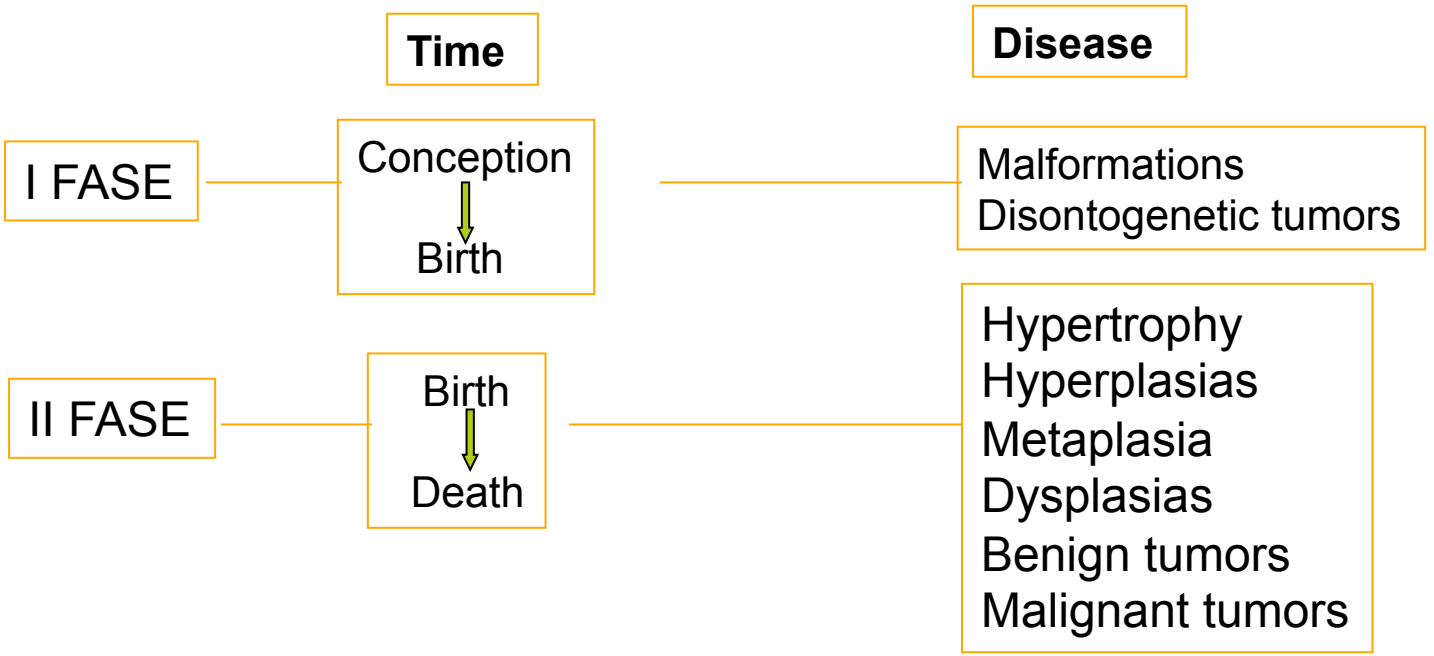
PATHOLOGY OF CELL PROLIFERATION

Alterations of cellular processes in response to damage

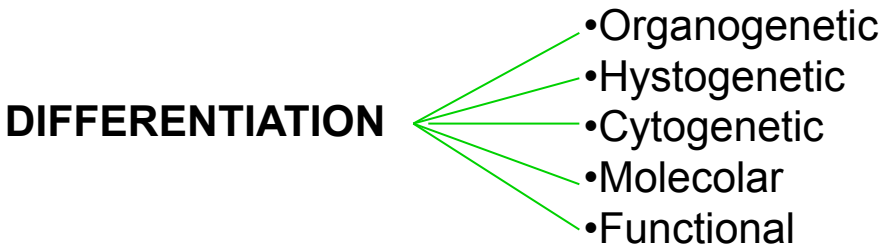
- CELL PROLIFERATION
- CELL DIFFERENTIATION

PATHOLOGICAL GROWTH=
growth deviated from its normal progression

Phases and disease of growth



DIFFERENTIATION:
Process transforming undifferentiated cells into specialized cells



DIFFERENTIATION

Different steps of differentiation occur during ontogenesis, which involve changes in shape, size and spatial organization of cells in different tissues, until their final appearance that can be observed in mature tissues

Progressive restriction of differentiation abilities with increasing maturation of cells

TOTIPOTENT CELLS (morula)
(All equal to each other)

FIRST STEP OF DIFFERENTIATION: MULTIPOTENT CELLS (epiblast)
Ectoderm, Mesoderm, Endoderm = “Determined cells”

SECOND STEP OF DIFFERENTIATION
(Pluripotent cells or stem cells)

THIRD STEP OF DIFFERENTIATION: UNIPOTENT DIFFERENTIATED CELLS
Cells consitituting organs.

Multipotent/unipotent adult stem cells

Intestinal stem cells:

Absorptive epithelial cells

Globet cells

Paneth cells

Entero-endocrine cells

Bone stem cells:

Osteocyte

Chondrocytes

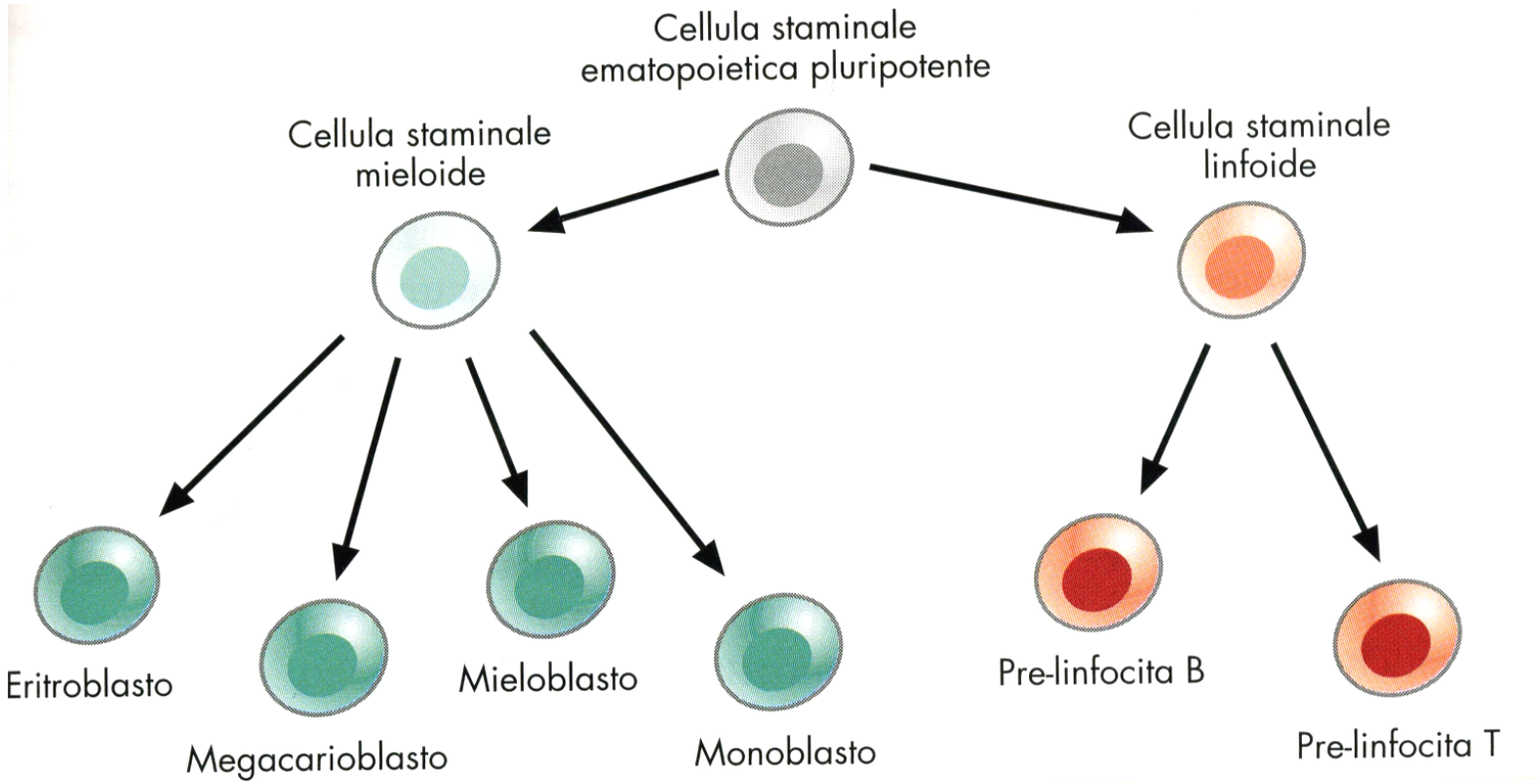
Adipocytes, tendon cells

Neural stem cells:

Neurons

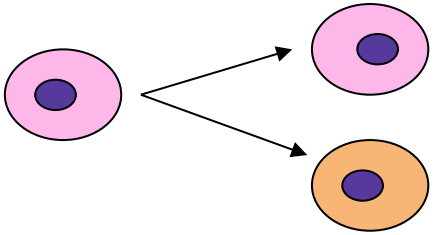
Astrocytes

Oligodendrocytes


Cellula staminale
ematopoietica pluripotente
Cellula staminale
mieloide
Cellula staminale
linfoide
Eritroblasto
Megacarioblasto
Mieloblasto
Monoblasto
Pre-linfocita B
Pre-linfocita T

CELLULAR PROLIFERATION AND DIFFERENTIATION

Stem cell



Stem cell

Differentiated cell

Omeostasis (stationary state): # differentiated cells = # destroyed cells

Differentiated cells

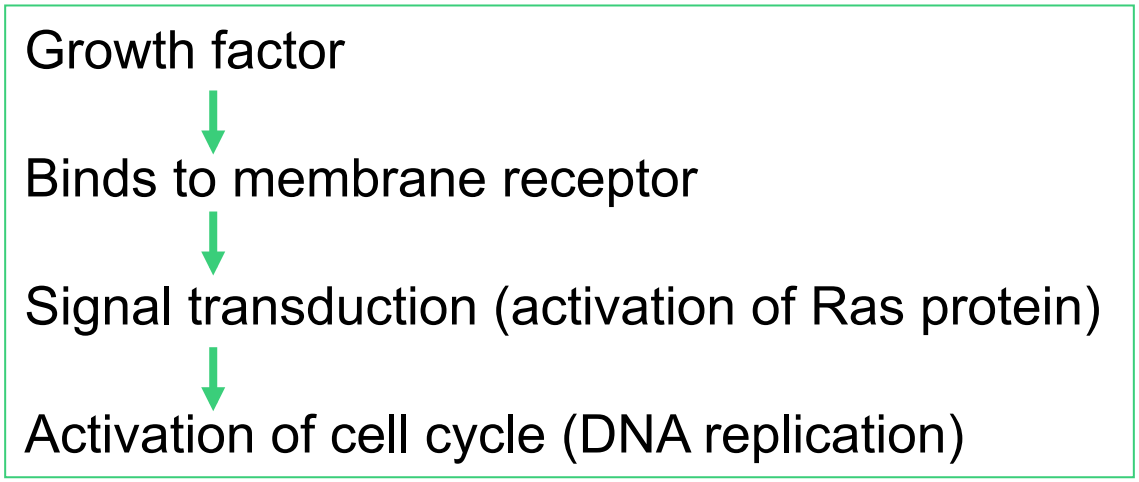
- Inability of replication (*neurons)*
- Replicate remaining the same (*liver, kidney*)
- Replicate and differentiate (*lymphocytes, epidermis ecc.)*

Factors stimulating cell proliferation and differentiation

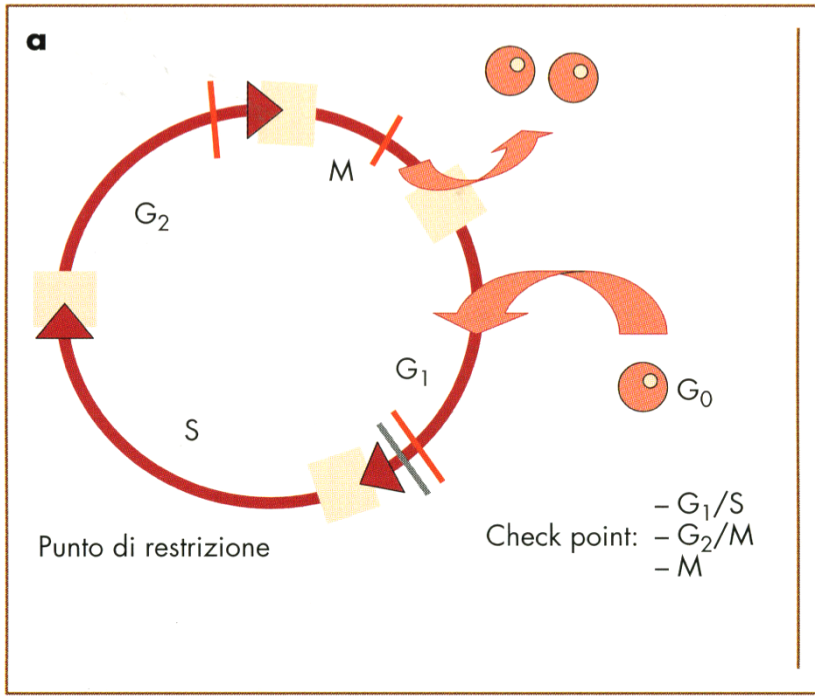
- Erythropoietin
- Leukopoietin
- Growth factors (EGF; PDGF, FGF, etc)
- Hormones

GROWTH FACTORS

Cell proliferation occurs by stimulations coming from outside (external microenvironment) or from inside the cell (internal microenvironment)



CELL CYCLE



CONTROL OF CELL PROLIFERATION

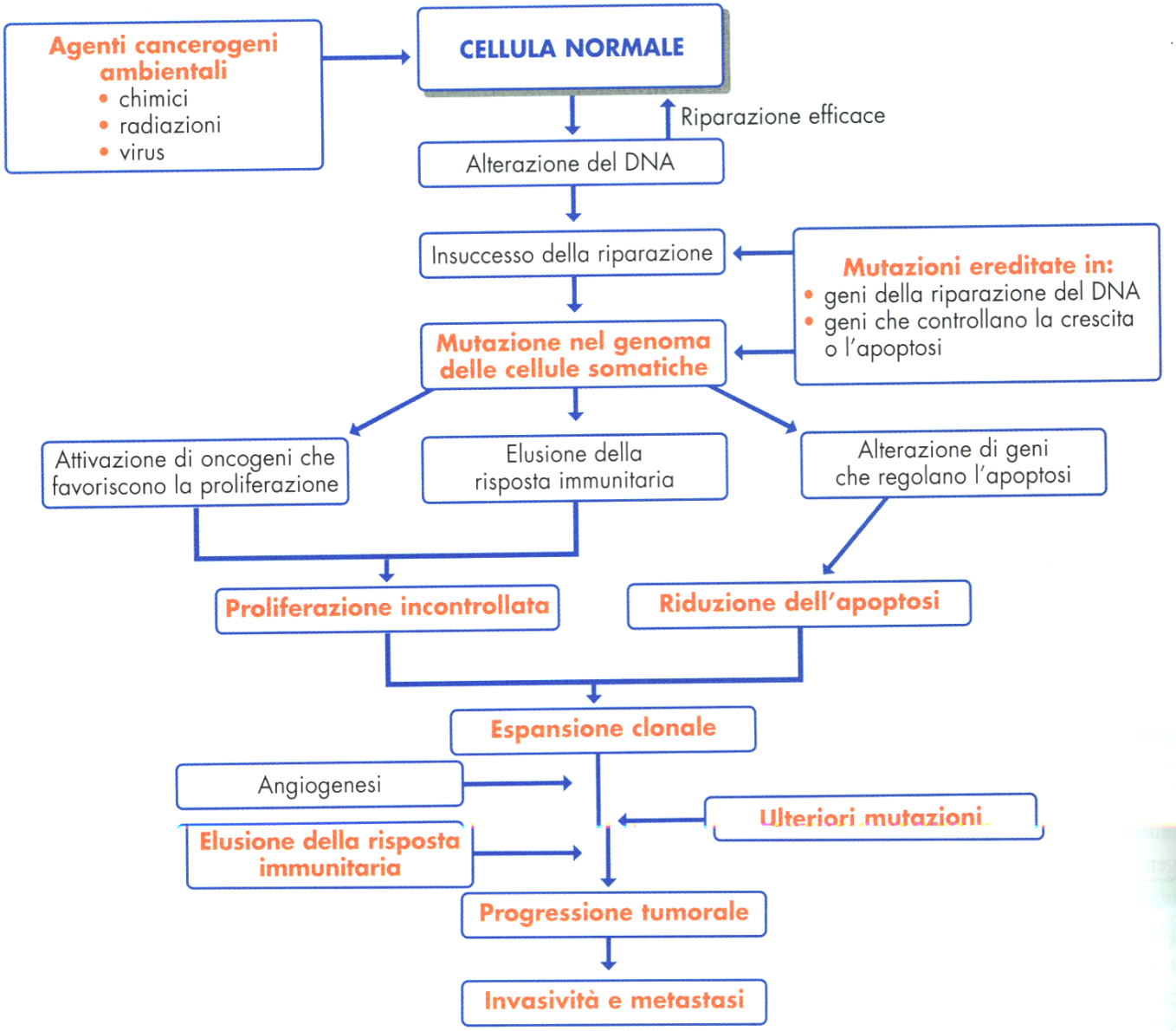
- ONCOGENES = stimulate cell proliferation
- TUMOR SUPPRESSOR GENES = inhibit cell proliferation
- DNA REPAIR GENES = restore normal nucleotide sequence
- APOPTOTIC GENES = promote cell death

EXCESSIVE CELLULAR PROLIFERATION= HYPERPLASIA

HYPERPLASIA: increase in volume of an organ or tissue due to numerical increase of cells → labile and stable tissue

CLINICAL IMPLICATIONS	Increased risk of DNA damage with development of tumors due to increased number of mitosis

Tappe del processo di trasformazione neoplastica



DIFFERENTIATION

ORGANOGENETIC DIFFERENTIATION

Process of integration and spatial arrangement of different cellular elements that lead organ formation

CYTOGENETIC MOLECULAR DIFFERENTIATION

- Production of particular enzymes, proteins ecc.
- Presence of antigenic structures
- Mebrane structures (cellular cohesion)

