PATHOLOGY

MD3

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Principles of Neoplasia

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Learning Objectives

- Use knowledge of epidemiology of neoplasia.
- Answer questions about carcinogenic agents
- Solve problems concerning carcinogenesis
- Answer questions about diagnosis of cancer

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DEFINITION

In neoplasia, an abnormal cell or tissue grows more rapidly than normal cells or tissue; it does so by acquiring multiple genetic changes over time and by continuing to grow after the stimuli that initiated the new growth have been removed.

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EPIDEMIOLOGY

Cancer is the **second leading cause of death** in the United States. In 2015, the estimated number of new cancers diagnosed was 1,658,370, and the estimated number of deaths from cancer was 589,430.

In men, the sites with the highest new cancer rates are (in order of decreasing frequency):

- Prostate
- Lung and bronchus
- Colon and rectum

These same sites have the highest mortality rate, although lung and bronchus cancers more commonly cause death than prostate cancer.

In women, the sites with the highest new cancer rates are (in order of decreasing frequency):

- Breast
- Lung and bronchus
- Colon and rectum

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These same sites have the highest mortality rate, although lung and bronchus cancers more commonly cause death than breast cancer.

In children, the most common cancers are acute lymphocytic leukaemia, CNS malignancy, neuroblastoma, and non-Hodgkin lymphoma.

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Predisposition to cancer involves many factors. Geographic and racial factors can be important:

- Stomach cancer is much more prevalent in Japan than in the United States.
- Breast cancer is much more prevalent in the United States than in Japan.
- Liver hepatoma is much more prevalent in Asia than in the United States.
- Prostate cancer is more prevalent in African Americans than in Caucasians.

Hereditary predisposition can be seen in many cancers, including familial retinoblastoma, multiple endocrine neoplasia, and familial polyposis coli. Acquired preneoplastic disorders also affect cancer incidence, with examples including cervical dysplasia (characterized by changes in cell size and shape), endometrial hyperplasia, cirrhosis, inflammatory bowel disease, and chronic atrophic gastritis.

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Tumor genes

Oncogene	Tumor	Gene Product	Mechanism of action
FGF3 & FGF4	Cancer of the stomach, breast, bladder, and Kaposi sarcoma	**Growth factors** Fibroblast growth factor	Overexpression
PDGFRA	Astrocytoma	Platelet-derived growth factor	Overexpression
ERBB1	Squamous cell carcinoma of lung	**Growth factor receptors** Epidermal growth factor receptor	Overexpression
ERBB2	Breast, ovary, lung	Epidermal growth factor receptor	Amplification
ERBB3	Breast	Epidermal growth factor receptor	Overexpression
RET	MEN 2A & 2B, familial thyroid (medullary) Cancer	Glial neurotrophic factor receptor	Point mutation
ABL	CML, ALL	**Signal transduction proteins** bcr-abl fusion protein with tyrosine kinase activity	Translocation (9:22)
KRAS	Lung, pancreas, and colon	GTP binding protein	Point Mutation
MYC	Burkitt's Lymphoma	Nuclear regulatory protein	Translocation (8:14)
MYCL	Small Cell lung Carcinoma	Nuclear Regulatory Protein	Amplification
MYCN	Neuroblastoma	Nuclear Regulatory Product	Amplification
CCND	Mantle Cel Lymphoma	Cell Cycle regulatory Protein	Translocation t(11:14)
CDK4	Melanoma	Cyclin dependent kinase	Amplification

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CARCINOGENIC AGENTS

Chemical carcinogen

Radiation

Viral infections

Loss of immune regulation

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Chemical carcinogens

Carcinogenesis is a multistep process involving a sequence of initiation (mutation) followed by promotion (proliferation). Initiators can be either direct-acting chemical carcinogens (mutagens which cause cancer directly by modifying DNA) or indirect-acting chemical carcinogens (procarcinogens which require metabolic conversion to form active carcinogens). Promotors cause cellular proliferation of mutated (initiated) cells, which may lead to accumulation of additional mutations.

