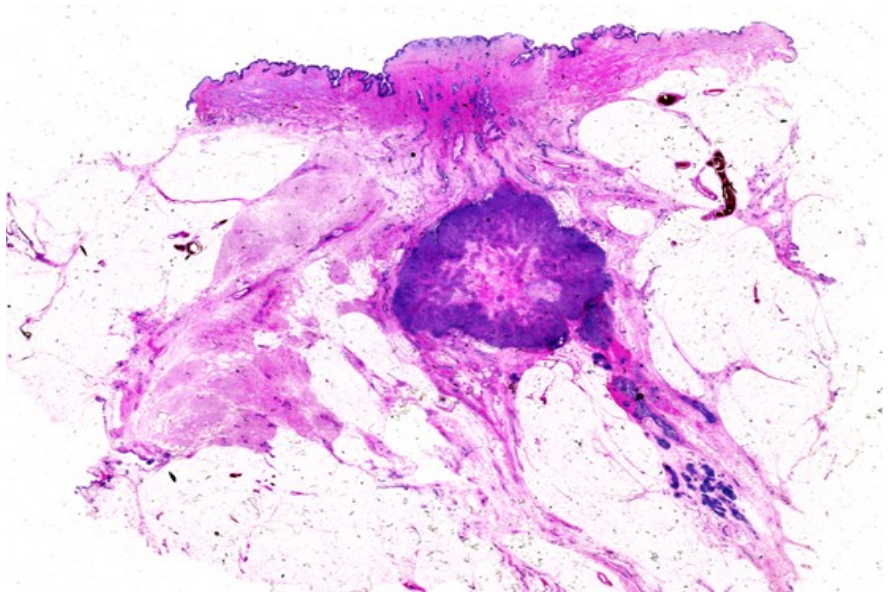
Basal (myoepithelial) cell (brown) are stain with high molecular weight cytokeratins (CK5/6)

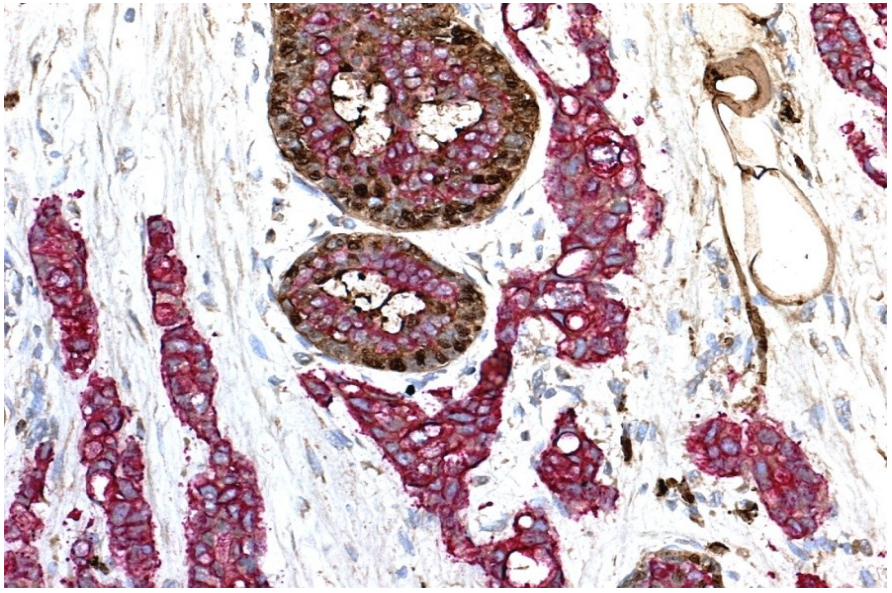
Luminal cells (red) are stained with low molecular weight cytokeratin (Cam5.2)

Pathology of breast cancer





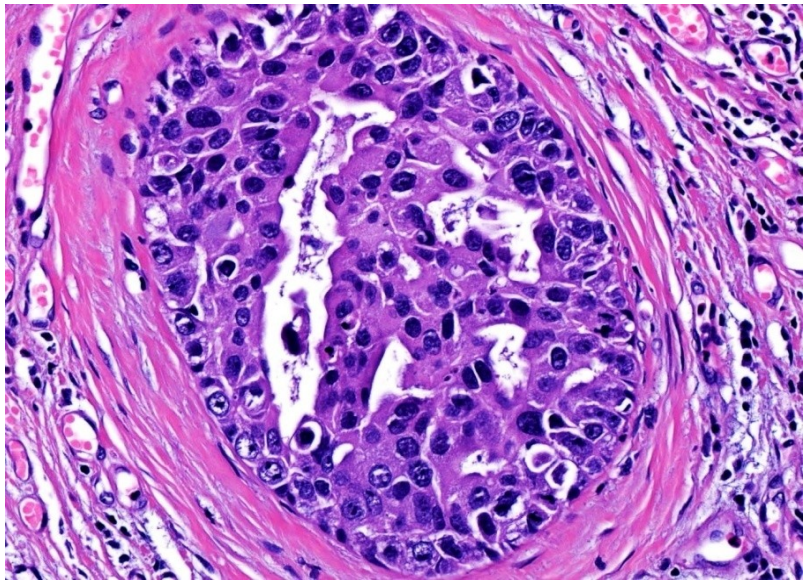




Morphological classification of breast carcinoma

In situ 20%

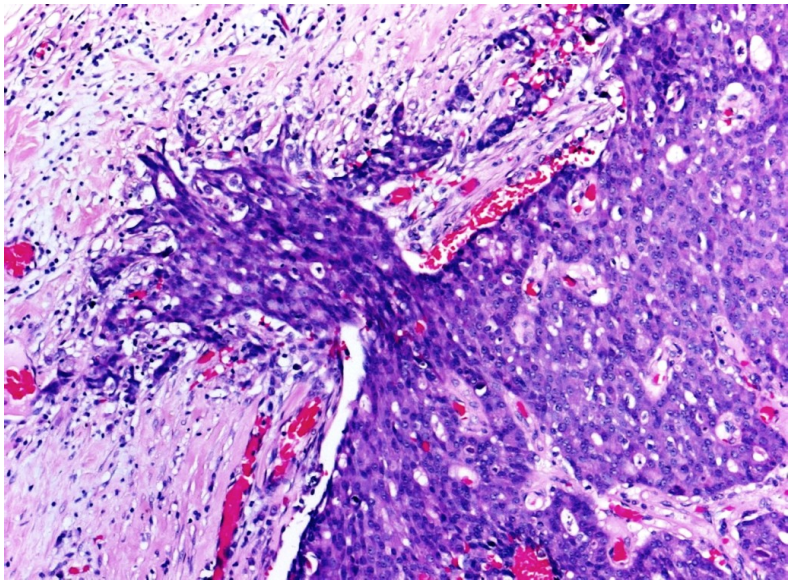
- Ductal in situ (DCIS) 80%
- Lobular in situ (LCIS) 20%



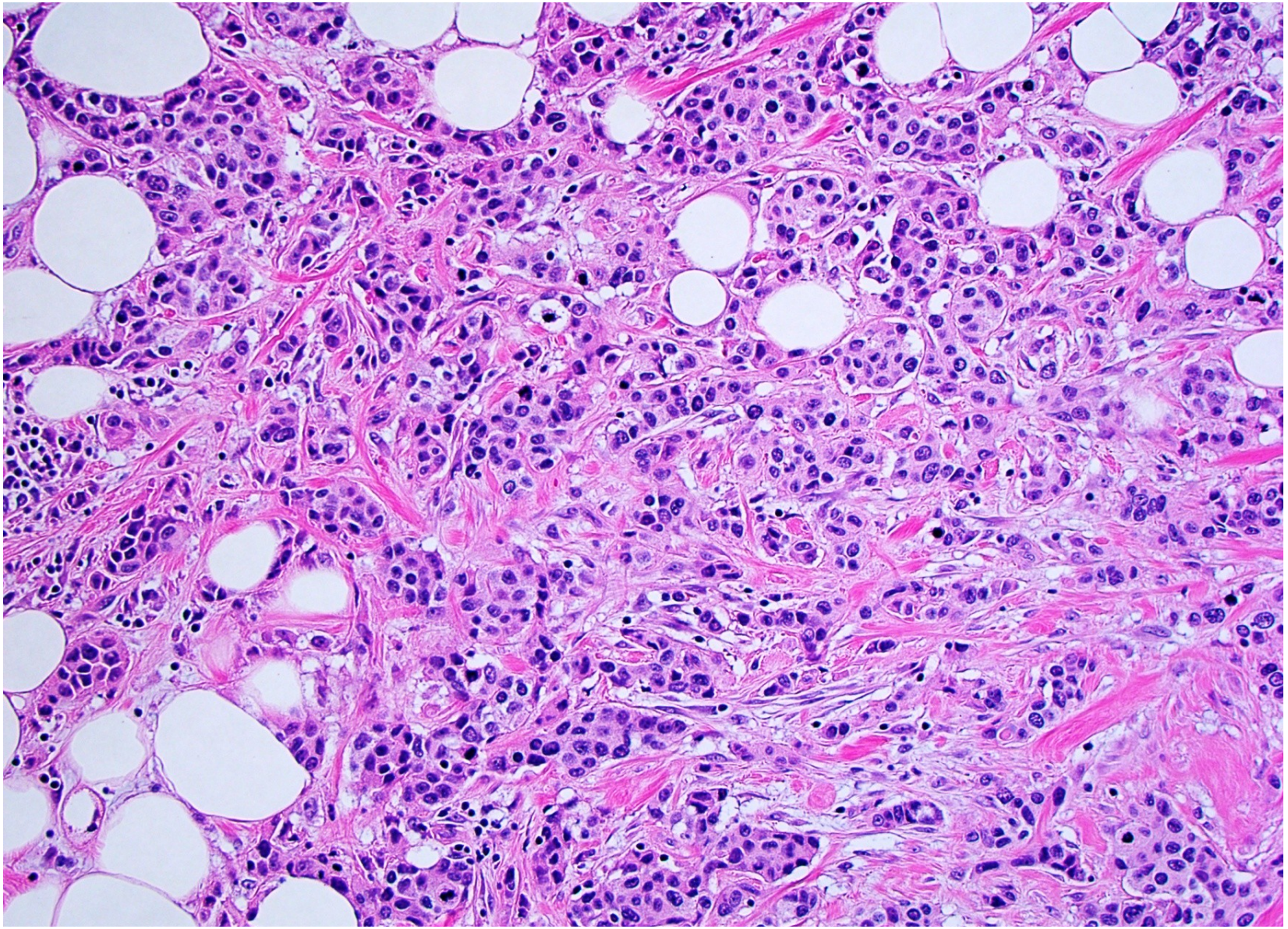
In-situ carcinoma

-Invasive 80%

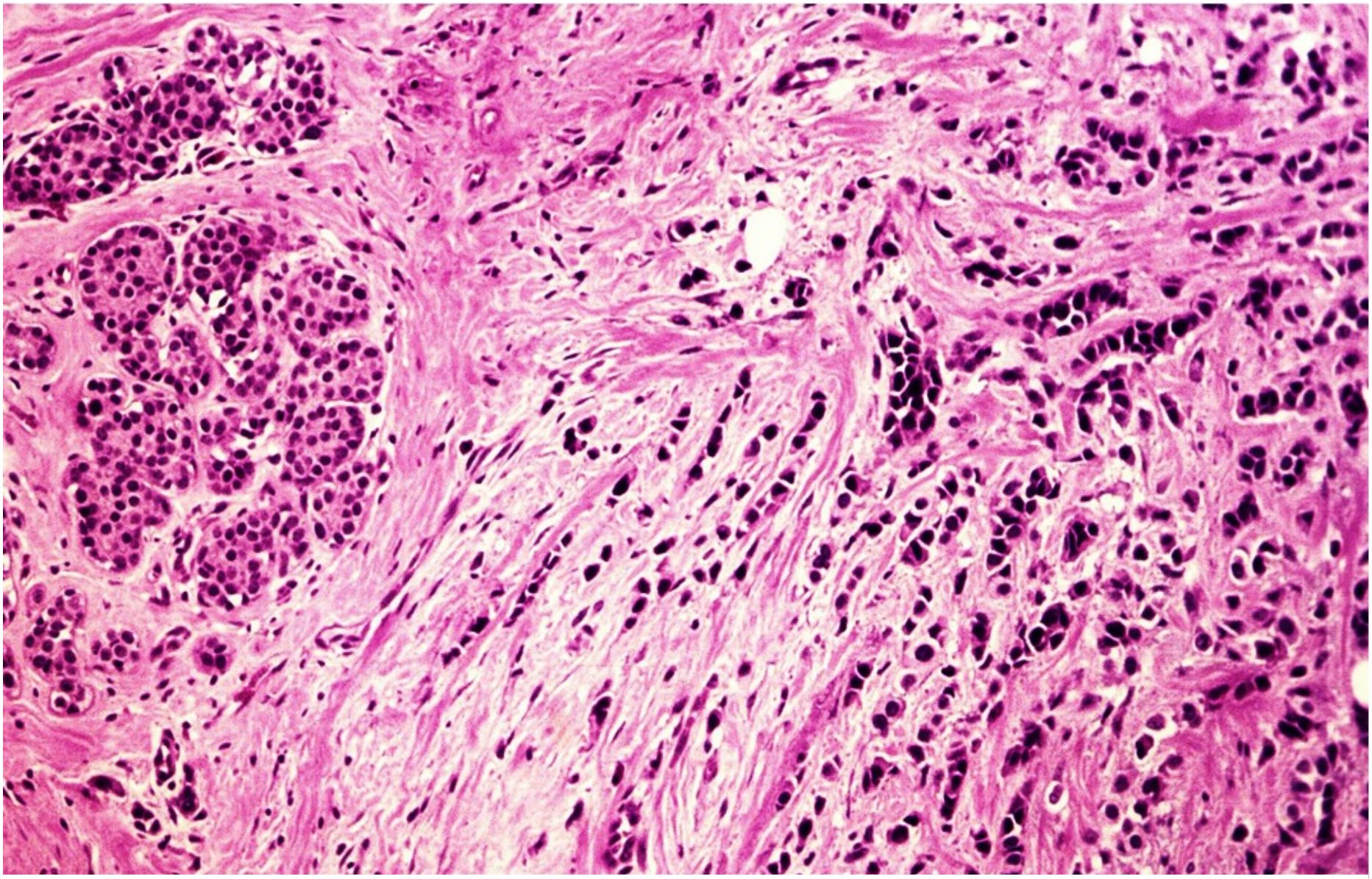
- No special type (NOS) 80%
- Lobular 10%
- Tubular 3%
- Cribriform 3%
- Mucinous 2%
- Micropapillary 1%
- Metaplastic <1%
- Rare types <1%



