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The principles of tumour classification, grading and staging

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Plan

- Describe the vocabulary of tumour biology and pathology

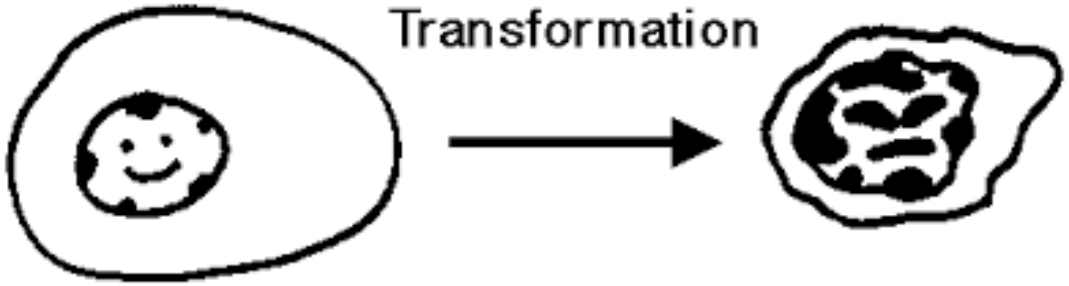
- Review the morphologic characteristics that
  - define neoplasia
  - allow benign and malignant tumours to be identified and distinguished.

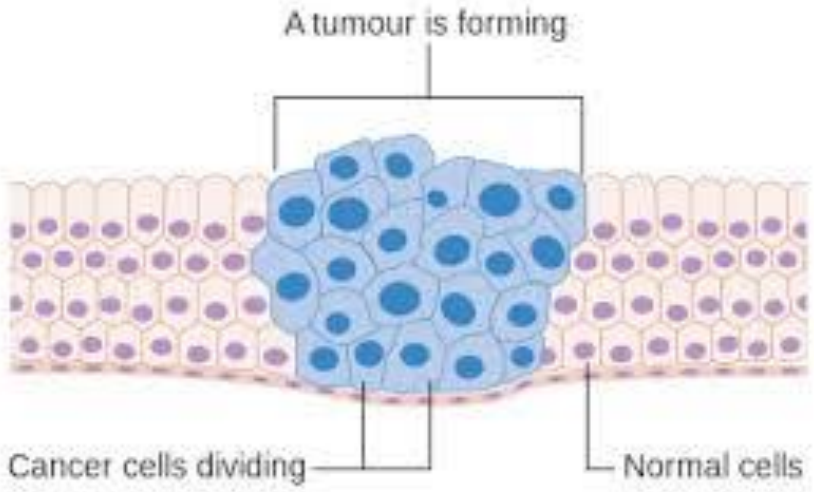
- **Neoplasia** means new growth, and the new growth is called a **neoplasm**.

- **Oncology** is the study of tumours or neoplasms.

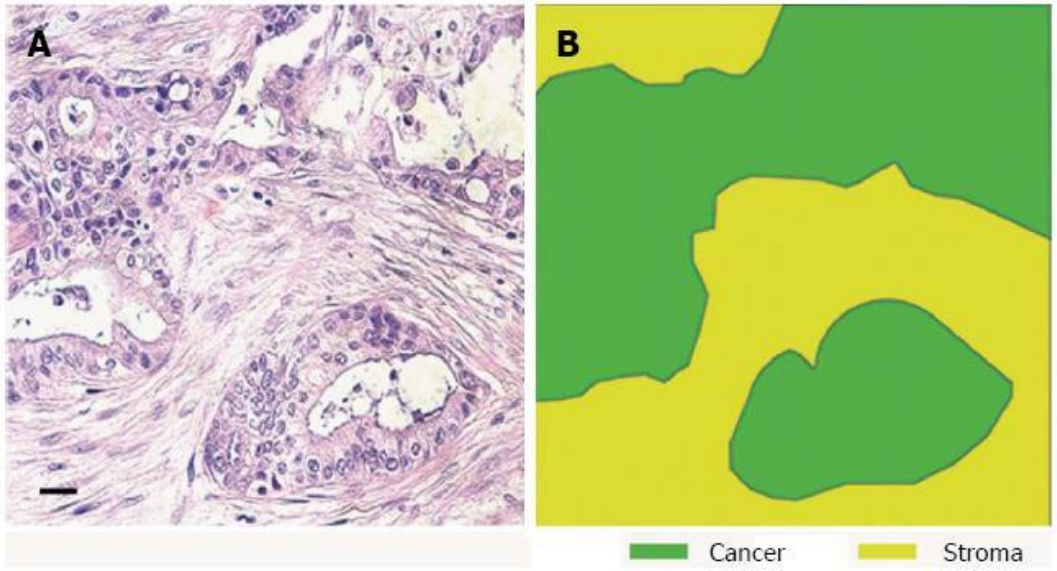
- A **neoplasm**: a disorder of cell growth triggered by a series of acquired mutations affecting a single cell and its clonal progeny.

- The causative mutations give the neoplastic cells a survival and growth advantage, resulting in excessive proliferation that is independent of physiologic growth signals (autonomous).





- All tumours have two basic components:
  - neoplastic cells that constitute the tumour parenchyma
  - reactive stroma made up of connective tissue, blood vessels, and variable numbers of cells of the adaptive and innate immune system.
- The classification of tumours and their biologic behaviour are based primarily on the parenchymal component.

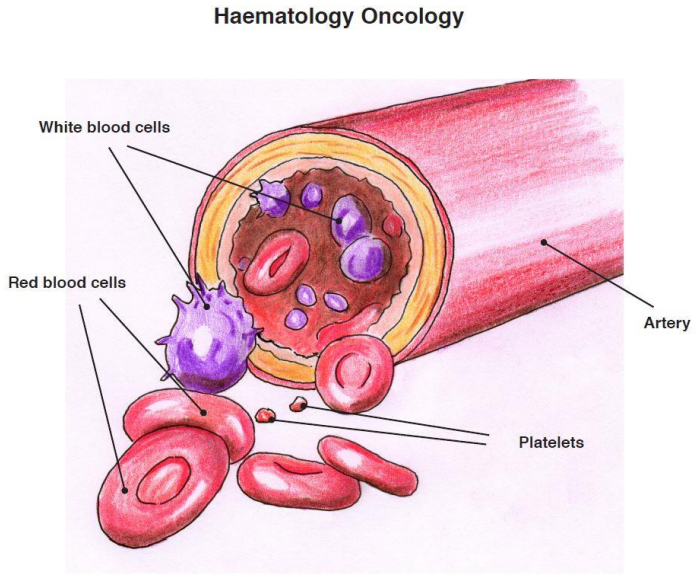


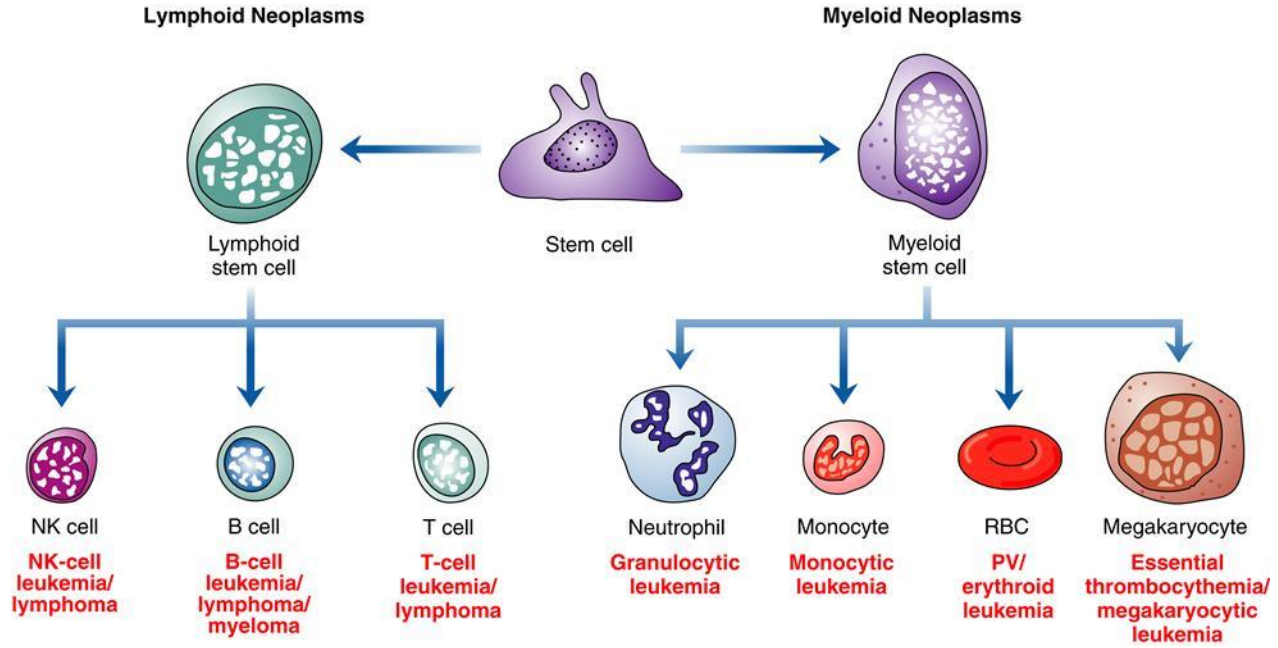
Coleman et al. World J Gastroenterol. 2014; 20(26): 8471-81

Tumour classification

- Haematological tumours: Arising from blood forming cells are called lymphomas of leukemias.

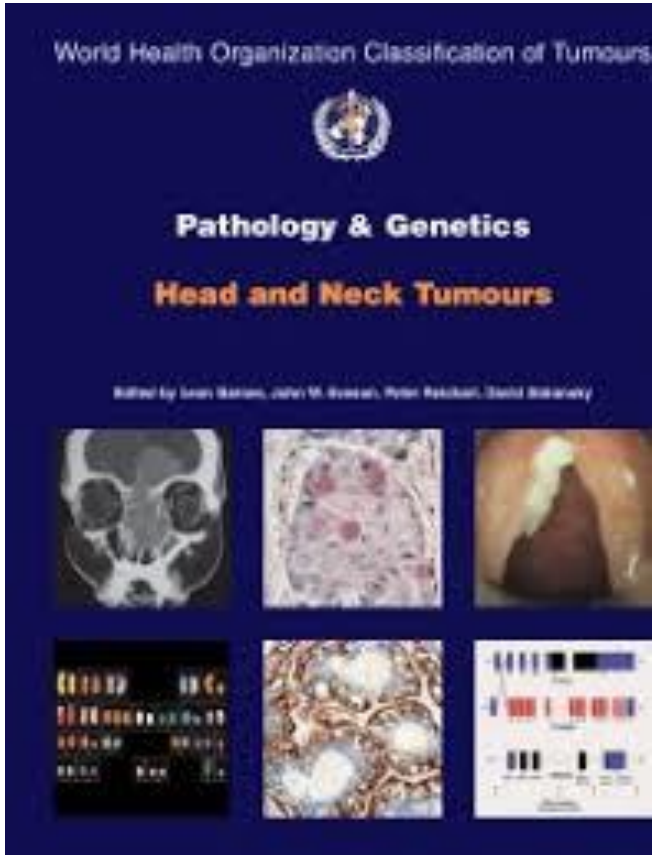
- Solid tumours: Arising from epithelium or mesenchymal tissue.