Schema formazione ghiandola

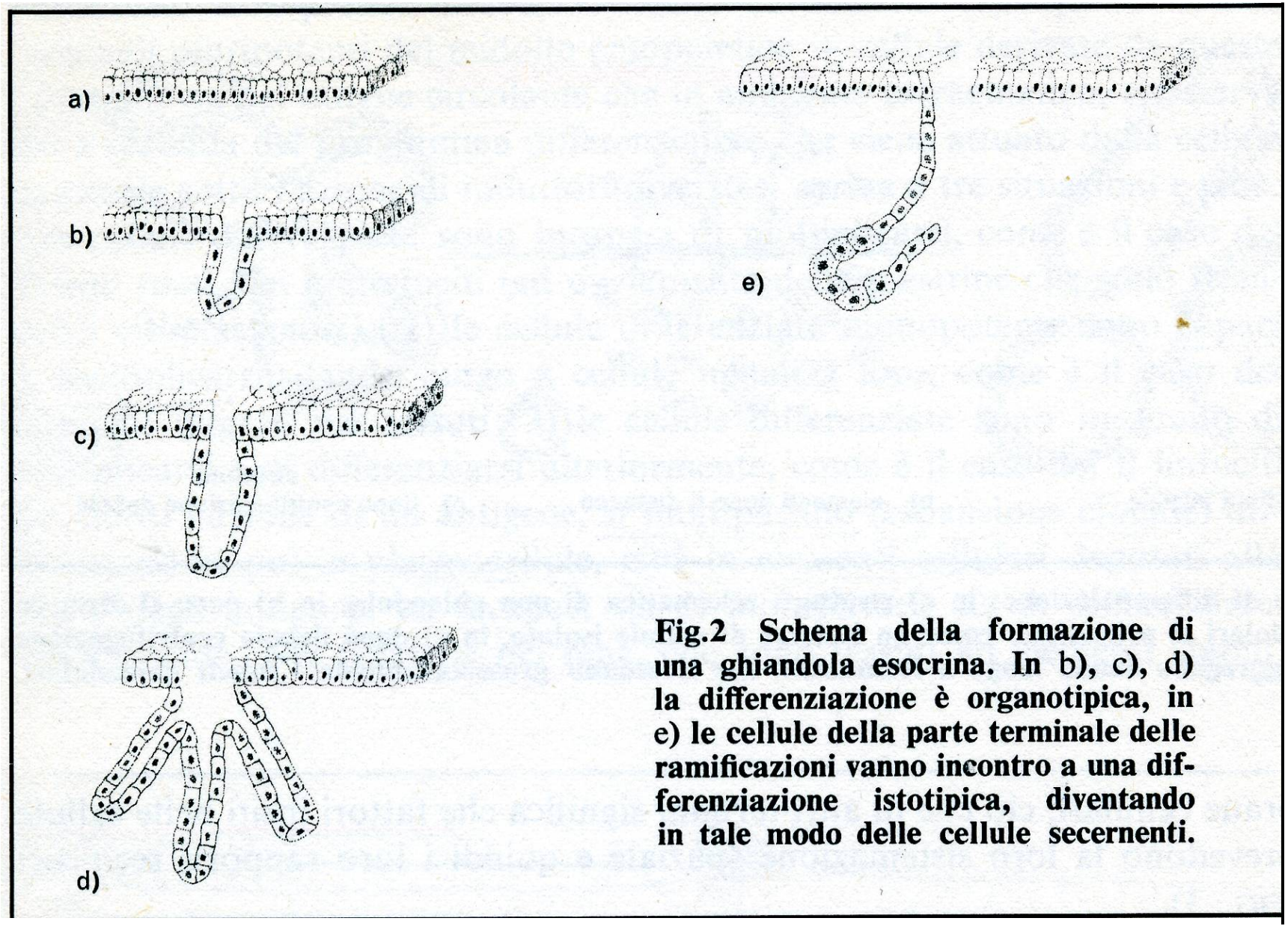
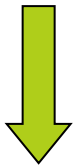


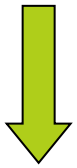
Fig.2 Schema della formazione di una ghiandola esocrina. In b), c), d) la differenziazione è organotipica, in e) le cellule della parte terminale delle ramificazioni vanno incontro a una differenziazione istotipica, diventando in tale modo delle cellule secernenti.

Differentiation is releted to distinct genetic assets and specific factors produced by the cell itself

Cells are no longer able to keep specific shapes and to assolve their peculiar functions, due to genetic alterations or lack of production of peculiar substances



LOSS OF DIFFERENTIATION CAPABILITIES



DYSPLASIA

NEOPLASTIC GROWTH:
Results from altered proliferation and differentiation

HYPERPLASIA

ATYPICAL HYPERPLASIA (DYSPLASIA)

CANCER

DYSPLASIA (literally = *altered development*)

Disorder of cell proliferation and differentiation
(skin, mucous membranes, glands).
Cell deviate from their normal morphofunctional maturation

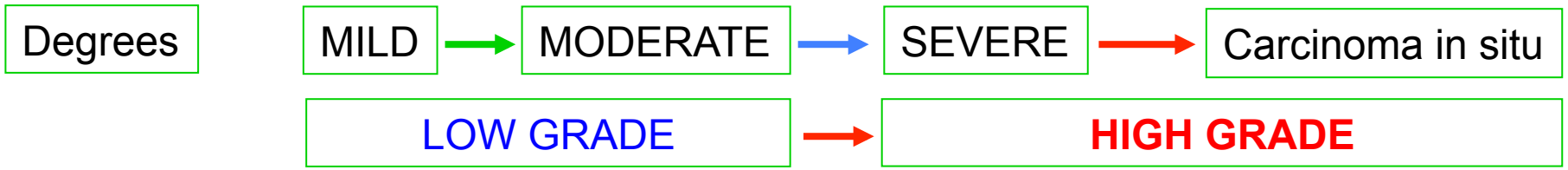
- Frequent association with hyperplasia
- Increased risk of evolution into carcinoma

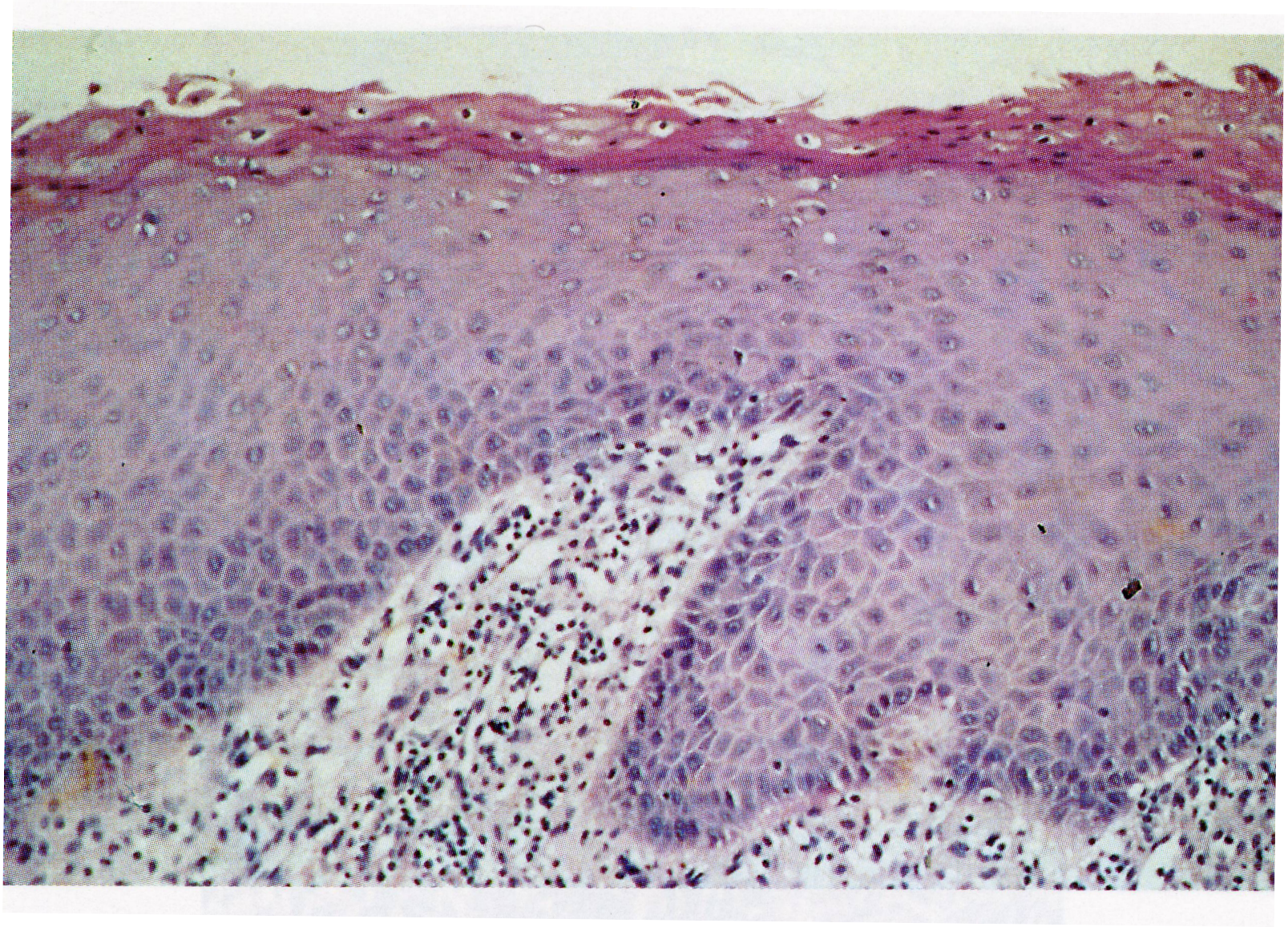
- **Most common locations**: cervix, bronchial, oral, digestive and bladder mucosa, mammary gland, liver, etc.

- **Causes**: Irritating chronic stimuli, genetic alteration (oncogenes, tumor suppressor genes), virus, hormones, etc.

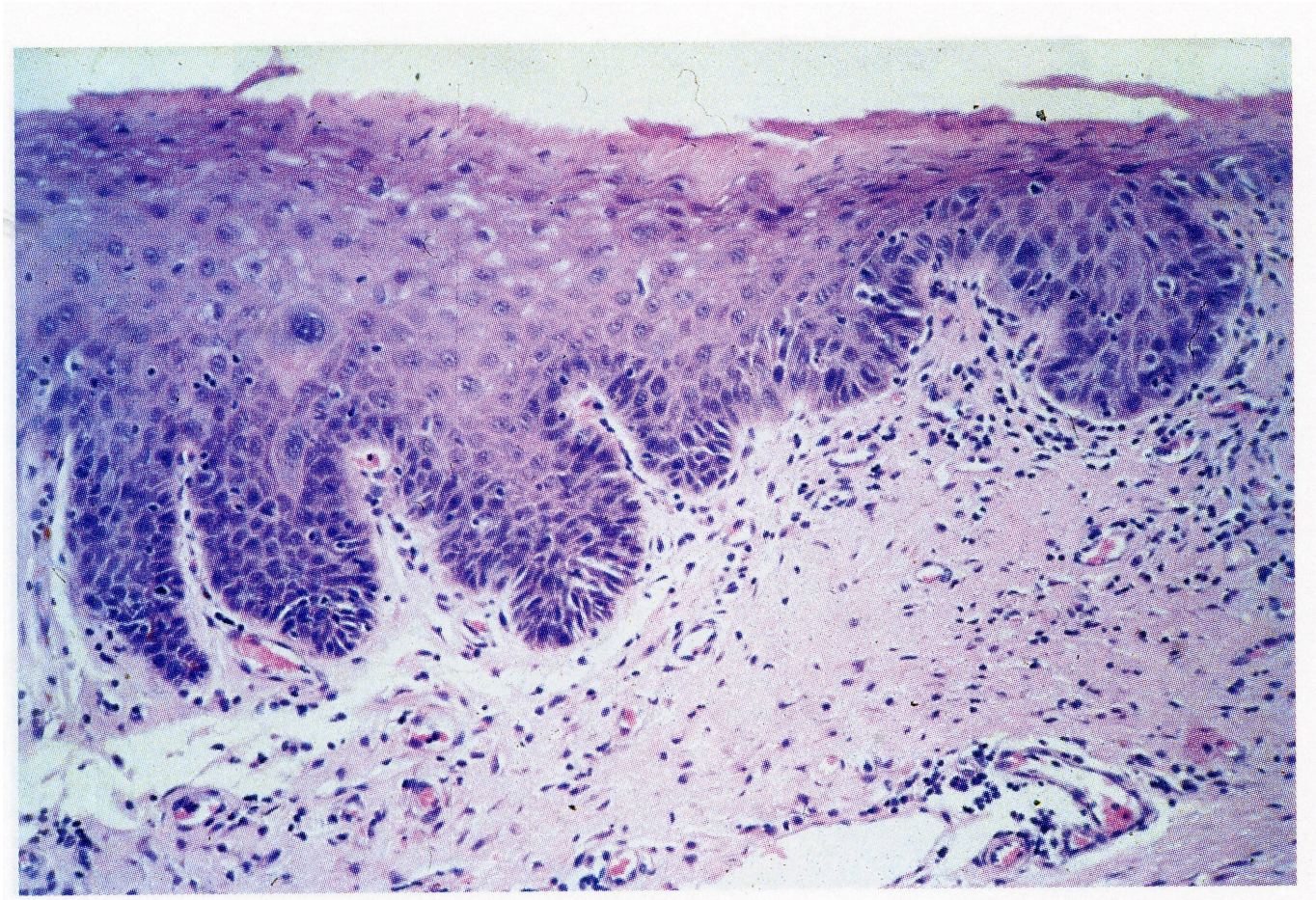
MORPHOLOGY OF DYSPLASIA

- Increased epithelial layers
- Alteration of cell polarity
- Increased mitotic activity (sometimes atypical).
- Alterated maturation (maturative arrest) of basal layers
- Size and shape modifications
- Nuclear hypercromasia (increased nucleic acid content)
- Increased number and size of nucleoli

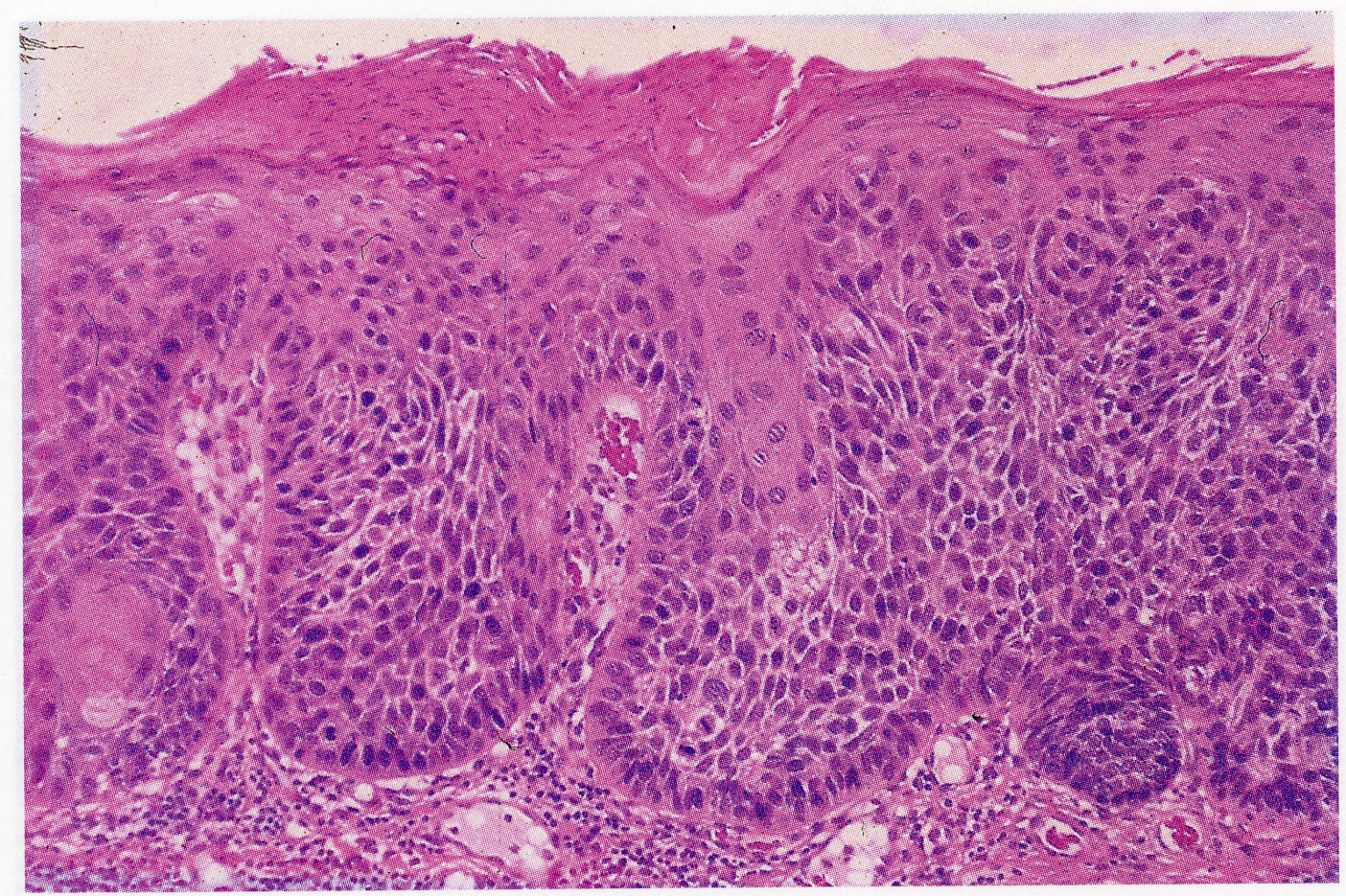




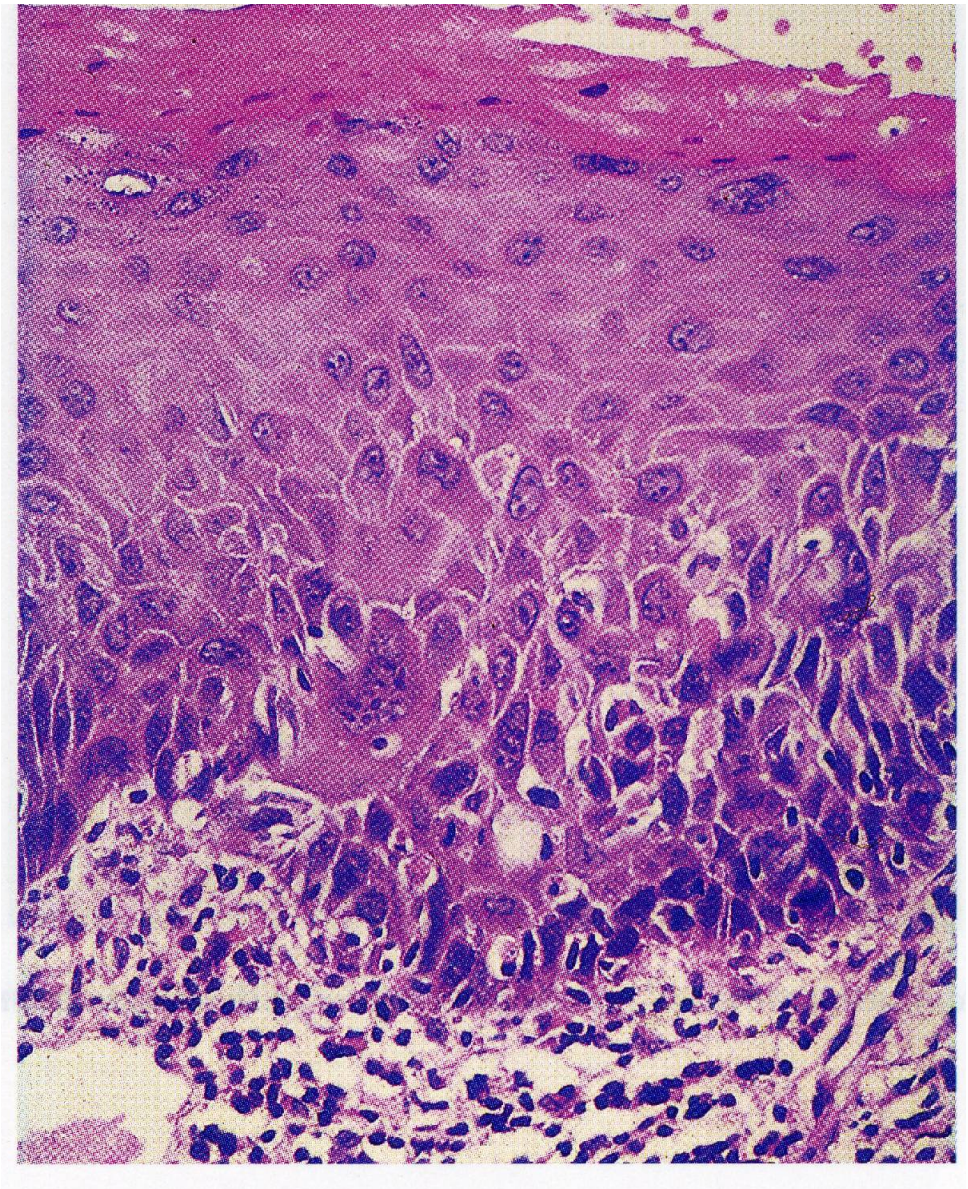
Stratified squamous epithelium (keratinized)