Invasive carcinoma

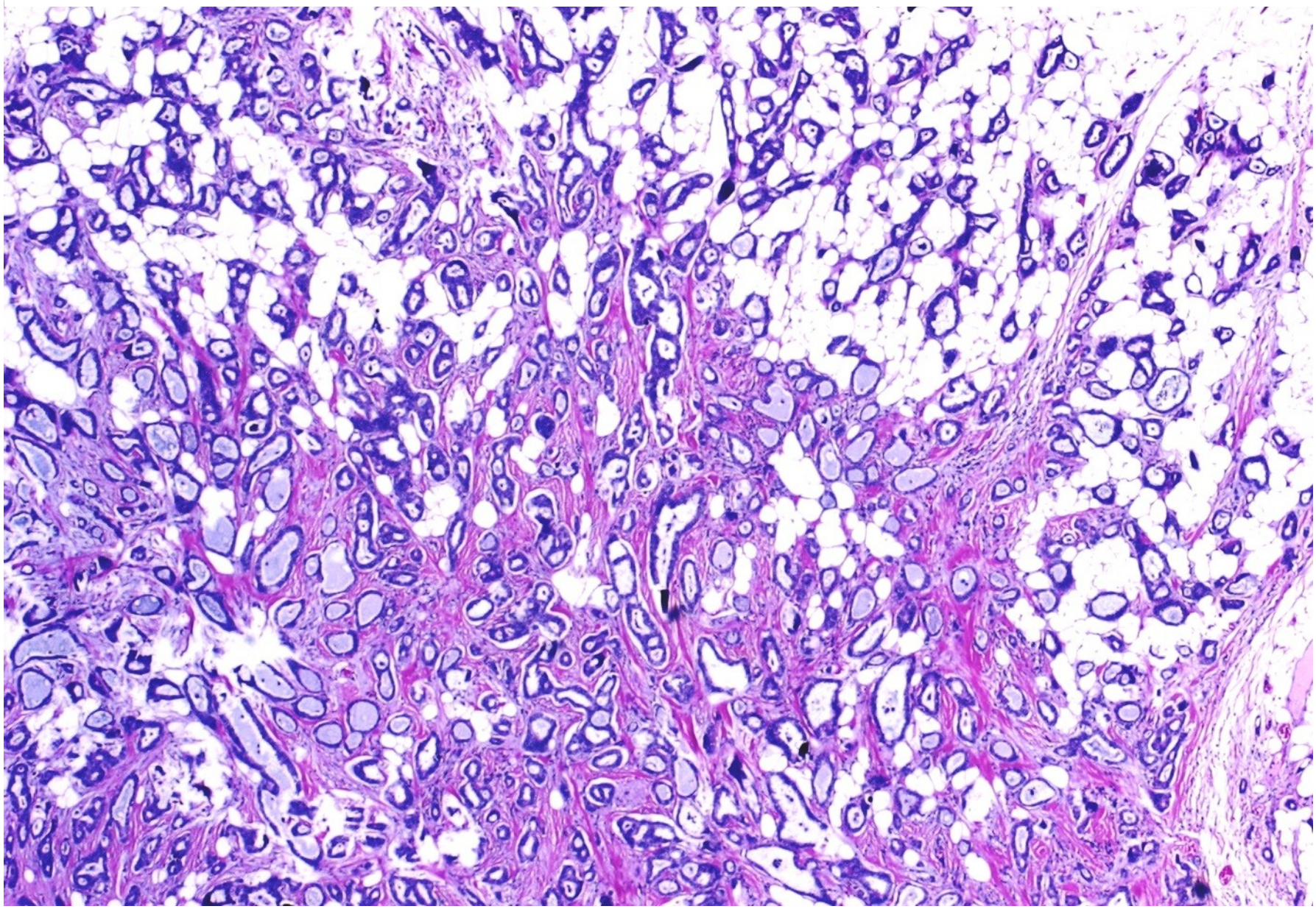


Invasive carcinoma NOS

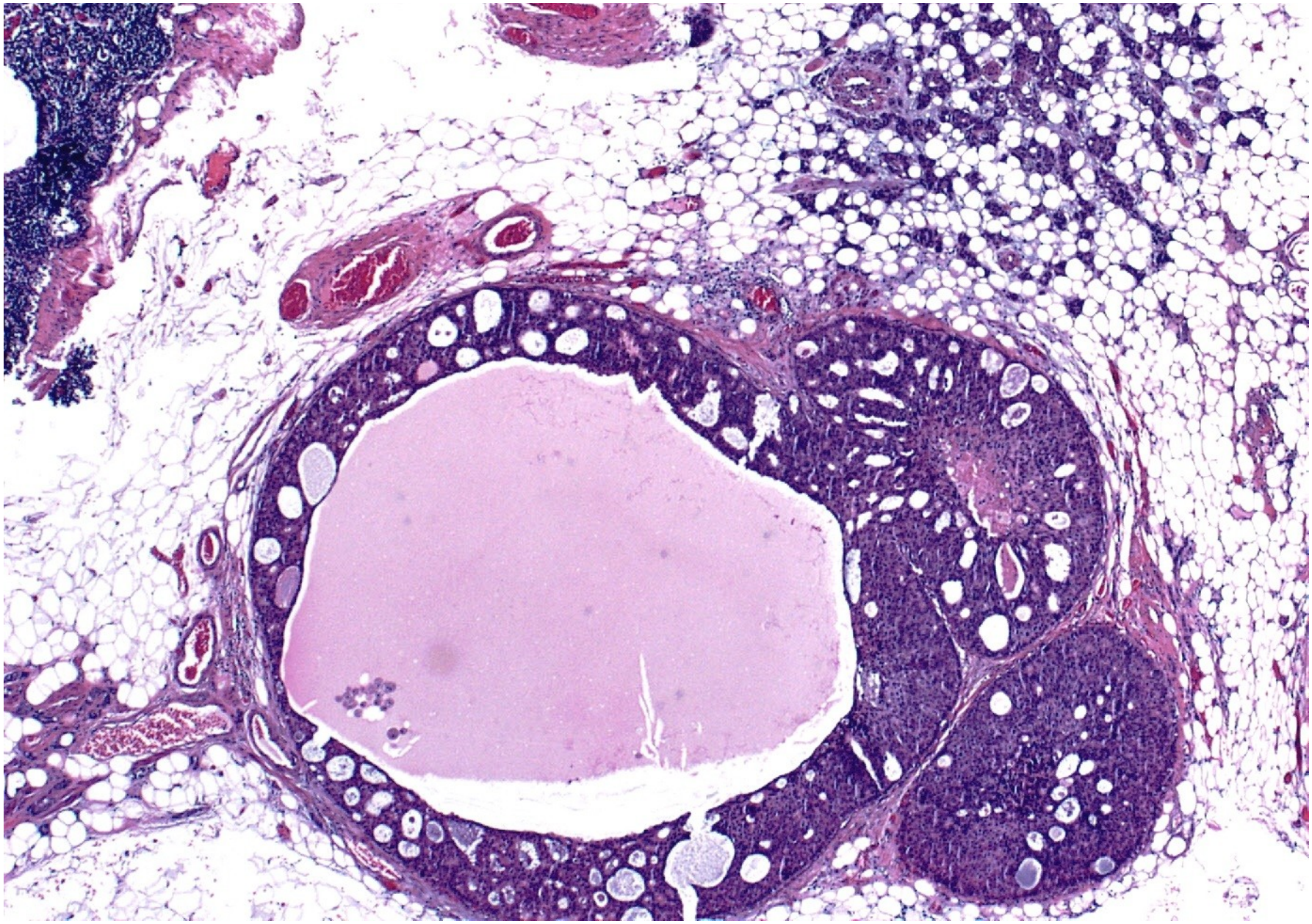


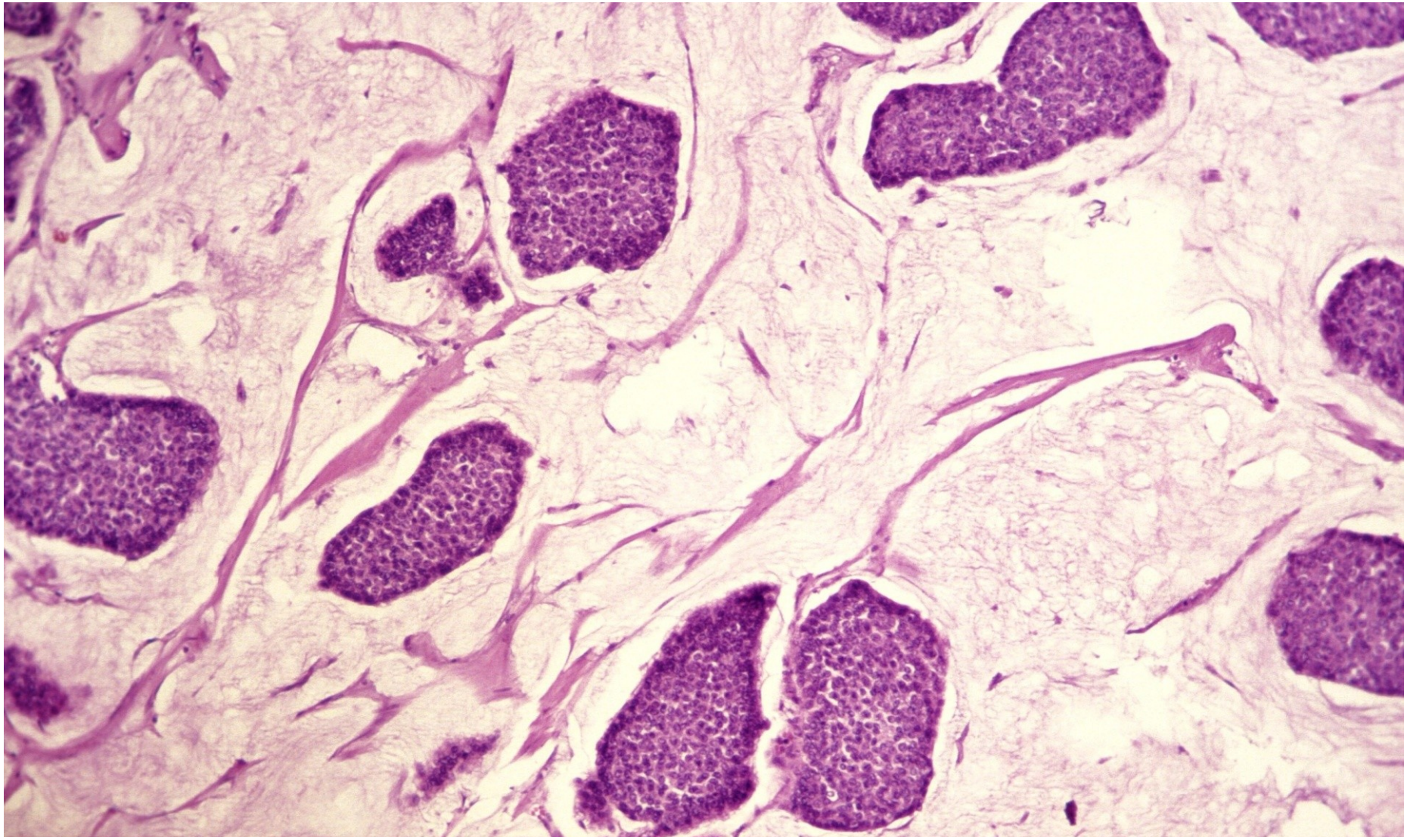
Invasive lobular carcinoma

Tubular carcinoma

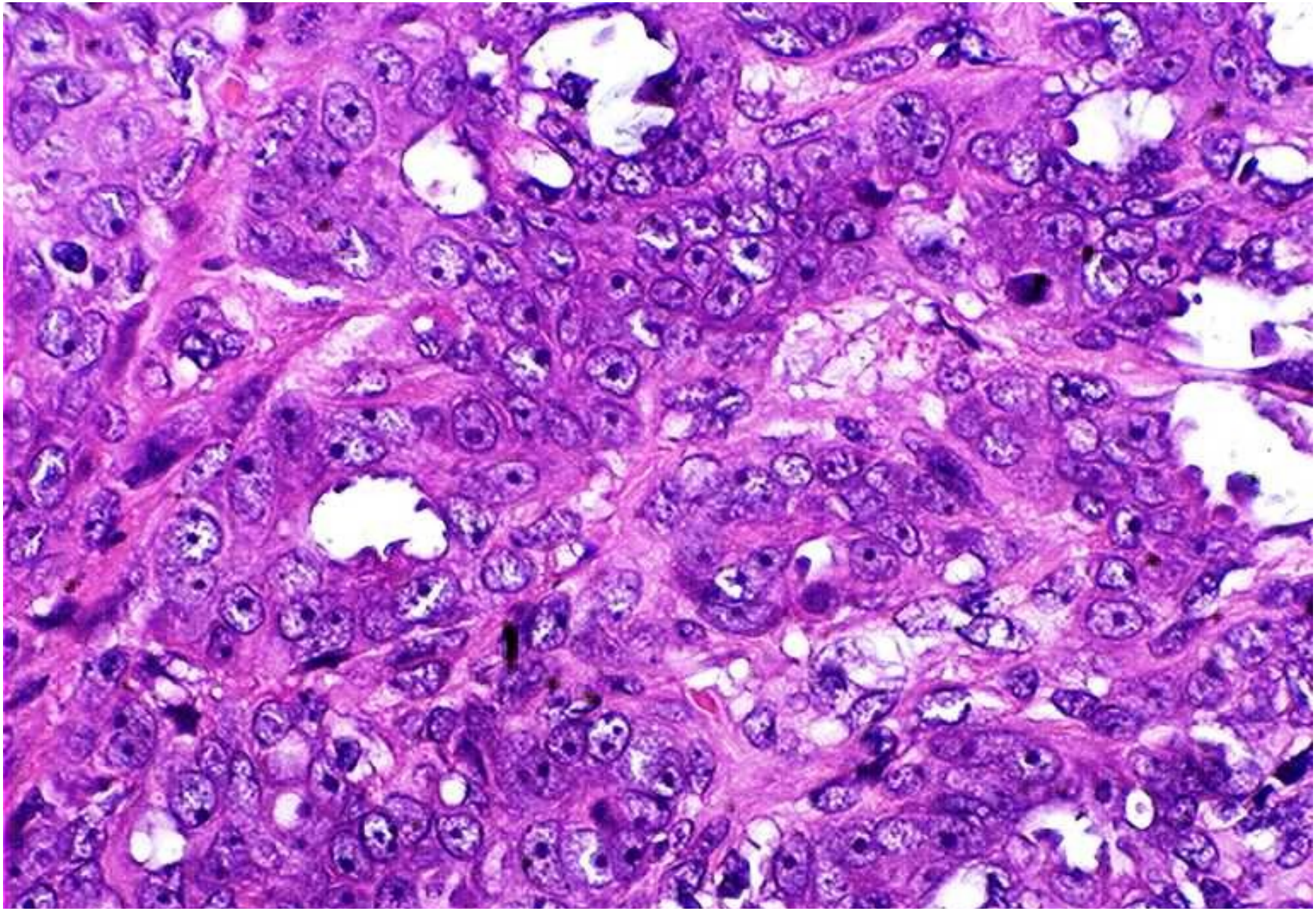