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Clinically important chemical carcinogens are numerous, and include

- Nitrosamines (gastric cancer),
- Cigarette smoke (multiple malignancies),
- Polycyclic aromatic hydrocarbons (bronchogenic carcinoma),
- Asbestos (bronchogenic carcinoma, mesothelioma),
- Chromium and Nickel (bronchogenic carcinoma),
- Arsenic (squamous cell carcinomas of skin and lung, angiosarcoma of liver),
- Vinyl chloride (angiosarcoma of liver),
- Aromatic amines and Azo dyes (hepatocellular carcinoma),
- Alkylating agents (leukemia, lymphoma, other cancers),
- Benzene (leukemia),
- Naphthylamine (bladder cancer).

Potential carcinogens are screened by the Ames test, which detects any mutagenic effects of potential carcinogens on bacterial cells in culture; mutagenicity in vitro correlates well with carcinogenicity in vivo.

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Radiation.

Ultraviolet B sunlight is the most carcinogenic because it produces pyrimidine dimers in DNA, leading to transcriptional errors and mutations of oncogenes and Tumor suppressor genes, thereby increasing the risk of skin cancer.

Xeroderma pigmentosum is an autosomal recessive inherited defect in DNA repair, in which the pyrimidine dimers formed with ultraviolet B sunlight cannot be repaired; this defect predisposes to skin cancer. Ionizing radiation includes

x-rays and

gamma rays,

alpha and

beta particles,

protons, and

neutrons.

Cells in mitosis or the G2 phase of the cell cycle are most sensitive to radiation. Radiation causes cross-linking and chain breaks in nucleic acids. Atomic bomb survivors experienced an increased incidence of leukaemia, thyroid cancer, and other cancers. Uranium miners historically had increased lung cancer, related to inhalation of radioactive radon, which is a decay product of uranium.

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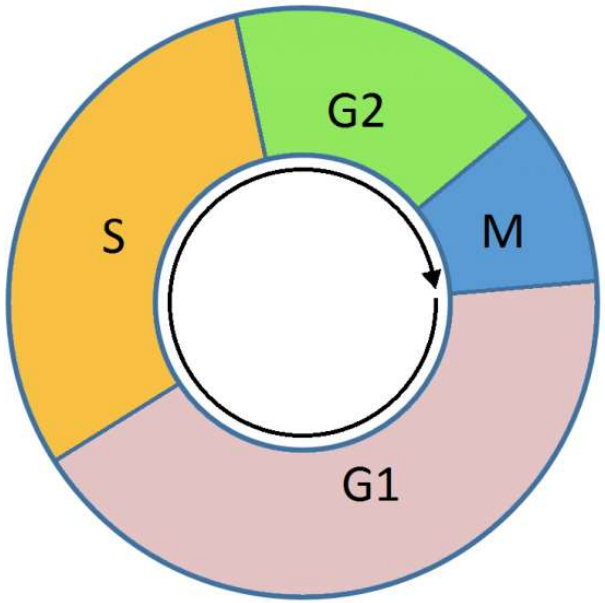

G1 - Growth

S - DNA synthesis

G2 - Growth and preparation for mitosis

M - Mitosis (cell division)

Cell Cycle

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General feature of Benign Tumor

- Slow growing
- Encapsulated or well-demarcated borders
- Expansile growth with well-circumscribed borders
- Tend to be well differentiated
- Resemble the normal tissue counterpart from which they arise
- Noninvasive and never metastasize

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General Feature of malignant Tumor

- Larger in size
- Rapid growth
- Necrosis and haemorrhage are commonly seen
- Poorly demarcated
- Vary from well to poorly (anaplastic) differentiated
- Tumor cells vary in size and shape (pleomorphism)
- Increased nuclear to cytoplasmic ratios
- Nuclear hyperchromatic and prominent nucleoli
- High mitotic activity with abnormal mitotic figures
- Invasive growth pattern
- Has potential to metastasize