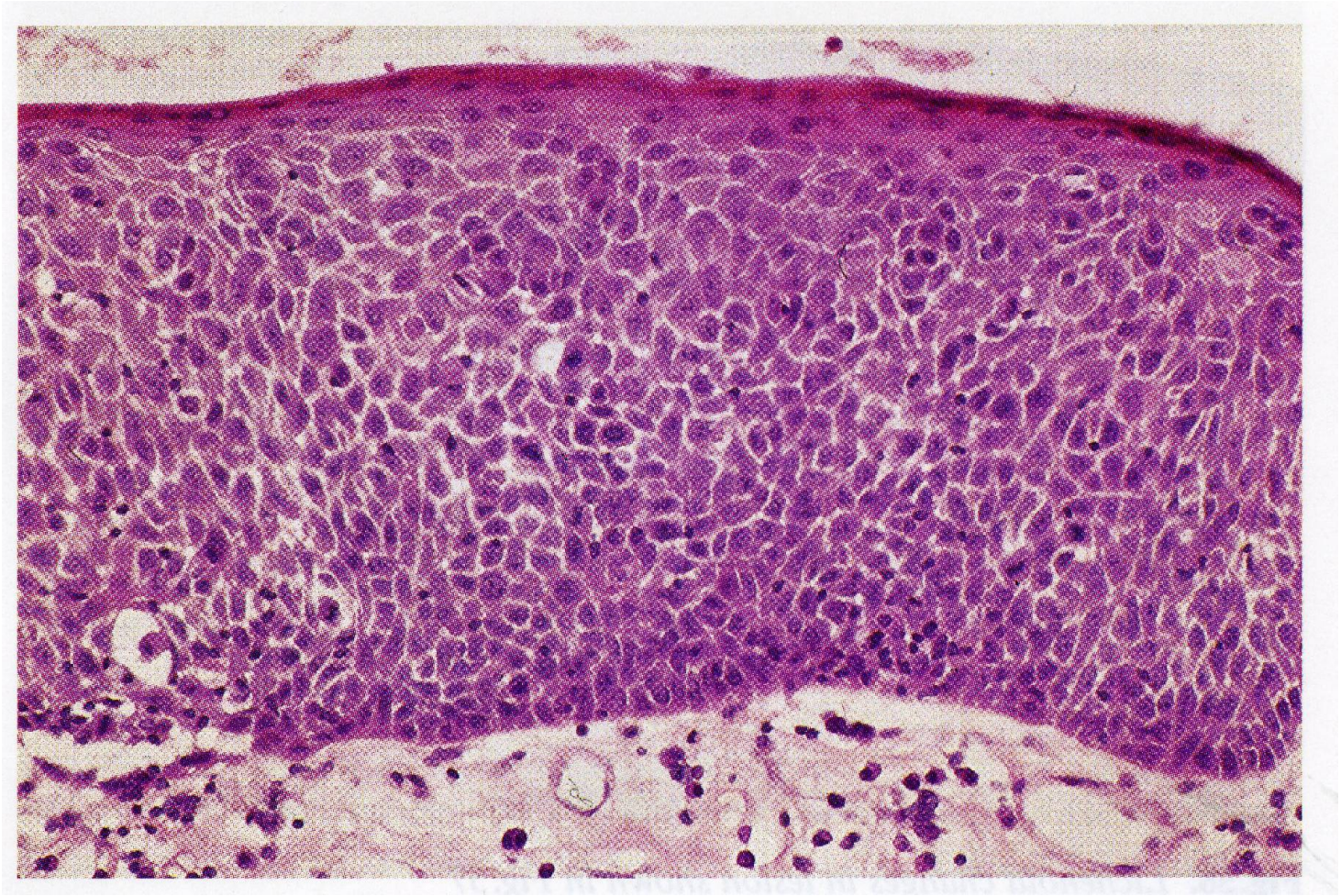
Dysplasia (mild degree)



Dysplasia (moderate degree)

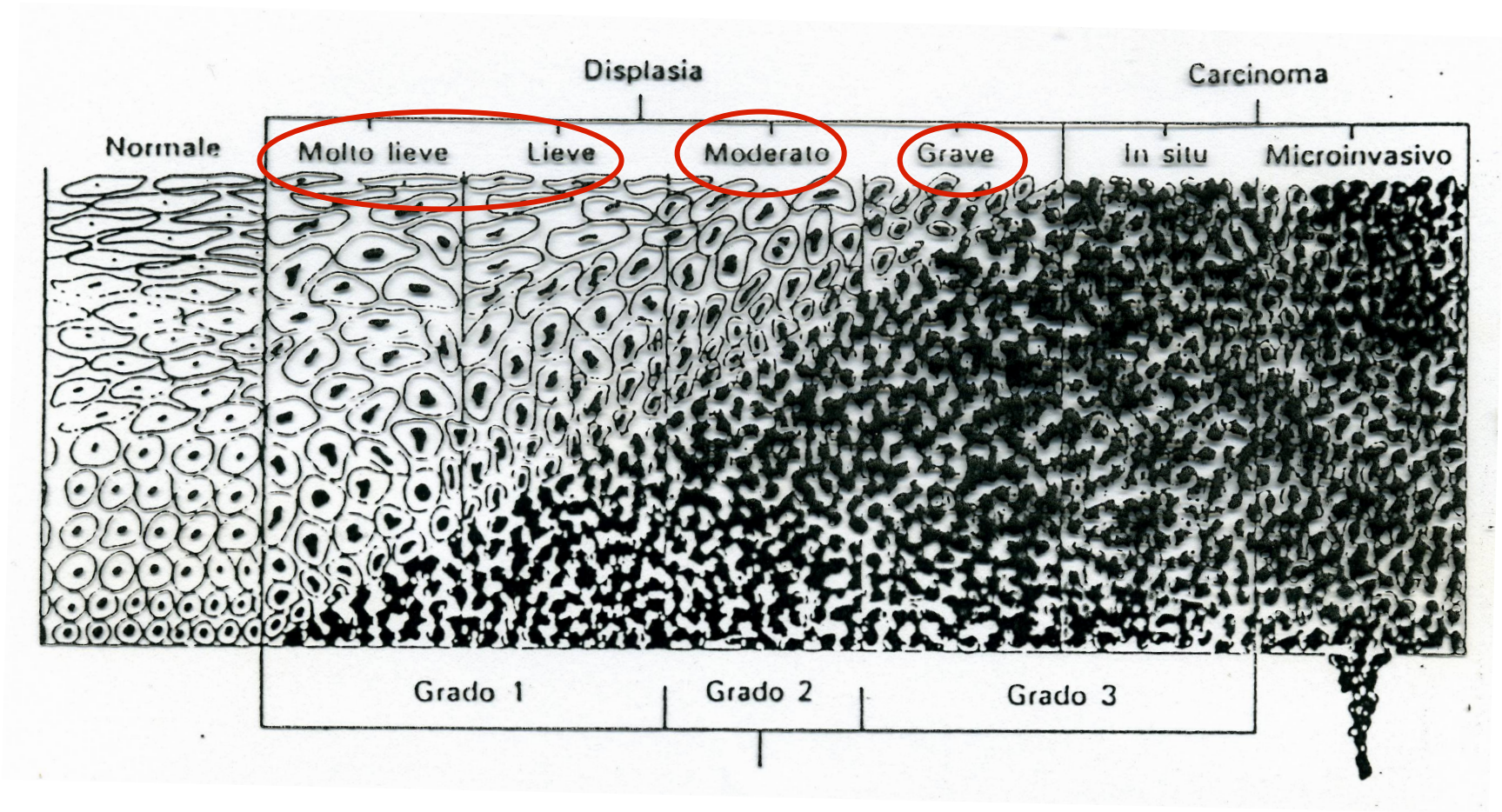


Dysplasia (severe)



Carcinoma in situ

Squamous epithelium

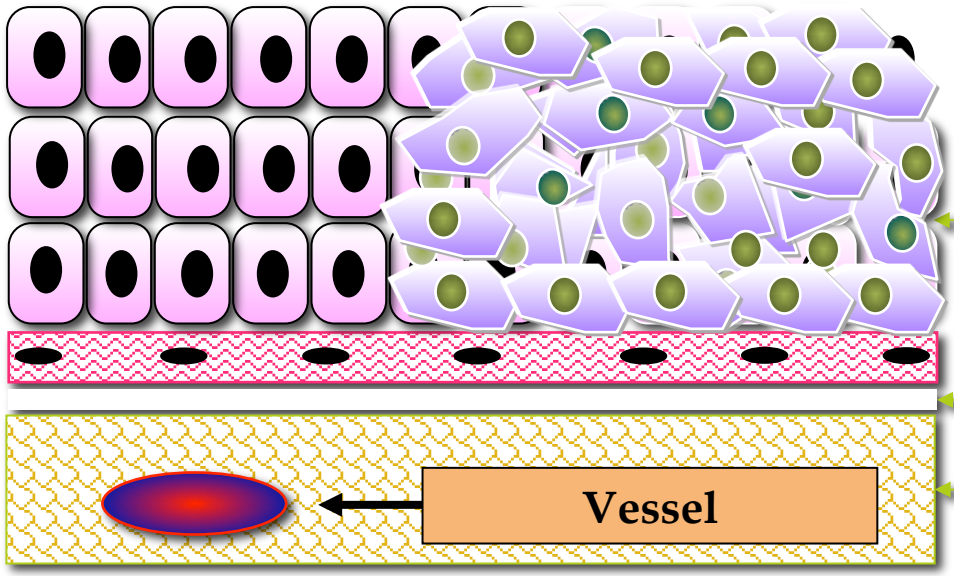


CARCINOMA IN SITU :

NEOPLASTIC PROLIFERATION CONFINED WITHIN THE EPITHELIUM AND NOT EXTENDING BEYOND THE BASAL MEMBRANE

Different type of intraductal proliferation

Hyperplasia → Dysplasia



Epithelial cells

Basal membrane

STROMA

NON-INVASIVE PROLIFERATIVE CONDITIONS

ACRONYMS FOR INTRAEPITHELIAL NEOPLASIA

SIN = **S**QUAMOUS **I**NTRAEPITHELIAL **N**EOPLASIA

OIN = **O**RAL **I**NTRAEPITELIAL **N**EOPLASIA

CIN = **C**ERVICAL **I**NTRAEPITHELIAL **N**EOPLASIA

DIN = **D**UCTAL **I**NTRAEPITHELIAL **N**EOPLASIA

LIN = **L**OBULAR **I**NTRAEPITHELIAL **N**EOPLASIA

PIN = **P**ROSTATIC **I**NTRAEPITHELIAL **N**EOPLASIA

Malignant tumors

Carcinoma in situ

- intraepithelial or preinvasive

- histogenetically related to squamous or columnar epithelia

- initial expression of neoplastic transformation

- hardly recognizable with macroscopic examination

- **histology:** *> epithelial layers, architectural disorders, polymorphism and > mitosis*

- intact basement membrane

Malignant tumors

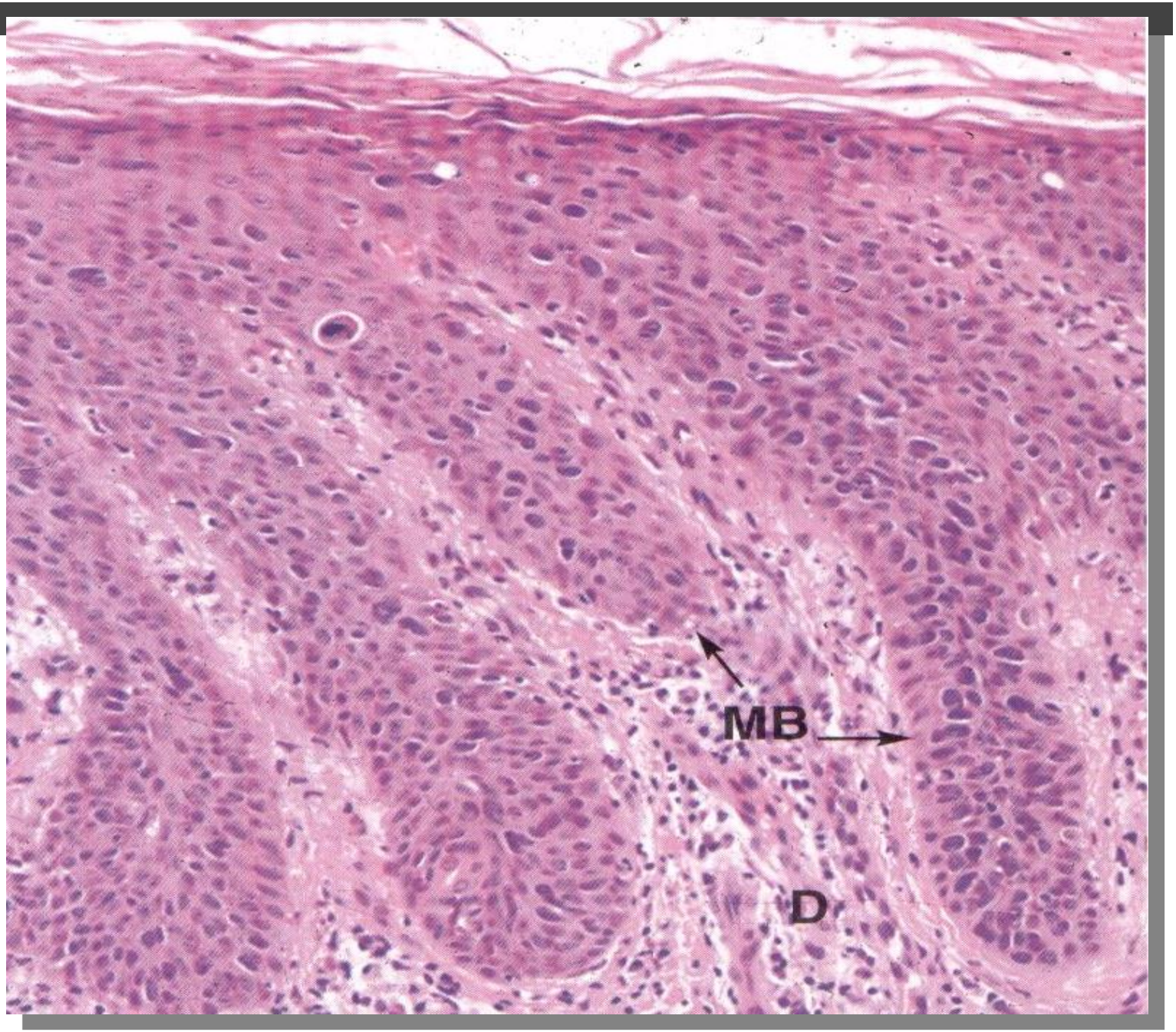
- **Carcinoma in situ**

  Cyto-histological abnormalities of the carcinoma

  No invasion of the underlying stroma

- **Tumour of uncertain malignant potential**

  Cyto-histological abnormalities without clear invasion of the stroma and sufficient prognostic data suggesting distinct aggressive behavior


MB
D

INTRAEPITHELIAL NEOPLASIA

Lesions unable to metastasize which are cured after ablation

Avoids the term “carcinoma” with all its (psycological) implications

Unifies and simplifies the terminology of intraepithelial lesions (dysplasia, atypical hyperplasia ecc.)

Downsides:

- Suggests progression from lower to higher grades

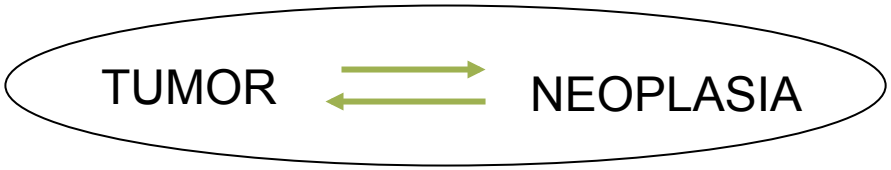
IMPORTANCE OF CYTOLOGY IN THE DIAGNOSIS OF MANY OF THESE INJURIES

PAP TEST,
Urinary cytology
Bronchial sputum cytology
Ecc.