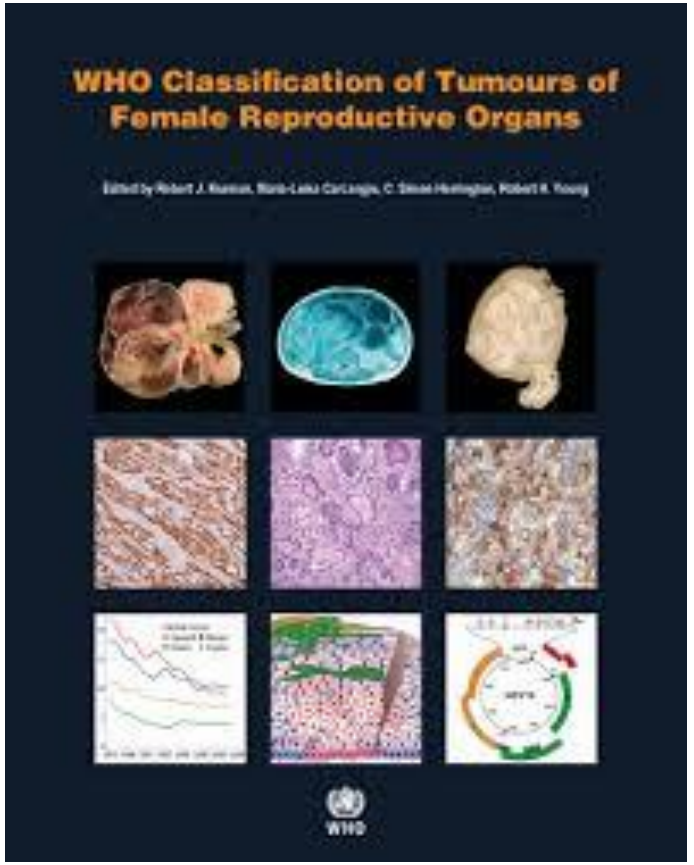


Tumour Classification

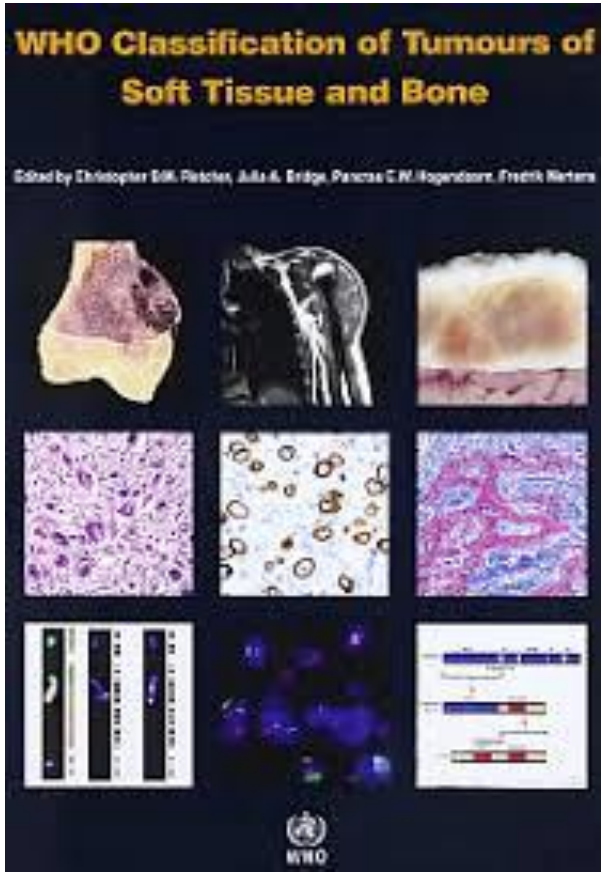
Region



Organ System



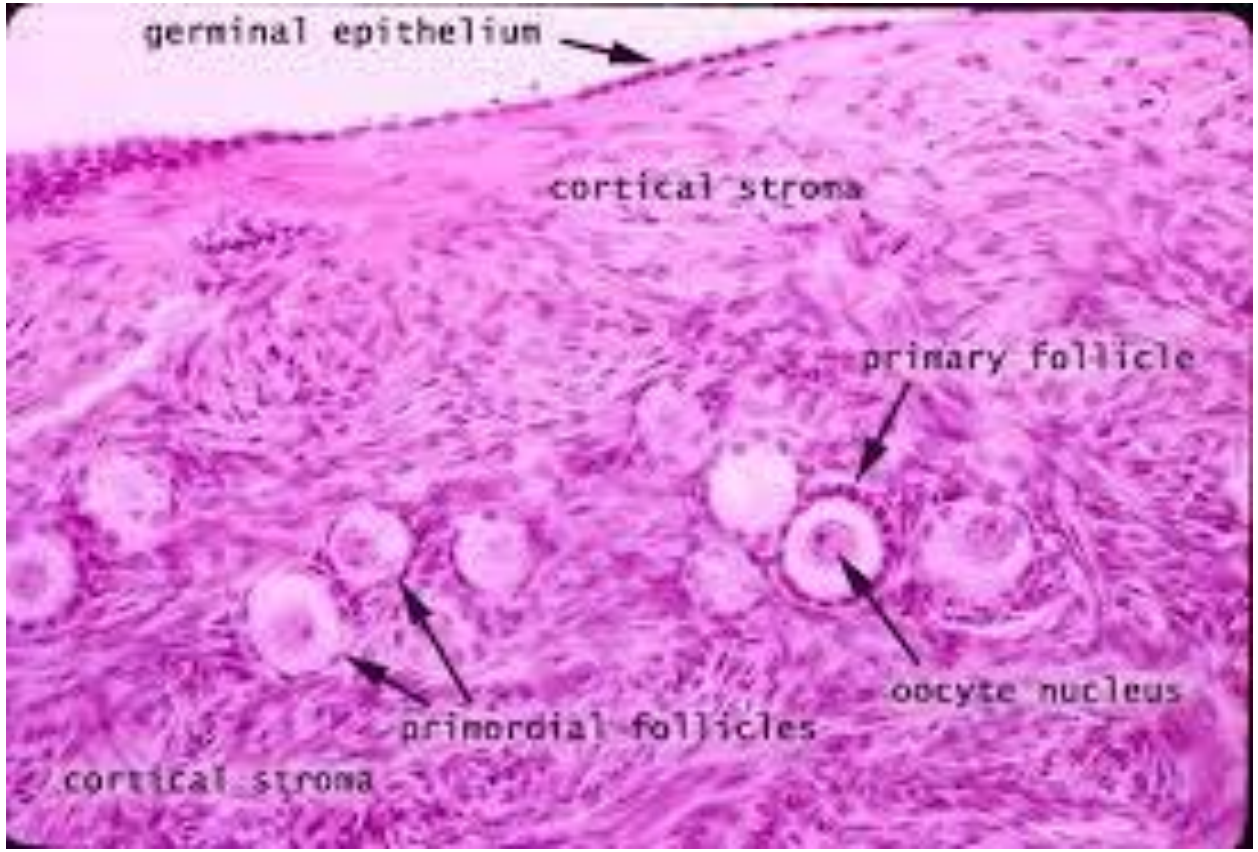
Tissue



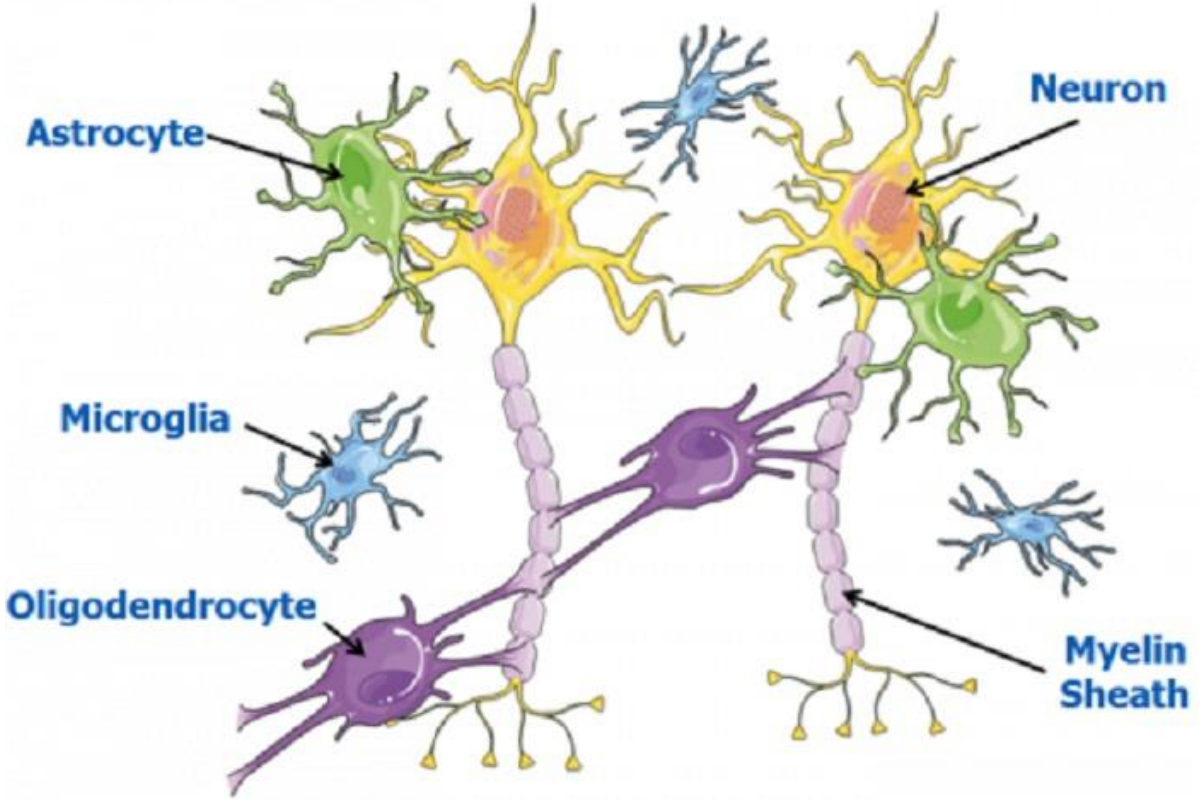
If you know the tissue / organ histological composition you can work out the classification

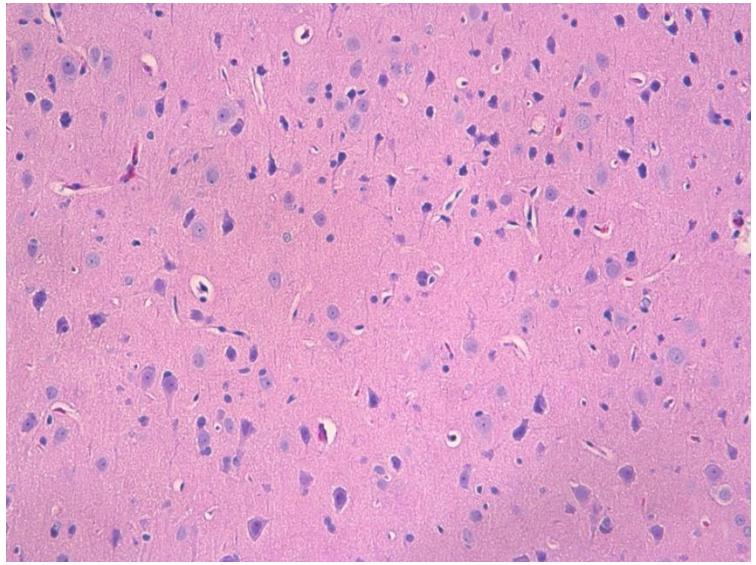
The ovary

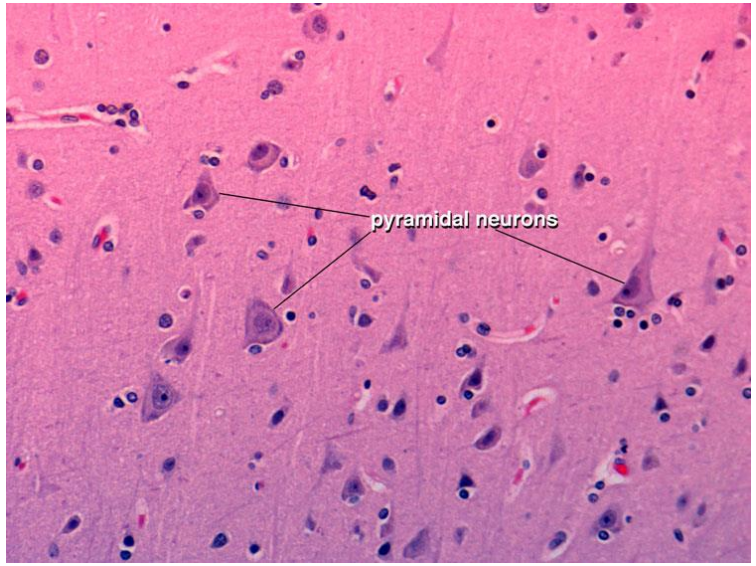
- Epithelial tumours
- Germ cell tumours
- Sex cord stromal tumours

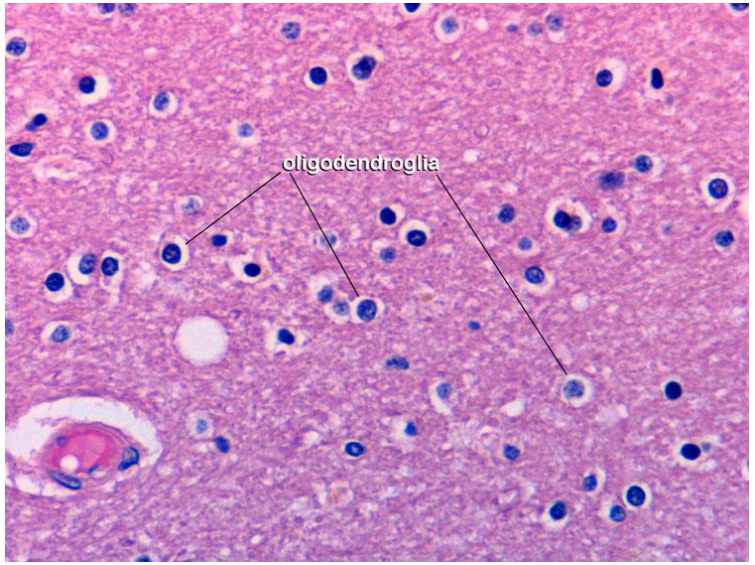


The brain


Astrocyte
Neuron
Microglia
Oligodendrocyte
Myelin Sheath




pyramidal neurons


oligodendroglia

Types of tumour

- Based on biological behaviour
  - Benign
  - Malignant
  - Borderline

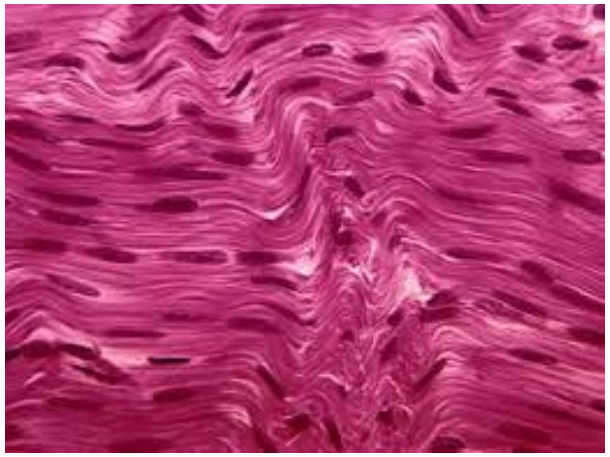
Benign tumours

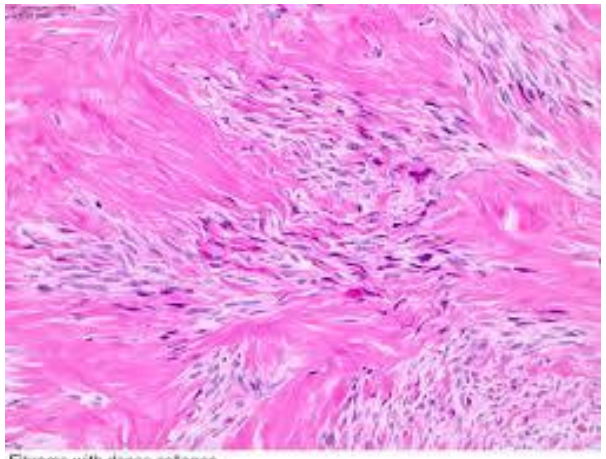
- Tumours that are considered relatively innocent, implying that
  - it will remain localised
  - will not spread to other sites
  - is amenable to local surgical removal.

- However, benign tumours may cause serious morbidity and can be even fatal.

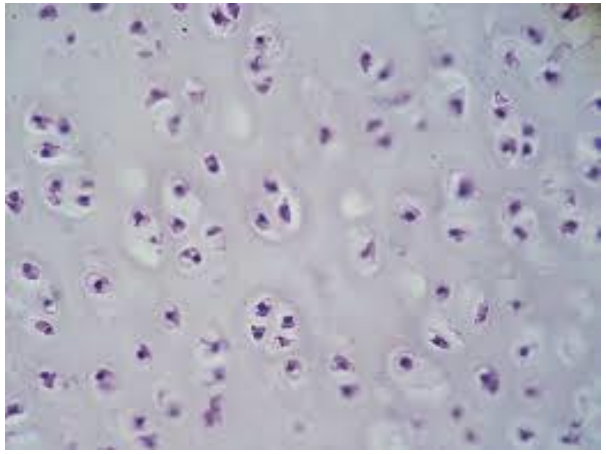
- In general benign tumours are designated by attaching the suffix – oma to the name of the cell type from which the tumour originates.

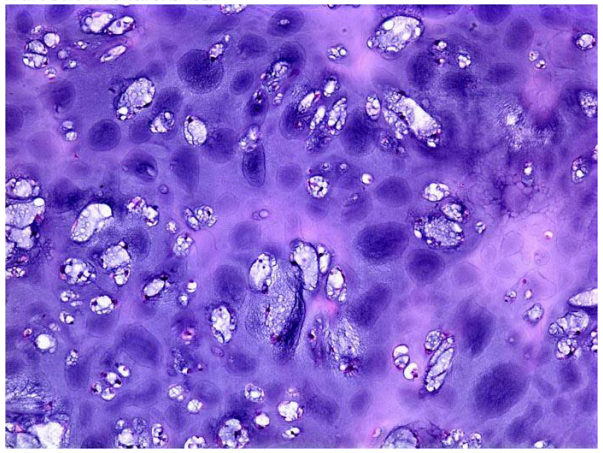
- In meshenchymal tumours For example:
  - tumour arising in fibrous tissue is called fibroma
  - tumour arising from cartilage is called chondroma.



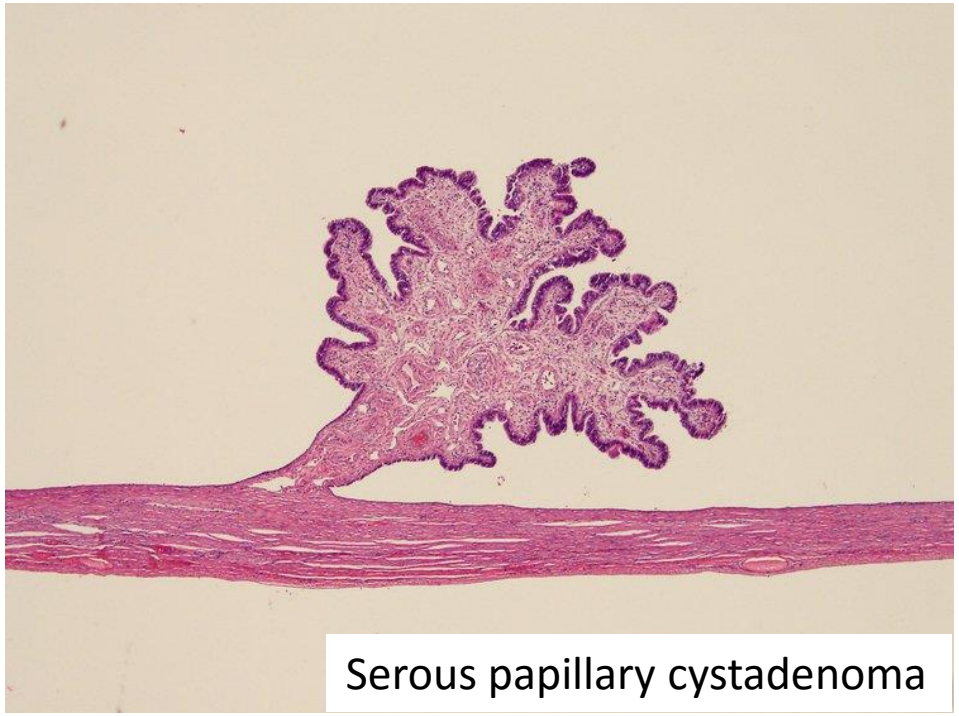


Fibroma with dense collagen

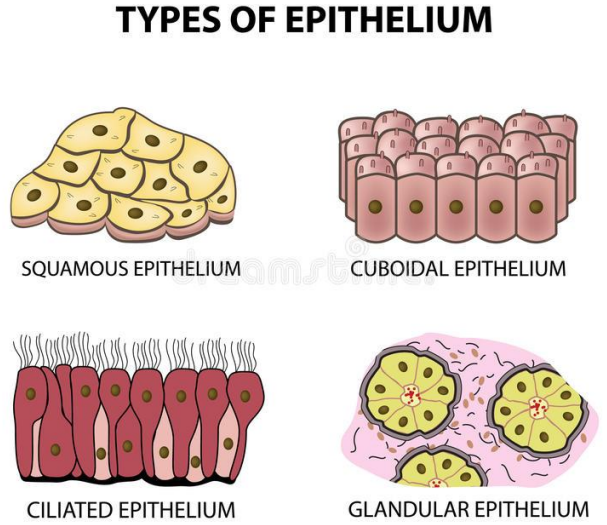


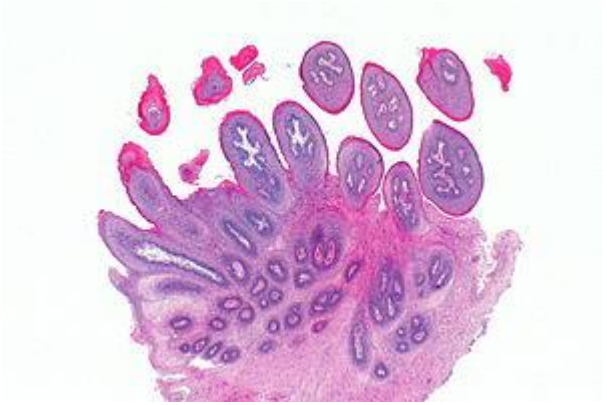


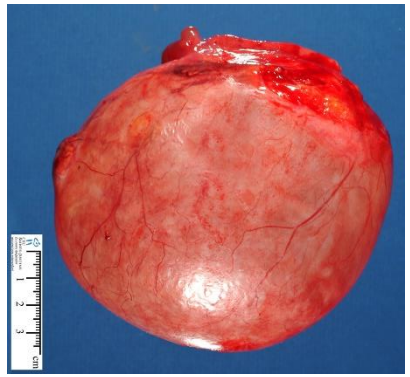
- Nomenclature of epithelial tumours is more complex;
  - some are classified based on their cells of origin: Squamous cell, transitional cell
  - others on microscopic pattern e.g. papillary
  - others on their macroscopic architecture e.g. cystic