Cribriform carcinoma



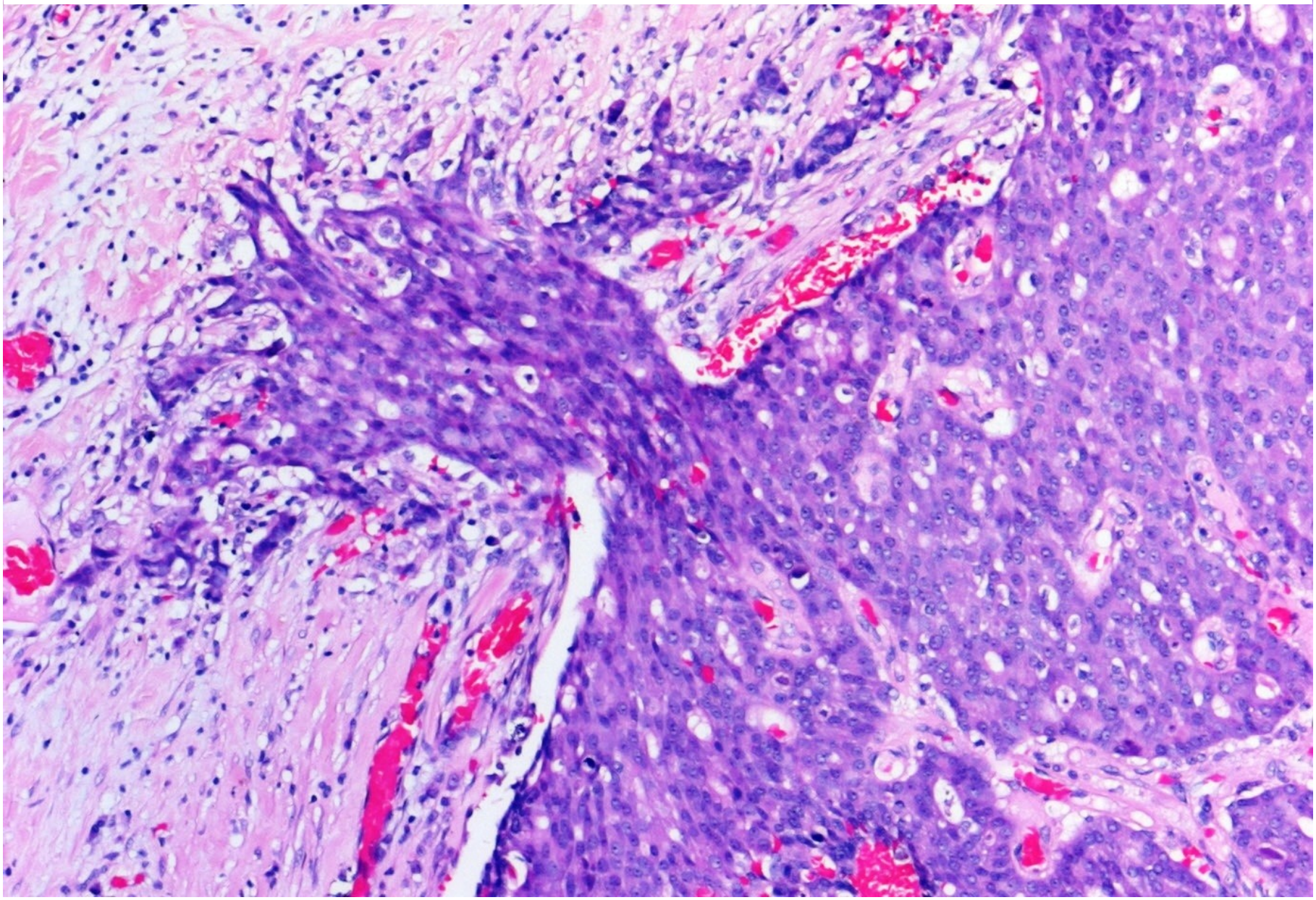


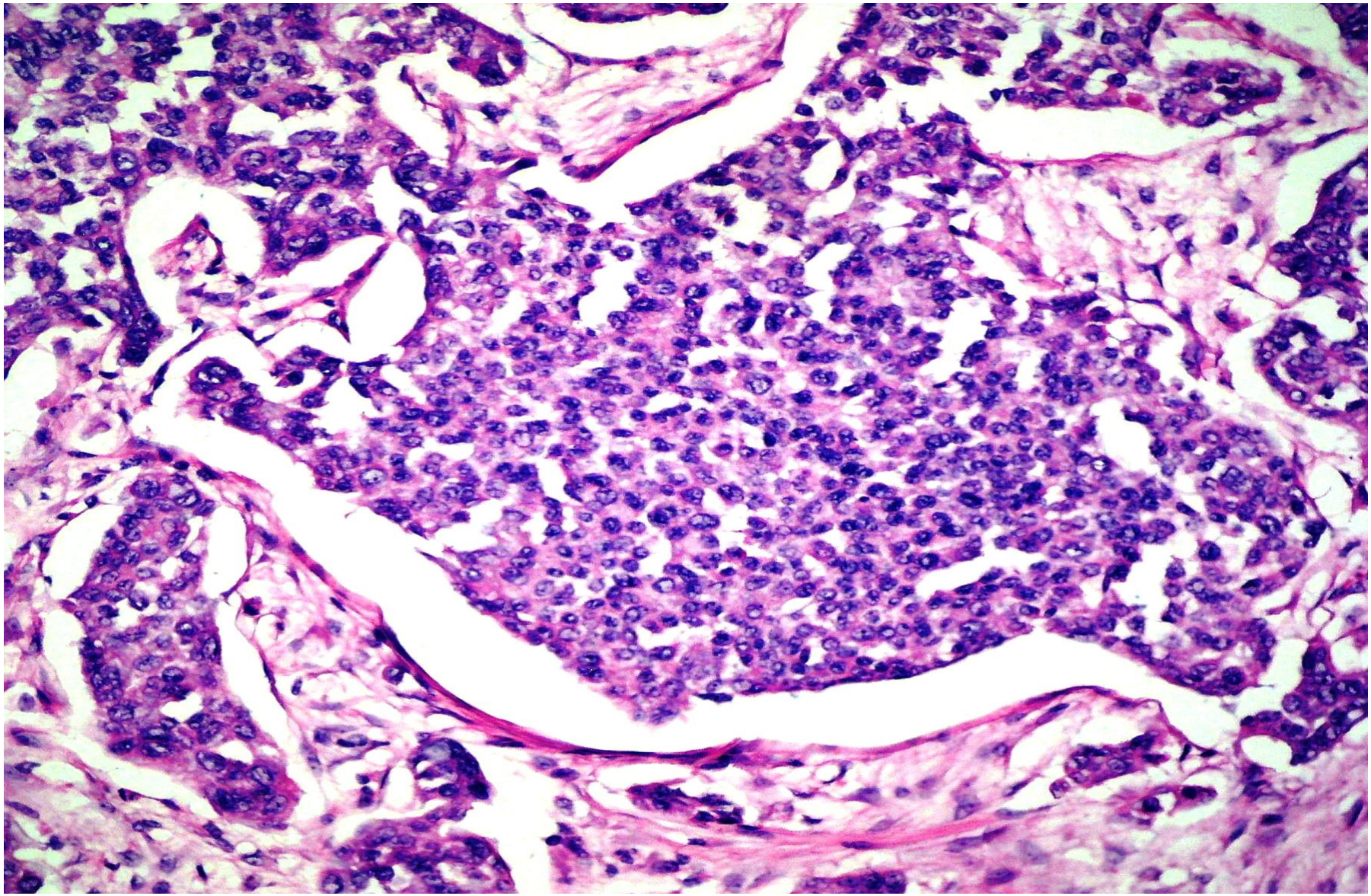
Mucinous carcinoma



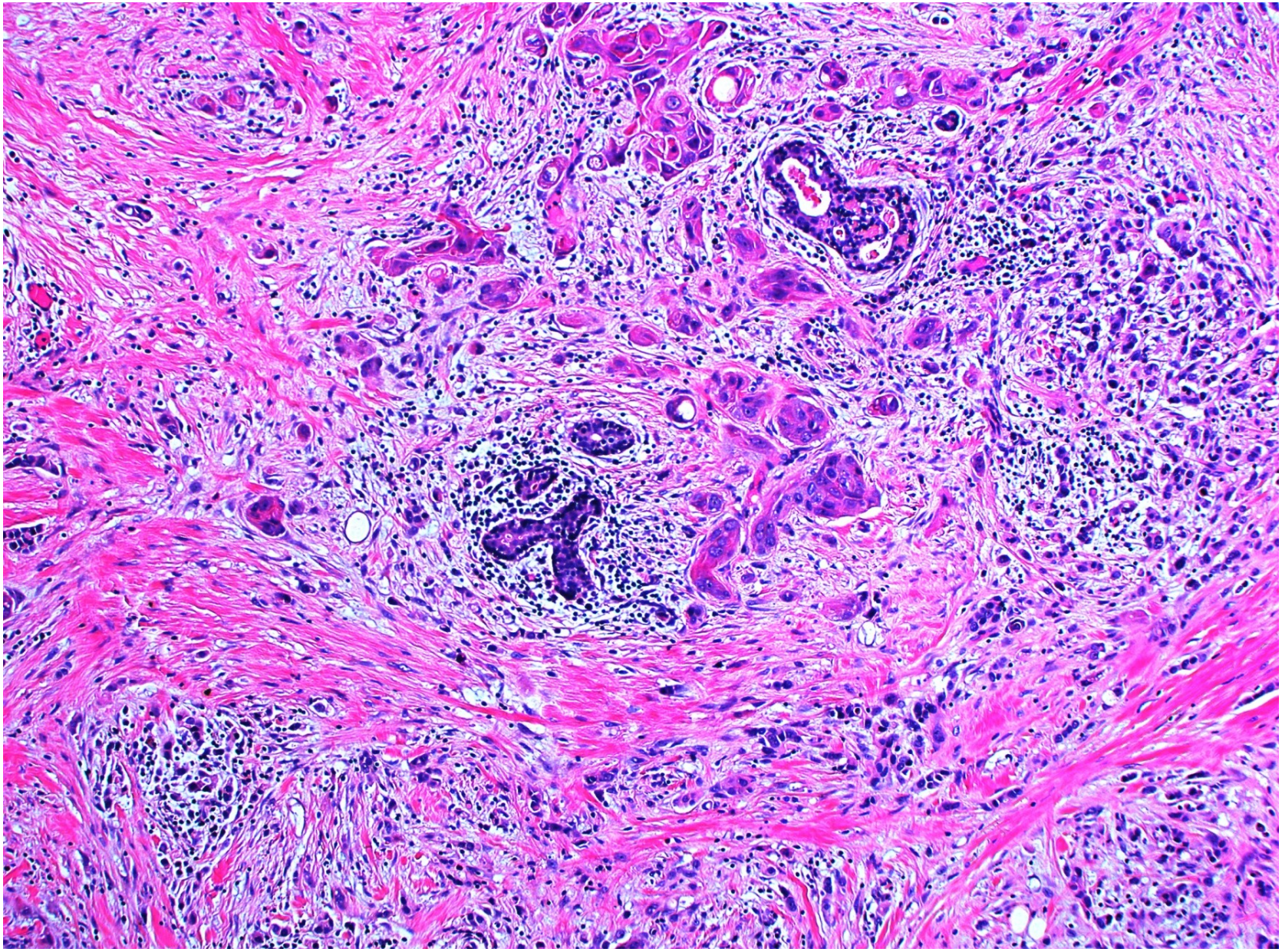
Medullary carcinoma

Papillary carcinoma (solid)