SECONDARY PREVENTION

TUMOR / NEOPLASM

Given a normally regulated cell system, we call TUMOR / NEOPLASM a cell population originating from it, characterized by lack or deficient control of the mechanisms regulating proliferation/differentiation



BENIGN TUMORS / MALIGNANT TUMORS

CANCER = MALIGNANT TUMOR

BENIGN TUMORS

A- MESENCHYMAL	ANGIOMA LIPOMA FIBROMA CHONDROMA OSTEOMA MYOMA (leiomyomas-lhabdomyomas) etc.
B- EPITHELIAL	ADENOMA POLYP PAPILLOMA
MIXED TUMORS (fibroepithelial)	Fibroadenoma

MALIGNANT TUMORS

A - MESENCHYMAL (SARCOMAS)

- ANGIOSARCOMA
- LIPOSARCOMA
- FIBROSARCOMA
- CHONDROSARCOMA
- OSTEOSARCOMA
- LEIOMYOSARCOMA
- RHABDOMYOSARCOMA

B - EPITHELIAL (CARCINOMAS)

- SQUAMOUS CELL CARCINOMA
- ADENOCARCINOMA
- PAPILLARY CARCINOMA

C – MIXED TUMORS (very rare)

- CARCINOSARCOMA

TUMORS WITH SPECIFIC DENOMINATION

- NEVI /MELANOMA
- LYMPHOMA, LEUKEMIA
- NERVOUS SYSTEM TUMORS
- DISONTOGENETIC TUMORS

BENIGN TUMORS/ MALIGNANT TUMORS

1. **DIFFERENTIATION**
2. **PROGRESSION**
3. **INVASION**

1- DIFFERENTIATION: degree of morphofunctional similarity of tumor cells with their purported cell of origin

BENIGN TUMORS: differentiated cells similar to mature tissue cells
Mitosis: rare or absent
Functions often preserved

MALIGNANT TUMORS: stem cells with variable G rating (G1: well differentiated, G2: moderately differentiated, G3: poorly differentiated.)

ATYPIA: → CYTOLOGICAL
→ ARCARCHITECTURAL
→ FUNCTIONAL

ATYPIA

CELLULAR ATYPIA
Changes in the ratio N / C

NUCLEUS
- > Size
- Staining modifications
- Altered shape
- Nucleoli
- Mitotic activity

CYTOPLASM
- Shape and size
- Staining modifications
- Inclusions
- Organelles disorder

ARCHITECTURAL ATYPIA

Greater or lesser inability of tumor cells to reproduce the histological structure of mature tissues

FUNCTIONAL ATYPIA

Loss of ability to develop products characterizing normal cells (es.: mucin, keratin, hormones etc.)

Newly developed functional abilities not owned by their normal counterpart or exclusively present at their early stages

GRADING

- Expresses the degree of aggressiveness of a given tumor
- Purpotedly anticipates the clinical course (**prognostic factor**) of a patient with malignancy
    - Disease-free survival
    - Overall survival
    - Time-to-progression
    - Progression-free survival
- Possibly guides the choice among therapies based on expected response (**predictive factor**)
- Based on the morphological (cyto-architectural) features of the tumor

Clinical meaning of grading

Grading = independent prognostic factor

Grade correlates with the clinical behaviour of the tumor

- Local and distant aggressiveness
- Growth rate
- Infiltrative capacity towards surrounding tissues
- Metastatic potential

GRADING

For most tumors are considered :

- Cytological **features**: nuclear pleomorphism, number of mitoses
- **Architectural** features: (ability to form glands, stratification)
- Pattern of **invasion**
- Host/tumor relationships

GRADING

Grades:

I Well differentiated (G1)
II Intermediate grade (G2)
III Poorly differentiated (G3)
IV Undifferentiated (G4)

GRADING

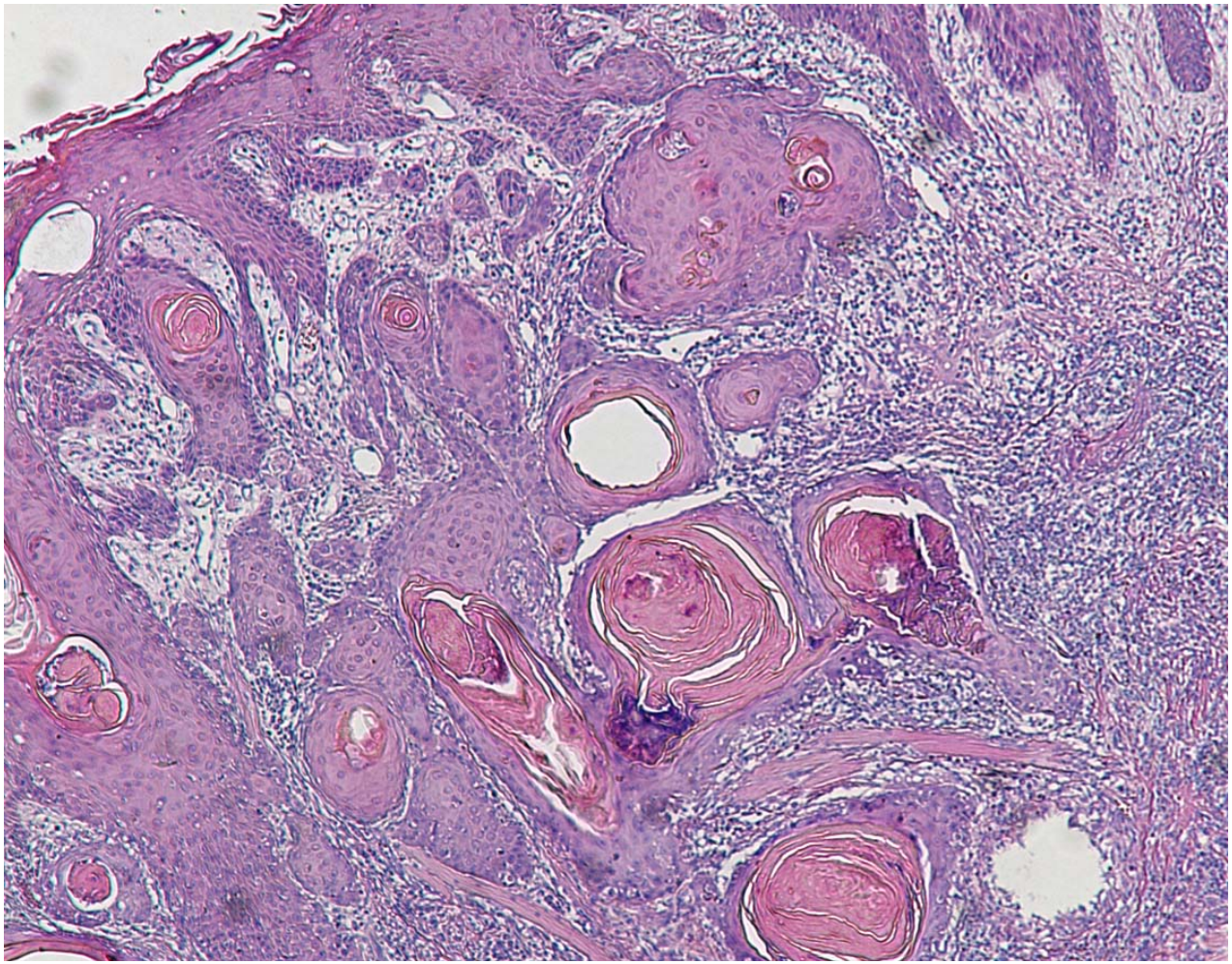
Distinct parameters for evaluating the degree of differentiation according to site / histotype

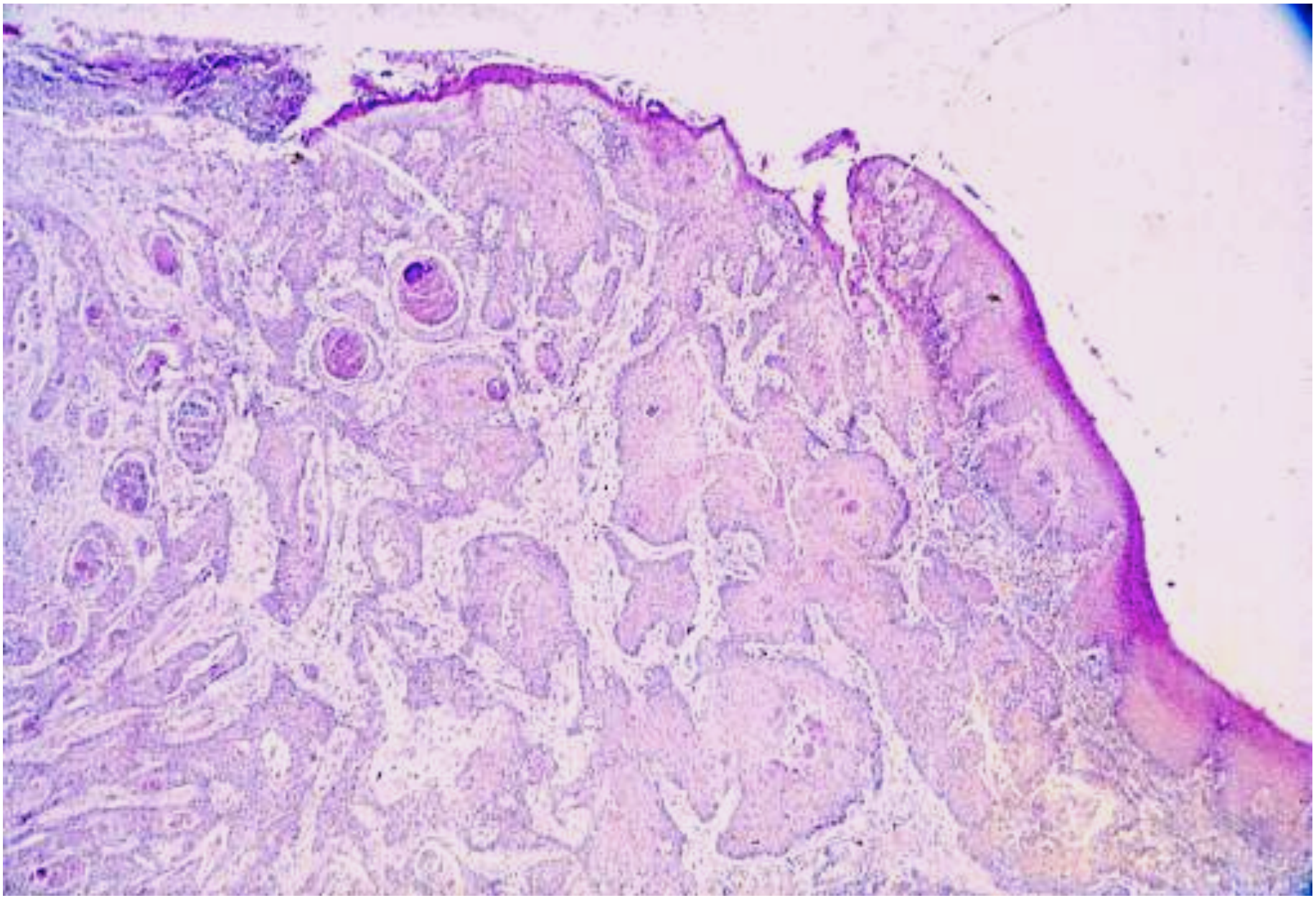
BREAST carcinoma: grading acc. to ELSTON & ELLIS – cytohistological grading: G1- G3

KIDNEY carcinoma: grading acc. To FUHRMAN = nuclear grading G1-G4

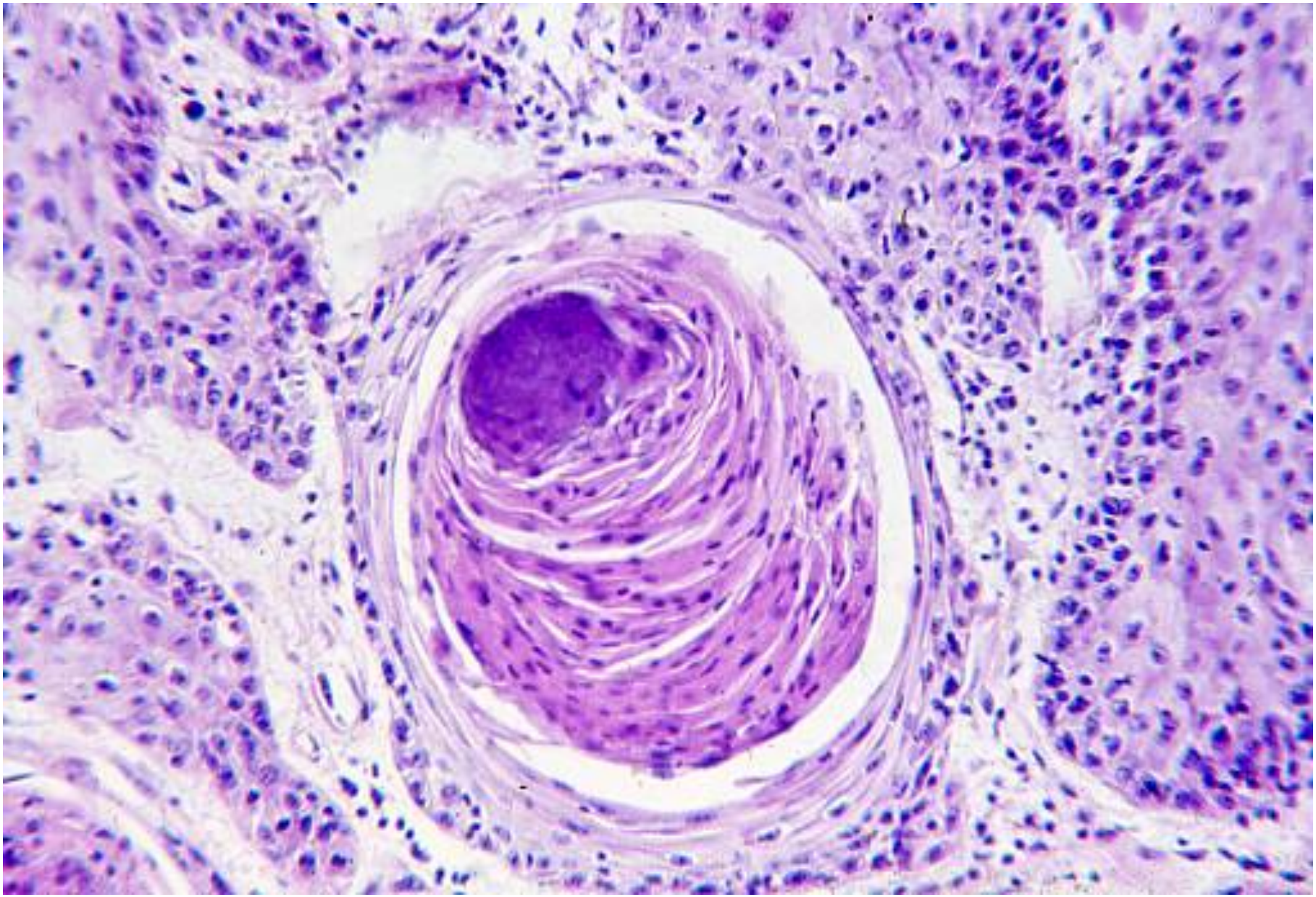
PROSTATE carcinom: grading acc. to GLEASON = architecturaf features