Serous papillary cystadenoma

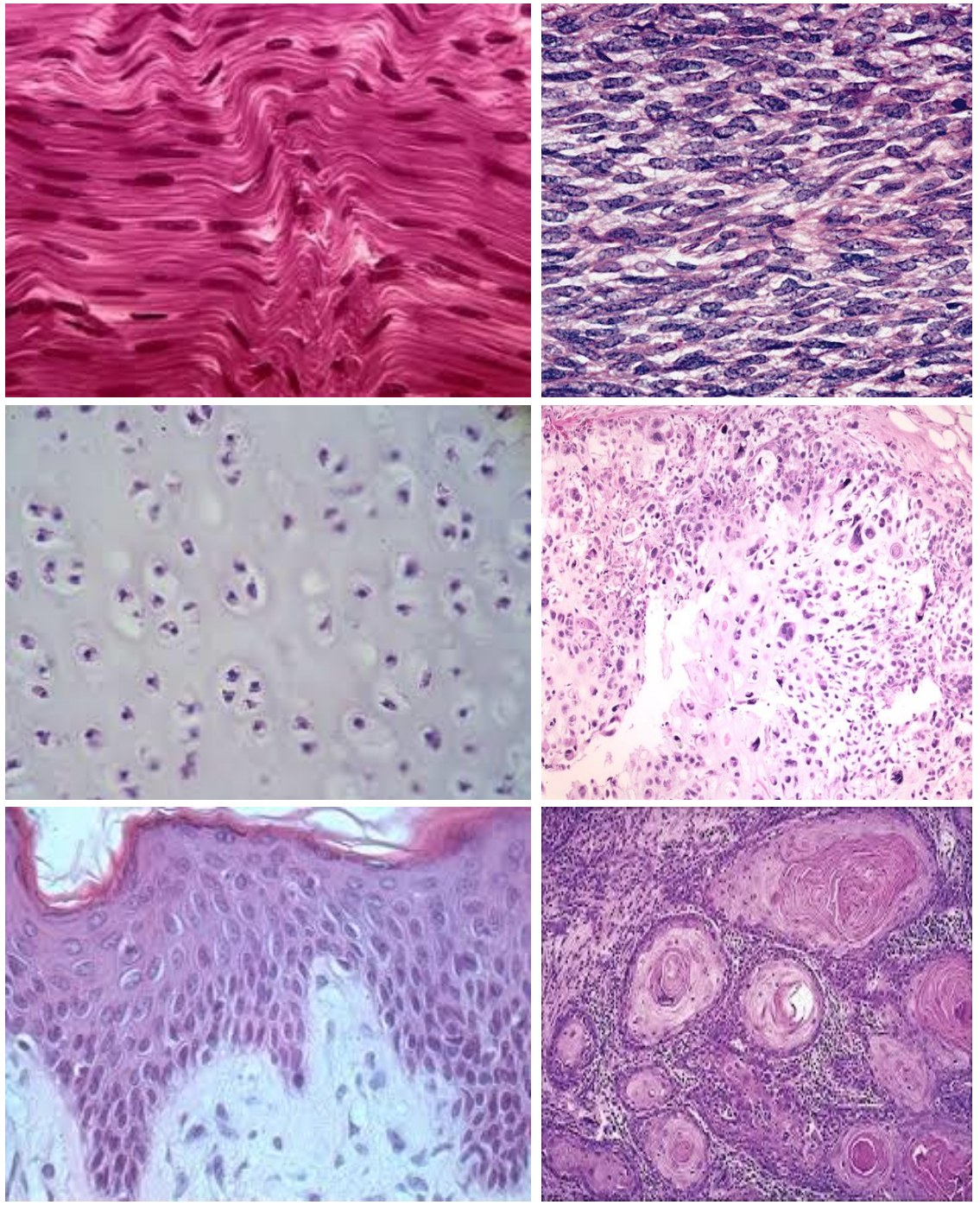




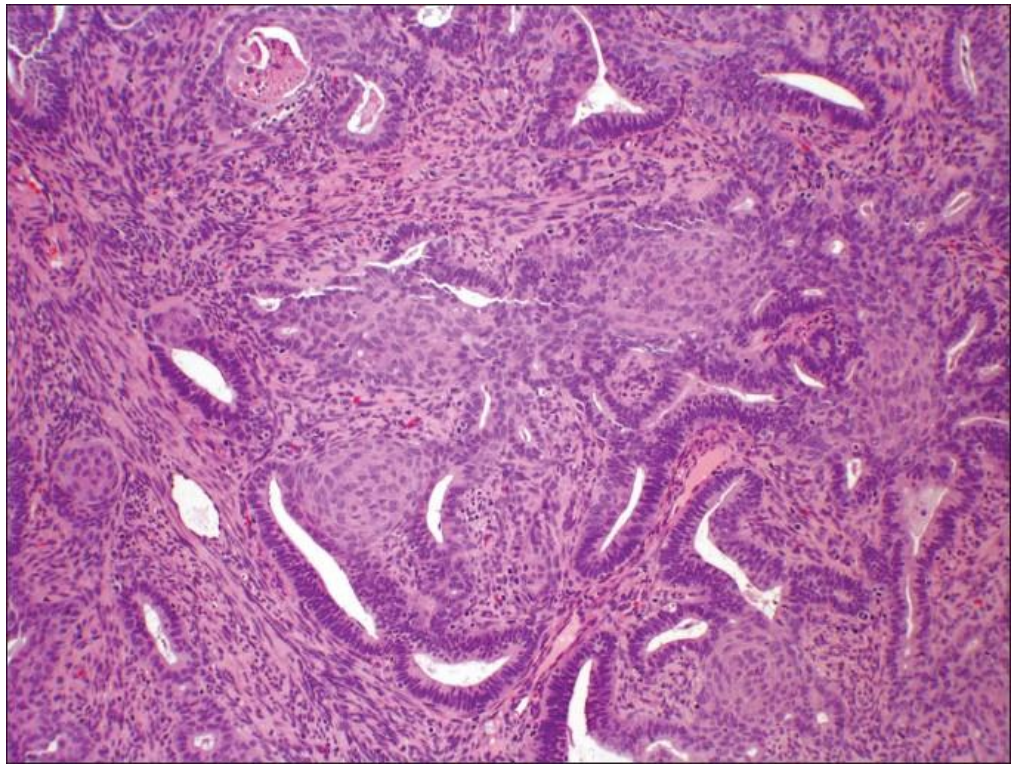


Malignant tumours

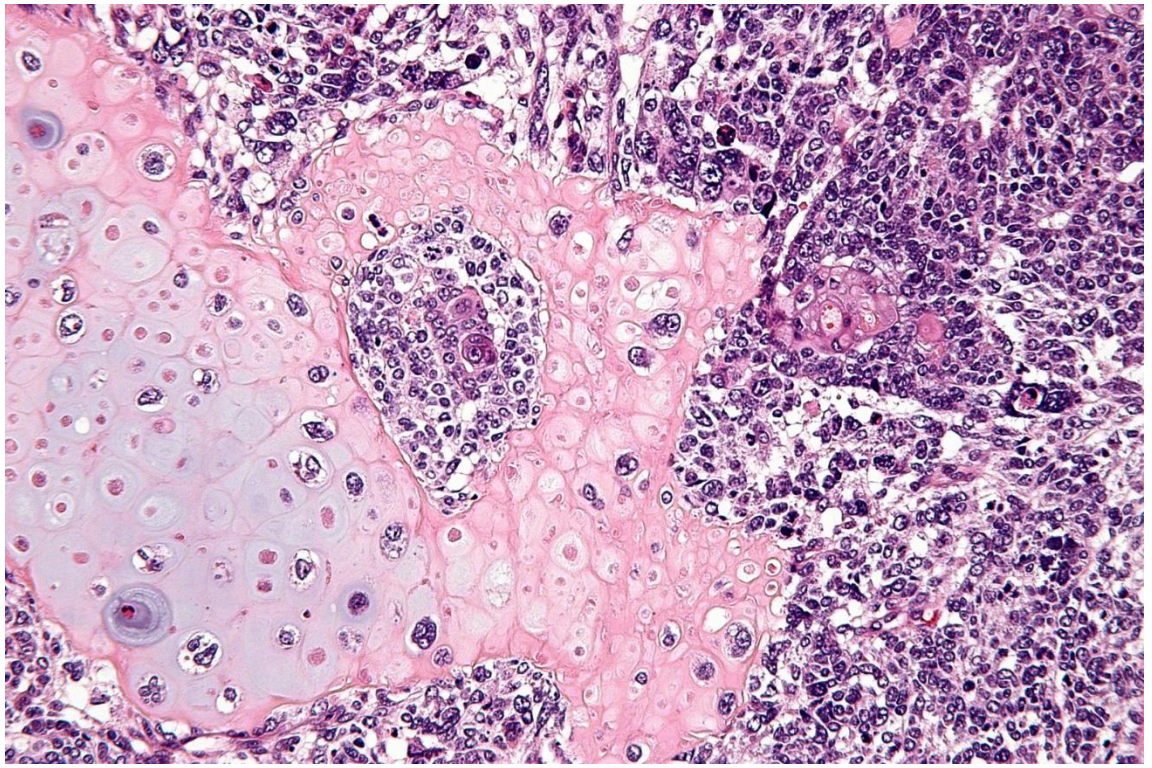
- Are collectively referred to as cancers.
- Malignant tumours can
  - invade and destroy adjacent structures (local spread)
  - spread to distant sites (metastasise).
- Malignant tumours arising in mesenchymal tissue are called sarcomas e.g. fibrosarcoma, chondrosarcoma
- Malignant neoplasms of epithelial cell origins are called carcinomas e.g. squamous cell carcinoma
- Cancer composed of cells of unknown tissue of origin is designated undifferentiated malignant tumour.



Mixed tumours



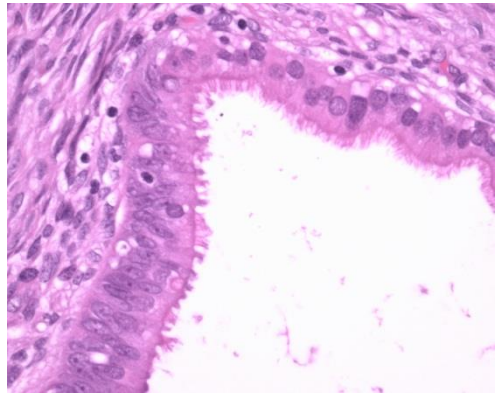
Adenomyoma

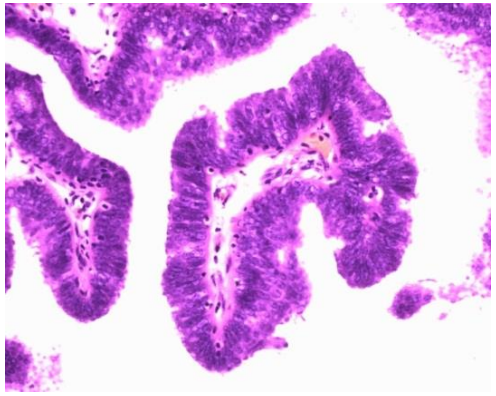


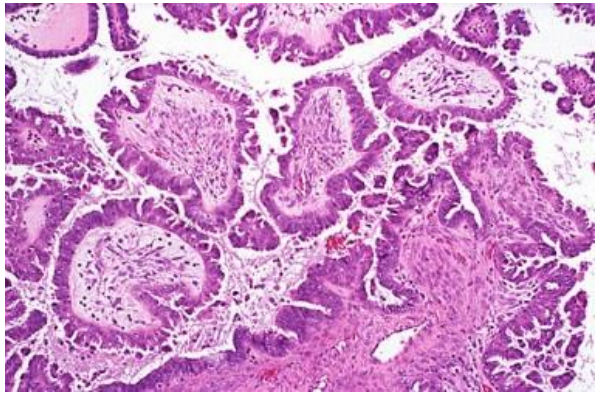
Carcinosarcoma

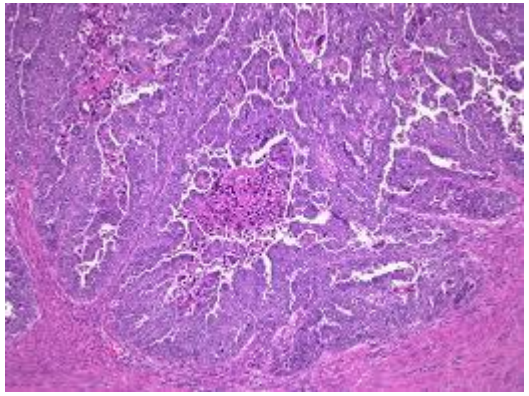
Borderline Tumours

- Tumours whose biologic behaviour cannot be predicted on histologic grounds
- Have very low but definite metastatic potential

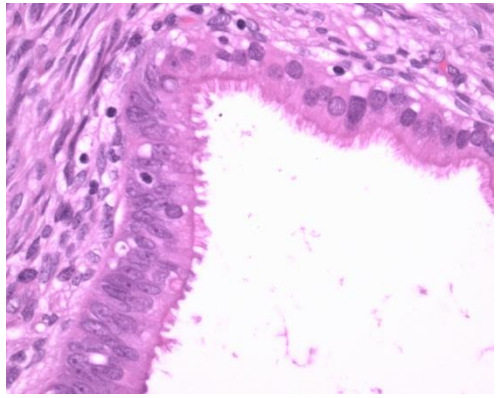
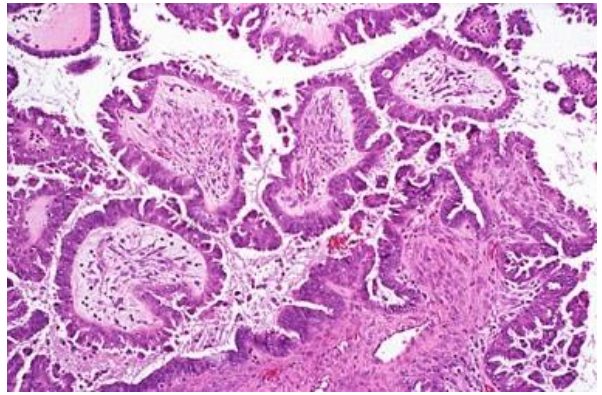
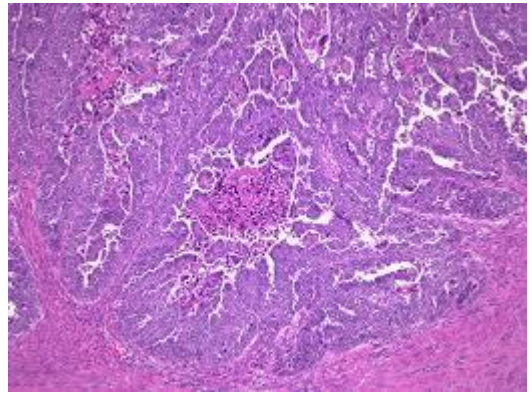




