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Neoplasia

Clinical workflow for cancer diagnosis:
1. Biopsy performed → tissue sent to patho lab → pathologist ascertains if malignant → clinician decides on treatment
2. After surgical excision (if done) → pathologist examines the removed tumour to decide on grade and local stage → multidisciplinary team decides on further treatment (e.g. chemotherapy)

Definition

Neoplasm: An abnormal mass of tissue, the growth of which exceeds, and is uncoordinated with that of the normal tissues and persists in the same excessive manner after cessation of the stimuli which evoked the change.

Characteristics of Benign VS Malignant tumours

Benign	Malignant
Appearance and behaviour	
Gross and microscopic features "innocent"	Gross and microscopic features abnormal
Remains localized – does NOT invade.	Locally invasive
No metastasis	Metastasis (e.g. via vessels)
Treatment	
Amenable to local surgical removal	Requires surgical excision/radio/chemo
Prognosis/Outcome	
Patient generally survives. However can cause significant morbidity through local effects e.g. brain tumour compression	Death and morbidity, cachexia. (often)

Nomenclature on tumours – how to name tumours

Tissue Type	Benign	Malignant
Epithelial	"-oma"	" - carcinoma"
Glandular	Adenoma (eg. Tubular adenoma of colon)	Adenocarcinoma (eg. Colon adenocarcinoma)
Squamous	Squamous papilloma	Squamous cell carcinoma
Mesenchymal	"-oma"	"- sarcoma"
Bone (osteo-)	Osteoma	Osteosarcoma
Blood vessels **Lymph vessels**	Haemangioma; Lymphangioma	Angiosarcoma Lymphangiosarcoma
Smooth muscle	Leiomyoma	Leiomyosarcoma
Skeletal muscle	Rhabdomyoma	Rhabdomyosarcoma
Cartilage	Chondroma	Chondrosarcoma
Fat	Lipoma	Liposarcoma

Appearance - Gross Morphology

Video/mindmap:
https://medicine.nus.edu.sg/pathweb/pathology-demystified/neoplasia/i-what-is-neoplasia/

Feature	Benign	Malignant
Shape	Well-circumscribed, rounded, may be encapsulated	Irregular, spiculated, non-encapsulated
Margins	Sharply demarcated, smooth	Sharply demarcated or ill-defined
Cut surface – necrosis	Usually absent	May be present (pale geographic areas) – rapid growth causes outstripping of blood supply
Cut surface – haemorrhage	Usually absent	May be present (new small, fragile& immature vessels rupture easily)
Local invasion of adjacent structures	Absent	May be present – invade into adjacent organs (eg. Colon tumour into bladder; Renal cell carcinoma invades into neighbouring renal or major vessels)
Evidence of spread to **regional lymph nodes**	Absent	May be present – tumour deposits in enlarged regional lymph nodes
Evidence of spread to **distant organ sites** ie **Metastasis**	Absent	May be present – tumour deposits at sites ***NOT*** of tissue origin (eg. Prostate adenocarcinoma in spinal vertebrae)

Appearance – Microscopic (often related to tumour grade)

(More: Papa Robbins 9th edition page 268-272)

Feature	Benign	Malignant
Architecture of cell groupings	Well-differentiated, regular structures closely resembling normal tissue (eg. Tubular adenoma with well-formed colonic crypts; Thyroid follicular adenoma with well-formed follicular structures)	Poorly-differentiated, irregular structures(eg. Irregular glands in adenocarcinoma of the colon almost unrecognizable from normal glands.)
Cytomorphology	Bland cells closely resembling tissue of origin	Cells showing features of malignancy – eg. Nuclear enlargement, irregular nuclear membranes, raised N:C ratios (nuclear / cytoplasmic), multiple & prominent nucleoli, nuclear pleomorphism (nuclei are of significantly differing sizes and shapes)
Mitoses	Few in number	Frequently seen (measured as mitotic counts per 10 high power fields)
Necrosis	Absent	May be present
Lymphovascular tumour emboli	Absent	May be present – tumour deposits within small vessels → these can then give rise to nodal or distant metastases
Perineural invasion	Absent	May be present

Pathogenesis

Six characteristics of cancer cells:
1. **Self-sufficient in growth factors**
2. **Insensitive to inhibitory signals**
3. **Resistant to apoptosis**
4. **Immortal**
5. **Angiogenesis**
6. **Able to invade and metastasize**

Requires multi-step genetic alterations to overcome **multiple protective mechanisms:**
(1) **Cell cycle regulatory checkpoints**
(2) **Tumour suppressing mechanisms**
(3) **Apoptosis (cell death) &**
(4) **DNA repair mechanisms**

Pathogenesis Video/Mindmap:
https://medicine.nus.edu.sg/pathweb/pathology-demystified/neoplasia/ii-how/