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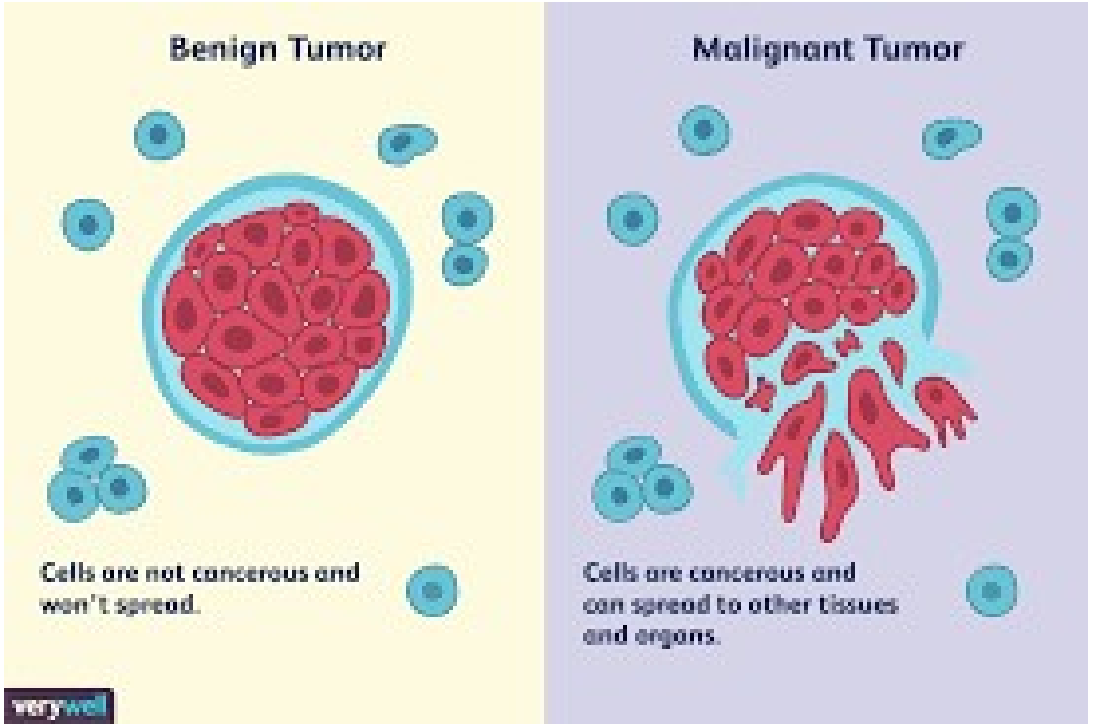
Benign Vs Malignant tumor