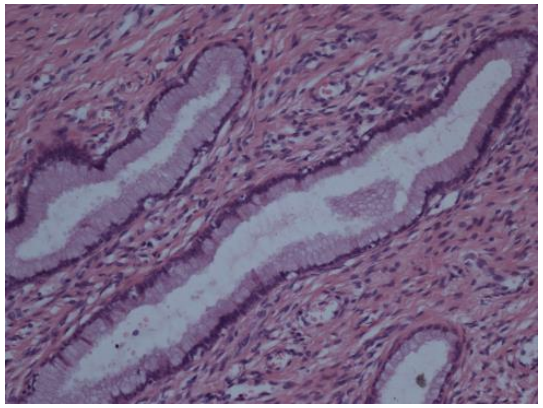




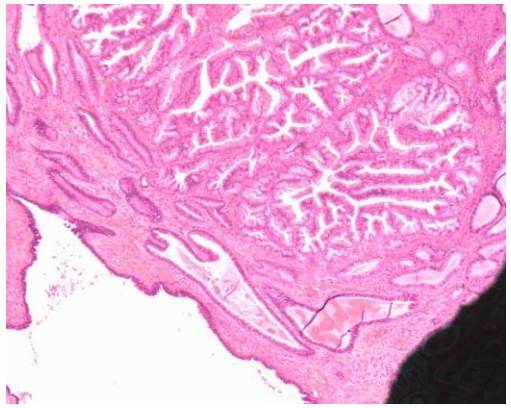
Serous tumours

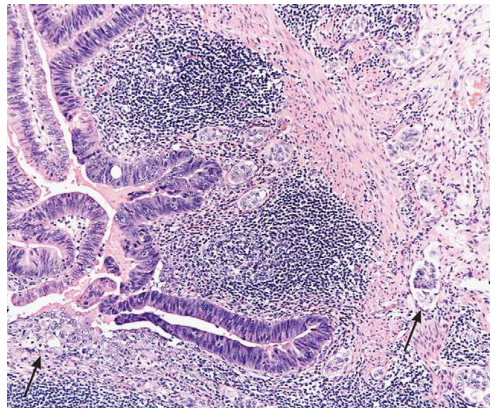
Mucinous tumours



Benign



Borderline



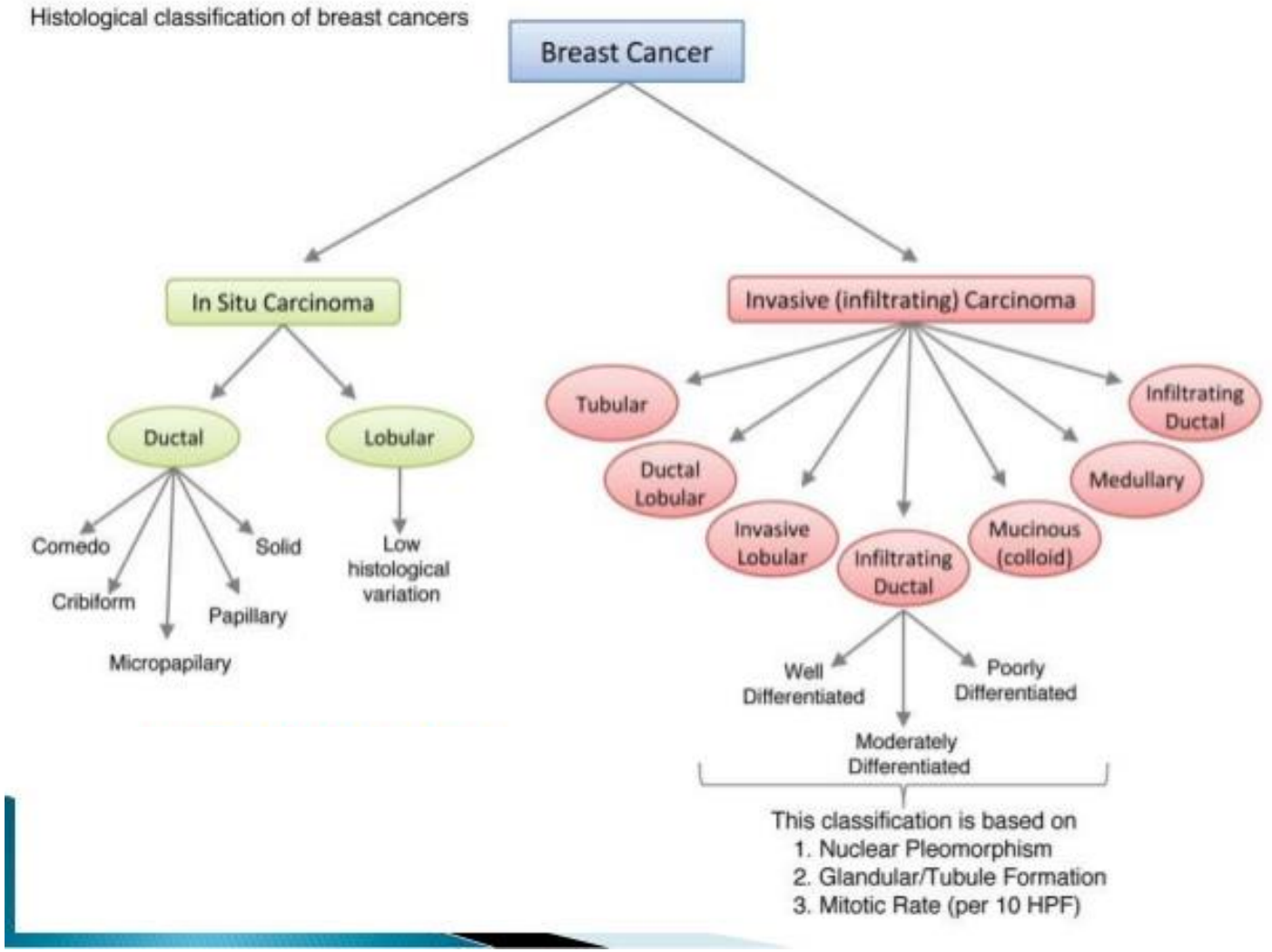
Malignant

- Four classes of normal regulatory genes:
  - The growth promoting proto-oncogenes
  - The growth inhibitory tumour suppressor genes
  - Genes that regulate programmed cell death – apoptosis
  - Genes involved in DNA repair.

These are the principal targets of cancer causing mutations.

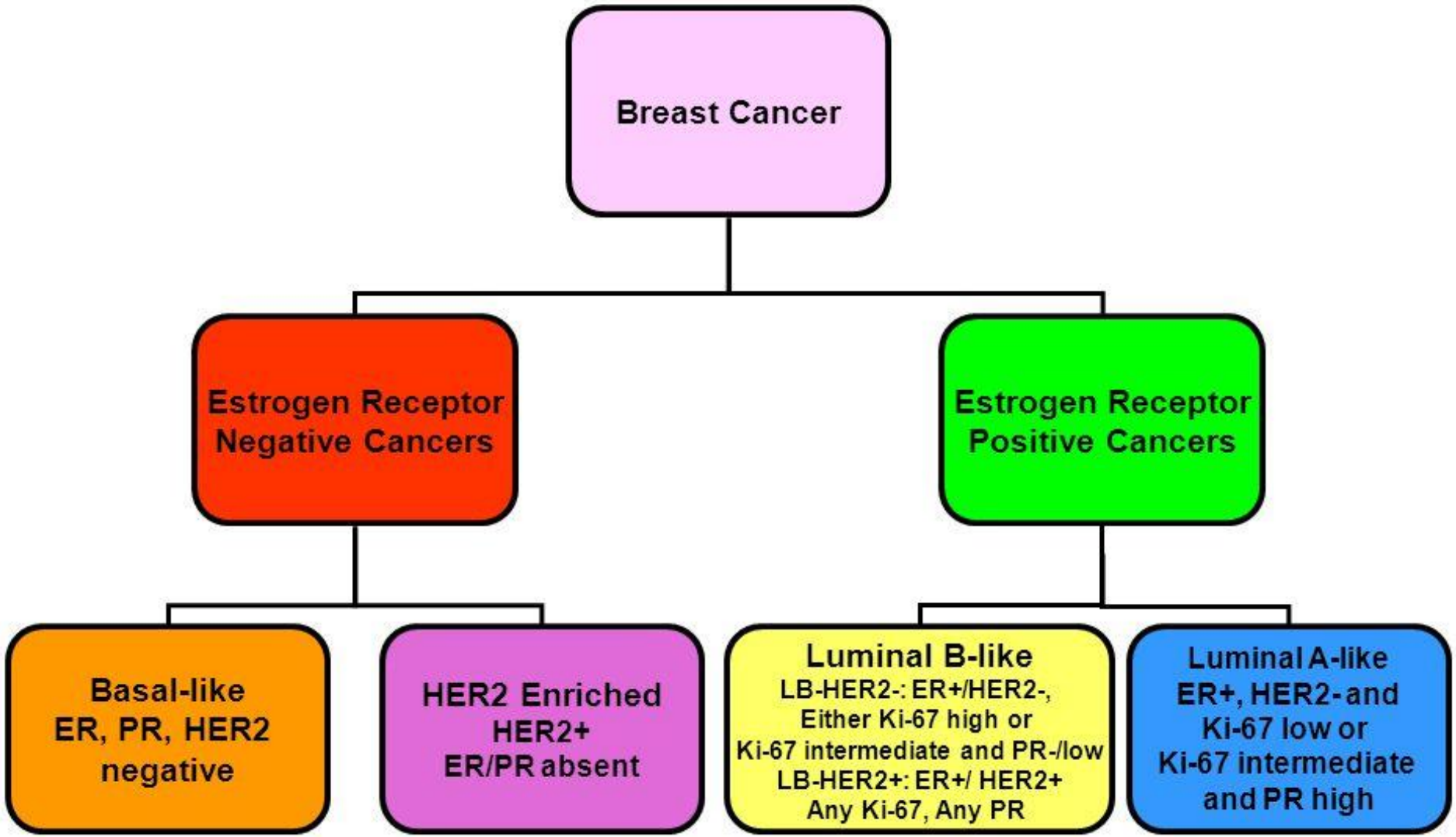
Breast carcinoma = Malignant epithelial tumours

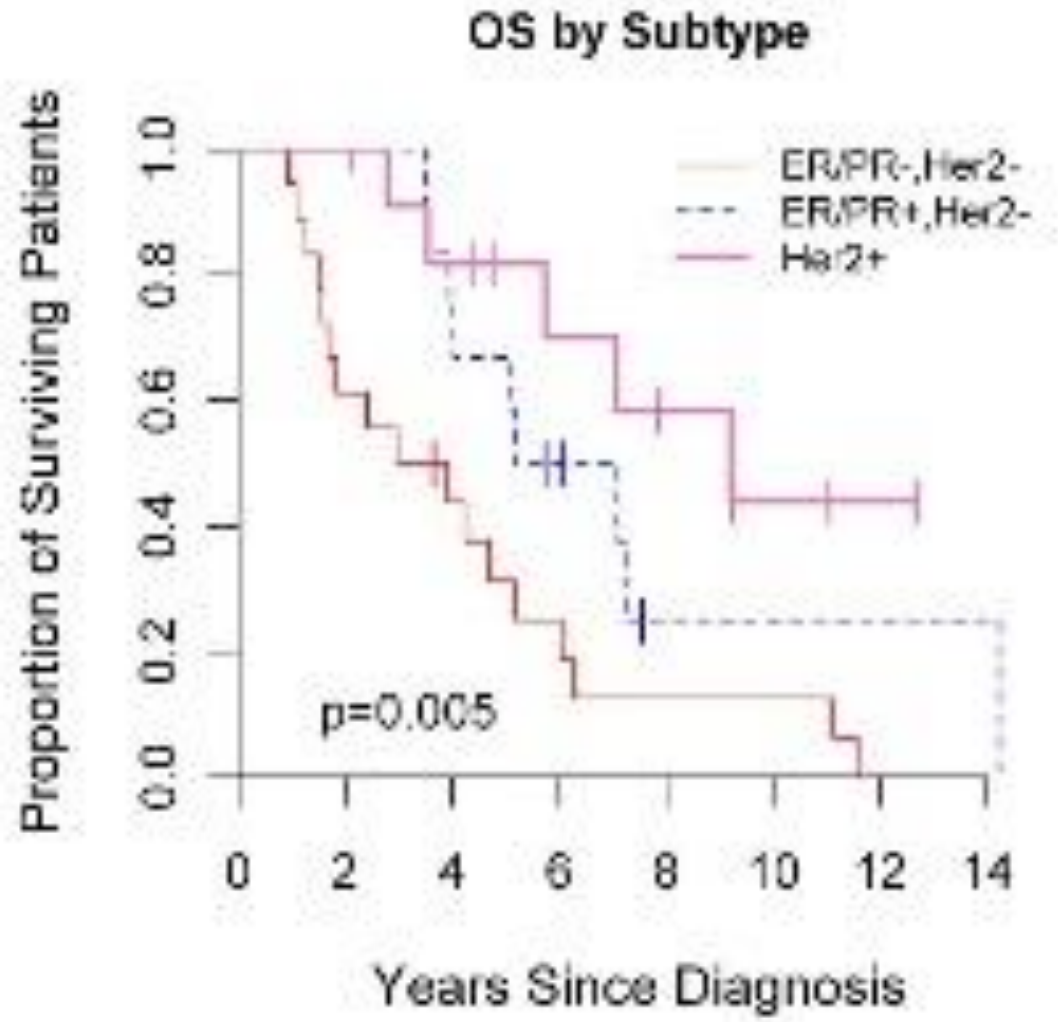
- Histological subtypes:
  - Invasive ductal
  - Invasive lobular
  - Mucinous
  - Tubular
  - Papillary
  - Apocrine
  - Micropapillary
  - Medullary
  - Secretory
  - Inflammatory

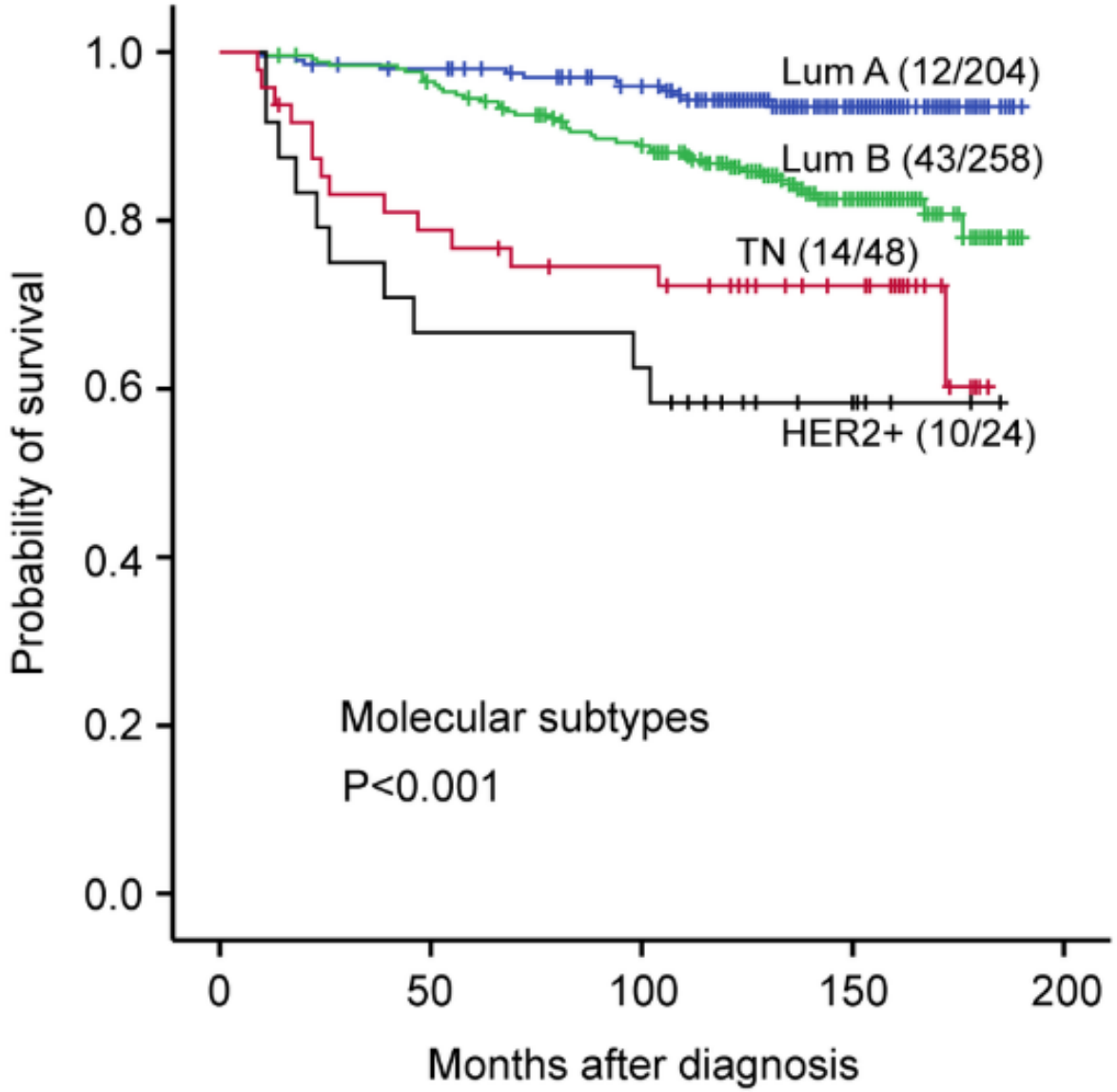


Molecular Classification

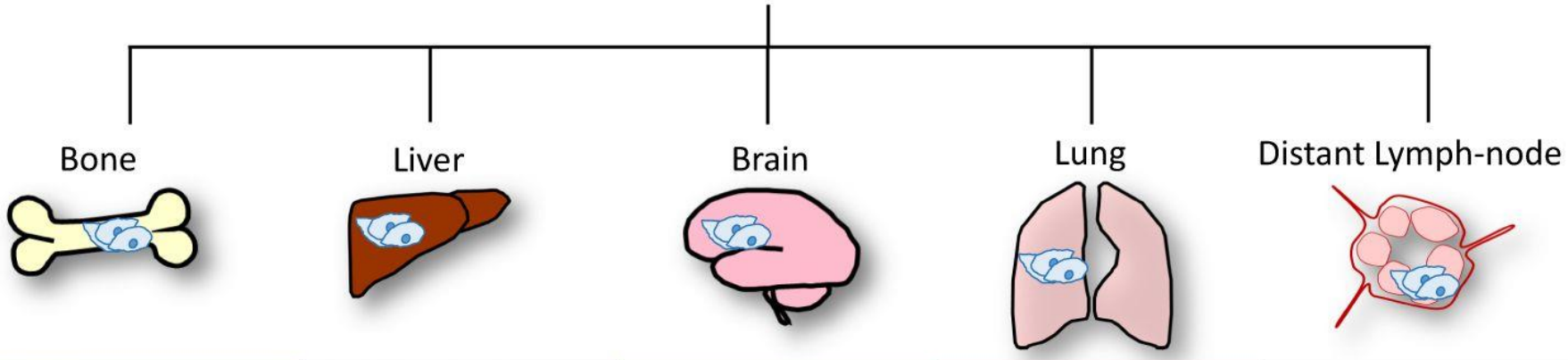
2016




OS by Subtype
Proportion of Surviving Patients
0.0
0.2
0.4
0.6
0.8
1.0
ER/PR-,Her2-
ER/PR+,Her2-
Her2+
p=0.005
0
2
4
6
8
10
12
14
Years Since Diagnosis


Probability of survival
1.0
0.8
0.6
0.4
0.2
0.0
Lum A (12/204)
Lum B (43/258)
TN (14/48)
HER2+ (10/24)
Molecular subtypes
P<0.001
0
50
100
150
200
Months after diagnosis

Breast Cancer Distant Metastases



	Bone	Liver	Brain	Lung	Distant Lymph-node
Associated subtypes	Luminal-HER2	HER2-enriched ER-positive Luminal B Luminal-HER2	HER2-enriched Luminal-HER2 TN-nonbasal Basal-like	TN-nonbasal Basal-like Luminal B HER2+, HR-, p53-	Luminal type HER2-enriched
Molecular features	Growth factors: IGF1, PGE2, TGFβ, PDGF and FGF2 Interleukins: IL-11, IL-1, IL-6 PTHrP OPN Heparanase RANKL-RANK pathway Src-dependent pathway	Chemokines and receptors: CXCR4/CXCL12 Interleukins: IL-6 Integrin complexes: α2β1, α5β1 N-cadherin HIF-regulated genes: LOX, OPN, VEGF, TWIST β-catenin-independent WNT signaling Downregulation of ECM (stromal) genes	ST6GALNAC5 CSC markers: Nestin, CD133, and CD44 Growth factors: VEGF and HBEGF Chemokines and receptors: CXCR4 Cytokines: CK5 MMP-1 and MMP-9 IL-8 Ang-2 COX2 L1CAM	Growth factors and their receptors: TGFβ, EGFR, EREG, VEGF Matrix metalloproteinases: MMP-1 and MMP-2 COX2 LOX BMP inhibitors: GALNTs and Coco	Kallikreins: KLK10, KLK11, KLK12, and KLK13 Downregulation of BCR signal pathway