Examples of genes involved:

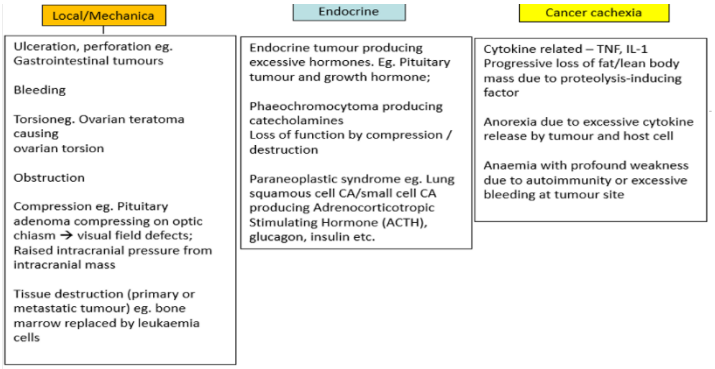
PROTO-ONCOGENES

Function	Gene	Protein encoded	Tumours
1.Growth factors	*VEGF*	Vascular endothelial growth factor	Kaposi's sarcoma
2. Growth factor receptors	*HER2*	Human EGF Receptor 2	Breast cancer
3. Signal transduction	*KRAS*	Ras protein	Colon adenocarcinoma
4. Transcriptional activatorss	*MYC*	c-MYC transcription factors	Small cell lung cancer, B-cell lymphomas
5. Regulators of cell cycle checkpoint (G1-S phase transition)	*CDK4* *Cyclins*	Cyclin-dependent kinase 4 Cyclin D protein	Melanoma, Glioblastoma (brain tumour) Mantle cell (B cell) lymphoma, breast carcinoma

2. Inhibitors of cell cycle regulation	*RB*	Rb protein (Regulates cell cycle)	Familial retinoblastoma	Retinoblastoma, Bladder cancer, Small cell lung cancer
3. Enablers of genomic stability	*p53*	p53 protein (regulates cell cycle, promote apoptosis)	Li-Fraumeni Syndrome	Sarcoma Breast cancer Leukaemia
4. DNA repair factors	*BRCA1 &2*	BRCA protein (DNA repair)	Familial breast cancer	Breast cancer, Colon cancer

Mechanisms of genetic aberrations –
Kindly refer to notes/robbins textbook for more details.
Inherited genetic aberration
- Inherited cancer syndromes, familial cancers
"Acquired" genetic aberration
- Aging – Accumulation of gene mutations over the years
- Physical injury – Radiation / radiotherapy
- Chemical carcinogens – Tobacco, Asbestos etc
- Biological – Chronic inflammation (Chronic liver cirrhosis: Hepatocellular carcinoma)
- Viral integration into host genome can cause: oncogene expression, tumour suppressor gene inhibition, drive polyclonal proliferation of lymphocytes leading to increased risk of acquiring genetic mutations which contribute to neoplastic transformation.
Ebstein-Barr Virus – Hodgkin lymphoma, Burkitt lymphoma, Nasopharyngeal CA;
Human Papilloma Virus – Squamous cell carcinoma of the uterine cervix
- Bacterial (Helicobactor pylori: Gastric lymphoma)

Effects of Neoplasia
Clinical Effects Video/Mindmap:
https://medicine.nus.edu.sg/pathweb/pathology-demystified/neoplasia/iii-clinical-effects-of-neoplasms/



Prognosis (Malignant tumours)
Video/Mindmap: https://medicine.nus.edu.sg/pathweb/pathology-demystified/neoplasia/iii-clinical-effects-of-neoplasms/

Stage and **Grade** are parameters used to assess clinical aggressiveness.

Stage - ***size*** *and/or* ***extent*** *of the tumour growth*
Tumour stage essentially refers to the size and/or extent of the tumour growth. Clinical findings, radiological imaging (CT scans, MRI, PET scans etc), intra-operative surgical findings and pathology reports of excised tumours are used to stage tumours. The AJCC TNM (American Joint Committee on Cancer) staging system is widely used. Different tumours have different TNM staging systems according to site and /or tissue of origin.

Grade - *reflects the* ***degree of differentiation*** *of the tumour*
How well the tumour cells resemble the tissue of origin. The closer the resemblance, the lower the grade. In high grade tumours, the tumour cells appear very abnormal and are hard recognise as a certain cell type.
Tumour grade is thus always assessed MICROSCOPICALLY (by the pathologist)

Important Resources – do not forget:
Quizzes and Media Gallery:
https://medicine.nus.edu.sg/pathweb/pathology-demystified/neoplasia/mediagallery/

- Know how to describe POTS/tumours grossly, distinguish grossly between benign and malignant, and appreciate the histological characteristics of benign and malignant tumours.