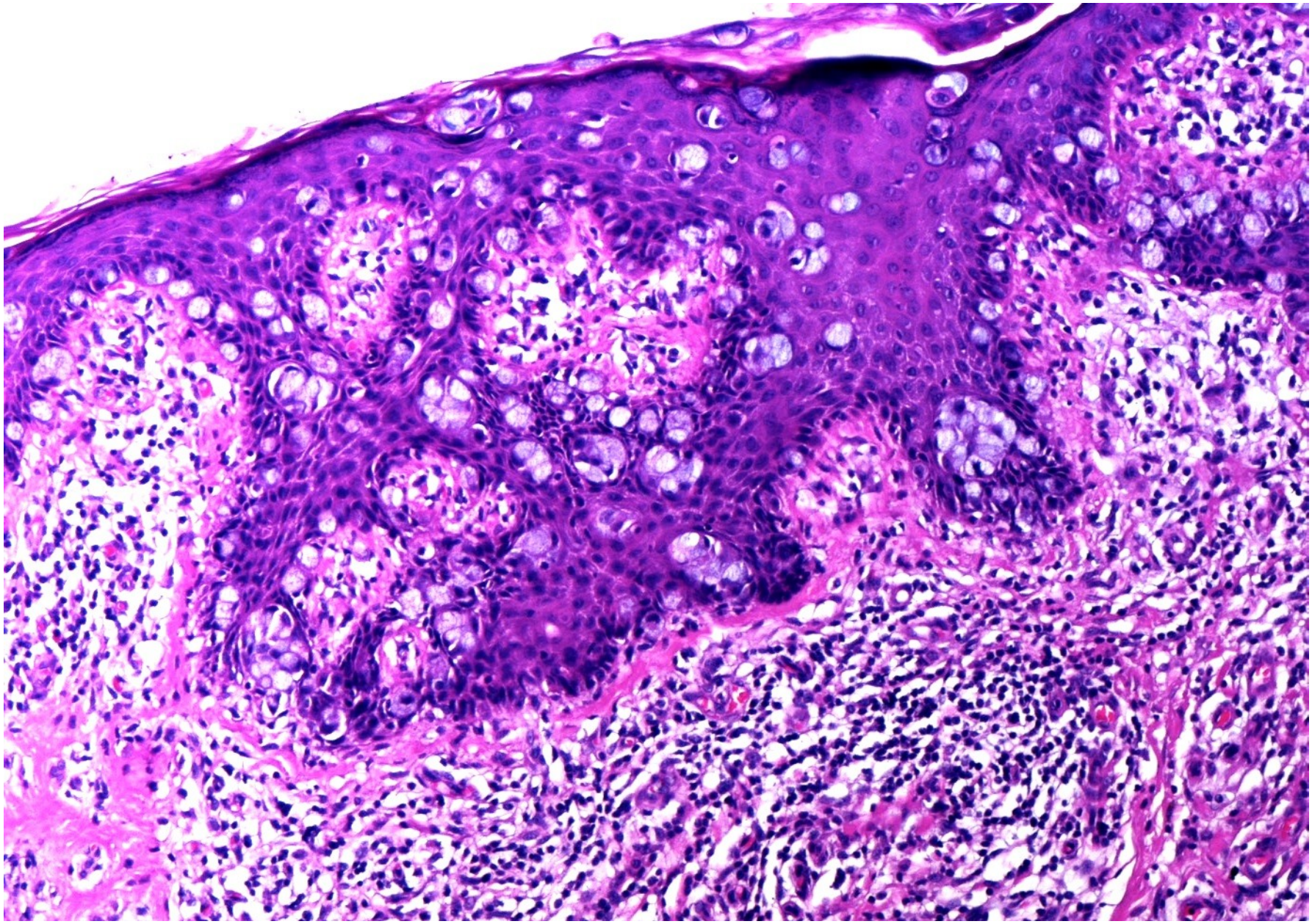




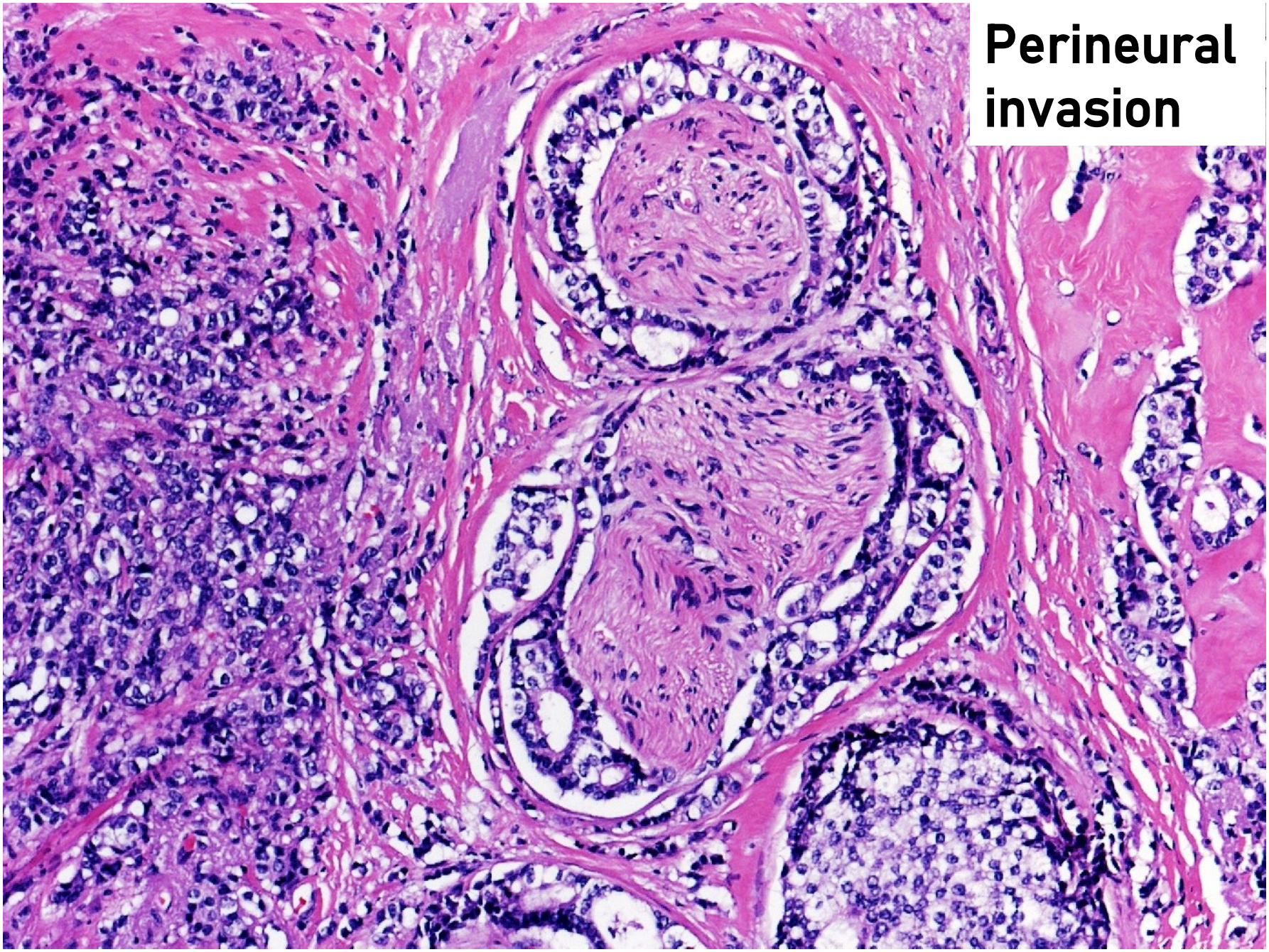
Micropapillary carcinoma

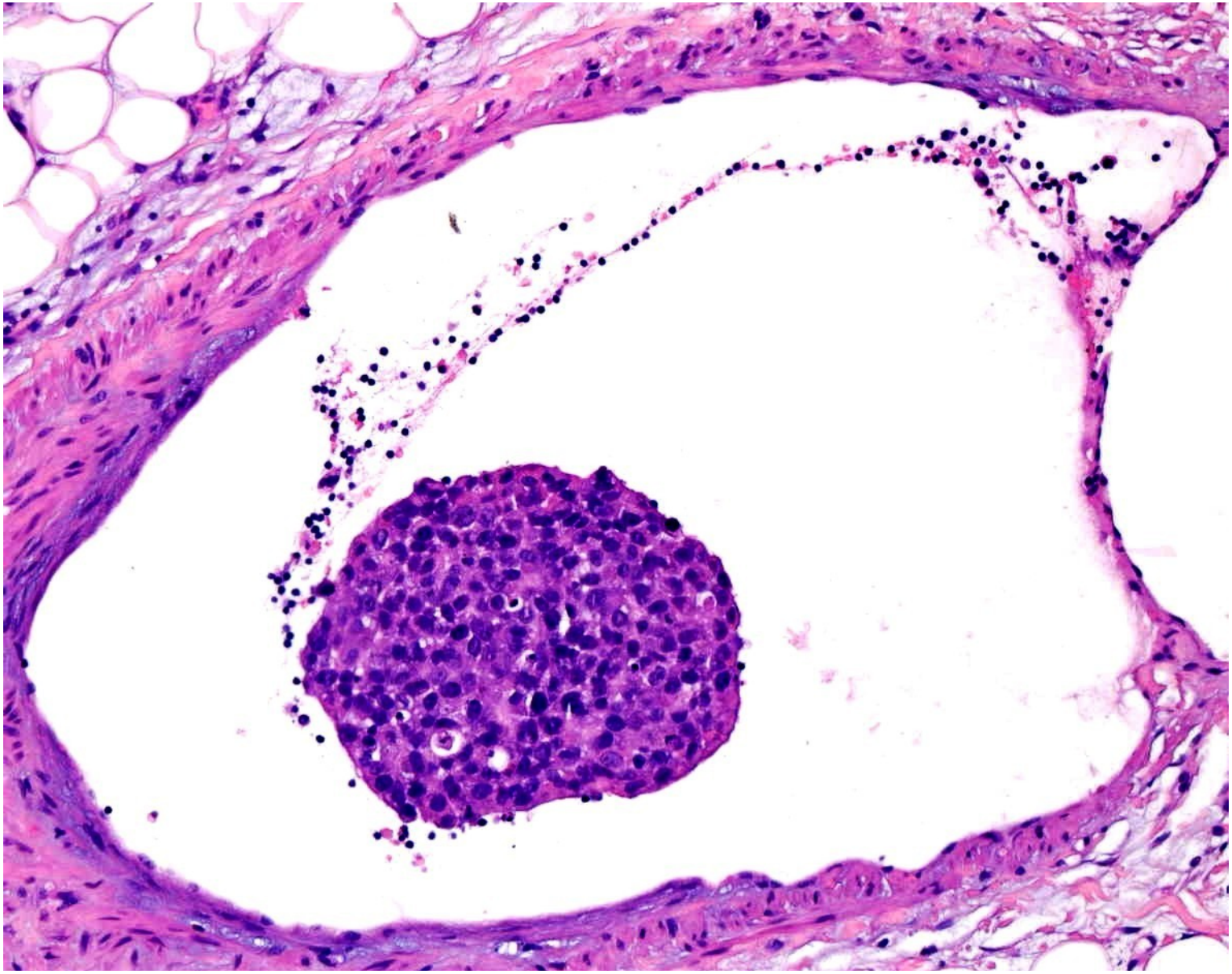


Metaplastic carcinoma



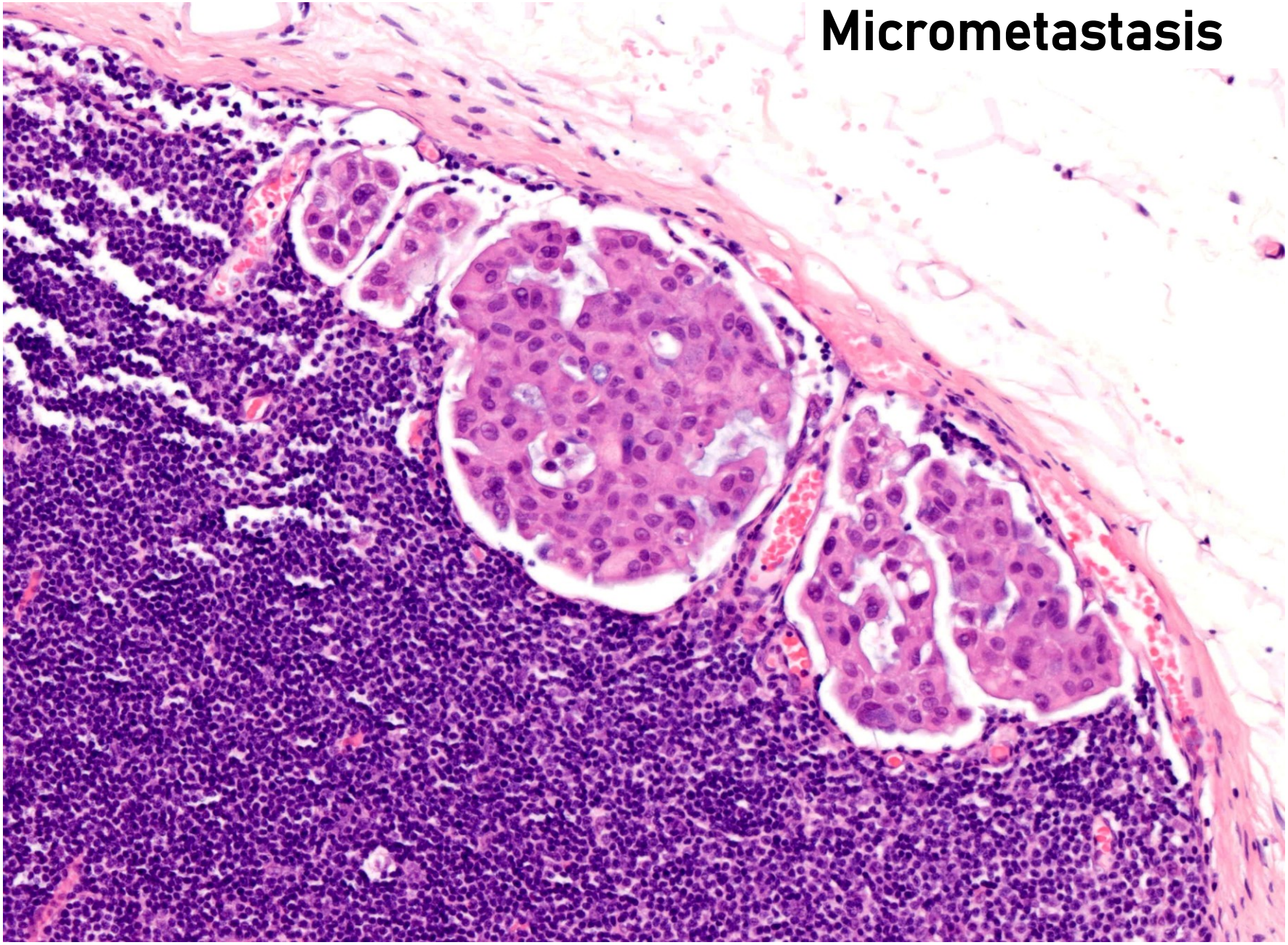
Paget's disease


Perineural
invasion



Lymphovascular space invasion (LVSI)

Micrometastasis



Breast cancer

Prognostic markers

Best guess in how the cancer will affect a patient

Predictive markers

Sensitivity or resistance to a specific treatment

Some markers (ER and HER-2) can have both prognostic and predictive utility

Prognostic markers in breast cancer

Patients with similar diagnostic and prognostic profiles can have markedly different clinical outcomes

Currently molecularly distinct diseases are grouped into clinical classes based mainly on morphology

Prognostic factors in breast cancer

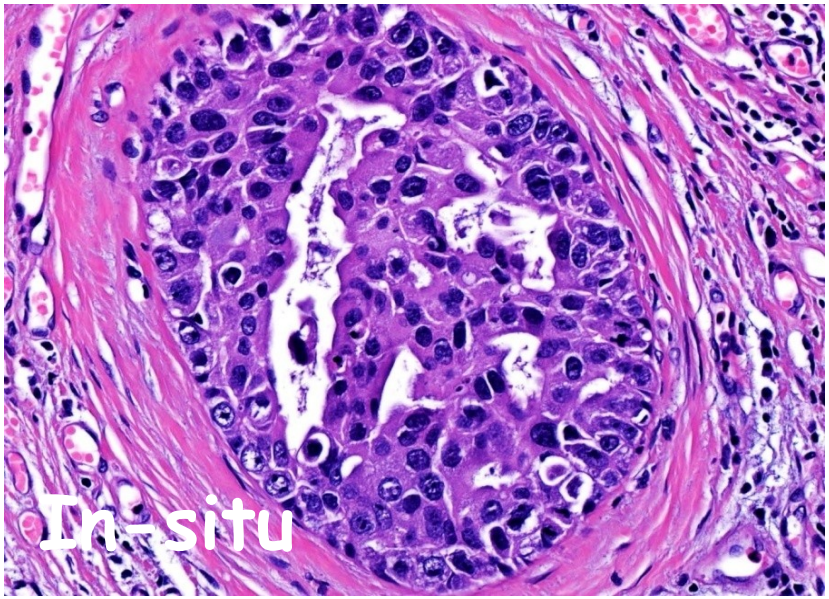
- Nodal status
- Size
- Grade
- Lymphovascular invasion
- Hormone receptor (ER/PR) status
- HER-2 status
- Age>35 years
- Others (Ki-67)

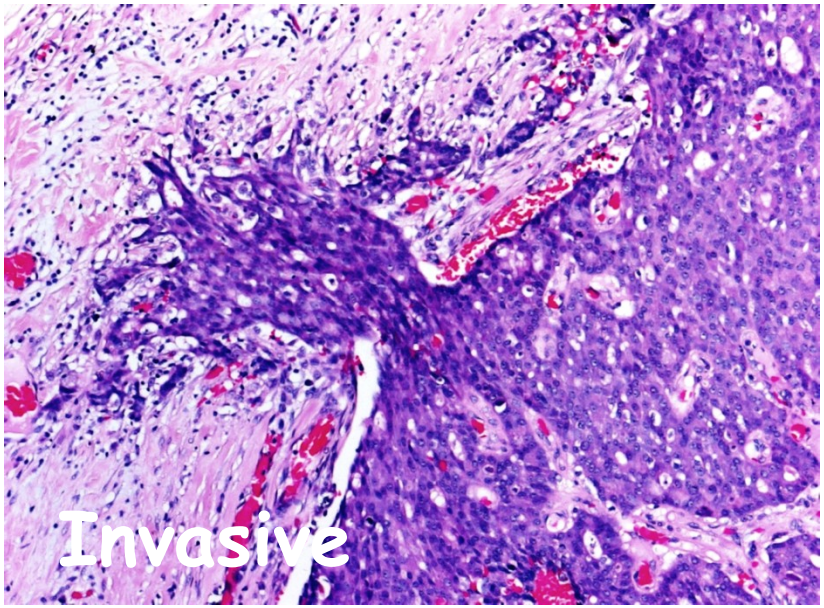
Major prognostic factors in breast carcinoma

In-situ vs. invasive

In situ cancer can not cause death but about one third of women with invasive carcinoma will succumb to the disease