WHO classification of tumours of the kidney

Renal cell tumours	
Clear cell renal cell carcinoma	8310/3
Multilocular cystic renal neoplasm of low malignant potential	8316/1*
Papillary renal cell carcinoma	8260/3
Hereditary leiomyomatosis and renal cell carcinoma–associated renal cell carcinoma	8311/3*
Chromophobe renal cell carcinoma	8317/3
Collecting duct carcinoma	8319/3
Renal medullary carcinoma	8510/3*
MiT family translocation renal cell carcinomas	8311/3*
Succinate dehydrogenase–deficient renal carcinoma	8311/3
Mucinous tubular and spindle cell carcinoma	8480/3*
Tubulocystic renal cell carcinoma	8316/3*
Acquired cystic disease–associated renal cell carcinoma	8316/3
Clear cell papillary renal cell carcinoma	8323/1
Renal cell carcinoma, unclassified	8312/3
Papillary adenoma	8260/0
Oncocytoma	8290/0
Metanephric tumours	
Metanephric adenoma	8325/0
Metanephric adenofibroma	9013/0
Metanephric stromal tumour	8935/1
Nephroblastic and cystic tumours occurring mainly in children	
Nephrogenic rests	
Nephroblastoma	8960/3
Cystic partially differentiated nephroblastoma	8959/1
Paediatric cystic nephroma	8959/0
Mesenchymal tumours	
Mesenchymal tumours occurring mainly in children	
Clear cell sarcoma	8964/3
Rhabdoid tumour	8963/3
Congenital mesoblastic nephroma	8960/1
Ossifying renal tumour of infancy	8967/0
Mesenchymal tumours occurring mainly in adults	
Leiomyosarcoma	8890/3
Angiosarcoma	9120/3
Rhabdomyosarcoma	8900/3
Osteosarcoma	9180/3
Synovial sarcoma	9040/3
Ewing sarcoma	9364/3
Angiomyolipoma	8860/0
Epithelioid angiomyolipoma	8860/1*
Leiomyoma	8890/0
Haemangioma	9120/0
Lymphangioma	9170/0
Haemangioblastoma	9161/1
Juxtaglomerular cell tumour	8361/0
Renomedullary interstitial cell tumour	8966/0
Schwannoma	9560/0
Solitary fibrous tumour	8815/1
Mixed epithelial and stromal tumour family	
Cystic nephroma	8959/0
Mixed epithelial and stromal tumour	8959/0
Neuroendocrine tumours	
Well-differentiated neuroendocrine tumour	8240/3
Large cell neuroendocrine carcinoma	8013/3
Small cell neuroendocrine carcinoma	8041/3
Phaeochromocytoma	8700/0
Miscellaneous tumours	
Renal haematopoietic neoplasms	
Germ cell tumours	
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.
*New code approved by the IARC/WHO Committee for ICD-O.

Molecular profiles of tumours – the future of cancer diagnostics

- Until recently, molecular studies of tumours involved the analysis of individual genes.

- Now there are technologies that can rapidly
  - sequence an entire **genome**
  - assess epigenetic modifications genome wide (the **epigenome**)
  - quantify all of the RNAs expressed in a cell population (the **trancriptome**)
  - measure many proteins simultaneously (the **proteome**)
  - take a snapshot of all of the cell's metabolites (the **metabolome**)

- The age of **omics**.

The cancer genome atlas (TCGA)

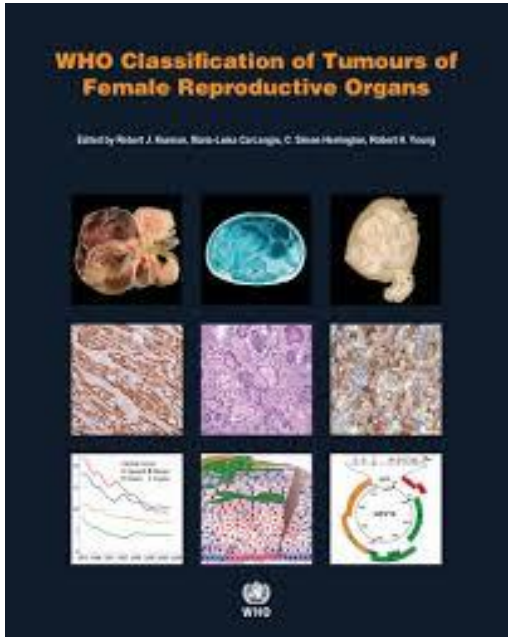
- A consortium sponsored by the National Cancer Institute to do systemic sequencing and cataloguing of genomic alterations in various human cancers.

- Outcomes:

 - identification of new mutations and genetic changes that underlie various cancers.

Endometrial carcinoma 2014 WHO classification

- **Endometrioid carcinoma:**
  - Squamous
  - Villoglandular
  - Secretory
  - Mucinous carcinoma
- **Serous endometrial intraepithelial carcinoma**
- **Serous carcinoma**
- **Clear cell carcinoma**
- **Neuroendocrine tumours**
  - Low grade neuroendocrine tumour
    - carcinoid tumour
  - High grade neuroendocrine carcinoma
    - Small cell neuroendocrine carcinoma
    - Large cell neuroendocrine carcinoma
- **Mixed cell adenocarcinoma**
- **Undifferentiated carcinoma**
- **Dedifferentiated**



The Cancer Genome Atlas (TCGA)

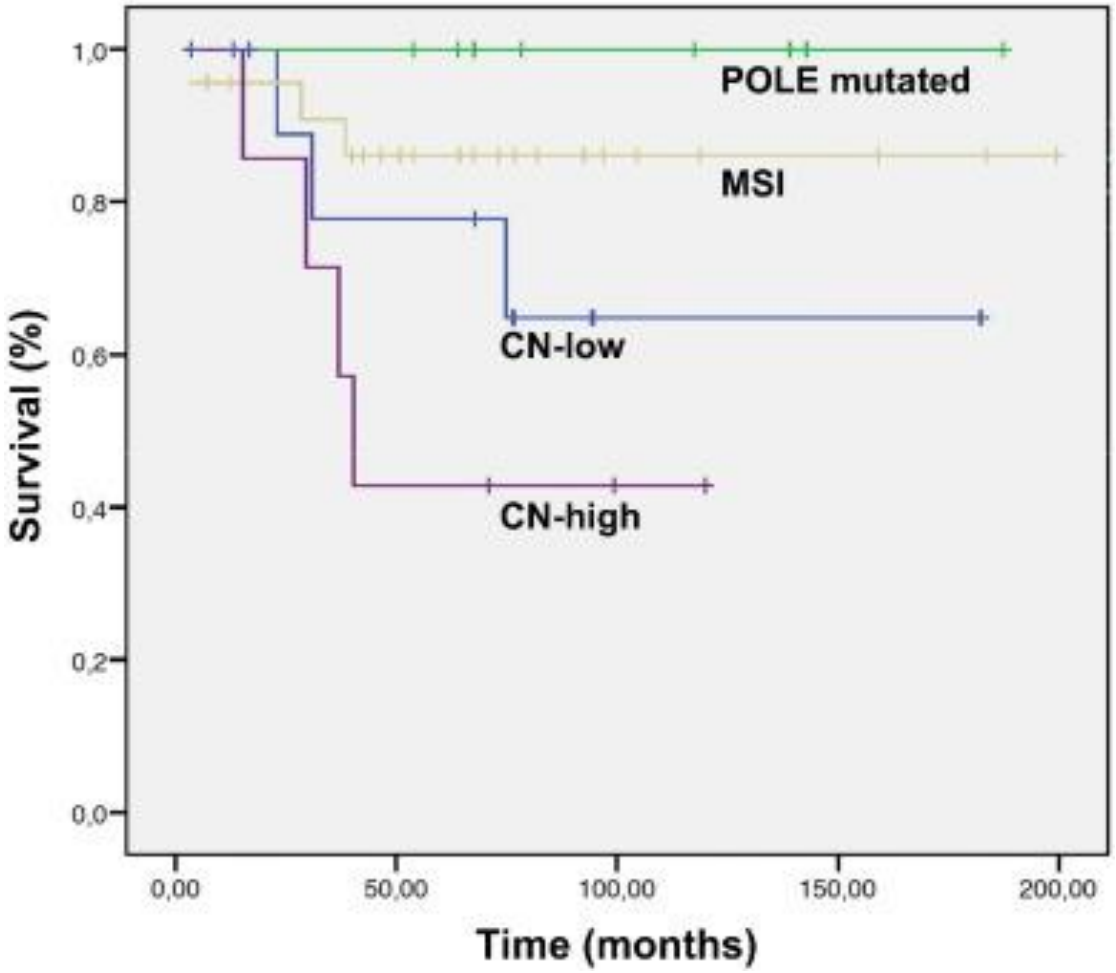
- On the basis of integration of mutation spectra, copy number alterations and microsatellite instability, ECs were categorized into four genomic subtypes

  with significant differences in prognosis.

  - **Group 1** comprised EEC with mutations in *POLE* (Polymerase E- ultramutated)
  - **Group 2** comprised EEC with MSI (hypermutated)
  - **Group 3** tumours comprised EEC with low copy number alterations
  - **Group 4** (serous-like) tumours show *TP53* mutations and high copy number alterations [Composed mostly of SCs, but also include some EEC; many grade 3 but also some grades 1 and 2]

- These subtypes can be reliably delineated and carry significant prognostic as well as predictive information – potential for clinical practice incorporation.

- Group 1 are highly prognostically favourable; group 2 and 3 have intermediate prognosis and group 4 are highly aggressive.

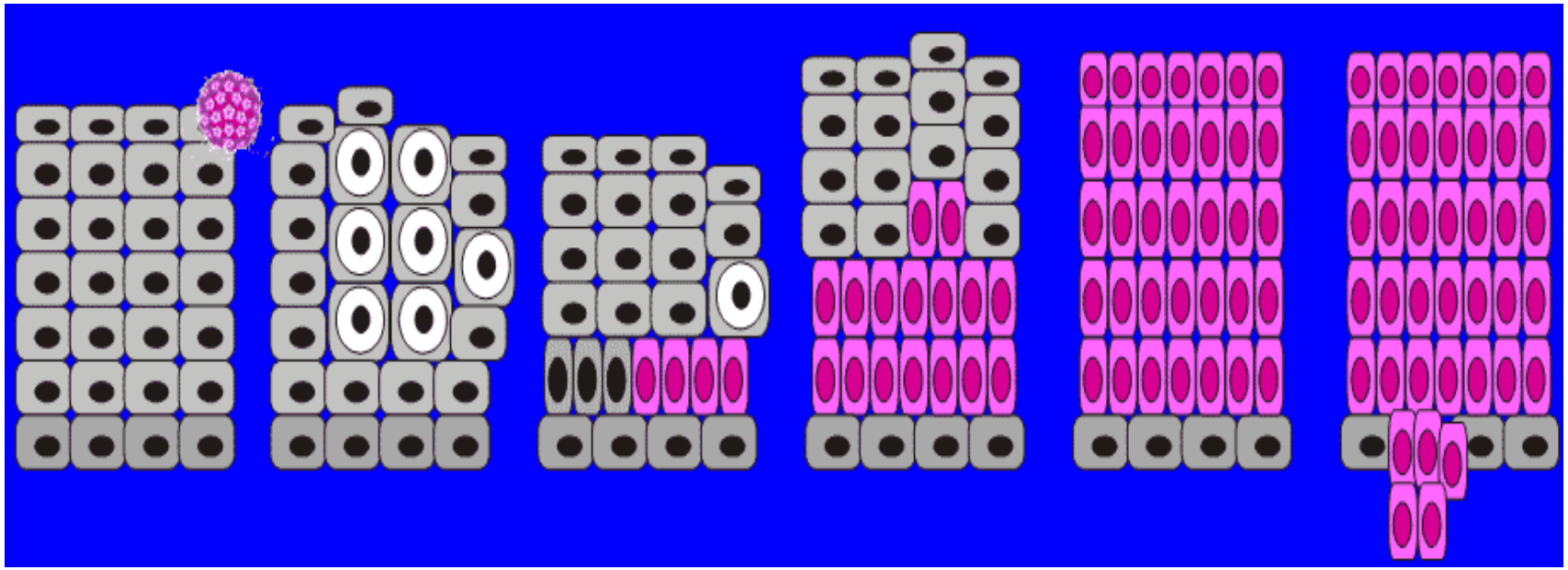


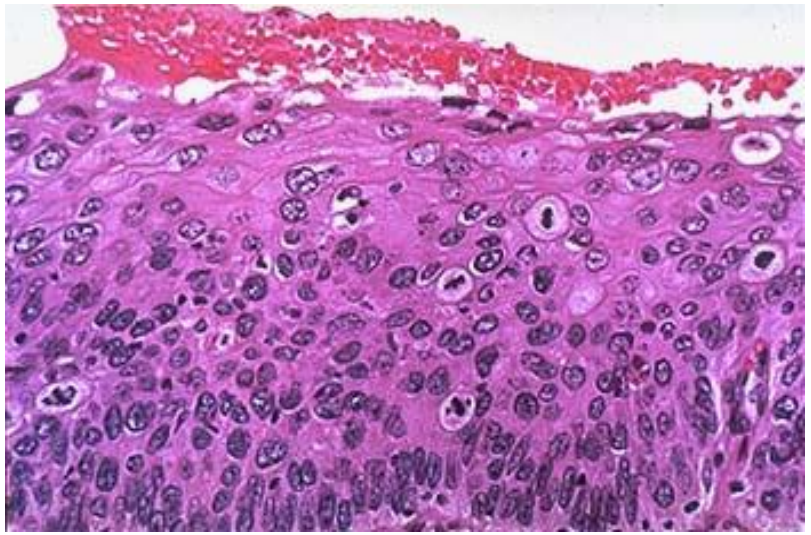
Dysplasia – disordered growth

- Dysplasia may be a precursor to malignant transformation; it does not always progress to cancer, and may be reversible.

- When dysplastic changes are marked and involve the full thickness of the epithelium, but the lesion does not penetrate the basement membrane it is considered a pre-invasive neoplasm and is referred to as carcinoma in situ.

- Once the tumour cells invade the basement membrane the tumour is said to be invasive.





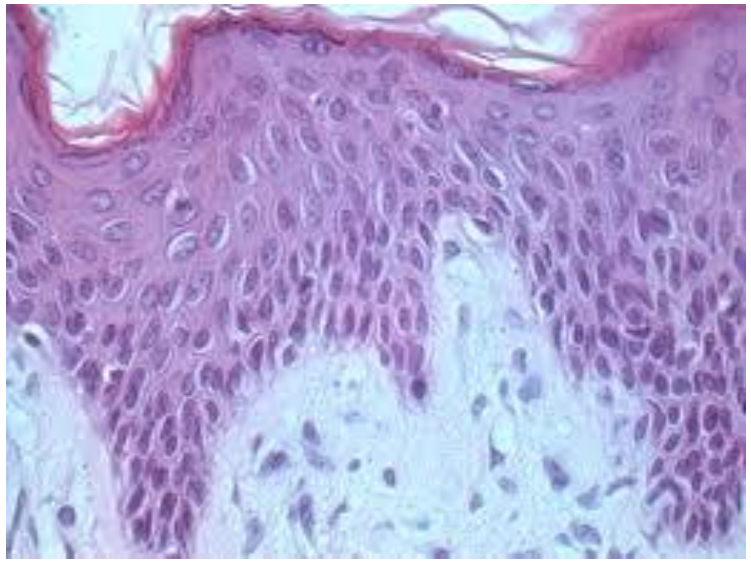
Cellular anaplasia

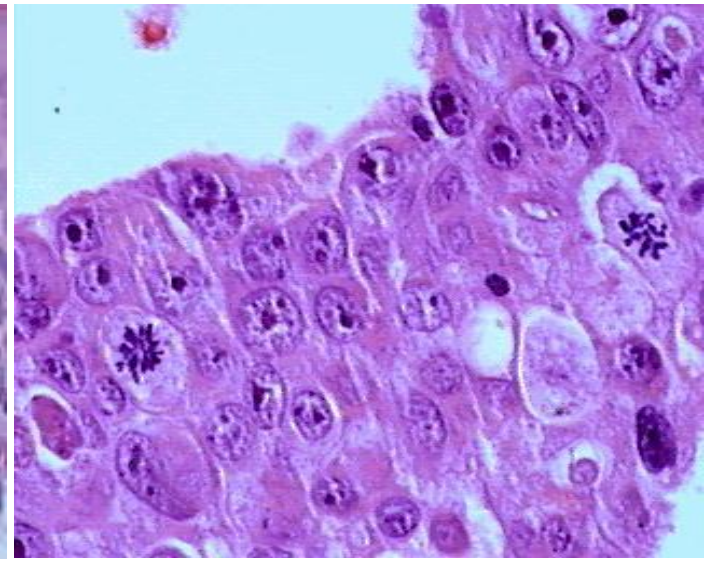
- **Loss of polarity:** the orientation of analplastic cells is disturbed markedly – grow in a disorganised fashion.