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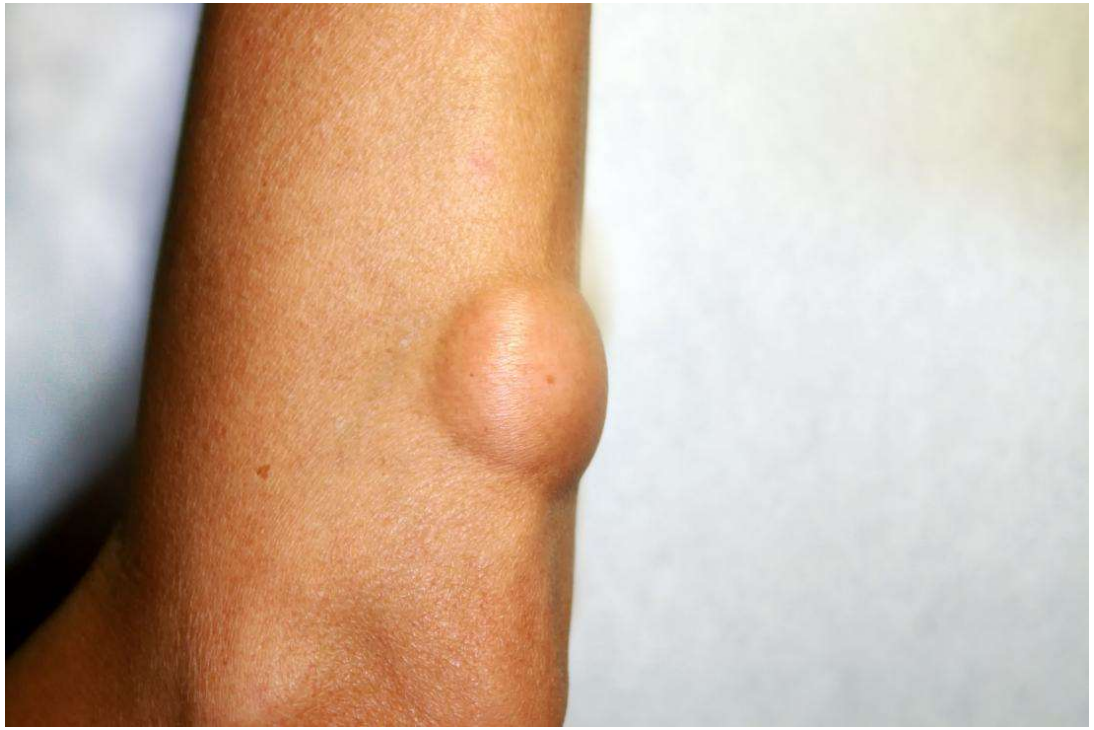
Benign Vs Malignant tumor



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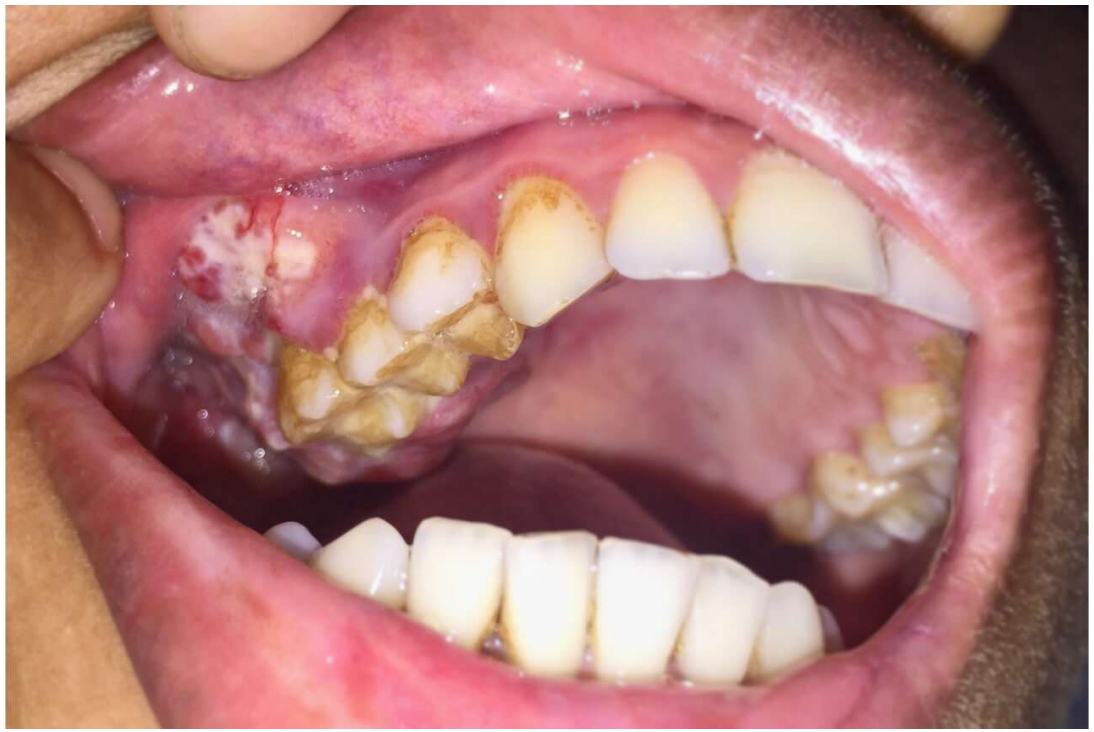
Benign Vs Malignant tumor



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Oncogenic viruses

RNA oncogenic viruses. Human T-cell leukemia virus (HTLV-1) causes adult T-cell leukemia/lymphoma.