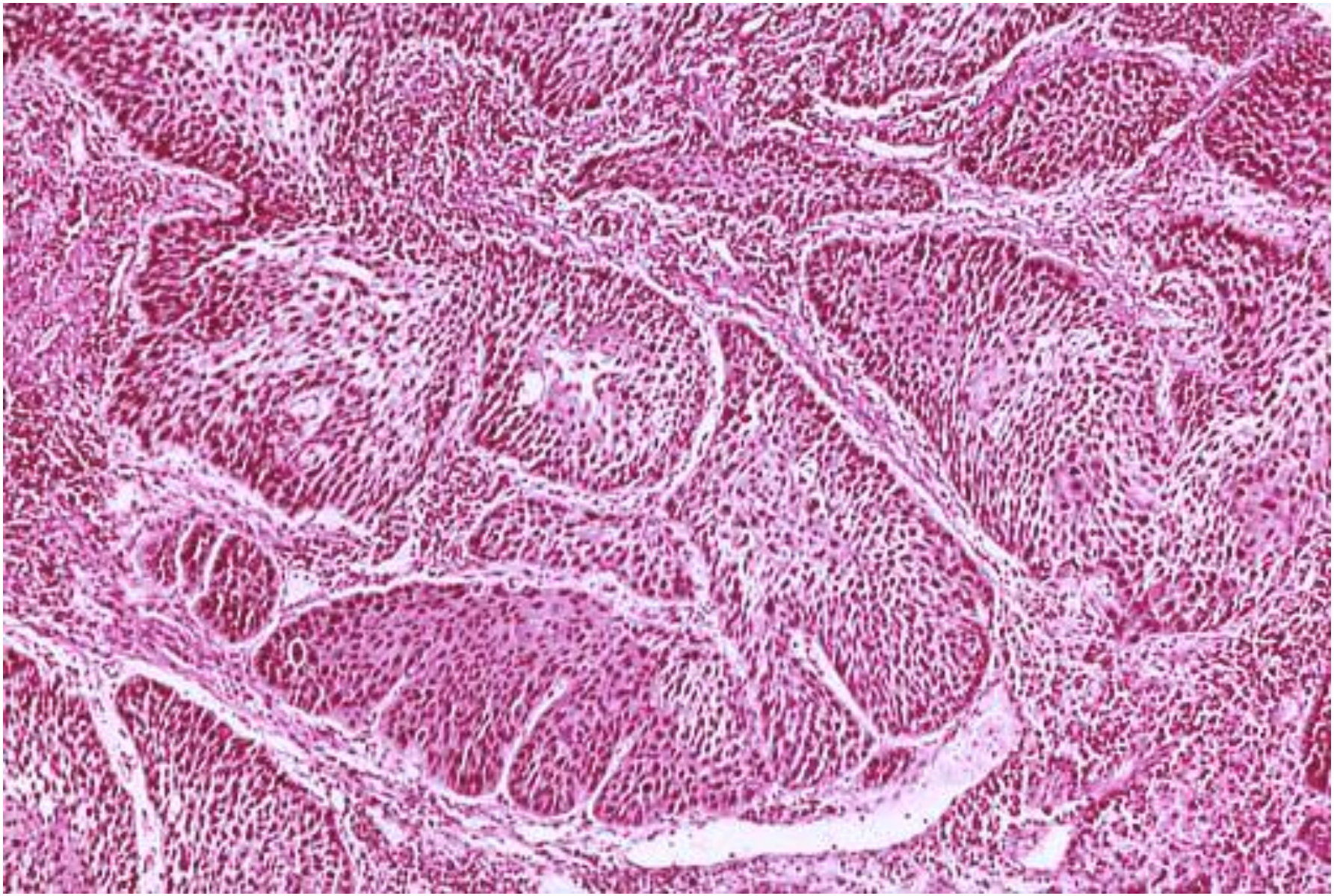
Squamous cell carcinoma



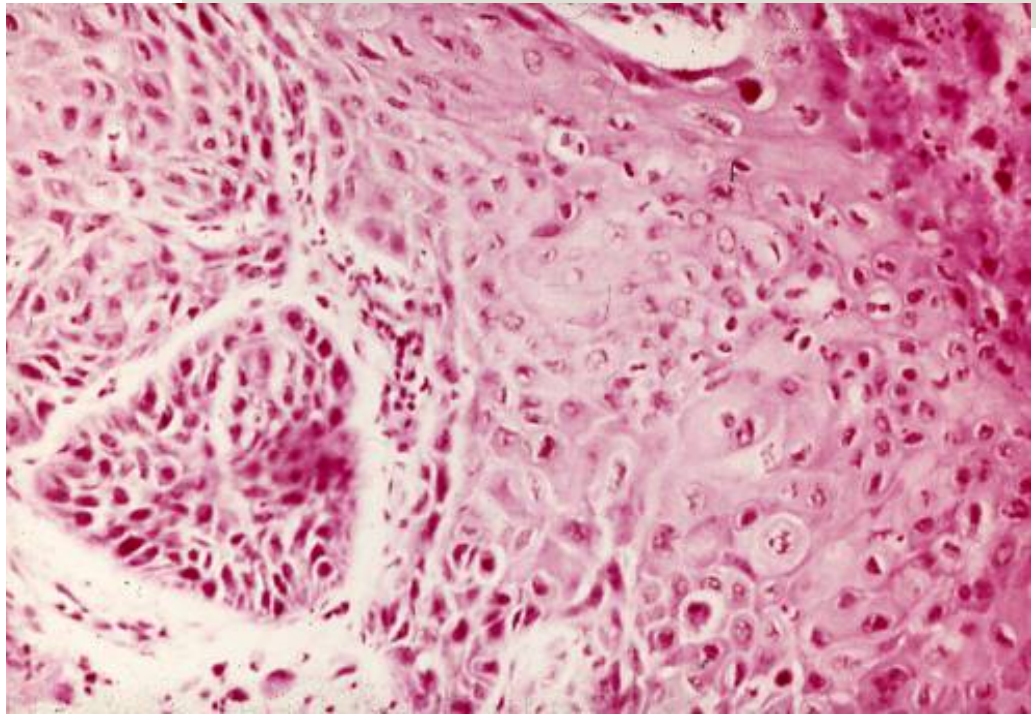


G1

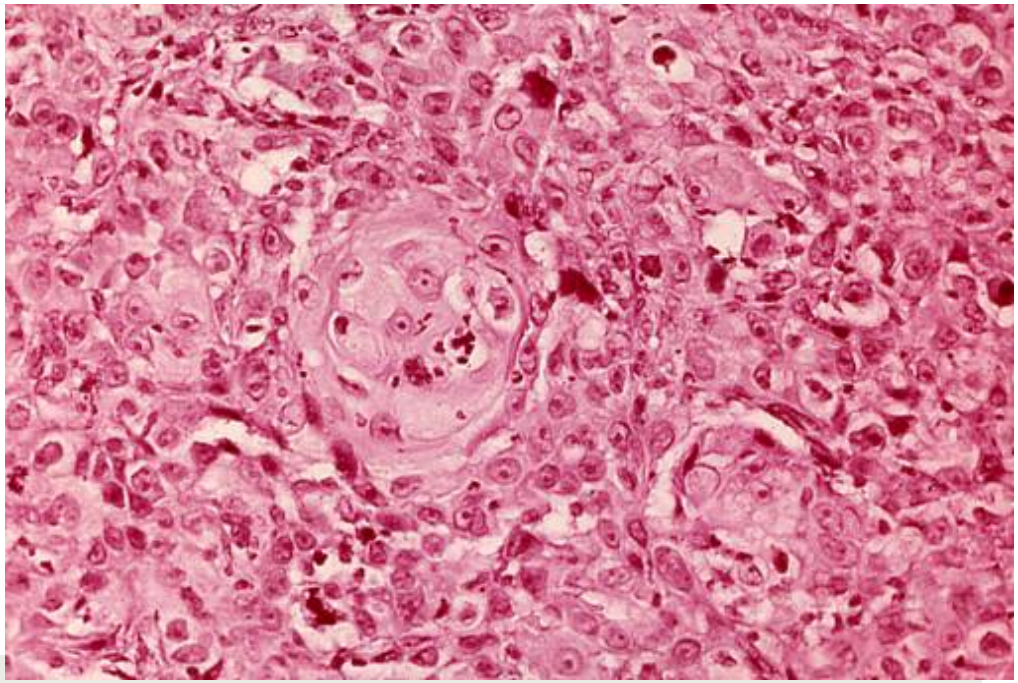


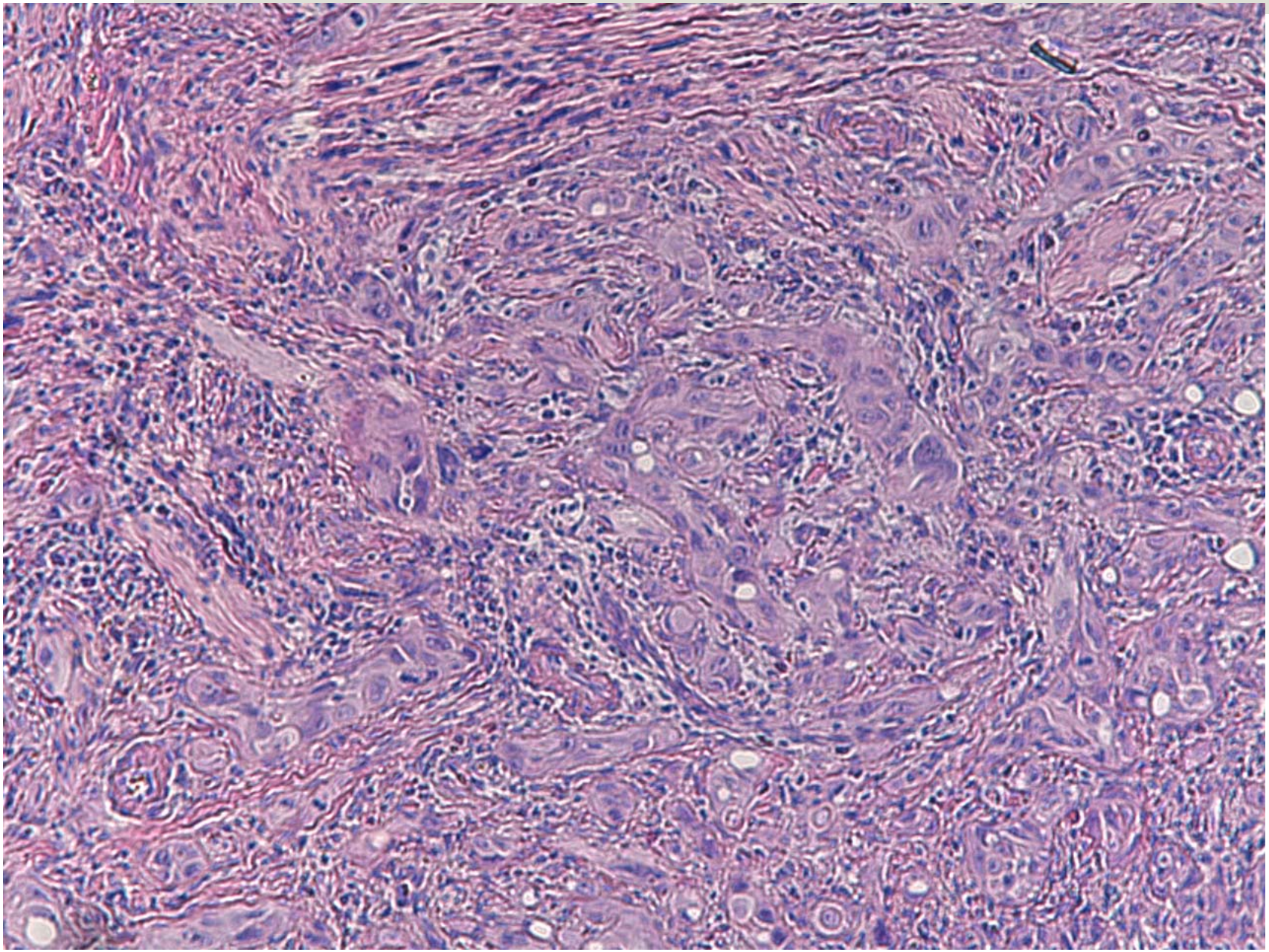


G2

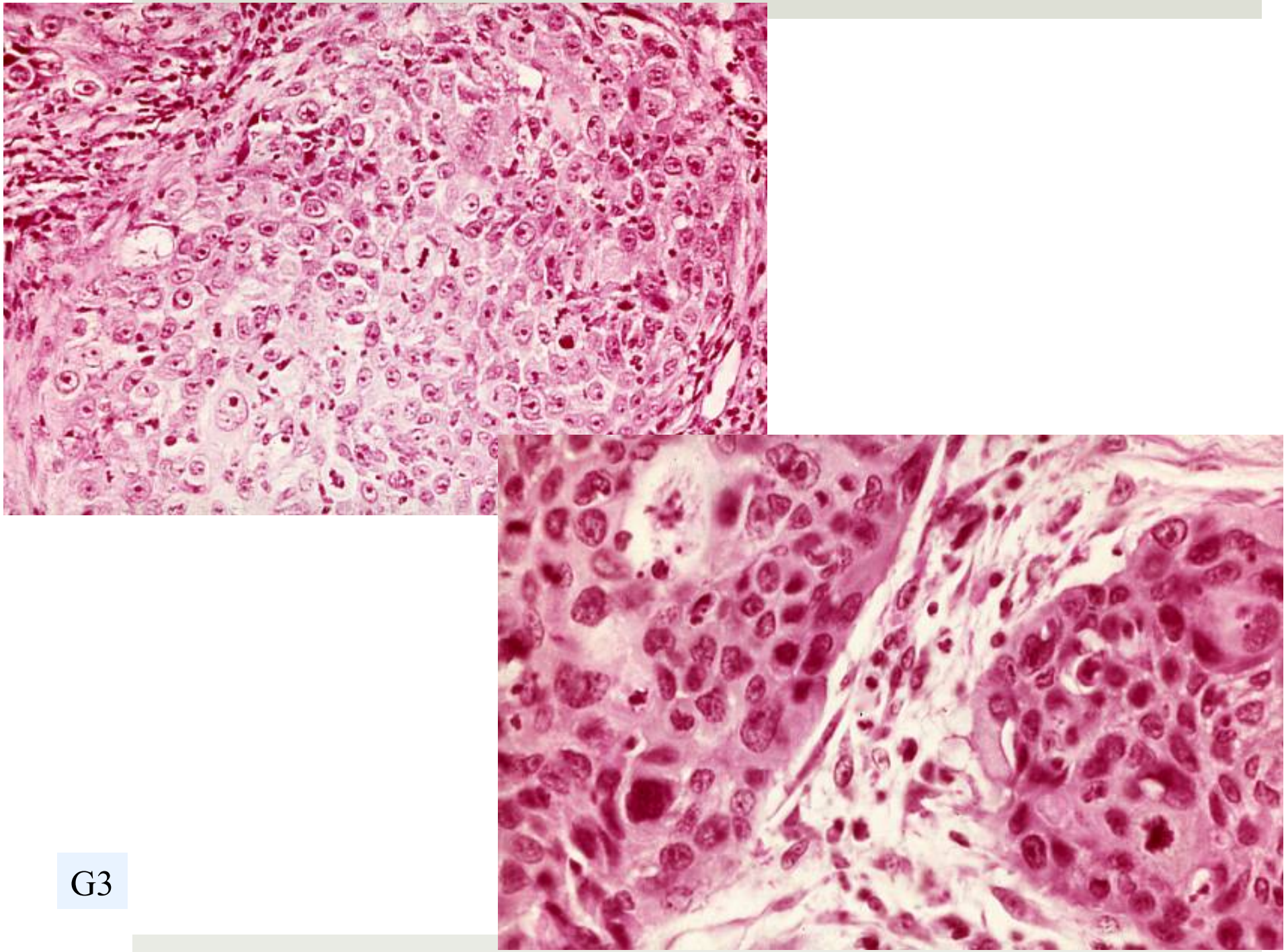


G2





G3



G3

BENIGN TUMORS/ MALIGNANT TUMORS

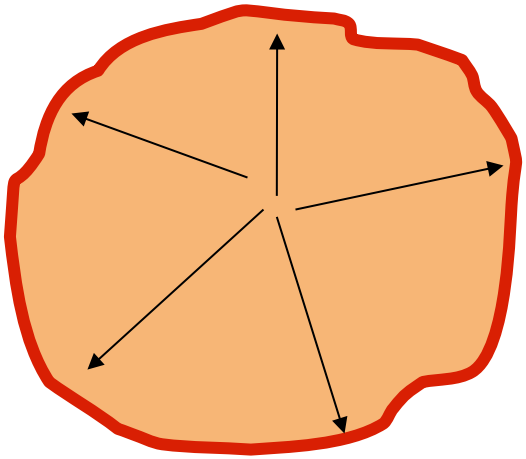
1. DIFFERENTIATION / ATYPIA
2. **PROGRESSION**
3. INVASIVENESS

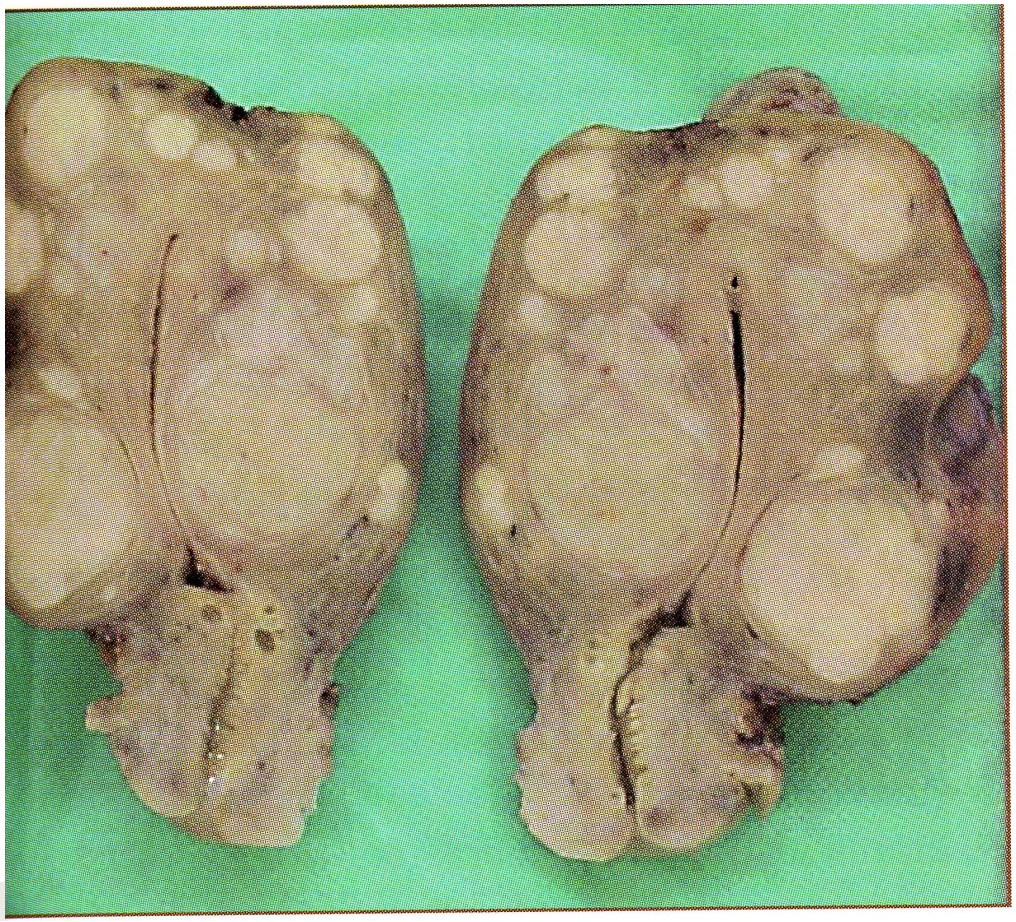
PROGRESSION → GROWTH MODALITIES
PROGRESSION → GROWTH RATE

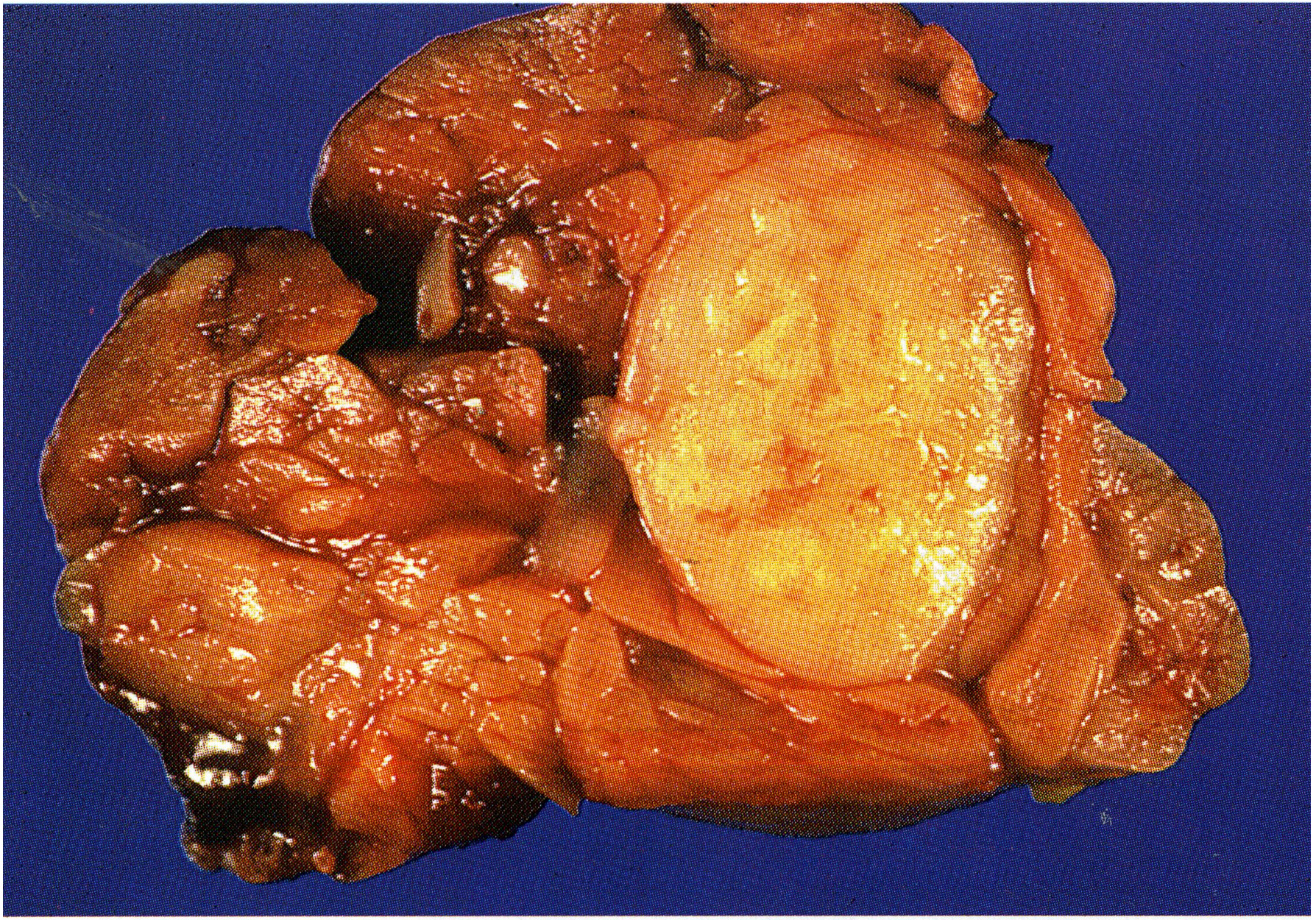
GROWTH MODALITIES

BENIGNANT TUMORS: clonal expansion = compression and atrophy of surrounding tissues