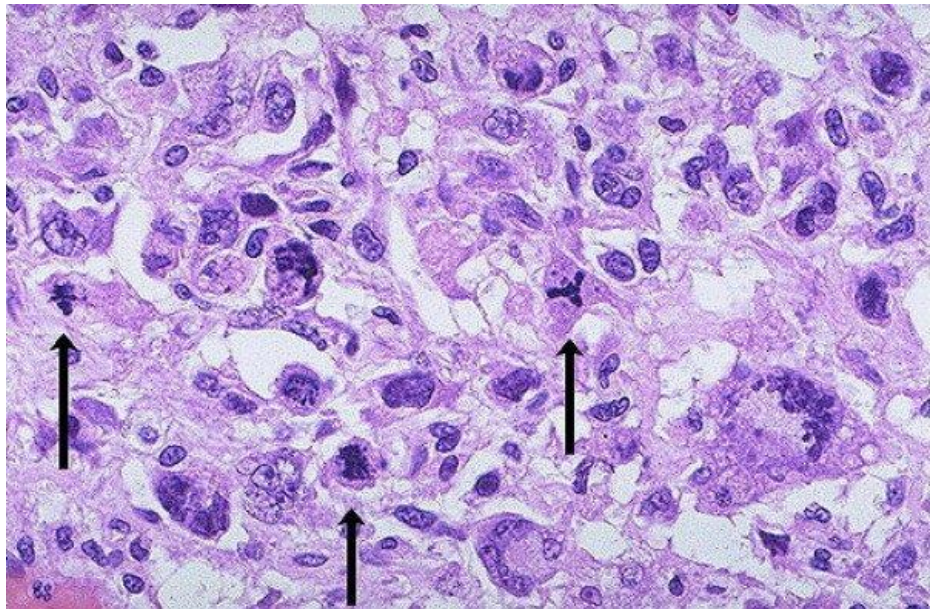
- **Pleomprhism:** variation in cell size and shape.

- **Abnormal nuclear morphology** – and **increase N/C ratio** (normally 1:4 – 1:6) it can rise to 1:1.

- **Mitoses:** increased number and abnormal forms - atypical, bizarre mitotic figures, sometimes with tripolar, quadripolar or multipolar spindles.







Tumour differentiation and grading

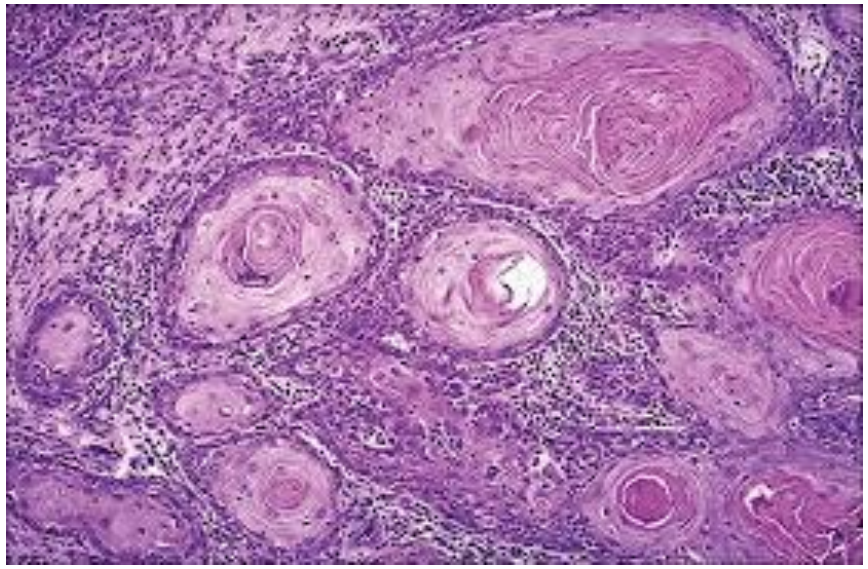
Differentiation: refers to the extent to which neoplastic parenchymal cells resemble the corresponding normal parenchymal cells, both morphologically and functionally.

Grading:

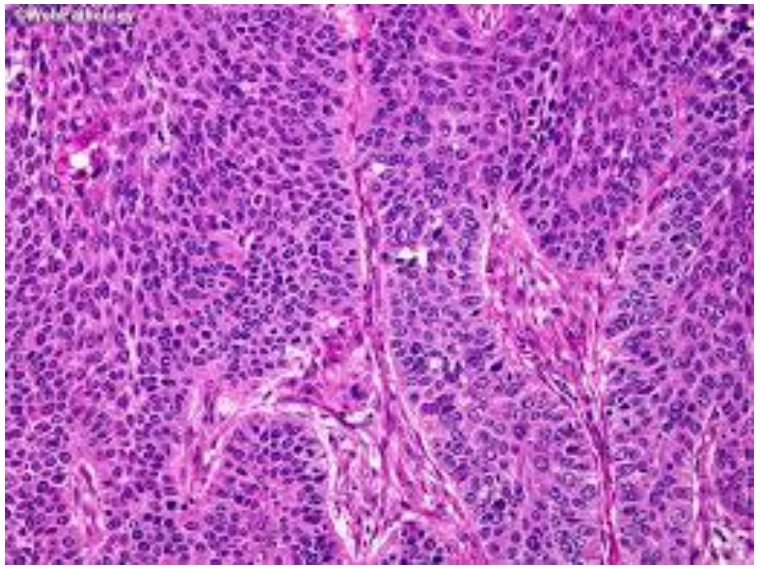
Criteria for individual grades vary in different types of tumours.

- Usually a three tier system: Well (G1), moderate (G2) and poor (G3)
- Can be a two tier system: Low grade (G1) and High grade (G2 & G3)
- Special / tumour type specific grading system

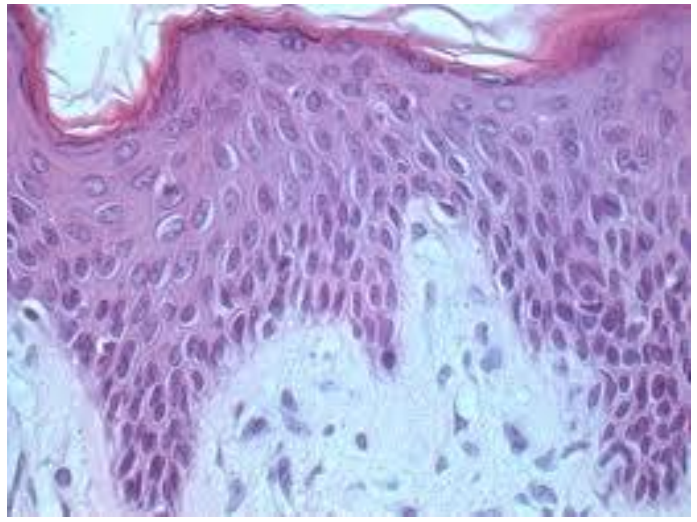
Squamous cell carcinoma

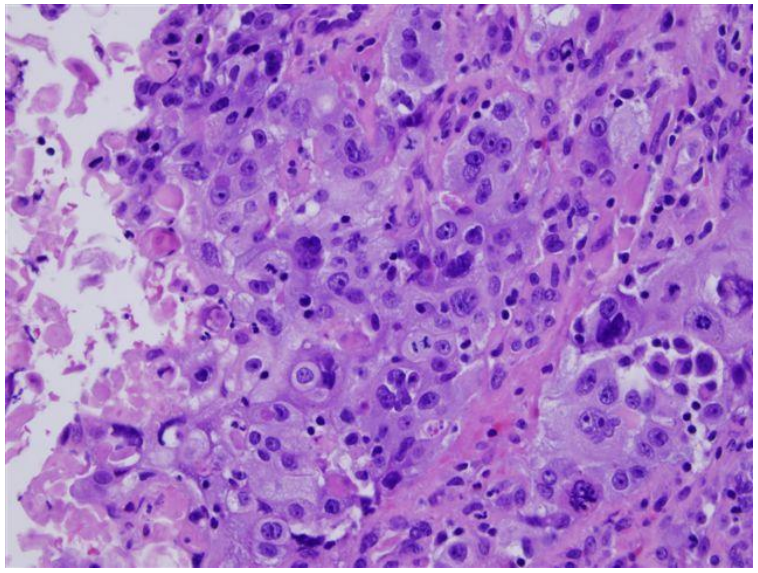


Well differentiated



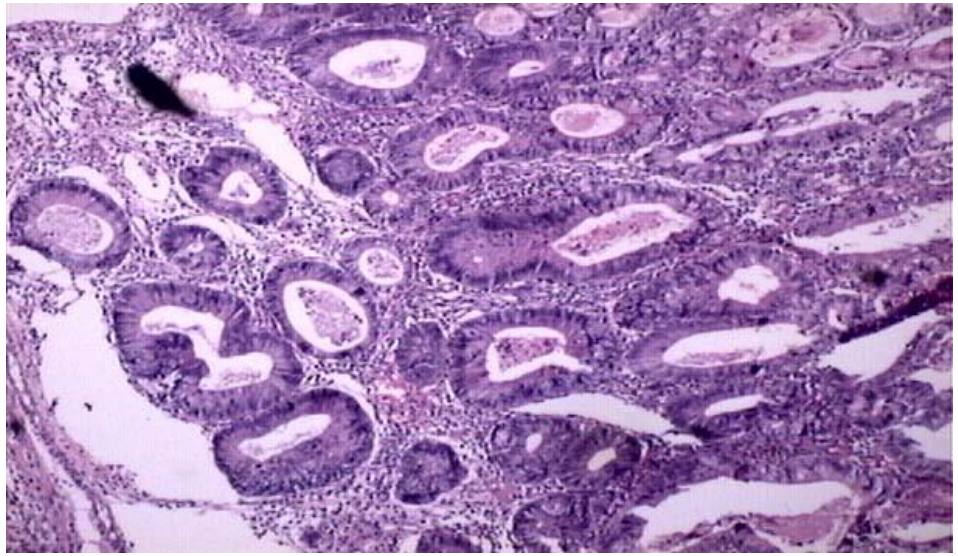
Moderately differentiated



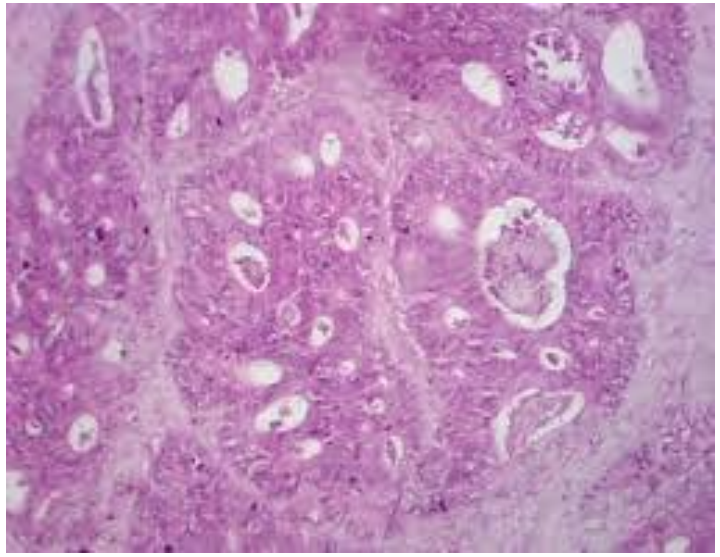


Poorly differentiated

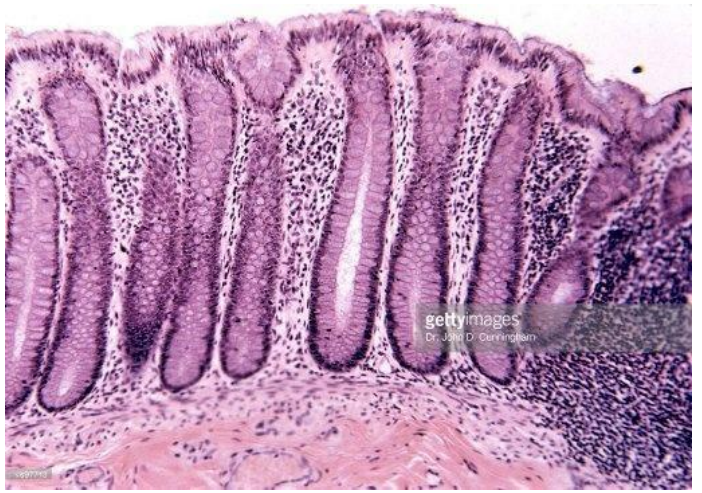
Adenocarcinoma

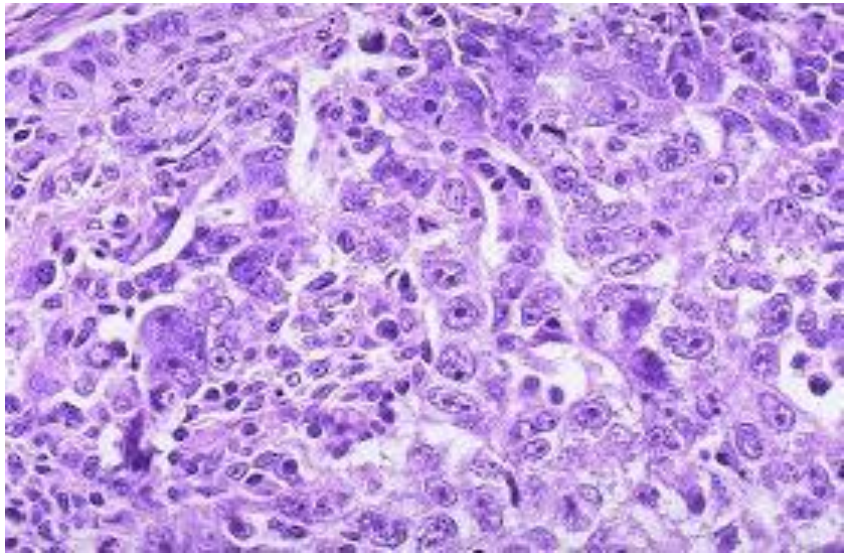


Well differentiated



Moderately differentiated

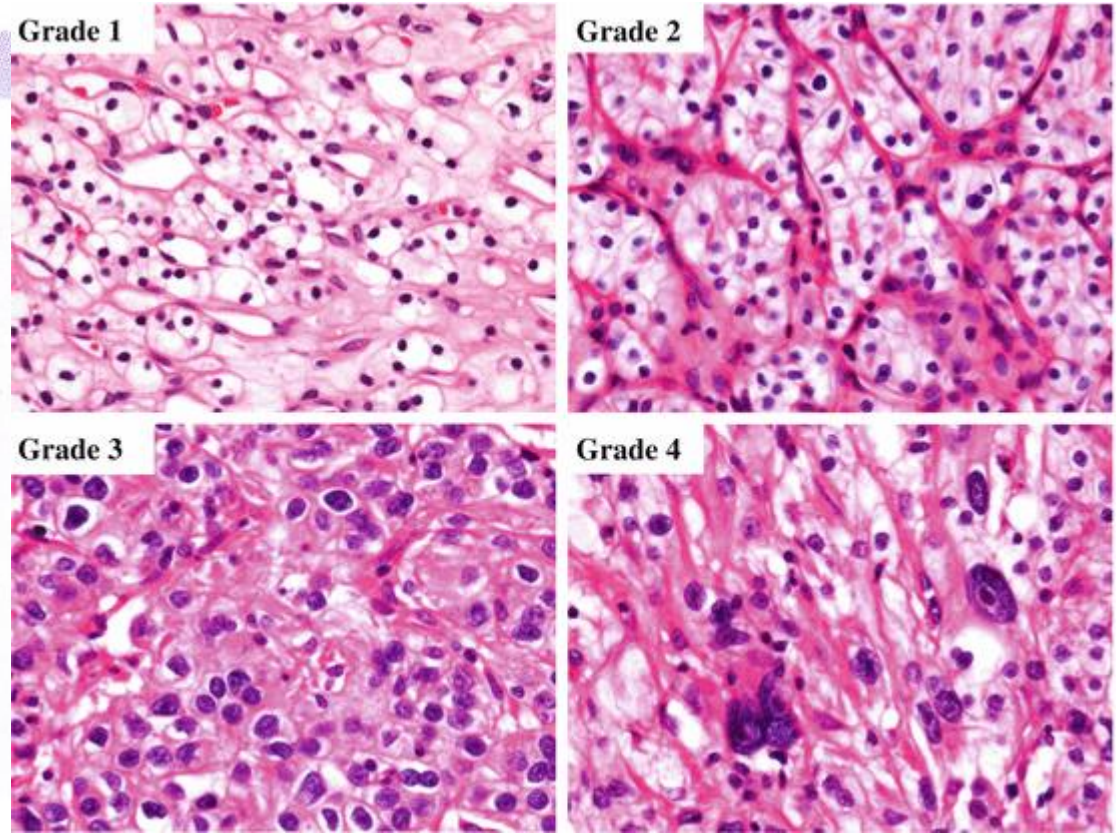




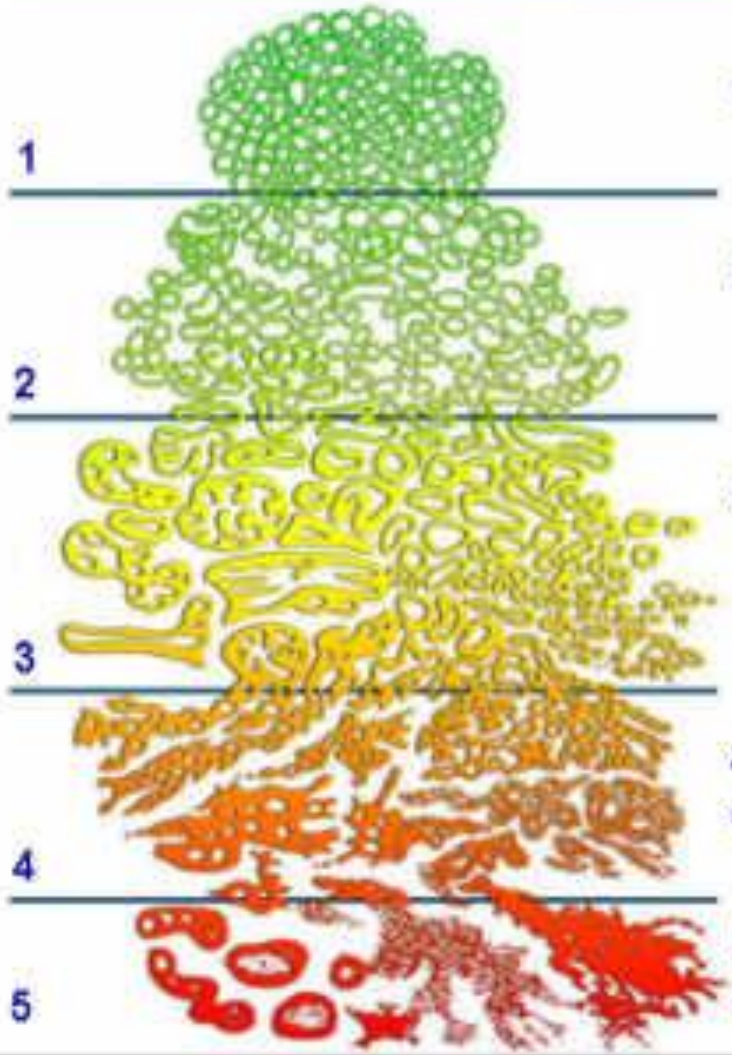
Poorly differentiated

Fuhrman Grading for Renal Cell Carcinoma

Grade	Nucleus
1	Round, uniform nuclei approximately 10 μm in diameter with minute or absent nucleoli
2	Slightly irregular nuclear contours and diameters of approximately 15 μm with nucleoli visible at 400 ×
3	Moderately to markedly irregular nuclear contours and diameters of approximately 20 μm with large nucleoli visible at 100 ×
4	Nuclei similar to those of grade 3 but also multilobular or multiple nuclei or bizarre nuclei and heavy clumps of chromatin



Gleason's Pattern Scale



1. Small, uniform glands.
2. More space (stroma) between glands.
3. Distinctly infiltration of cells from glands at margins.
4. Irregular masses of neoplastic cells with few glands.
5. Lack of or occasional glands, sheets of cells.