Deaths associated with carcinoma in-situ are due to the **subsequent development of invasive carcinoma** or the **presence of an occult area of invasion**

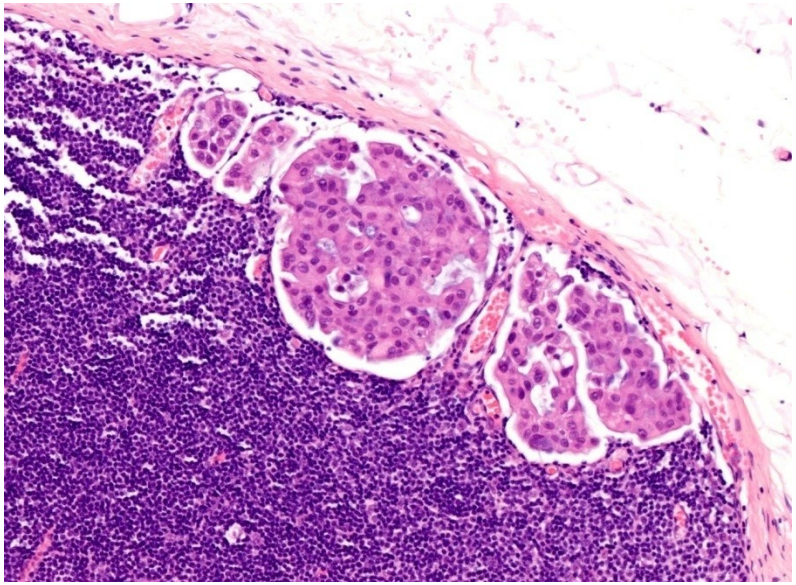




Lymph node metastases

In the absence of distant metastases, lymph node status is the **most important prognostic factor**

If nodes are of free of carcinoma, 10 years disease free survival rate is 75% but falls to **35% with 1 to 3 lymph nodes** and **10% with more than 10 positive lymph nodes**



Micrometastasis

Distant metastases

Once distant metastases are present, **cure is unlikely** (long-term remissions and palliation can be achieved)

Common sites of metastasis are **lungs, liver, adrenal, brain and meninges**

Fewer than 10% of women present with metastases to distant sites

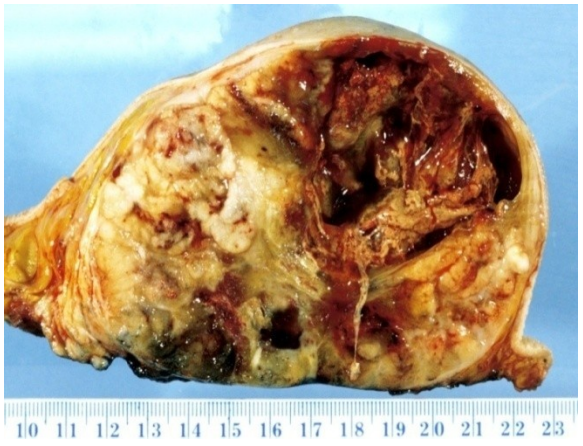
Tumour size

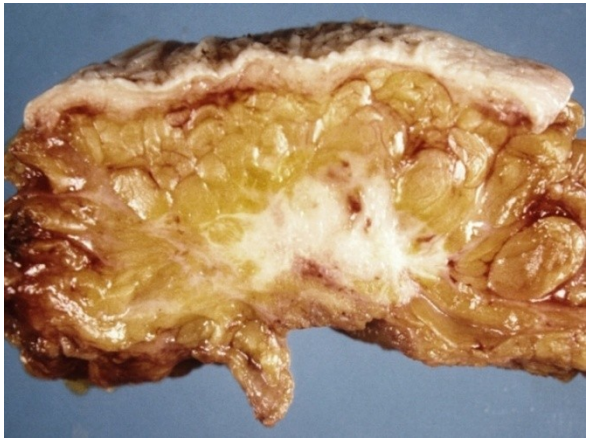
Likelihood of metastasis increases with tumour size

Size is also an **independent prognostic factor**

Women with node negative carcinoma <10mm have a survival rate similar to woman without breast cancer

Women with cancer >20mm are likely to have lymph node metastasis and majority will die of the disease