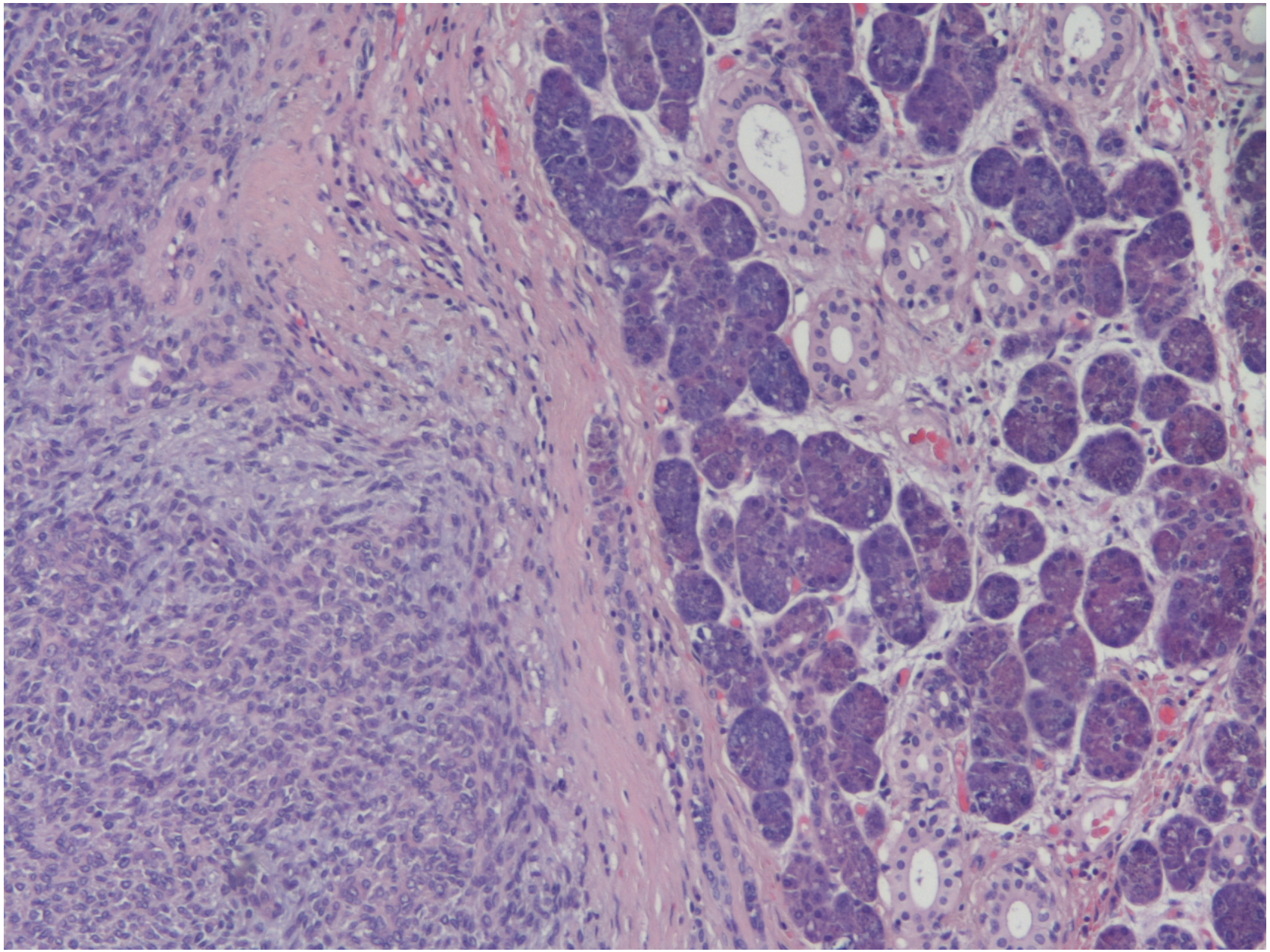
Fibrous pseudocapsule
Possible cleavage plane







Parotid adenomas

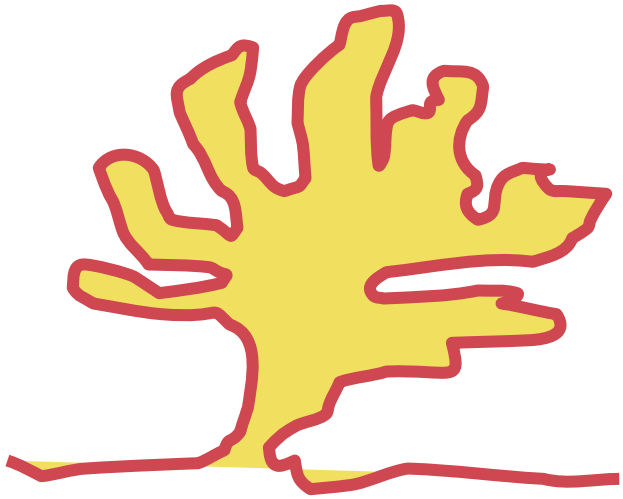


BENIGNANT TUMORS LOCALIZED ON SURFACE EPITHELIA

PAPILLOMA

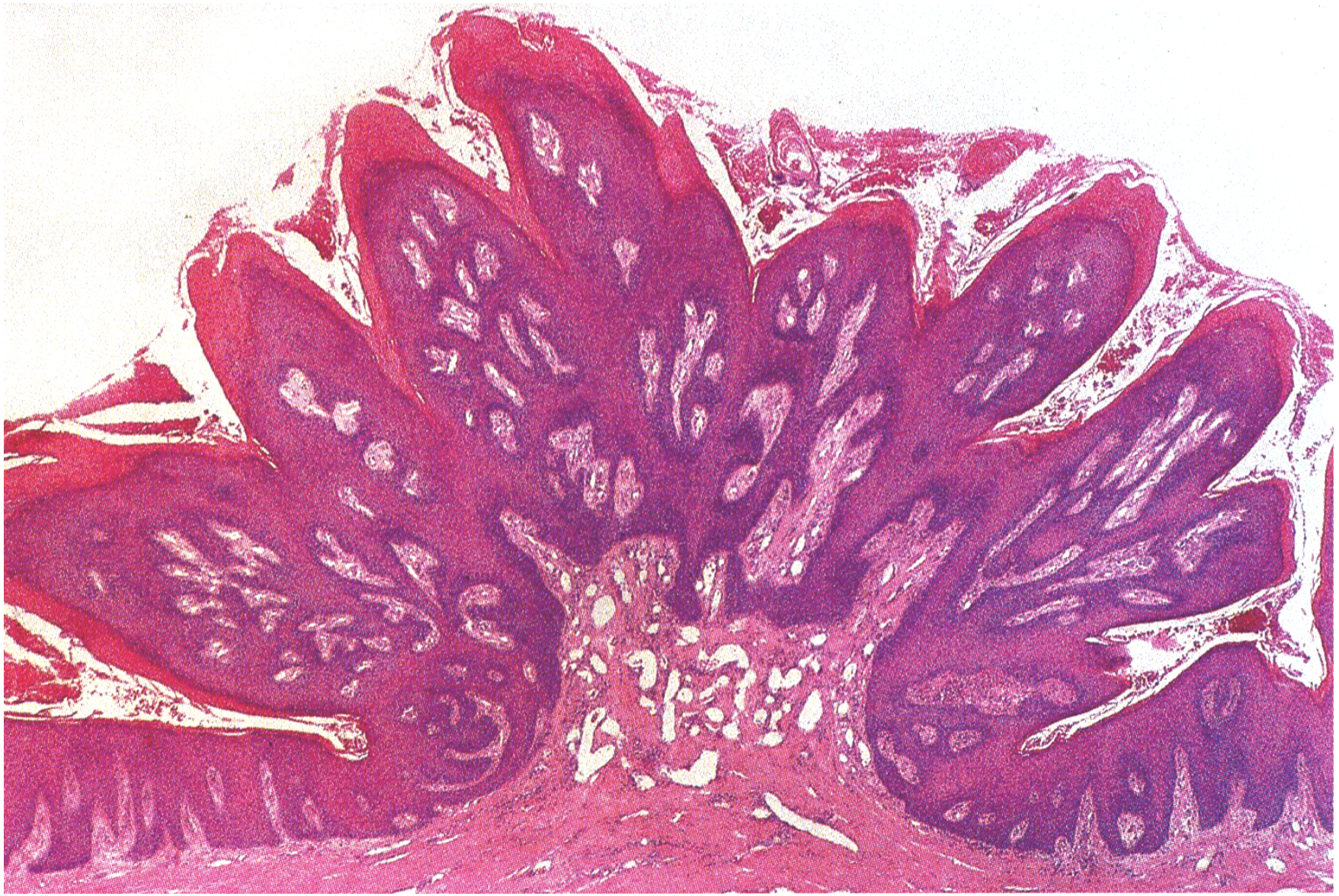
POLYP

PAPILLOMA: exophytic epithelial tumor, localized on the epidermis or mucous membranes, characterized by a branching axis (connective tissue + vessels) surrounded by lining epithelium.

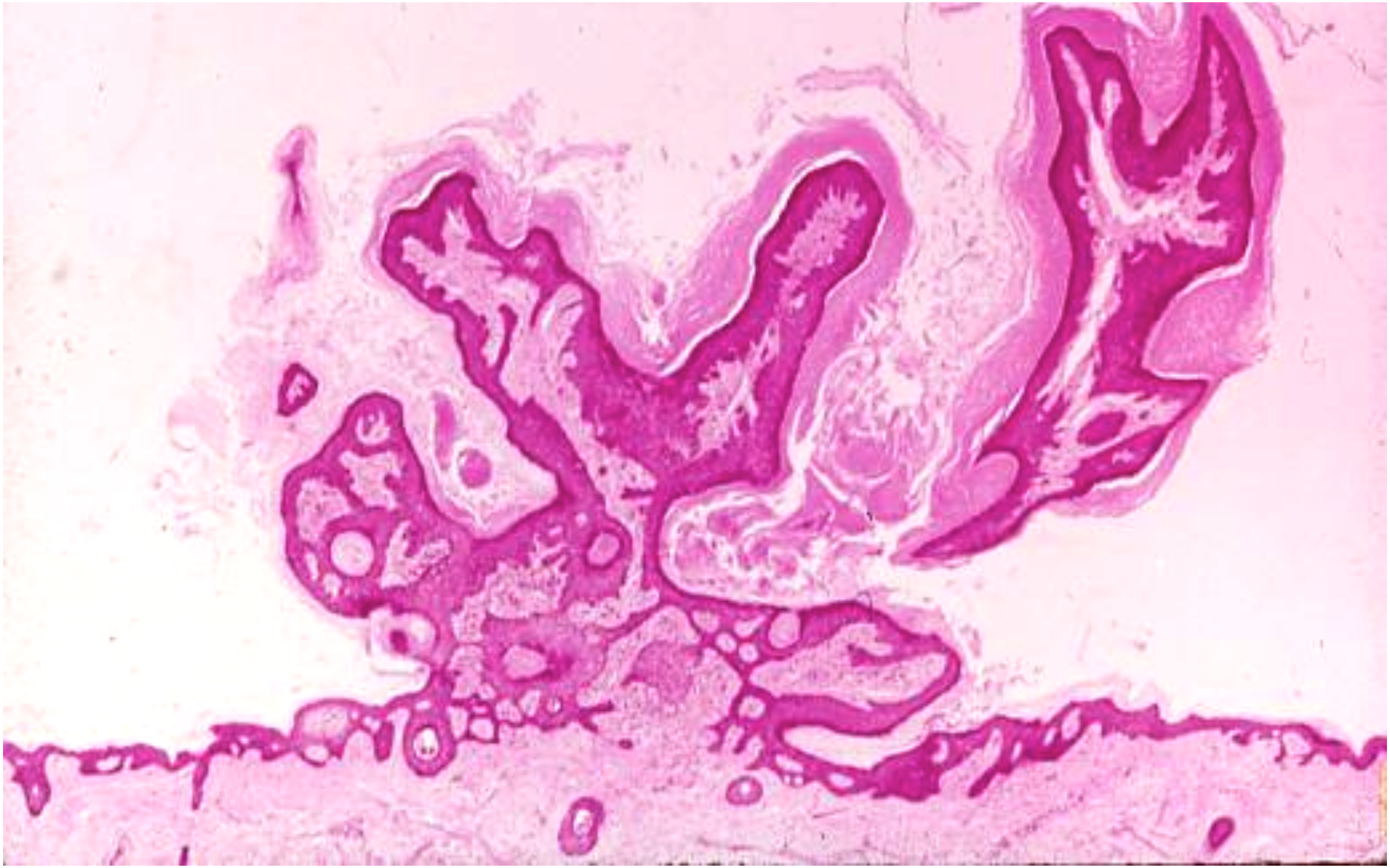


Pedunculated papilloma

Sessile papilloma

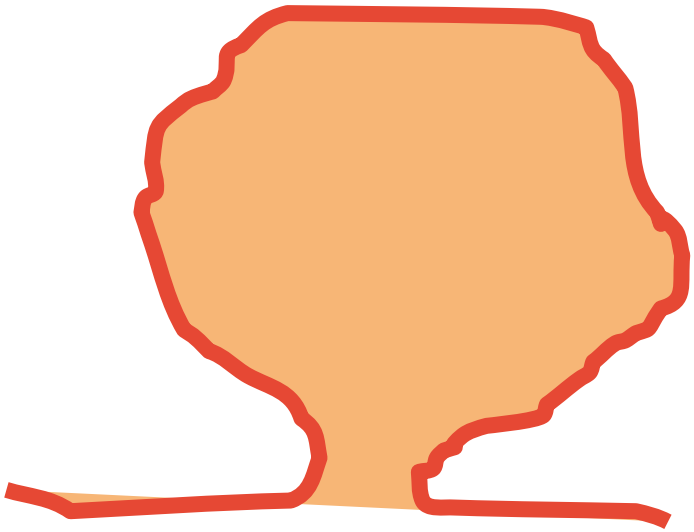


Vulgar wart

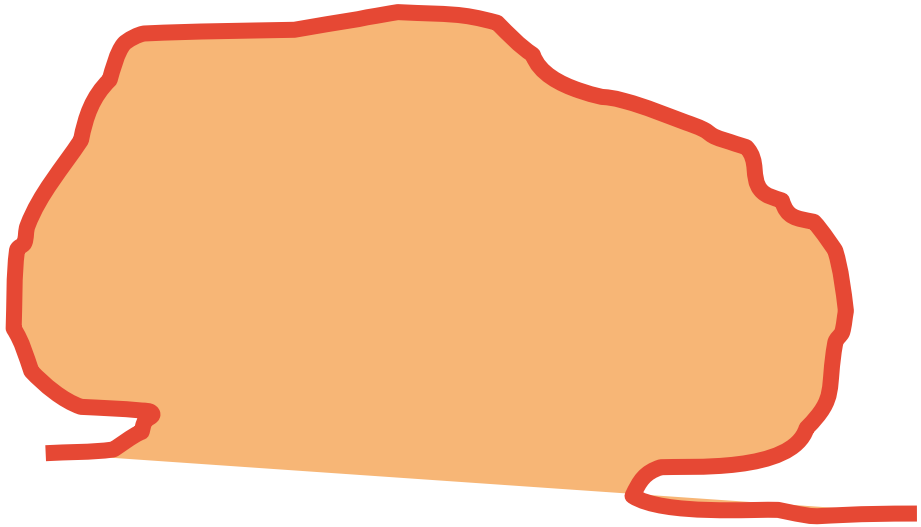


Cutaneous papilloma

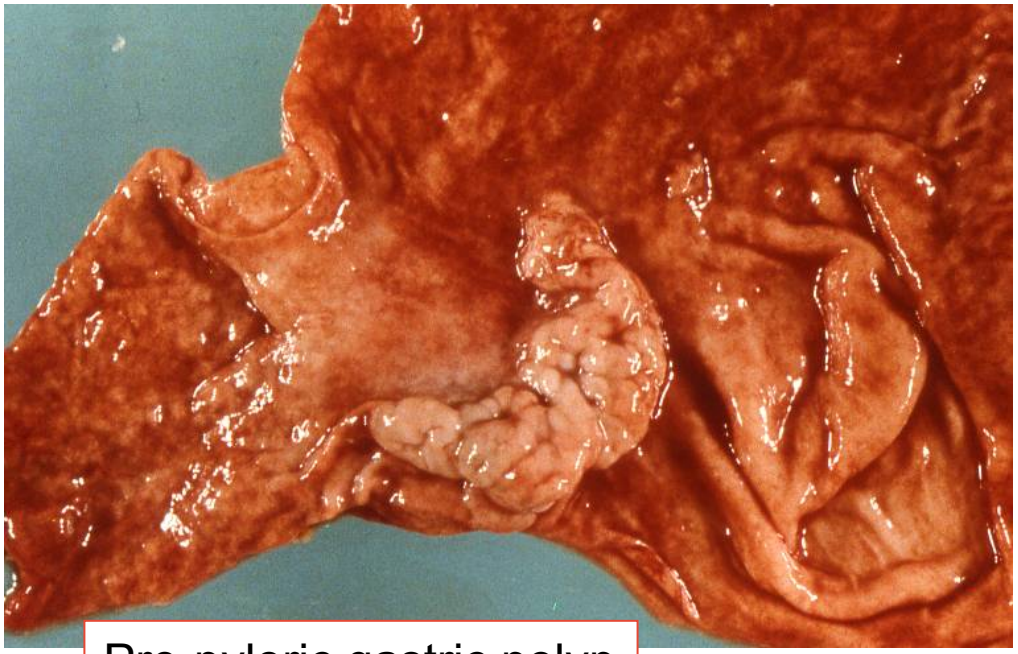
POLYP: exophytic epithelial tumor, localized on mucous membranes (colon, uterus), characterized by a single axis (connective tissue + vessels), surrounded by lining epithelium