Well differentiated

Moderately differentiated

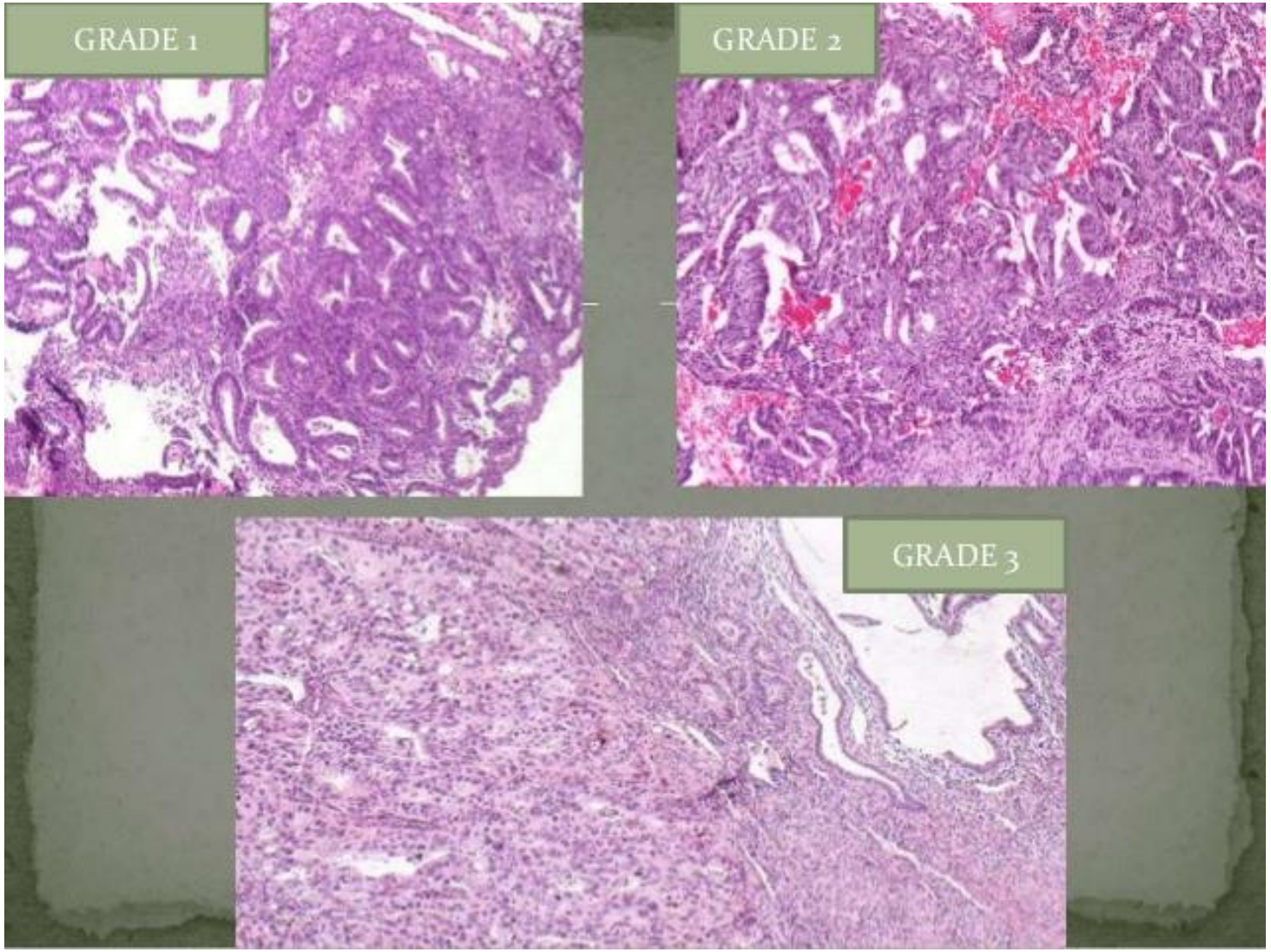
Poorly differentiated
Anaplastic

Endometrial carcinoma grades

- Depends on:

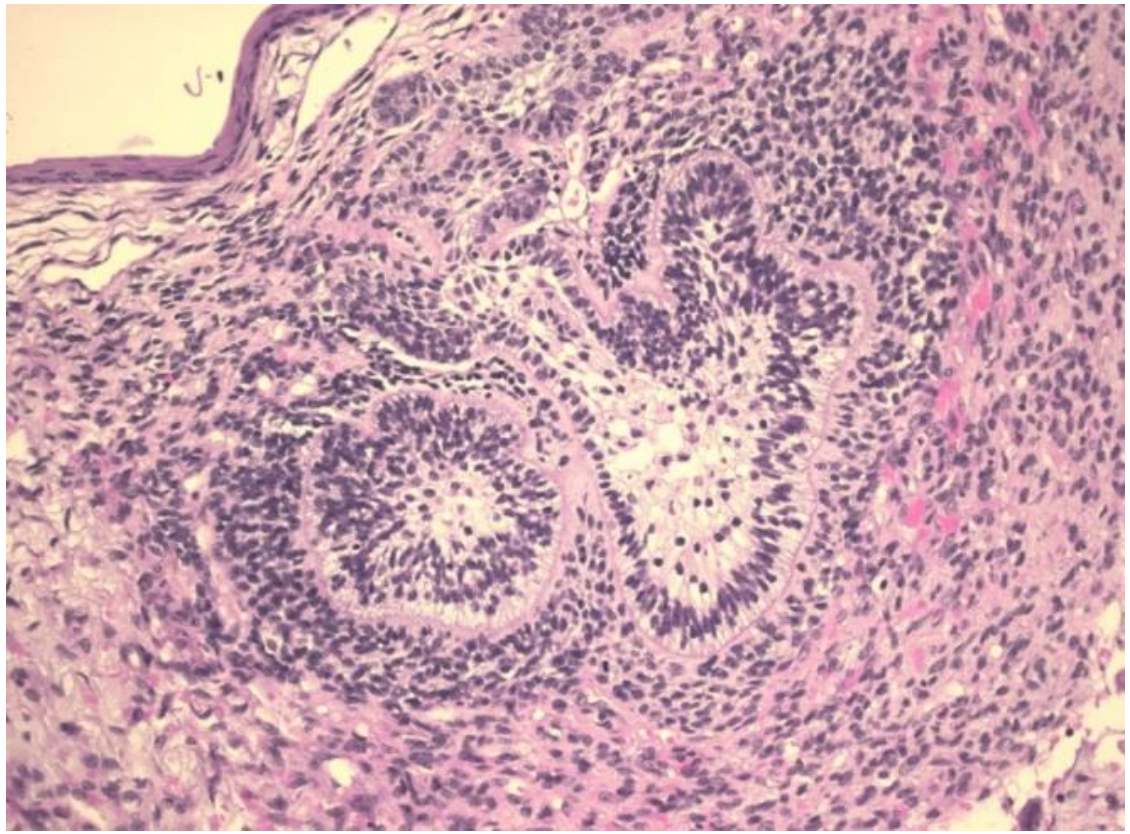
- Pattern: glands vs solid areas

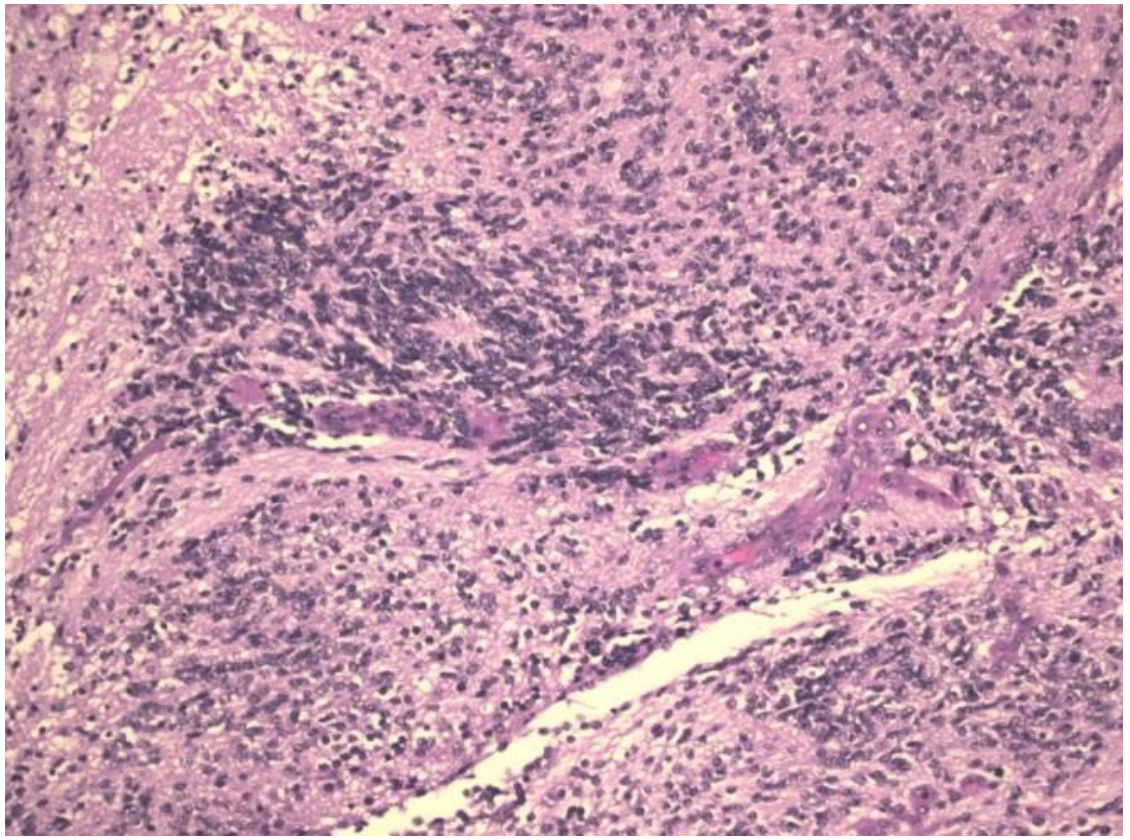
- Degree of cytological atypia



Immature teratoma

- There are immature neural elements
- Three tier grading system according to amount of primitive elements





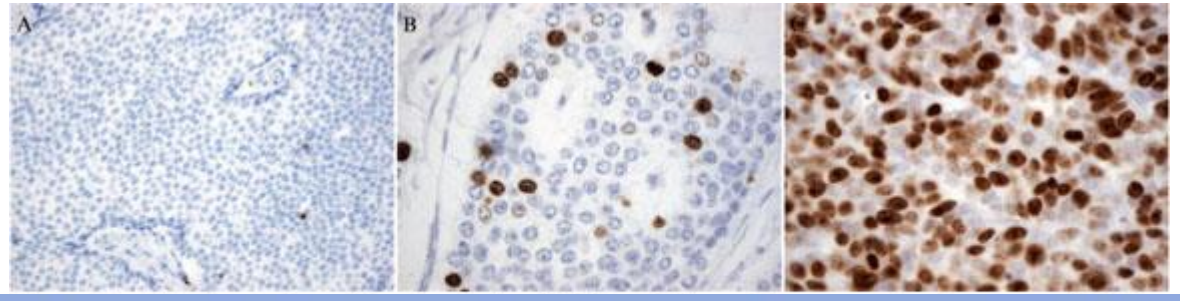
Grading of sarcomas: Importance of identifying mitosis

DEDIFFERENTIATION		MITOSES		NECROSIS	
Resembling normal	1	0-9/10 HPF	1	None	0
Definitive	2	10-19/10 HPF	2	<50%	1
Undifferentiated	3	>20/10 HPF	3	>50%	2

GRADE	SCORE
1	2-3
2	4-5
3	6-8

*The FNCLCC system provides maximum data and more predictive outcome.[25]
FNCLCC, Fédération Nationale des Centres de Lutte Contre le Cancer; HPF, high-power field.
Adapted from Soft tissue sarcoma. In: Edge SB, Byrd DR, Compton CC, et al, eds. AJCC Cancer Staging Manual. 7th ed. New York: Springer; 2010:291-298, with permission.