DNA oncogenic viruses include the following:

- Hepatitis B virus (hepatocellular carcinoma)
- Epstein-Barr virus (EBV), which has been implicated in Burkitt lymphoma, B-cell lymphomas in immunosuppressed patients, nasopharyngeal carcinoma
- Human papilloma virus (HPV), which causes benign squamous papillomas (warts-condyloma acuminatum) and a variety of carcinomas (cervical, vulvar, vaginal, penile, and anal)
- Kaposi-sarcoma-associated herpesvirus (HHV8) which causes Kaposi sarcoma

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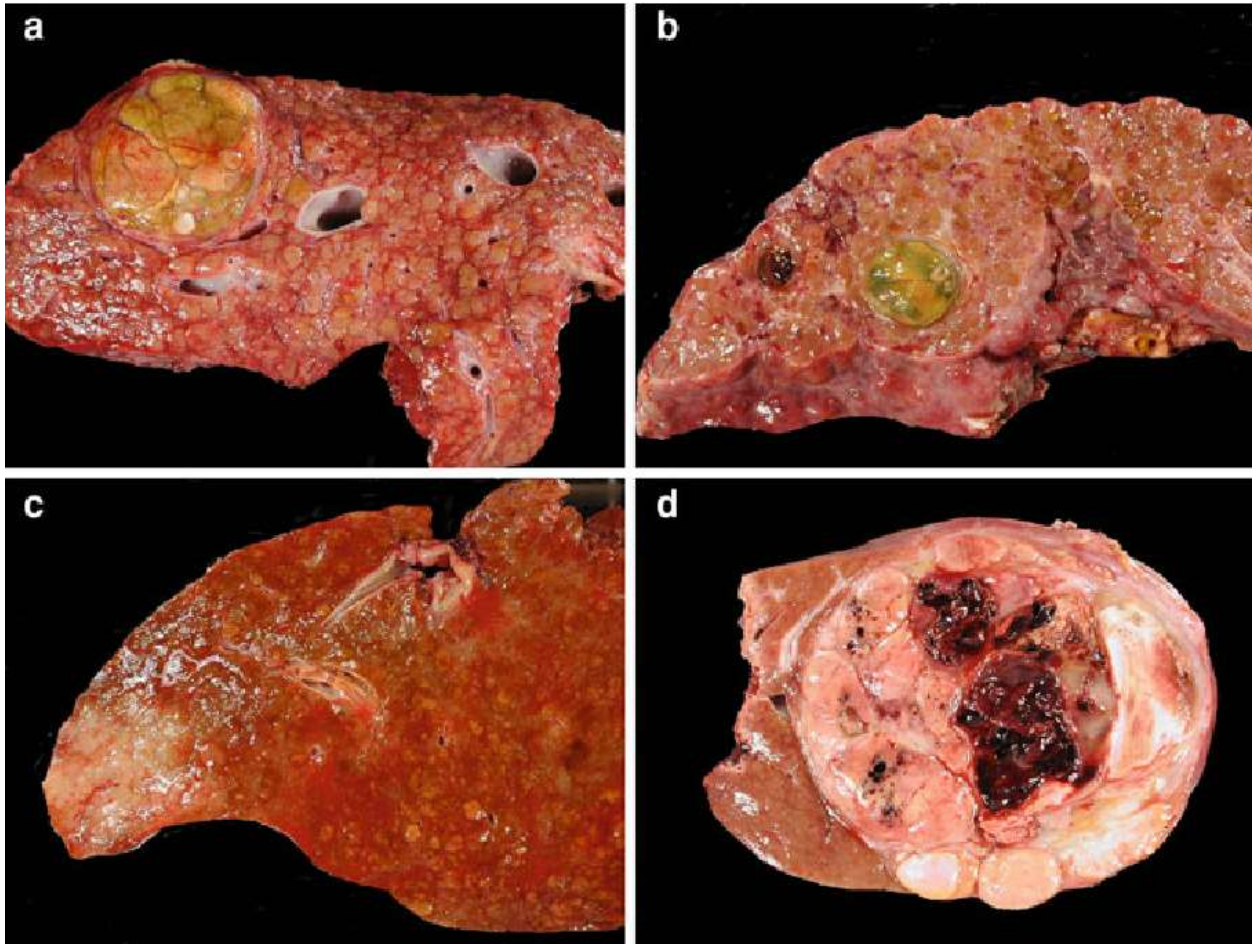
Hepatocellular Cancer