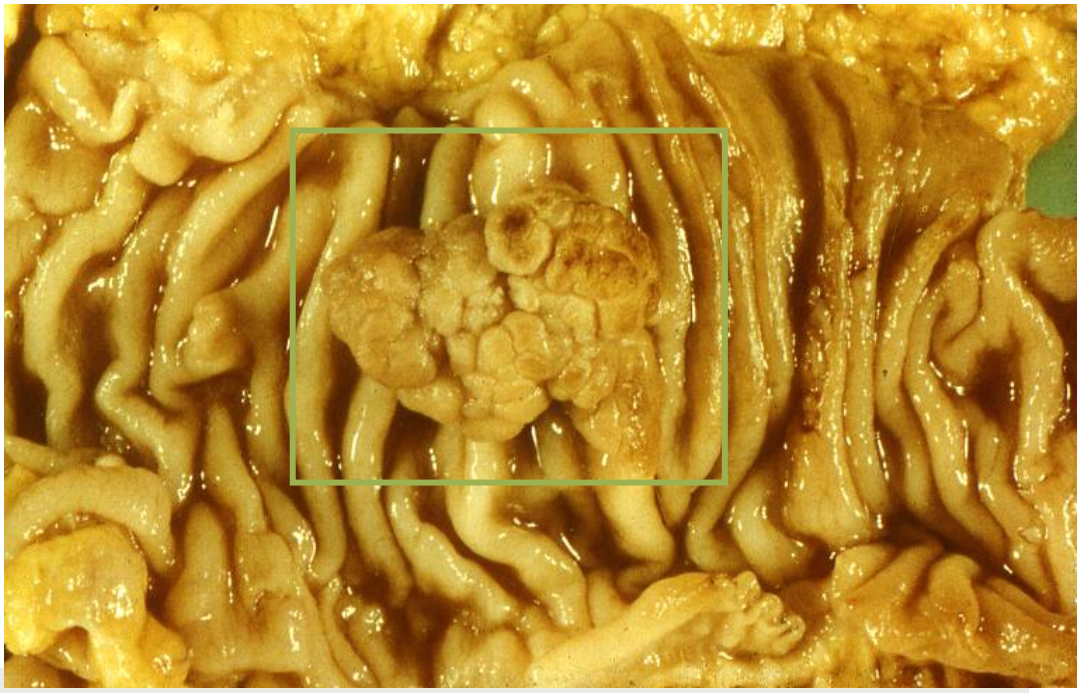
Pedunculated polyp



Sessile polyp



Pre-pyloric gastric polyp



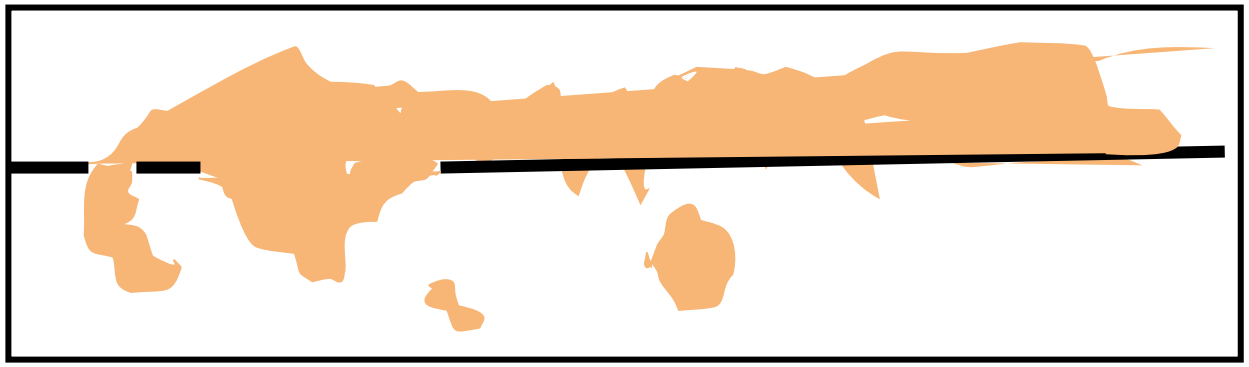
Colon polyp

MALIGNANT TUMORS: invasive growth = infiltration of surrounding tissues, lymphatic and blood vessels (capillaries, venules, arterioles) and perineural spaces (**METASTATIC DISSEMINATION)**

Destruction and replacement of pre-existing tissues

Modifications of intra and peritumoral stroma

Infiltrating carcinoma in parenchymal organs



Infiltrating carcinoma in hollow organs

STROMAL MODIFICATIONS

Stroma is essential for tumor growth (vascular supply)

Amount and type of stroma

- Desmoplastic reaction : scirrum
- Tumors with loose stroma (eg. myxoid)
- Tumors with little stroma “Medullary carcinomas”

Desmoplastic reaction : dense sclero-hyaline stroma

Loose stroma rich in acid amorphous substance

Metaplasia = myxoid, cartilage, bone

Tumor cells modulate the characteristics of the stroma through the production of growth factors: **FGB** (Fibroblast Growth Factor) **VEGF** (Vascular Endothelial Growth Factor), **PDGF** (Platelet Derived Growth factor), **TGF-β** (Trasforming growth Factor) ecc

STROMAL MODIFICATIONS

Inflammatory infiltrates (lymphocytes, plasma cells, eosinophils, etc.).
Organisms response to necrosis or tumor-released factors
No clear relationships with tumor progression

Peri/intra-tumoral neoangiogenesis: production of angiogenic factors
by tumor cells (VEGF = vascular endothelial growth factor)

Newly formed vessels often abnormal and very thin
Frequent damage associated to bleeding outbreaks

If «tumor mass/vessels» ratio is negative = NECROSIS.

PROGRESSION: growth rate

BENIGN TUMORS: Slow growth rate, often related to endocrine stimuli (uterine myomas, mammary fibroadenomas)

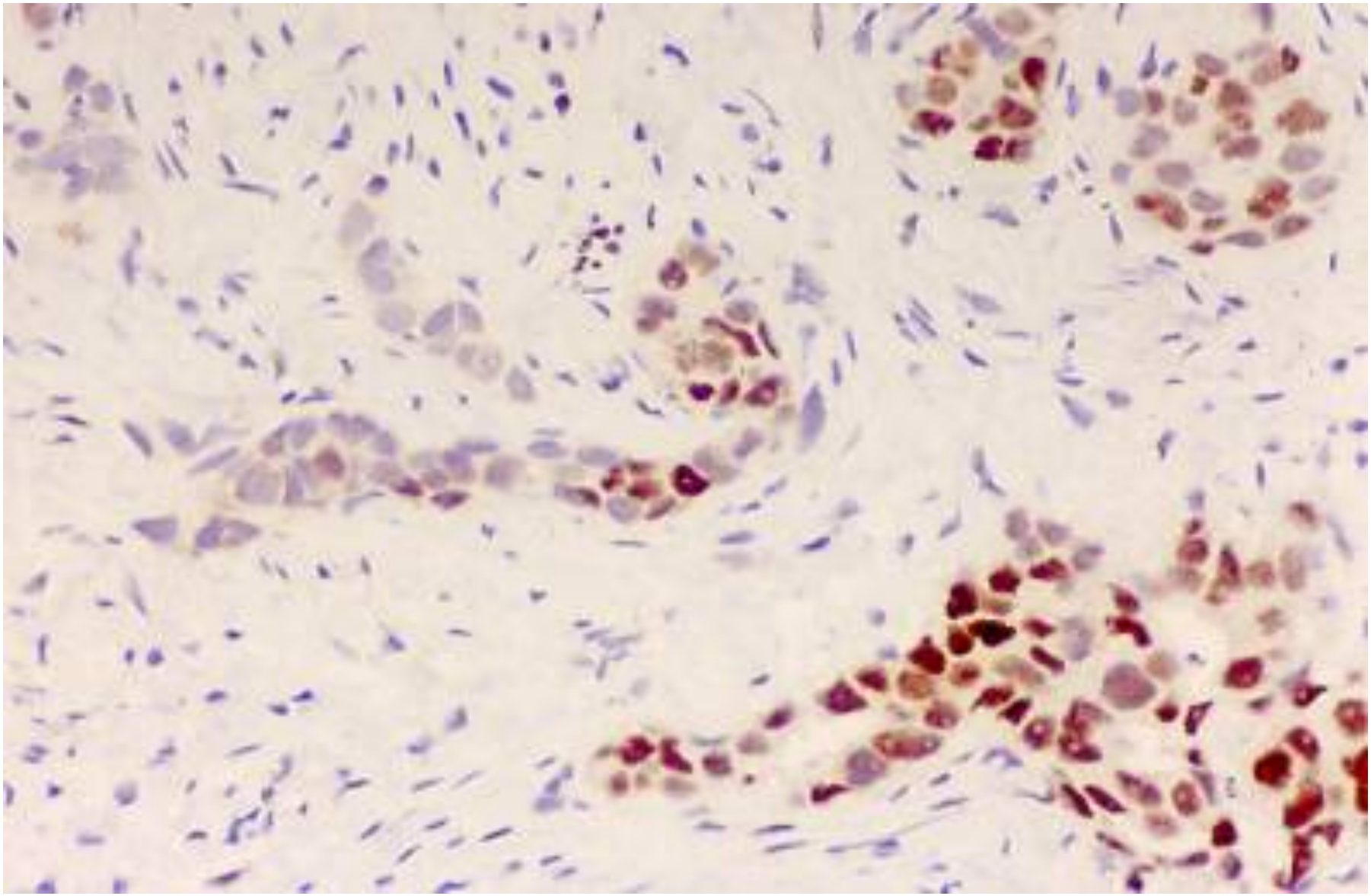
MALIGNANT TUMORS: Fast growth rate
- Silent phase
- Eruptive phase
- Phases with decreasing volume

Speed of growth: T_R = time needed by the tumor to double its mass

T_R
- Fraction of proliferating cells
- Cell loss (necrosis, apoptosis)
- Non-proliferating cells

Kinetics study on neoplastic tissues
- mitotic index (# of mitosis /10 HPF (40X)
- IIC: protein evaluation Ki-67

CLINICALLY: “in situ “
invasive / infiltrating



Ki-67

BENIGN TUMORS/ MALIGNANT TUMORS

1. DIFFERENTIATION / ATYPIA
2. PROGRESIVENESS
3. **INVASION**

INVASION → INVASION OF SURROUNDING TISSUES

INVASION → METASTASES

METASTASES = separated from primitive tumors.

lymphatic course → lymphatic vessels → lymph nodes

Hematic course → blood vessels → Liver, Lungs, Brain, Skeleton, Ecc.

Direct implantation → Natural body cavities → Pleural cavity, Peritoneal cavity

Important: look at the microscope for emboli and endovascular penetrations in peritumoral sites or at distance.

RECURRENCE = relapse of the tumour at the site of origin

Recurrence may occur after a very variable time from case to case, and may involve both benign (incomplete excision) and malignant tumours

METASTASIS = repetition of the tumour at distant sites, without connection with the primary tumour.

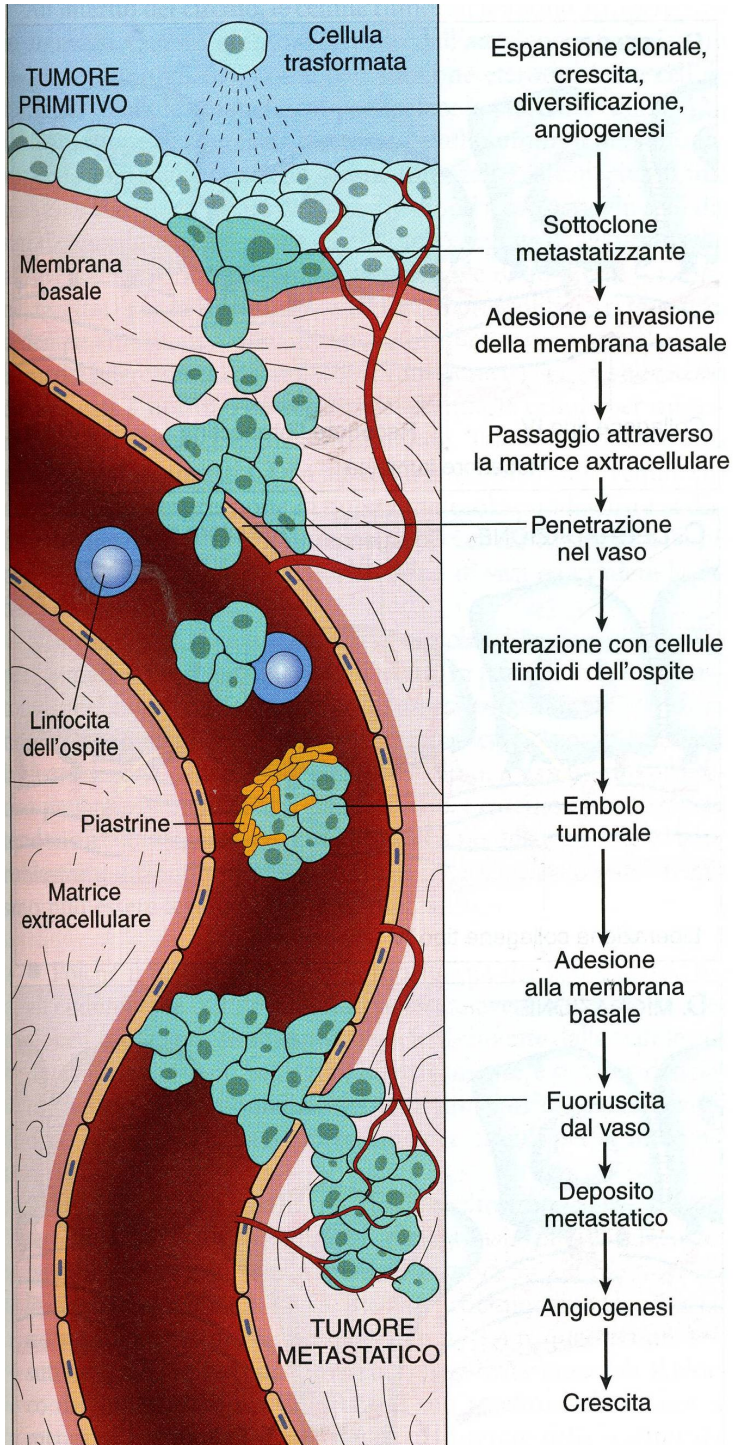
Only occurs in malignant tumours.

The involvement of other organs without solution of continuity with the primary tumour is called INFILTRATION/EXTENSION.

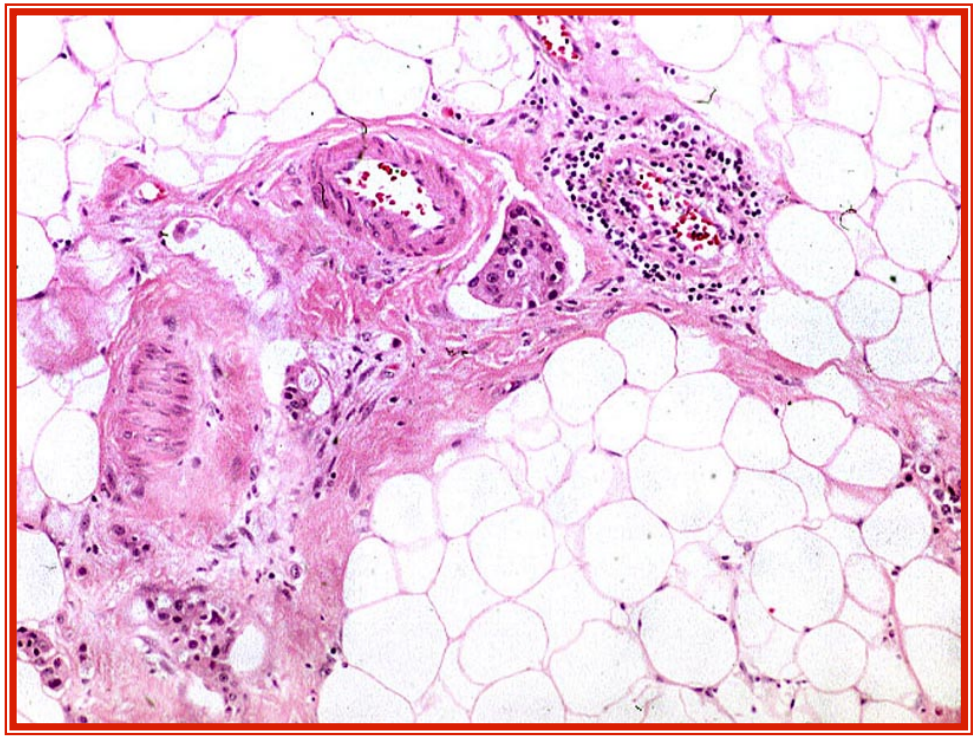
Malignant tumors

Routes of dissemination:

- **Local invasion:** infiltration in surrounding tissues
- **Lymphatic:** neoplastic cells colonize regional lymph nodes
- **Vascular:** neoplastic cells in veins reach other organs
- **Perineural**: through peripheral nerves (sheats)
- **Transcoelomatic:** through peritoneum and pleura