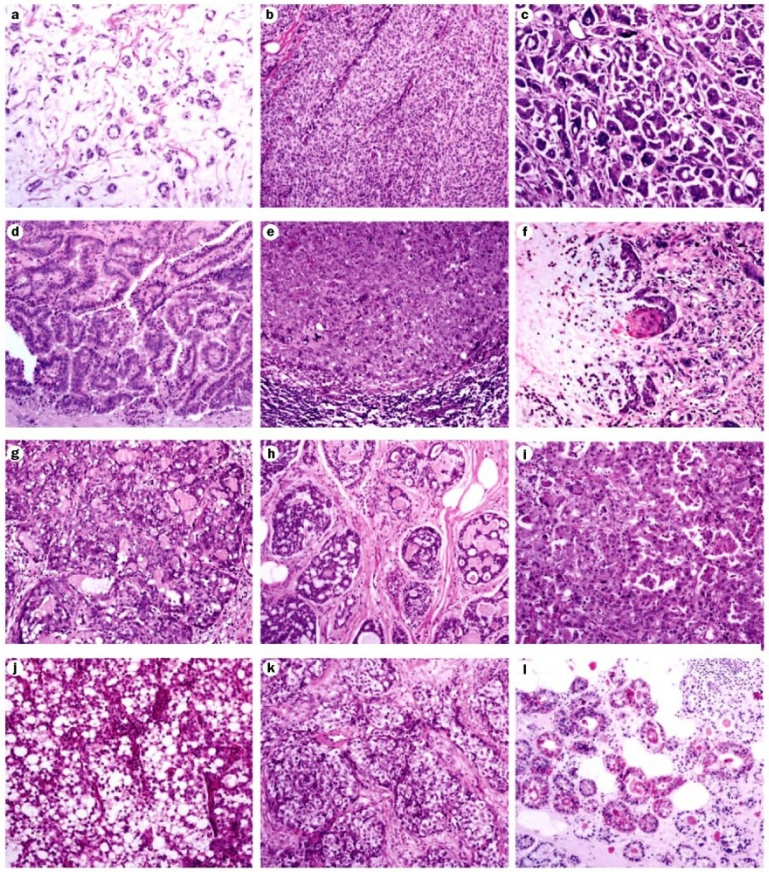




Minor prognostic factors in breast carcinoma

Histological subtype

With the exception of metaplastic carcinoma, which has a poor outcome, carcinomas classified as a **special type** of breast carcinoma have a better prognosis than those of **no special type**



Tumour grade

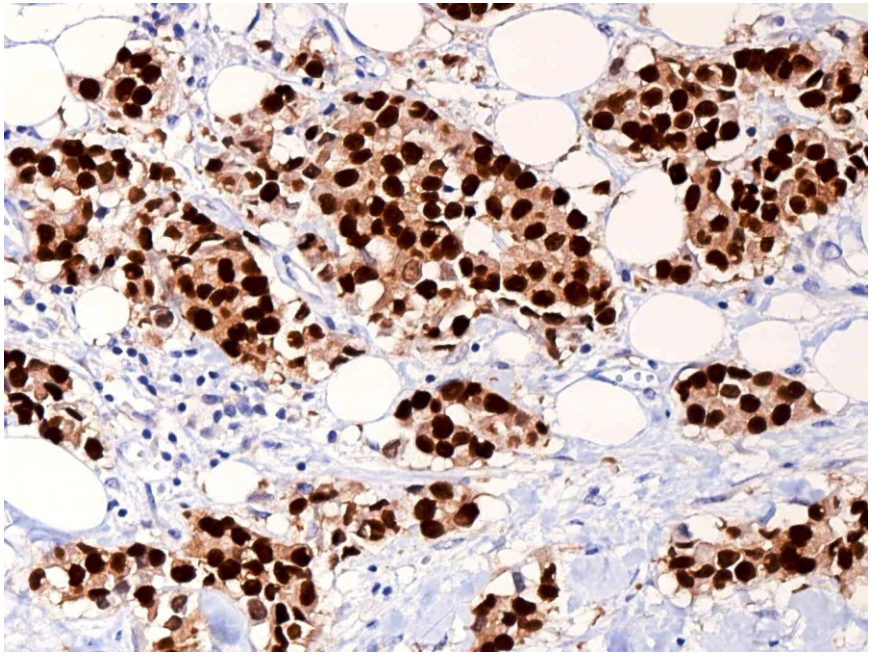
Assessment of **tubular formation, nuclear pleomorphism and mitotic rate** divides carcinomas into 3 grades

Grade 1 carcinomas have the best prognosis whereas **grade 3** cancers have the worst outcome

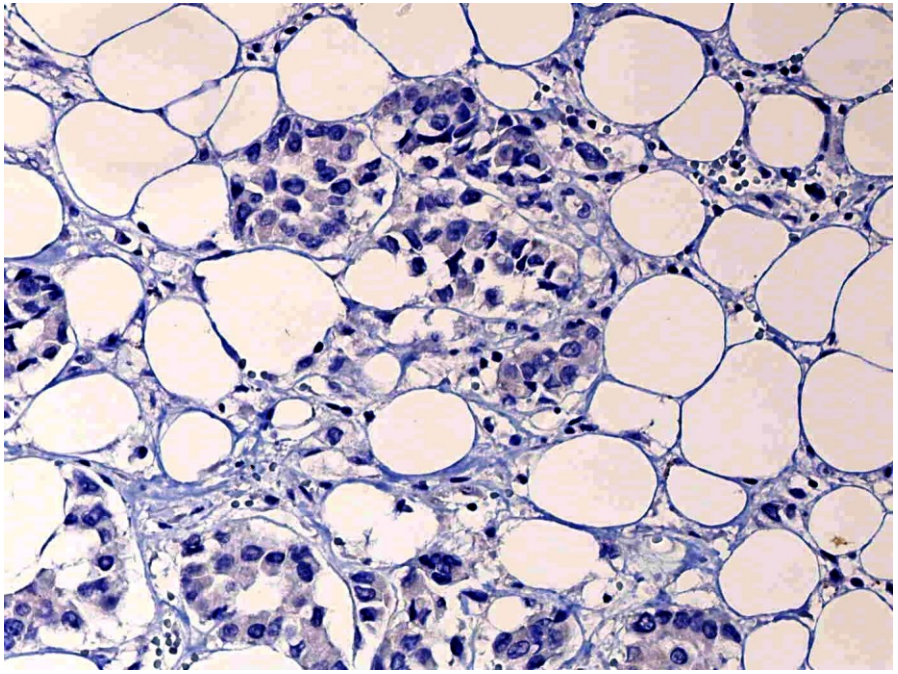
Oestrogen and progesterone receptors

Receptor positive tumours have better prognosis than receptor negative tumours

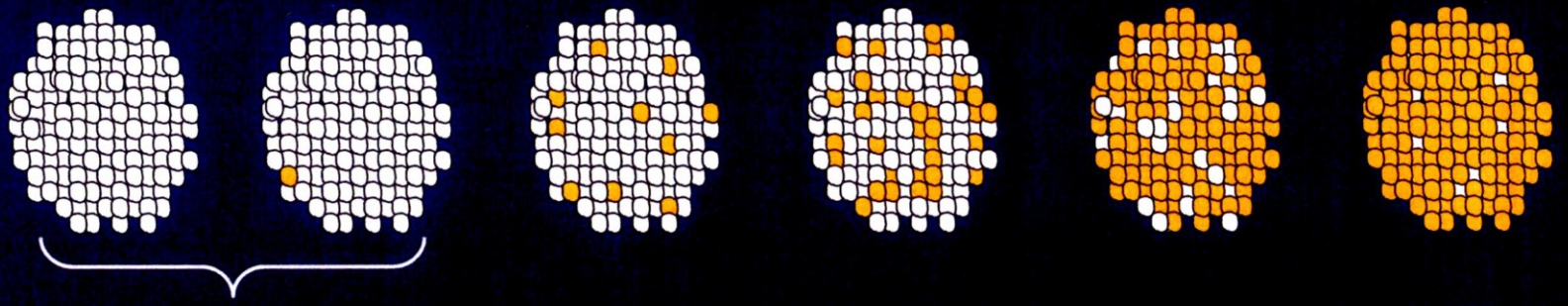
Presence of hormone receptors predicts the likelihood of response to hormone-based therapies



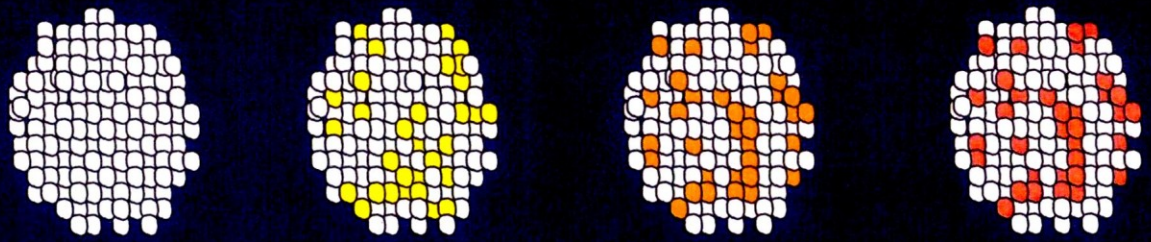
Receptor Status
Oestrogen



Allred Immunohistochemistry Score



Proportion score (0–1 → 1/100) — (2 → 1/10) — (3 → 1/3) — (4 → 2/3) — (5 → 1)



Intensity score 0 = negative 1 = weak 2 = intermediate 3 = strong

Total score = proportion score + intensity score (range 0, 2–8)

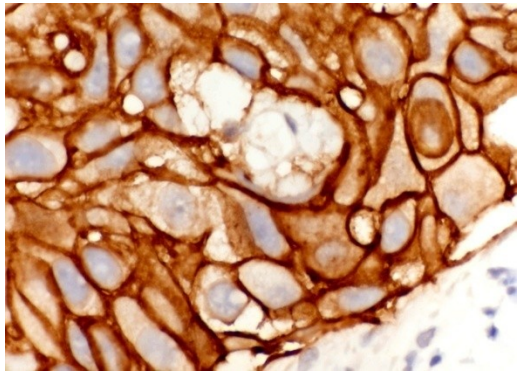
HER-2 Oncogene

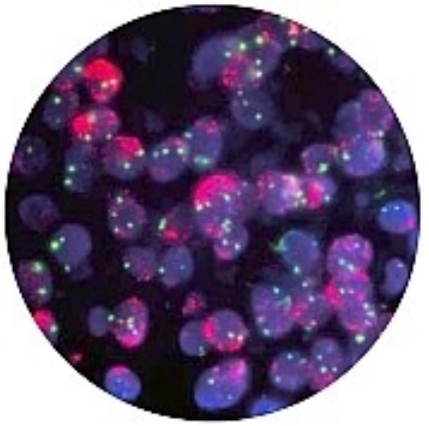
Overexpressed in 25% of breast carcinomas and in general suggests a worse prognosis

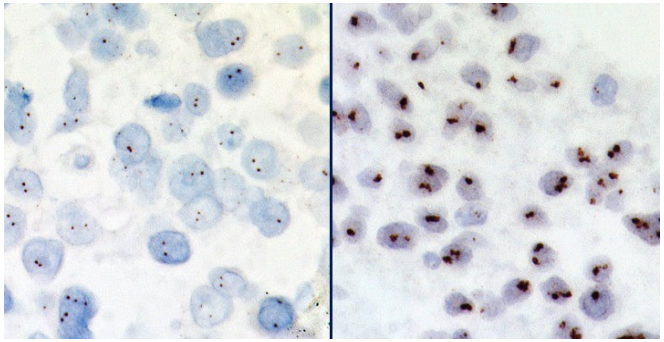
Overexpression is due to amplification of the gene on chromosome 17q21 in >90%

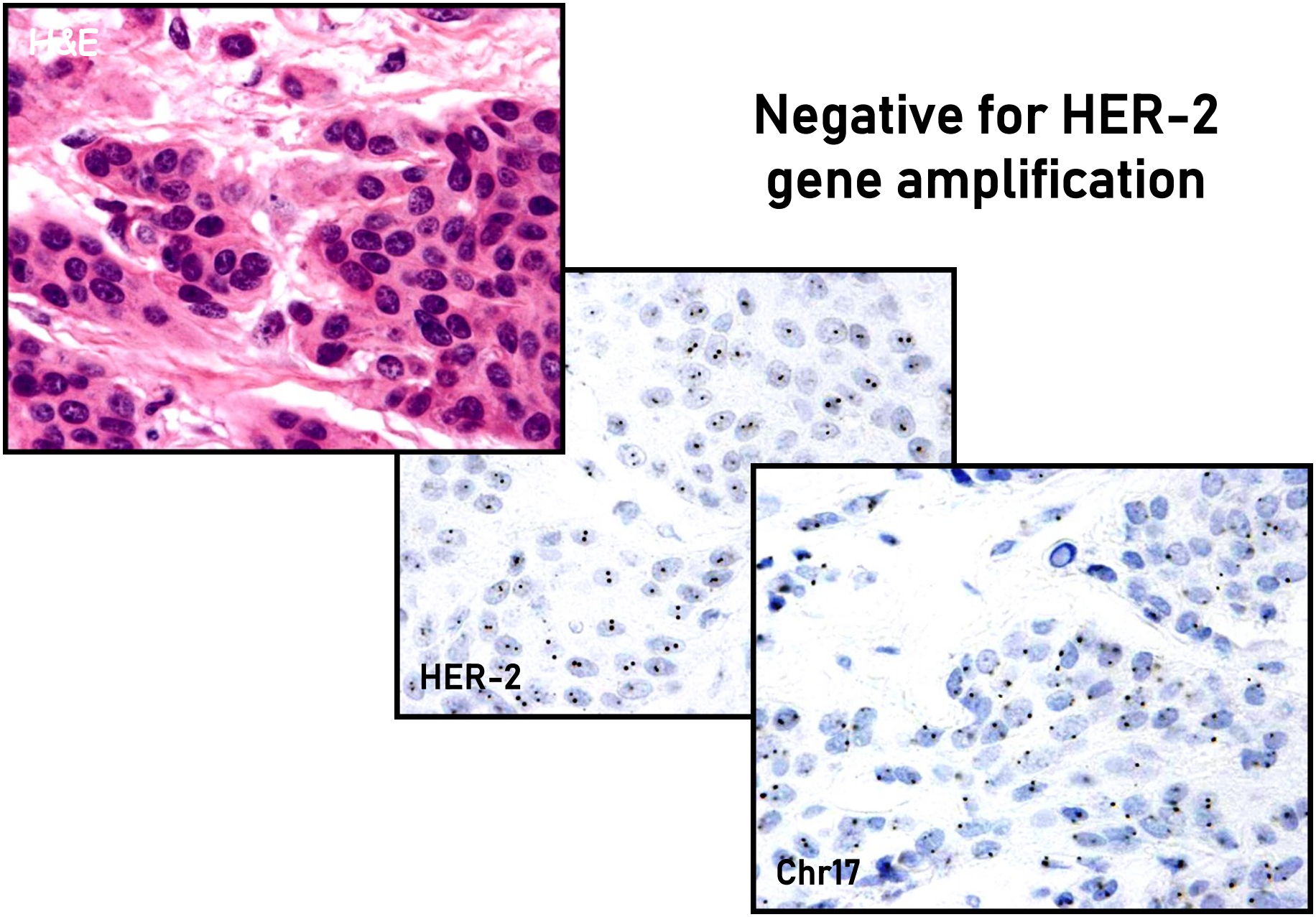
Expression can be detected IHC (protein) or by ISH (gene copy) in order to predict response to Herceptin