Cell cycle associated antigens: e.g. Ki67

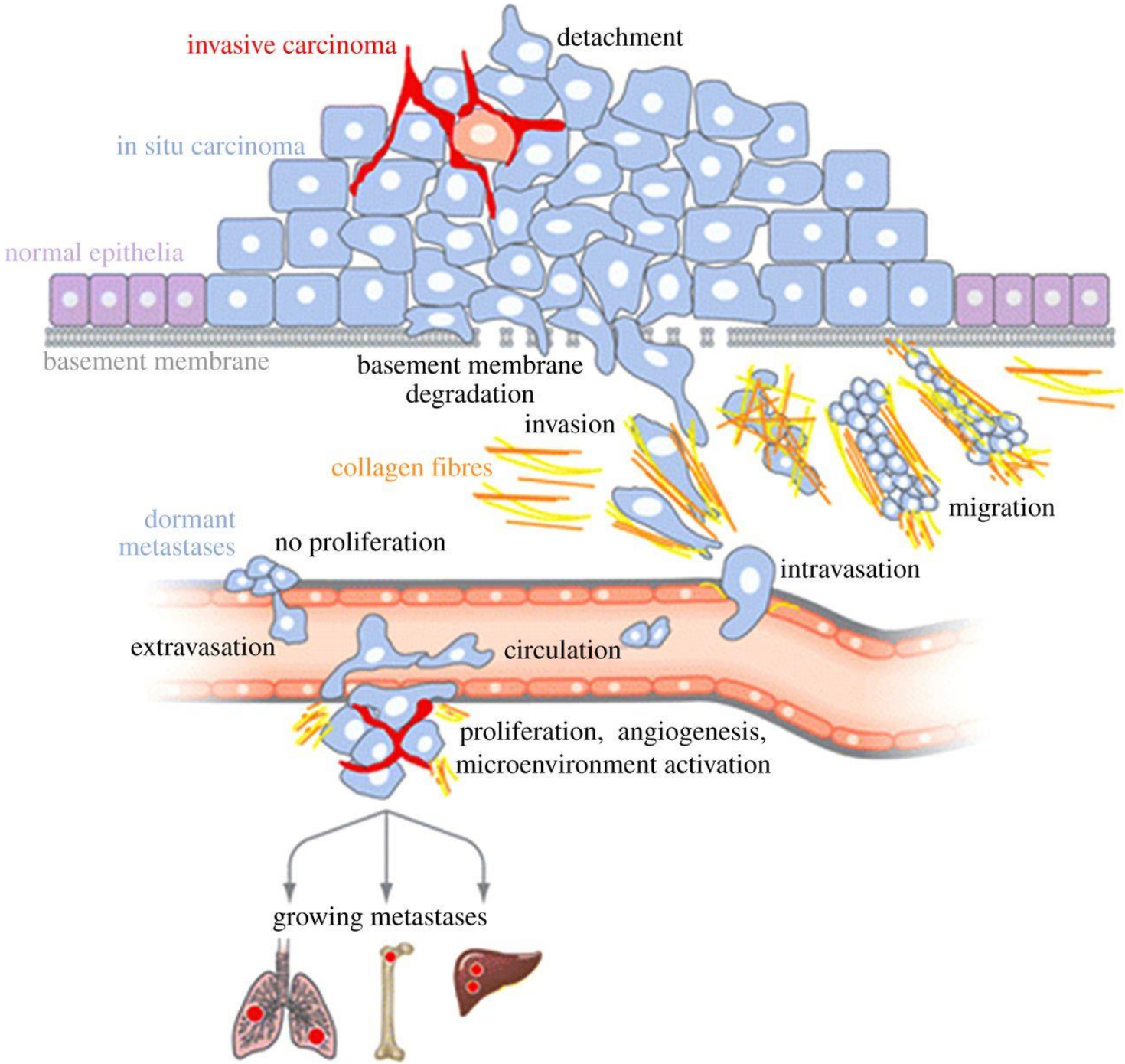


Grades of Neuroendocrine Neoplasms – WHO 2017

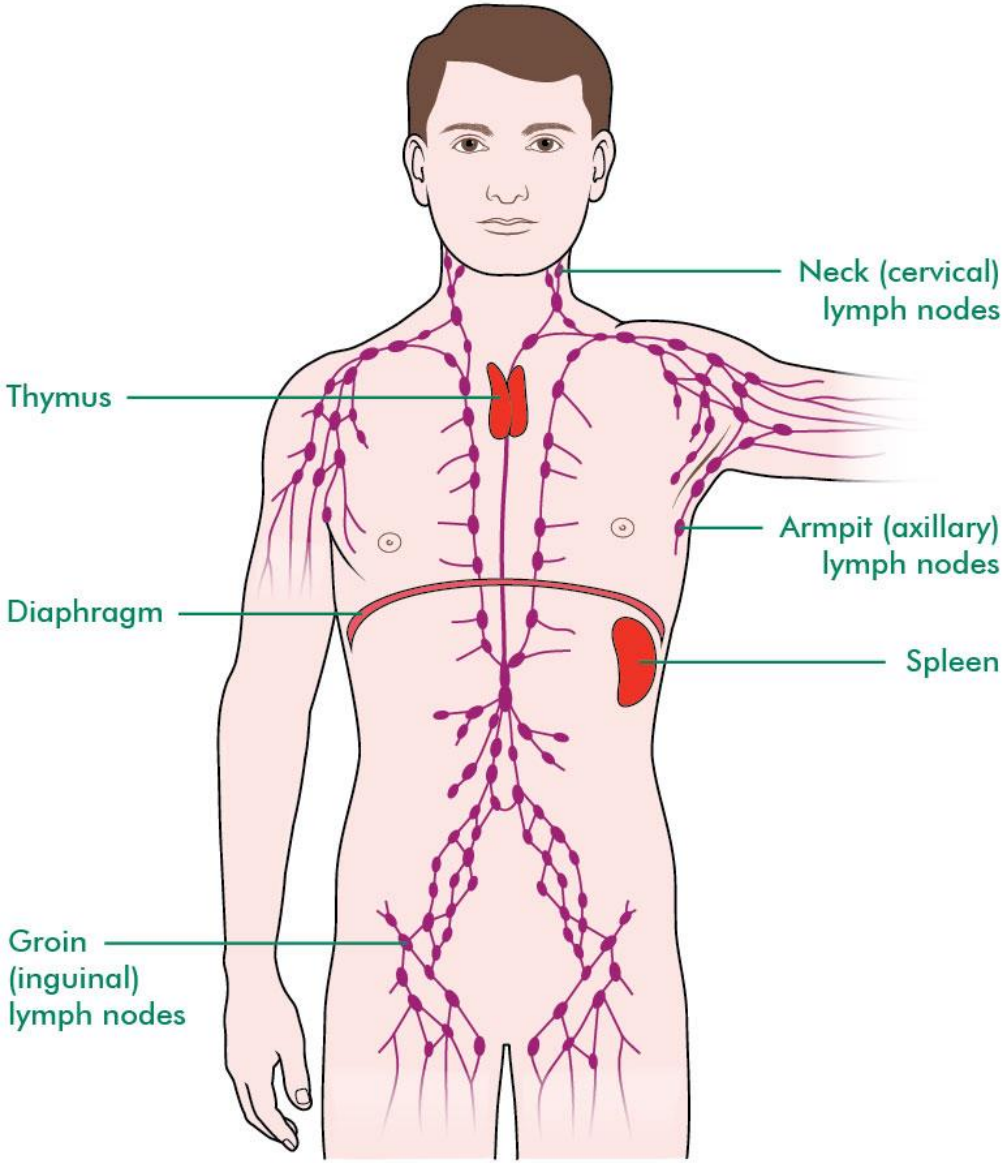
Grade	Differentiation	Miotic Count/Ki-67
1 (low) - NET	Well differentiated	<2 mitoses/10 HPF <3% Ki-67 index
2 (Intermediate) - NET	Well differentiated	2-20 mitoses/10 HPF 3-20% Ki-67 index
3 (high) - NET	Well differentiated	>20 mitoses/10 HPF >20% Ki-67 index
3 (high) – Neuroendocrine Carcinoma (NEC)	Poorly differentiated	>20 mitoses/10 HPF >20% Ki-67 index
Mixed Neuroendocrine Non-Neuroendocrine Neoplasm (MiNEN) - See text		

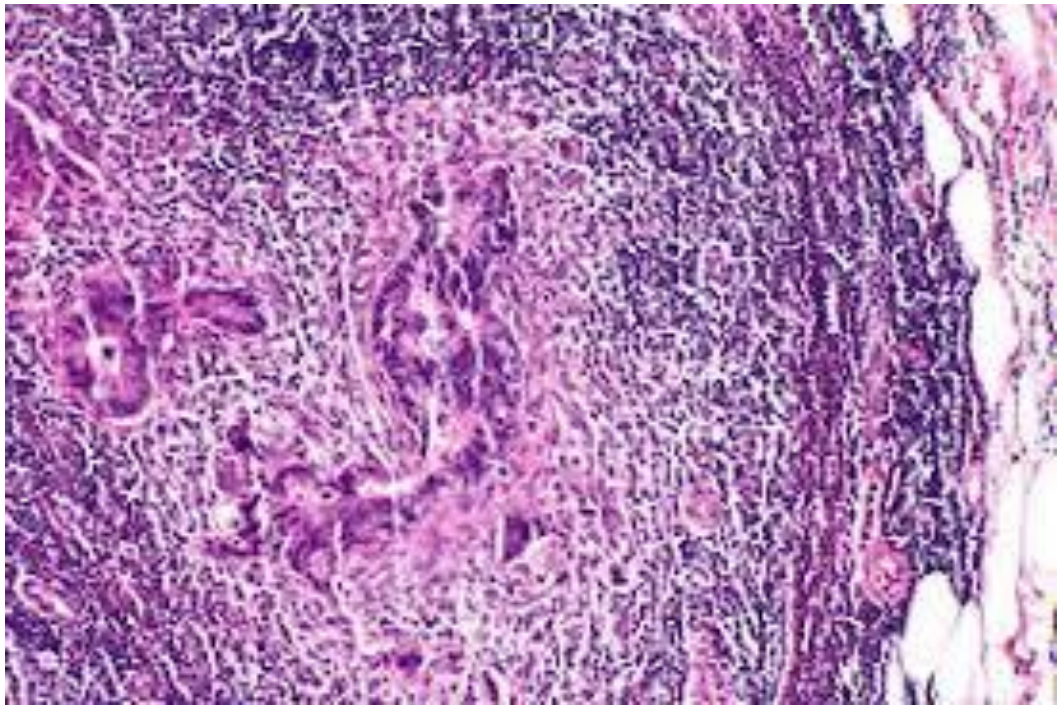
Tumour local invasion and distant metastasis

Haematogenous spread

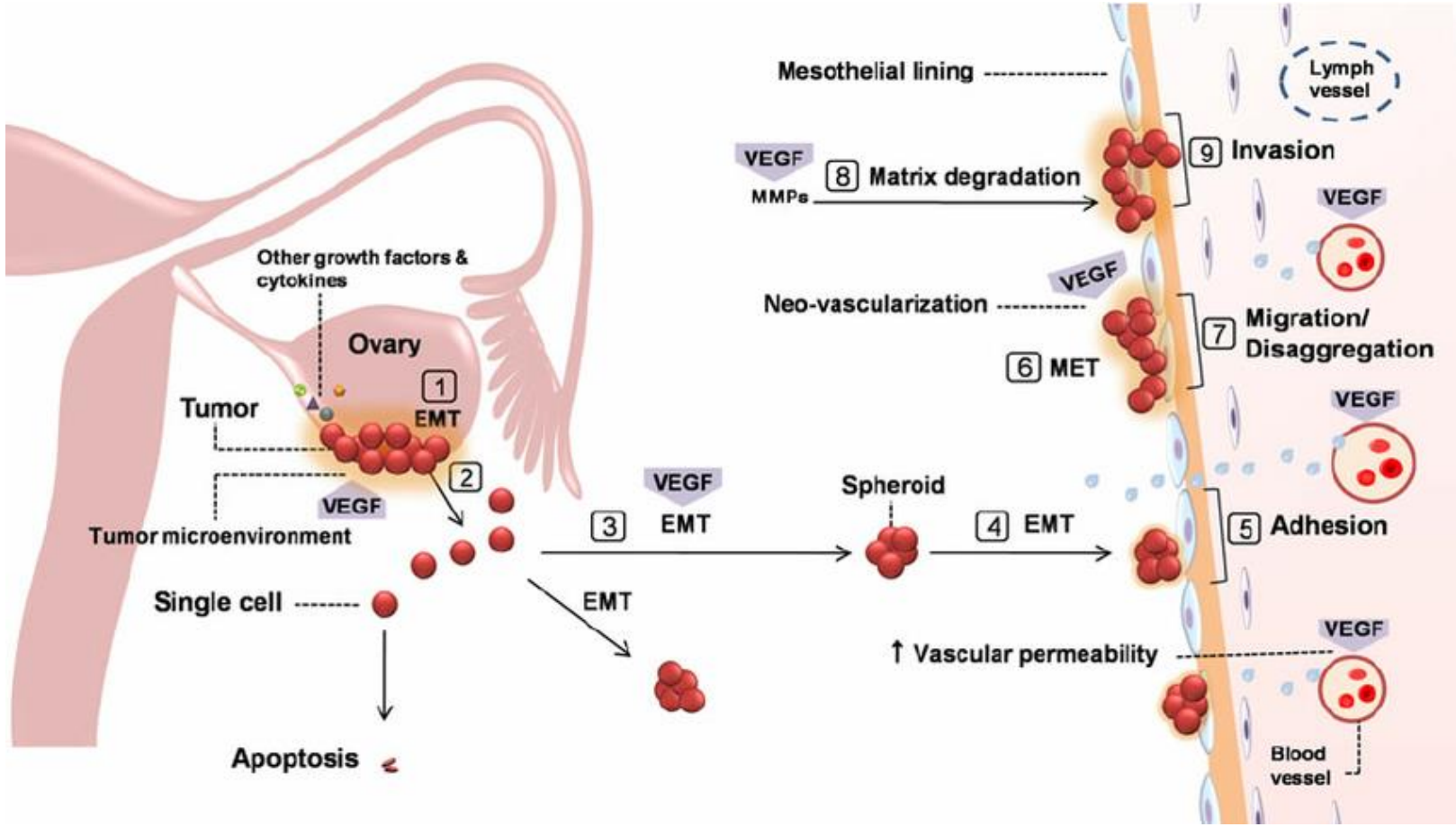


Lymphatic spread





Direct seeding of body cavities and surfaces



Tumour spread and staging

- Local invasion: the growth of cancers is accompanied by progressive infiltration, invasion and destruction of surrounding tissue.

- Metastasis is defined by the spread of tumour to sites that are physically discontinuous with the primary tumour.

- Staging is based on:
  - size of the primary lesion
  - its extent of spread to regional lymph nodes
  - the presence of blood borne metastasis

T N M Tumour staging

- The major staging system is currently the American joint committee on cancer staging.

- This system uses a classification called the TNM system
  - T for primary tumour
  - N for regional lymph node involvement
  - M for metastases

- It varies for different types of cancers, but there are general principles.

T N M Tumour staging

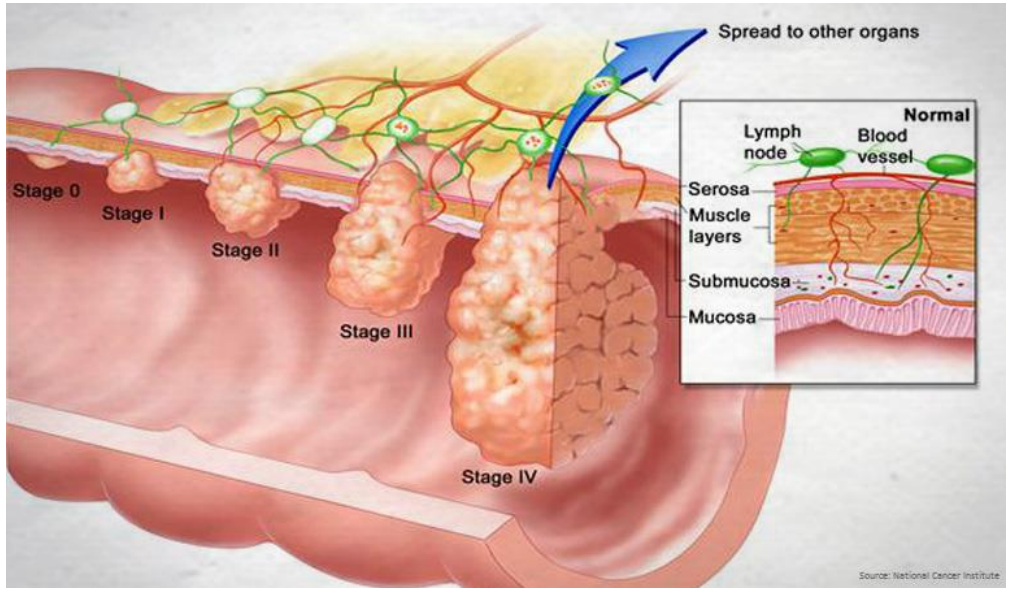
- **T:** The primary lesion is characterised from T1 to T4 based on size.
  T0 is used to indicate an in situ lesion.

- **N:** N0 would mean no nodal involvement whereas N1 to N3 would denote involvement of an increasing number and range of nodes.

- **M:** M0 signifies no distant metastasis, whereas M1 or sometimes M2 indicates the presence of metastasis and some judgment as to their number.

TNM staging of rectal carcinoma

Stage	Level of Involvement
Tumor	
T1	Limited to mucosa and submucosa
T2	Extension into but not through muscularis propria
T3	Invasion of perirectal fat
T4	Invasion of adjacent structures
Nodes	
N0	No involved lymph nodes
N1	Fewer than four regional nodes positive for tumor
N2	More than four regional nodes positive for tumor
Metastasis	
M0	No metastasis
M1	Distant metastasis



Tumour diagnosis

- **Tumour type**

- **Tumour grade:** determined principally by architectural and cytological appearance based on the idea that behaviour and differentiators are related with poorly differentiated tumours having more aggressive behaviour.

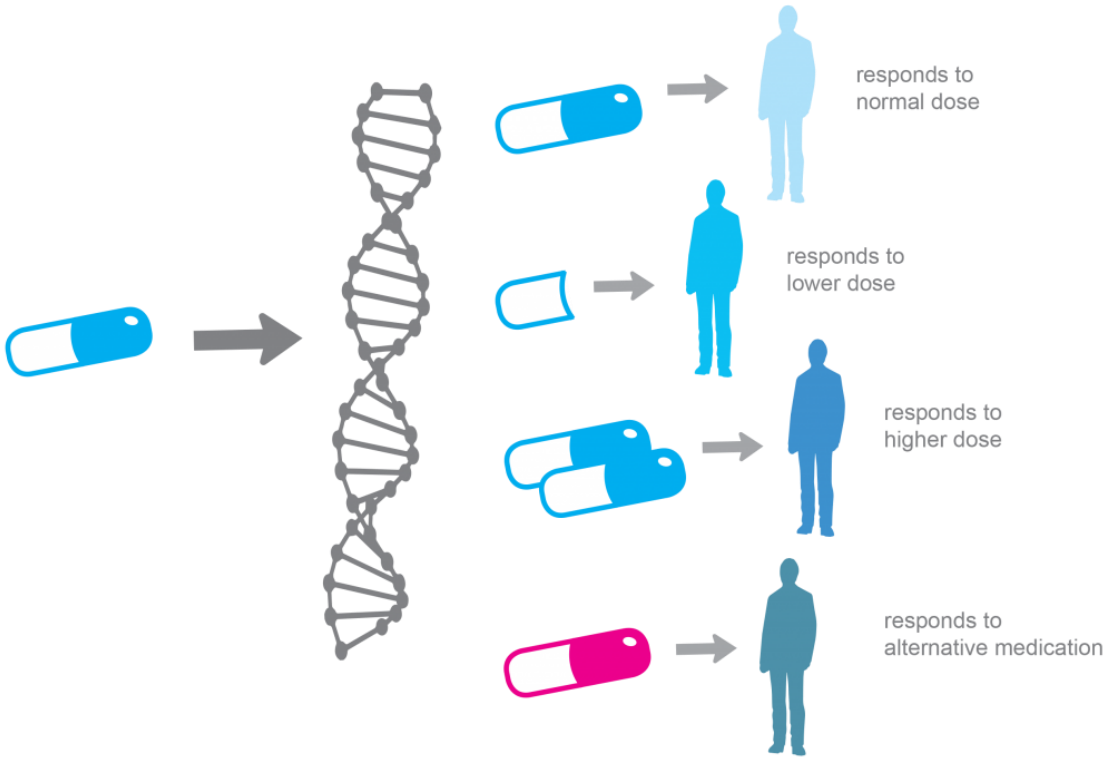
- **Tumour stage:** is based on size, local and regional lymph node spread, and distant metastasis (clinical and pathological).

In general, the likelihood of a primary tumour metastasizing correlates with lack of differentiation, aggressive local invasion, rapid growth, and large size.

- These items are essential parameters for setting the generic protocols for tumour management:
  - Surgical
  - Chemotherapy
  - Radiotherapy

Personalised medicine

- Refers to the practice of medicine where patients based on their genetic background receive
  - the most appropriate management
  - combination of drugs



European Alliance for
Personalised Medicine

The Hammersmith Hospital

Imperial College Healthcare NHS Trust