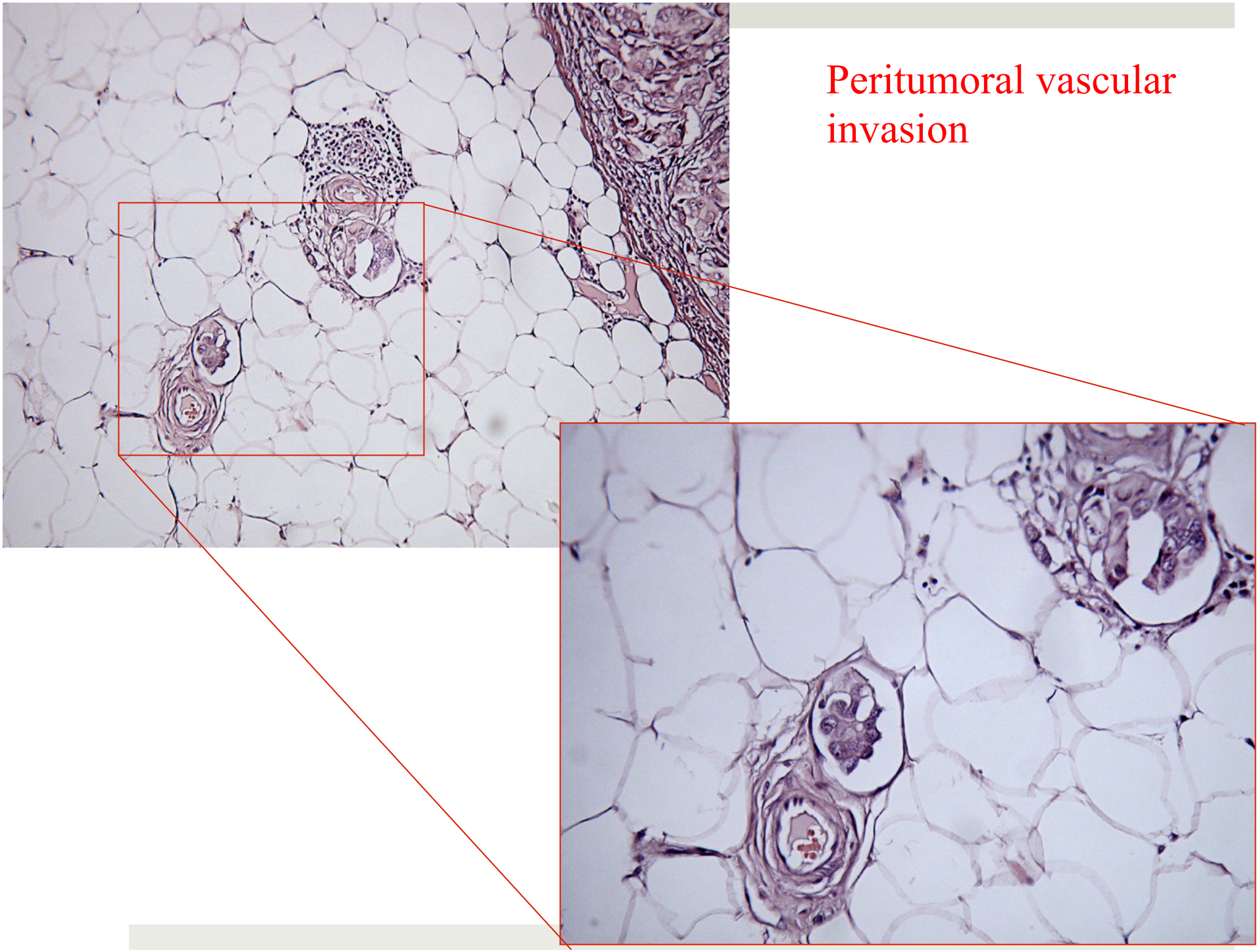


"METASTATIC CASCADE"
Sequence of events in the vascular diffusion of neoplasia



Peritumoral vascular invasion

Peritumoral vascular invasion

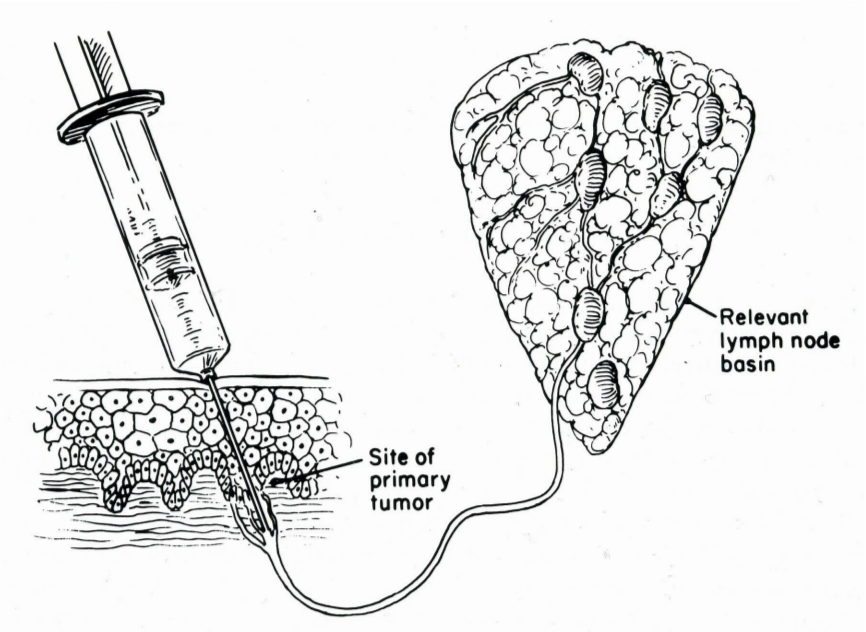


SENTINEL LYMPH NODE

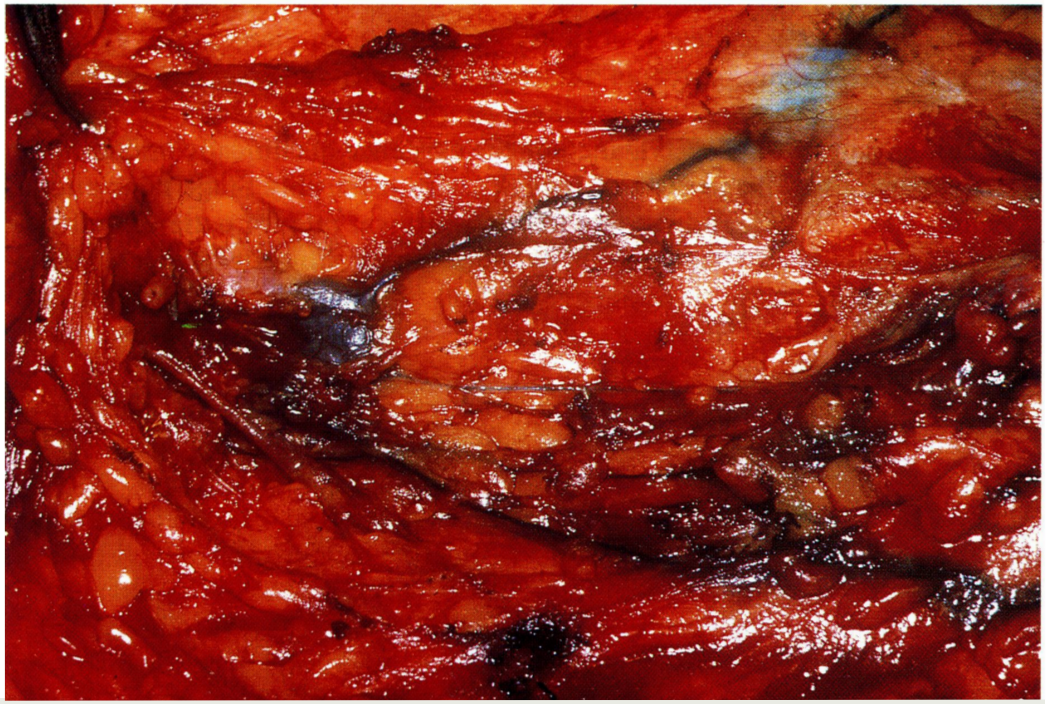
The sentinel lymph node is the first lymph node intercepted by the neoplastic cells of a malignant tumor trough the lymph vessels

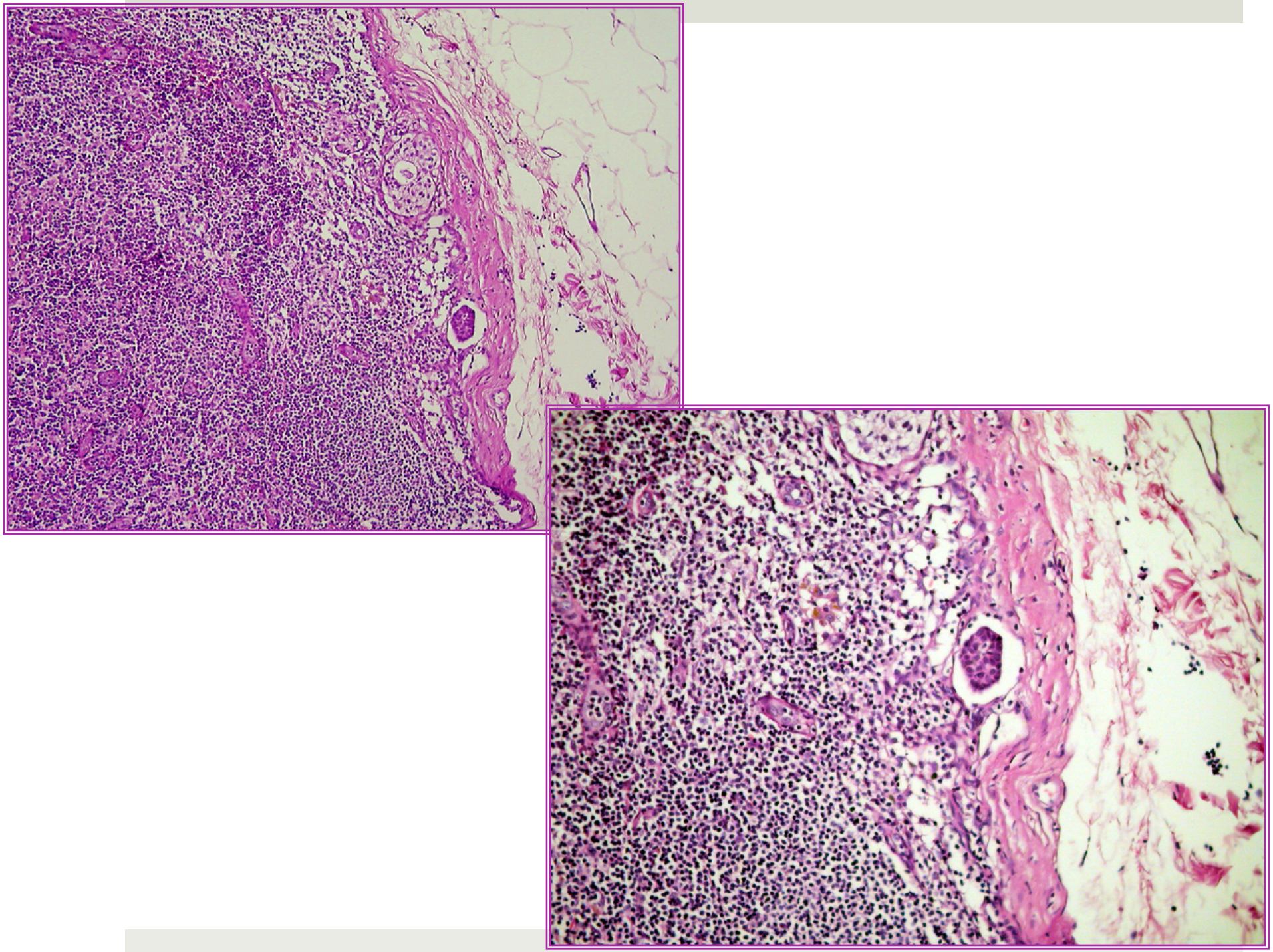
Histological examination of the regional lymph nodes is one of the most important prognostic factors.

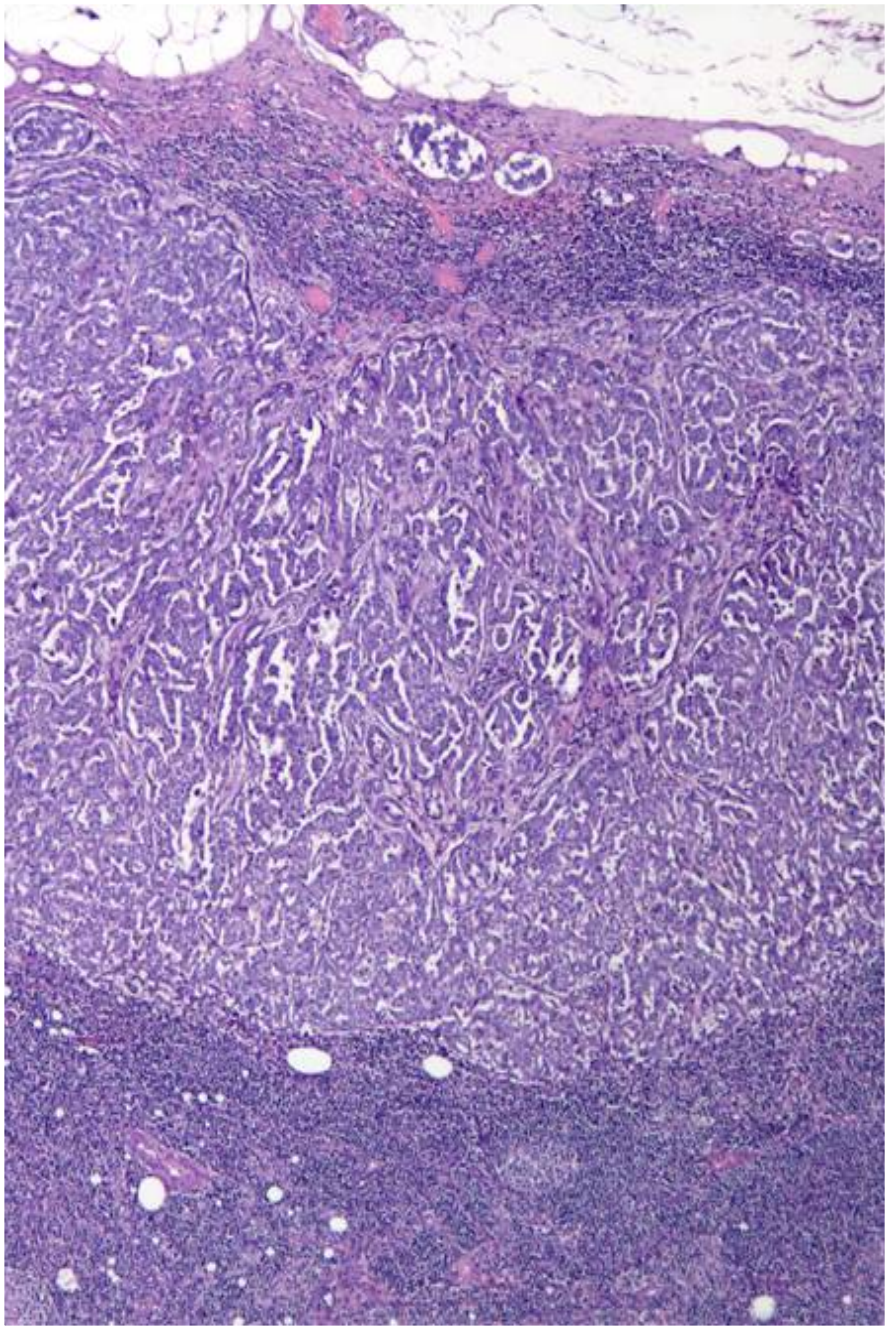
Removal of free lymph nodes during neoplasia negates a possible defensive barrier and causes lymphedema.

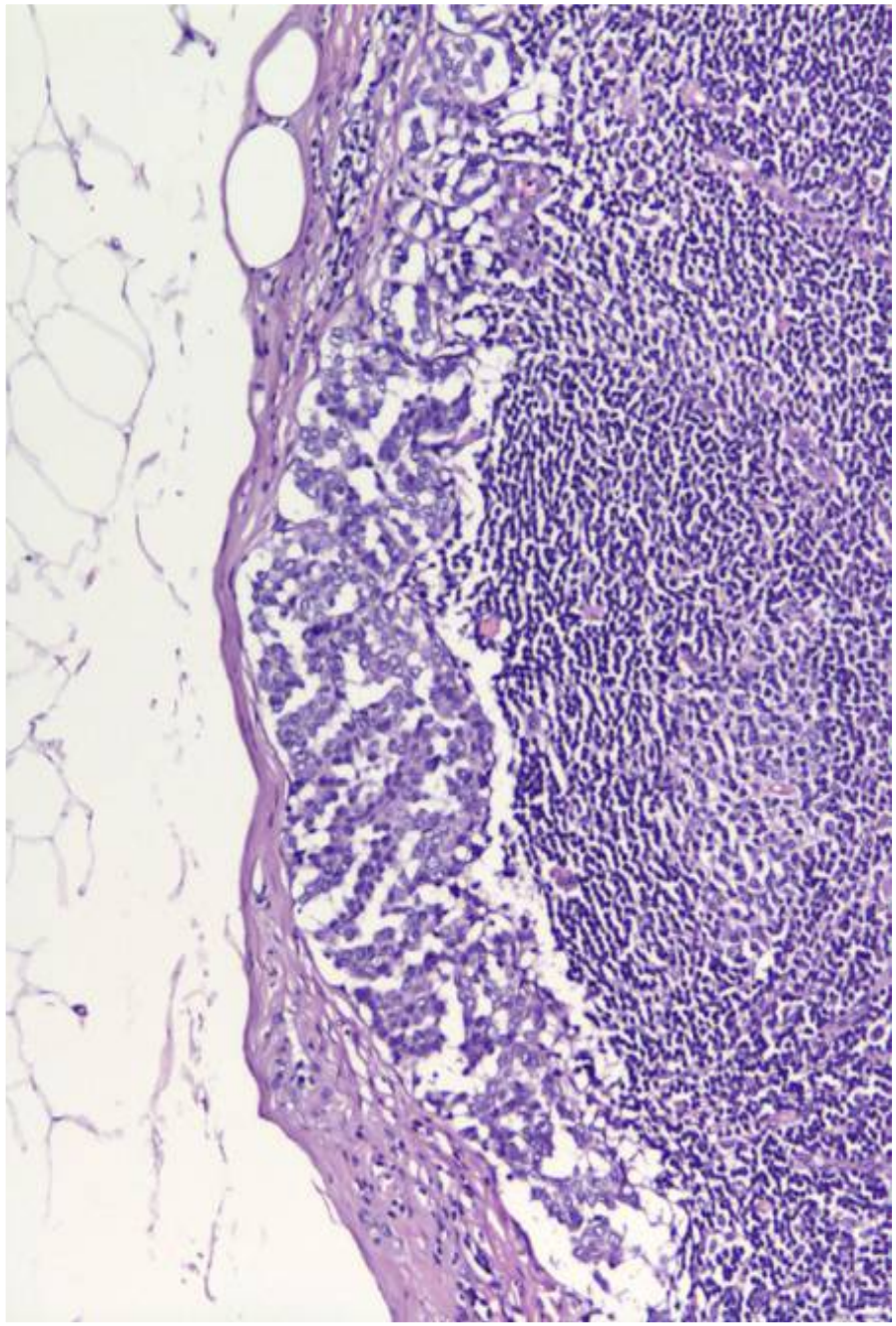


Sentinel lymph node biopsy









STAGING OF MALIGNANT TUMORS

The stage of a malignant tumor describes its extension in the original site and its spread trough the body.

Staging allows:

- evaluation of the stage of the disease;
- prognosis;
- therapeutic planning

The TNM staging system is one of the most widely used.
Approved by **WHO**, **UICC** and **AJCC**

Secondary tumors (metastases)

- Any organ (most favoured: **liver, lung, bone, brain**)
  - **Bone metastases: lythic** (most) / **sclerotic** (prostate, *breast*)
- **Early (pre-clinical), sinchronous, late (metachronous)**
- **Solitary/multiple**
- **Nodular , papillary, diffuse**

STAGING

Clinico (cTNM) – pathologic (pTNM) evaluation of the extension of a tumor

T Tumor diameter or depth of invasion in hollow organ's wall

N Nodes = lymph nodes.
Presence/Absence of metastases in regional lymph nodes

M Metastases

TNM

T – size of the primary tumour and direct extension into nearby tissues

- Tx, T0, T1, T2, T3, T4

N – lymph node metastases

- Nx, N0, N1, N2, N3

M – metastasis to distant organs

- Mx, M0, M1

Descriptors:

is (in situ), **m** (multiple), **y** (following previous treatments), **r** (recurrence), **sn** (sentinel node)