HER-2 status can be assessed by IHC or ISH
Fluorescent dye (FISH)
Chromogen (CISH)



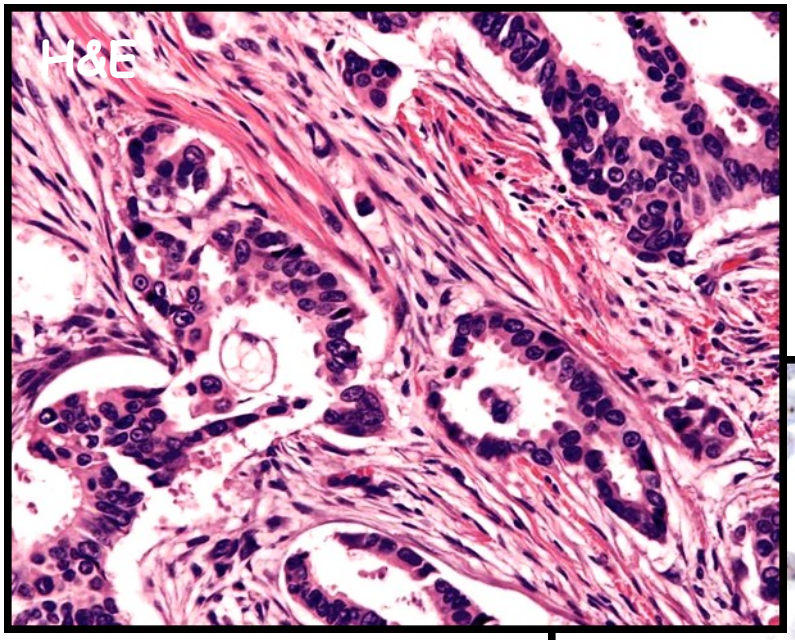


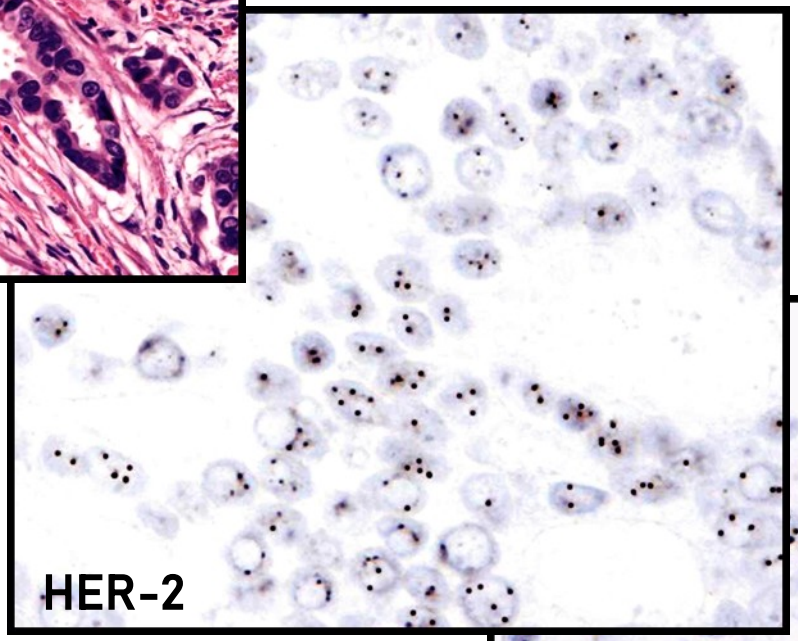


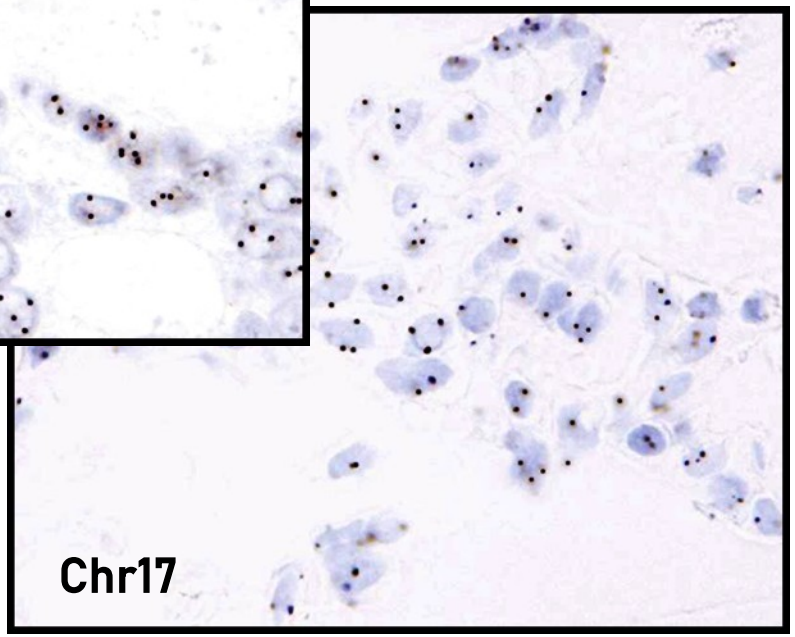


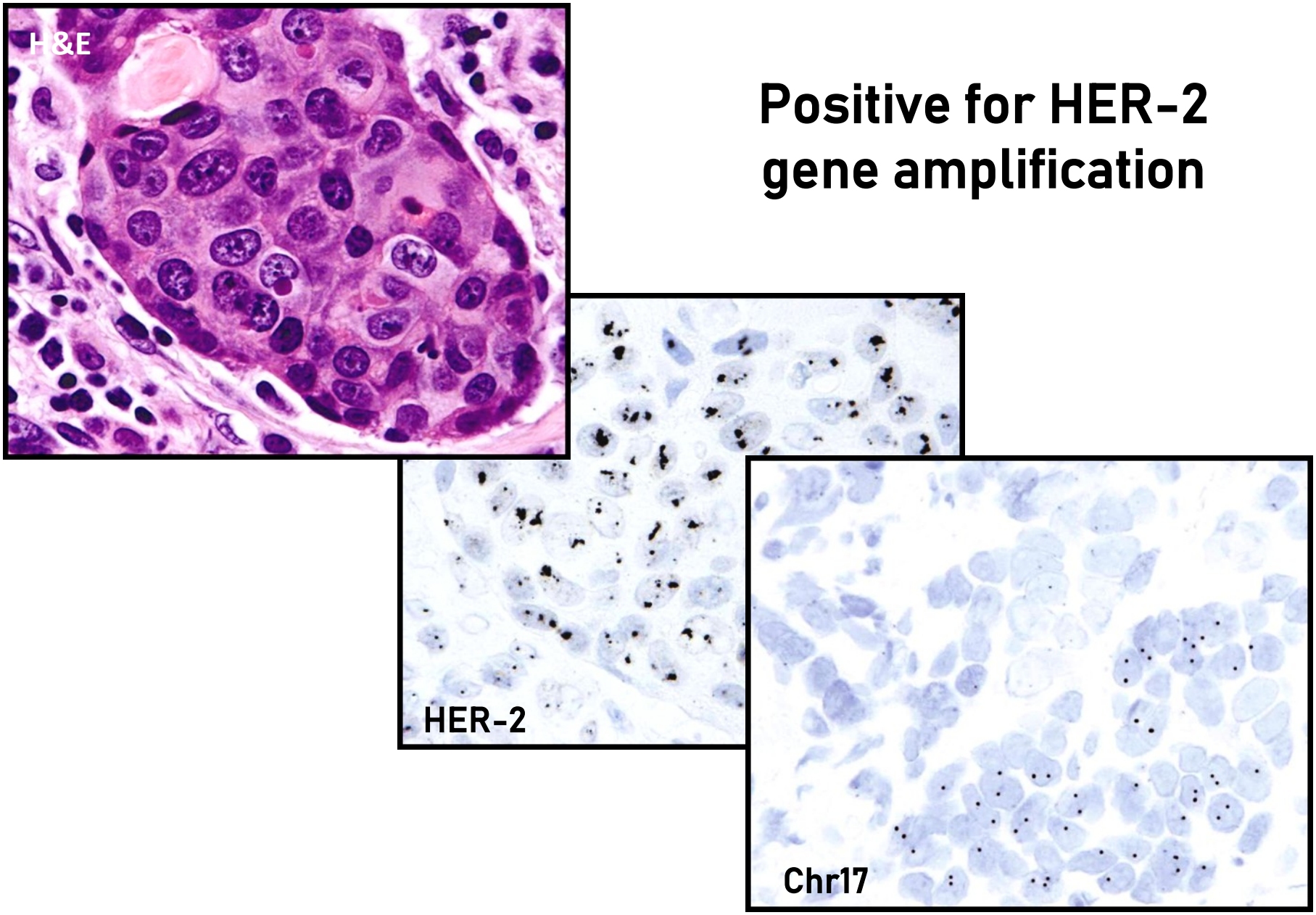
Negative for HER-2 gene amplification

Equivocal for HER-2 gene amplification



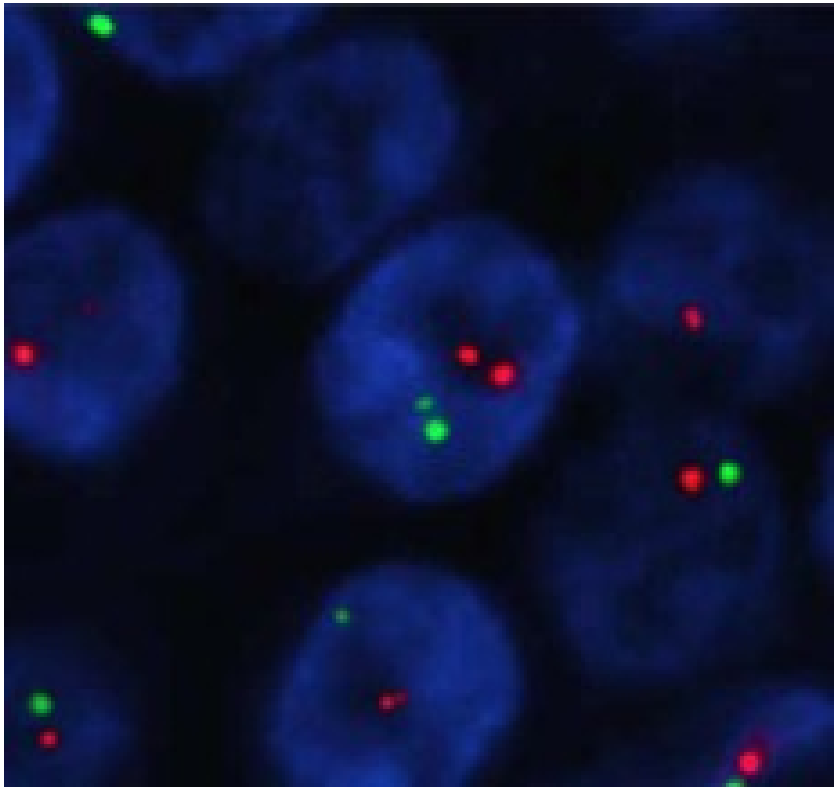


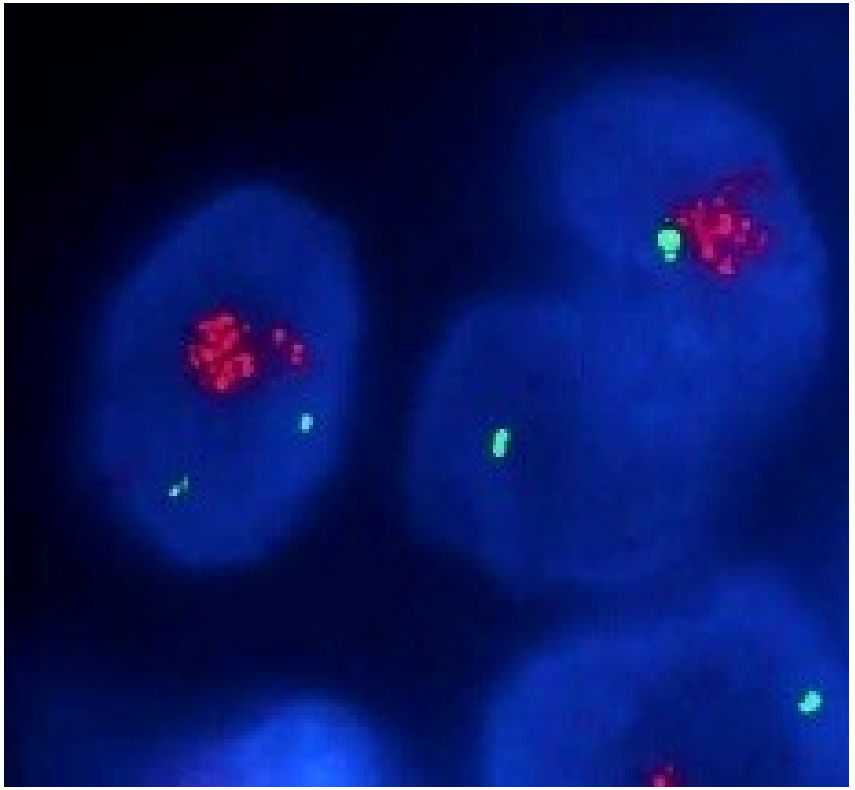




Positive for HER-2 gene amplification

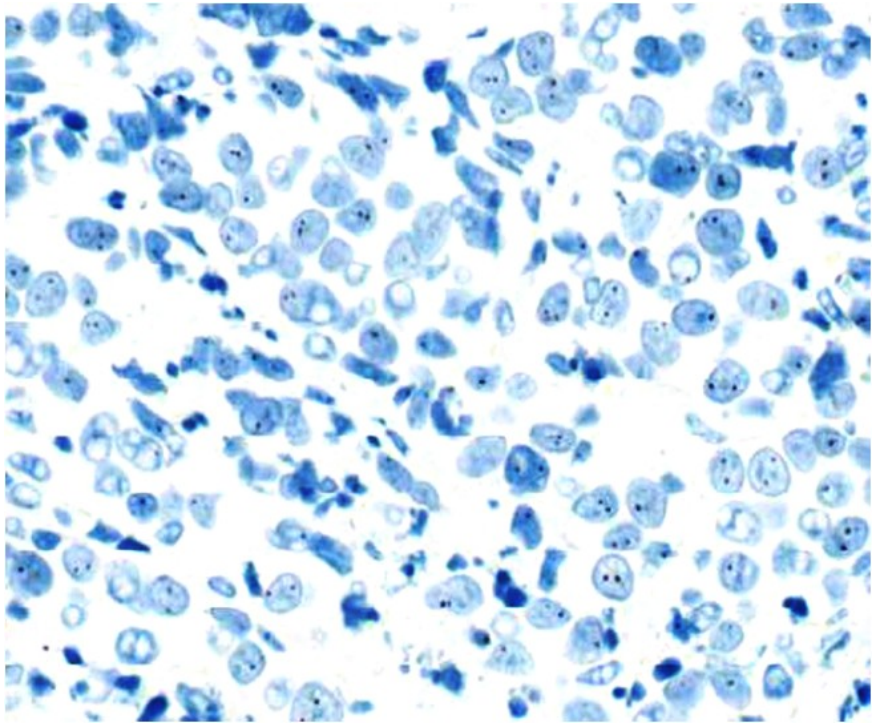
FISH for Her-2/Chr 17
Her-2 = Red Chromosome 17 = Green



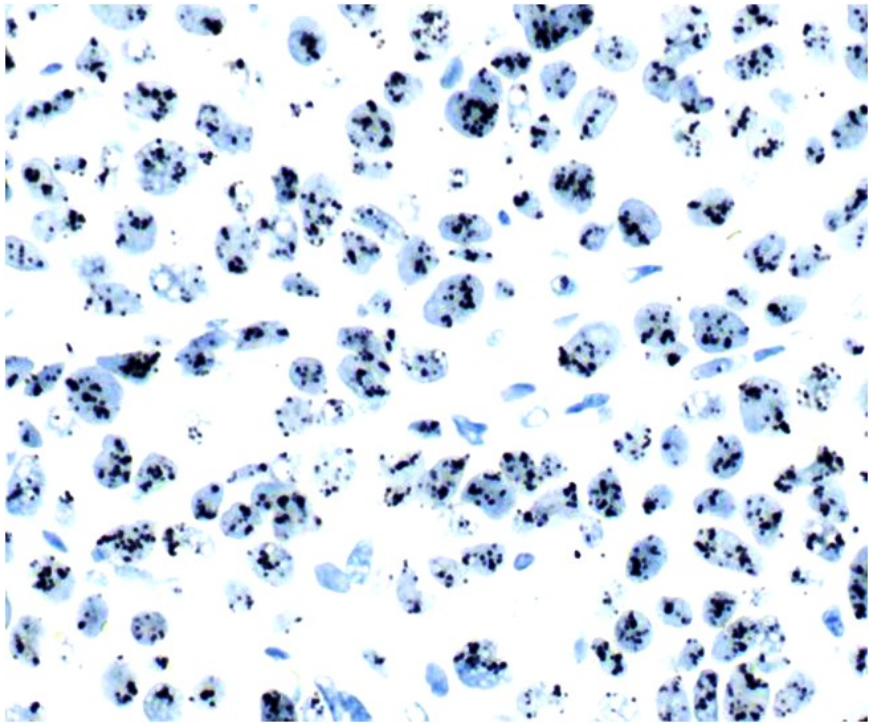