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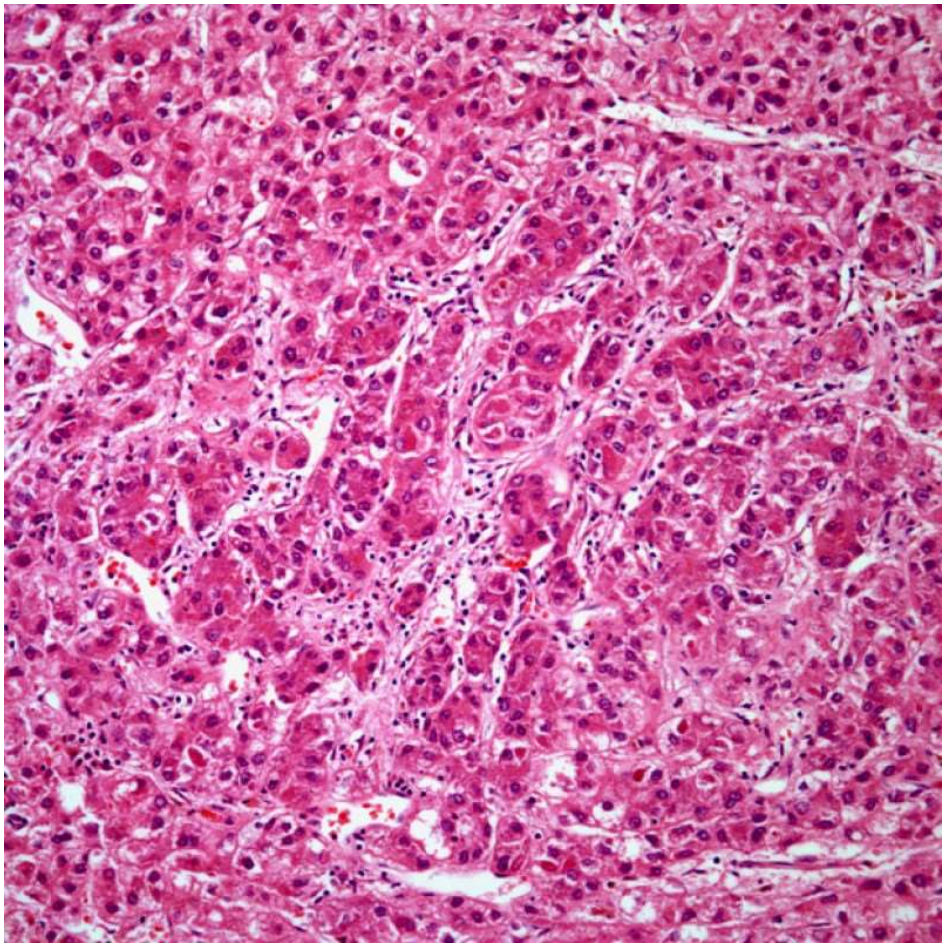
Hepatocellular cancer



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Loss of immune regulation. Immunosurveillance normally destroys neoplastic cells via recognition of “non-self” antigens, and both humoral and cell-mediated immune responses play a role. Patients with immune system dysfunction have an increased number of neoplasms, especially malignant lymphomas.