HER-2 silver in-situ hybridisation

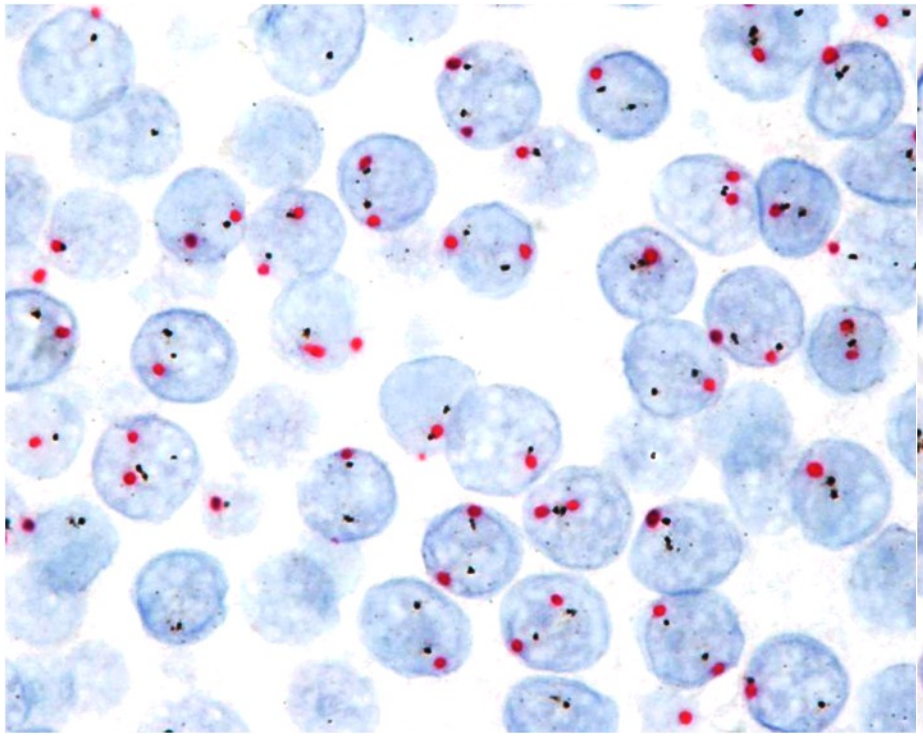
Non-amplified



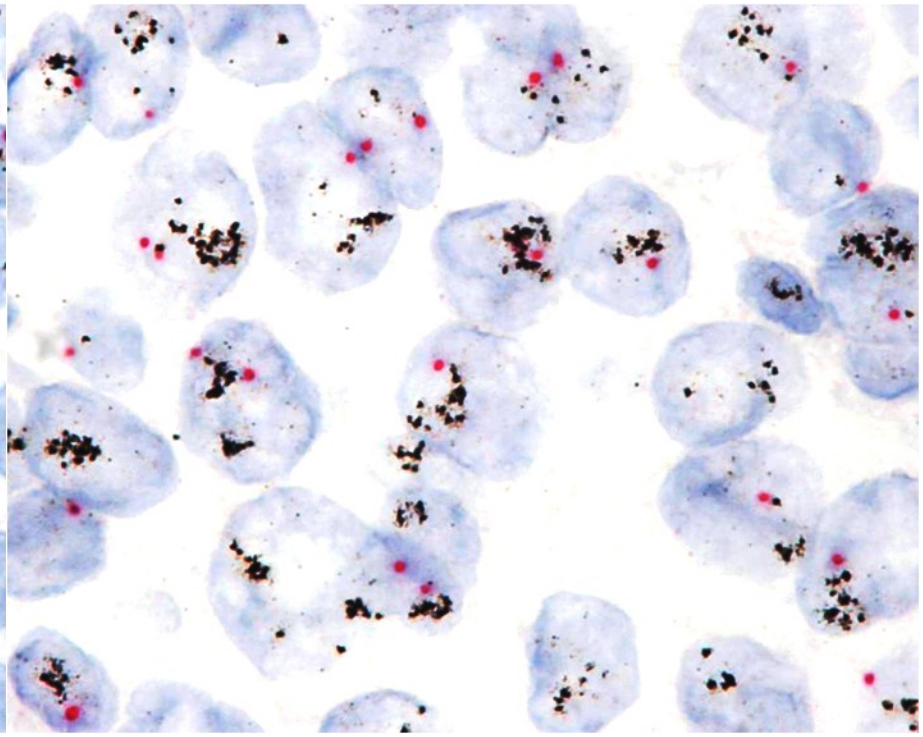
Amplified



In-situ hybridisation



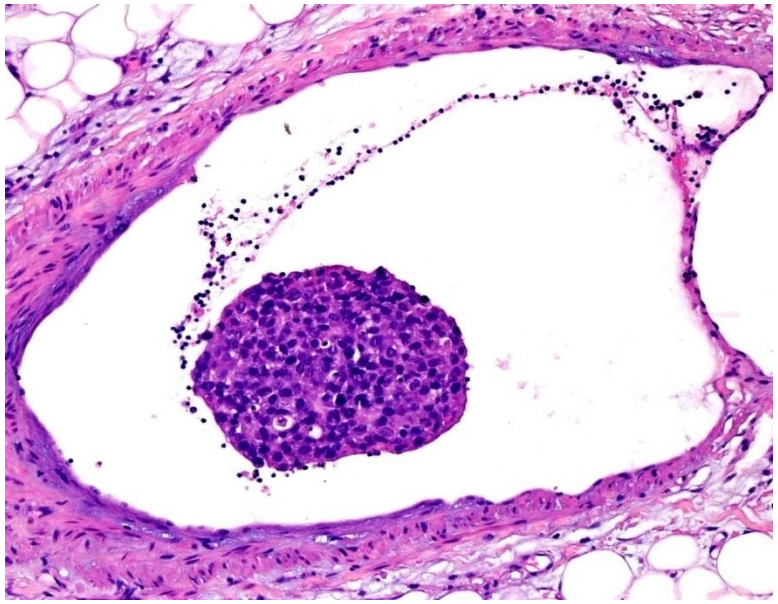
HER-2 non-amplified



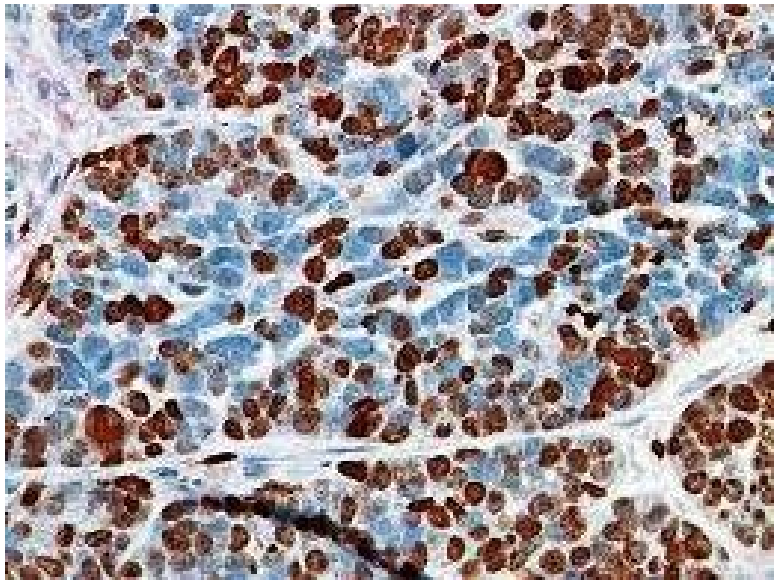
HER-2 amplified

HER-2 Chr17

Lymphovascular space invasion (LVSI)
Tumour cells in lymphatics is a poor prognostic factor in women without lymph node metastases



Proliferative rate
A high proliferative rate (>14%) is a poor prognostic factor (proliferation can be measured by a variety of methods)



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