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CARCINOGENESIS

Carcinogenesis is a multistep process, and development of all human cancers appears to require the accumulation of multiple genetic changes. These changes can involve either inherited germline mutations or acquired mutations. Once a single severely mutated cell forms, monoclonal expansion of the cell's line can cause a Tumor. Most important mutations in tumorigenesis involve growth promoting genes (proto-oncogenes), growth inhibiting Tumor suppressor genes, or the genes regulating apoptosis and senescence.

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Expression of Intermediate Filaments by Normal and Malignant Cells

Intermediate Filament	Normal Tissue Expression	Tumor
Keratin	All epithelial cells	Carcinomas
Vimentin	Mesenchymal cells	Sarcomas
Desmin	Muscle cells	Uterine leiomyoma Rhabdomyosarcoma
Neurofilament	CNS and PNS neurons Neural crest derivatives	Pheochromocytoma Neuroblastoma
Glial fibrillary acidic protein(GFAP)	Glial cells	Astrocytoma Ependymomas

*Mesenchymal stem cells are multipotent stromal cells that can differentiate into a variety of cell types, including osteoblasts (bone cells), chondrocytes (cartilage cells), myocytes (muscle cells) and adipocytes (fat cells which give rise to marrow adipose tissue)

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Activation of growth promoting oncogenes. Proto-oncogenes are normal cellular genes involved with growth and cellular differentiation.

Oncogenes are derived from proto-oncogenes by either a change in the gene sequence, resulting in a new gene product (oncoprotein), or a loss of gene regulation resulting in overexpression of the normal gene product.

Mechanisms of oncogene activation include

- point mutations,
- chromosomal translocations,
- gene amplification,
- and insertional mutagenesis.

Activated oncogenes lack regulatory control and are overexpressed, resulting in unregulated cellular proliferation.

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Inactivation of Tumor suppressor genes.

Tumor suppressor genes encode proteins that regulate and suppress cell proliferation by inhibiting progression of the cell through the cell cycle.

The mechanism of action of Tumor suppressor genes may vary.

As examples, p53 prevents a cell with damaged DNA from entering S-phase, while Rb prevents the cell from entering S-phase until the appropriate growth signals are present.

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Knudson's "two hit hypothesis" states that at least 2 Tumor suppressor genes must be inactivated for oncogenesis.

In cancers arising in individuals with inherited germline mutations, the "first hit" is the inherited germline mutation and the "second hit" is an acquired somatic mutation.

Examples of inherited germline mutations include familial retinoblastoma (in which germline mutation of RB1 on chromosome 13 is associated with a high rate of retinoblastoma and osteosarcoma) and Li-Fraumeni syndrome (in which germline mutation of TP53 on chromosome 17 is associated with a high rate of many types of tumours).

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Regulation of apoptosis. Tumor genesis related to changes in regulation of apoptosis occurs in the follicular lymphomas that have the translocation t(14;18).

Normally, Bcl-2 prevents apoptosis (programmed cell death). In the follicular lymphomas with this translocation, the Bcl-2 regulator of apoptosis is overexpressed, because the translocation connects the immunoglobulin heavy chain gene on chromosome 14 (which turns on easily in B lymphocytes) to the BCL2 gene on chromosome 18, thereby leading to a situation in which lymphocytes fail to die as expected and instead produce a tumor. Other examples of apoptosis regulators include Bax, Bad, bcl-xS, and Bid; p53 promotes apoptosis in mutated cells by stimulating bax synthesis. The protein c-myc promotes cellular proliferation and when associated with p53 leads to apoptosis and when associated with Bcl-2 inhibits apoptosis.

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Limitless replication is possible due in part to upregulation of telomerase. Sustained angiogenesis is possible due in part to activation of the Notch signalling pathway.

Invasiveness/metastasis. Malignant cells must dissociate from tumours (loss of E-cadherin function) and degrade the extracellular matrix before spreading to distant sites. Cancer-associated glycans are being investigated for their role in cancer spread and as targets for therapy.

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Histologic diagnosis of cancer. Microscopic examination of tissue or cells is required to make the diagnosis of cancer. Material suitable for diagnosis of a Tumor may be obtained by

- Complete excision,
- Biopsy,
- Fine needle aspiration, or
- Cytologic smears (Pap test).

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Immunohistochemistry may be helpful in confirming the tissue of origin of metastatic or poorly differentiated tumours. The technique uses monoclonal antibodies that are specific for a cellular component. Among the many antibodies that are clinically useful are:

All the serum Tumor markers

- Thyroglobulin (thyroid cancers)
- S100 (melanoma and neural tumours)
- Actin (smooth and skeletal muscle)
- CD markers (lymphomas/leukaemia's)
- Estrogenic receptors (breast cancer)
- Intermediate filaments

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Serum tumor markers. Tumor markers are usually normal cellular components that are increased in neoplasms but may also be elevated in nonneoplastic conditions. Serum tumor markers are used for screening (e.g., prostate specific antigen [PSA]) for cancer, monitoring treatment efficacy, and detecting recurrence of cancers.

Clinically useful tumor markers include

- Alpha-fetoprotein (AFP, used for hepatoma, non seminomatous testicular germ cell tumors);
- Beta human chorionic gonadotropin (hCG, used for trophoblastic tumors, choriocarcinoma);
- Calcitonin (used for medullary carcinoma of the thyroid);
- Carcinoembryonic antigen (CEA, used for carcinomas of the lung, pancreas, stomach, breast, and colon);
- CA-125 (used for malignant ovarian epithelial tumors);
- CA19-9 (used for malignant pancreatic adenocarcinoma);
- Placental alkaline phosphatase (used for seminoma); and
- Prostate specific antigen (PSA, used for prostate cancer).

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Grading and staging. Tumor grade is a histologic estimate of the malignancy of a Tumor, and typically uses criteria such as the degree of differentiation from low grade (well-differentiated) to high grade (poorly differentiated/anaplastic) and the number of mitoses.

Tumor stage is a clinical estimate of the extent of Tumor spread. TNM staging system criteria are used for most Tumor types:

- T indicates the size of the primary Tumor.
- N indicates extent of regional lymph node spread.
- M indicates the presence or absence of metastatic disease.

In general, staging is a better predictor of prognosis than Tumor grade.

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TNM Grading

Tumours	T0/Tis	T1	T2	T3	T4
Tumour Size	**T0**: No primary tumour. **Tis**: Tumour only in breast ducts or lobules.	0-2 cm	2-5 cm	>5 cm	Tumor of any size with extension to chest wall/skin or ulceration ****inflammatory breast cancer** is staged as T4.
Nodes	**N0**	**N1**	**N1mi**	**N2**	**N3**
	No lymph node metastases.	Cancer cells present in 1-3 axillary lymph nodes.	Lymph node tumor > 2 mm.	Cancer cells present in 4-9 axillary lymph nodes.	Cancer cells in infra or supraclavicular lymph nodes, or in >10 axillary lymph nodes.
Metastasis	**M0**	**M1**			
	No evidence of cancer metastasis.	Cancer found in other areas of body.			

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Tumor progression refers to the tendency of a Tumor to become more malignant over time. This progression can be related to both natural selection (evolution of a more malignant clone over time due to a selective growth advantage) and genetic instability (malignant cells are more prone to mutate and accumulate additional genetic defects).

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Metastasis

- Lymphatic spread is the most common initial route of spread for epithelial carcinomas.
- Early hematogenous spread is typically seen with most sarcomas (e.g., osteogenic sarcoma), renal cell carcinoma (because of the proximity of the large renal vein), hepatocellular carcinoma (because of the presence of the hepatic sinusoids), follicular carcinoma of the thyroid, and choriocarcinoma (because of its propensity to seek vessels).
- Seeding of body cavities and surfaces occurs in ovarian carcinoma.
- Transplantation via mechanical manipulation (e.g., surgical incision, needle tracts) may occur but is relatively rare.

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