Histochemistry (304 C)

Third year biochemistry students
Faculty of science
Damietta University

Lecture (6)

Tumor markers

Introduced By :

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Apoptosis

is a process of programmed cell death that occurs in multicellular organisms. Biochemical events lead to characteristic cell changes (morphology) and death. These changes include **blebbing, cell shrinkage, nuclear fragmentation, chromatin condensation, hromosomal DNA fragmentation, and global mRNA decay**. Between 50 and 70 billion cells die each day due to apoptosis in the average human adult. For an average child between the ages of 8 and 14, approximately 20 billion to 30 billion cells die a day.

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Control of The Apoptotic Mechanisms:

The initiation of apoptosis is tightly regulated by activation mechanisms, because once apoptosis has begun, it inevitably leads to the death of the cell. The two best-understood activation mechanisms are the **intrinsic pathway** (also called the mitochondrial pathway) and the **extrinsic pathway.** The intrinsic pathway is activated by intracellular signals generated when cells are stressed and depends on the release of proteins from the intermembrane space of mitochondria. The extrinsic pathway is activated by extracellular ligands binding to cell-surface death receptors, which leads to the formation of the death-inducing signaling complex.

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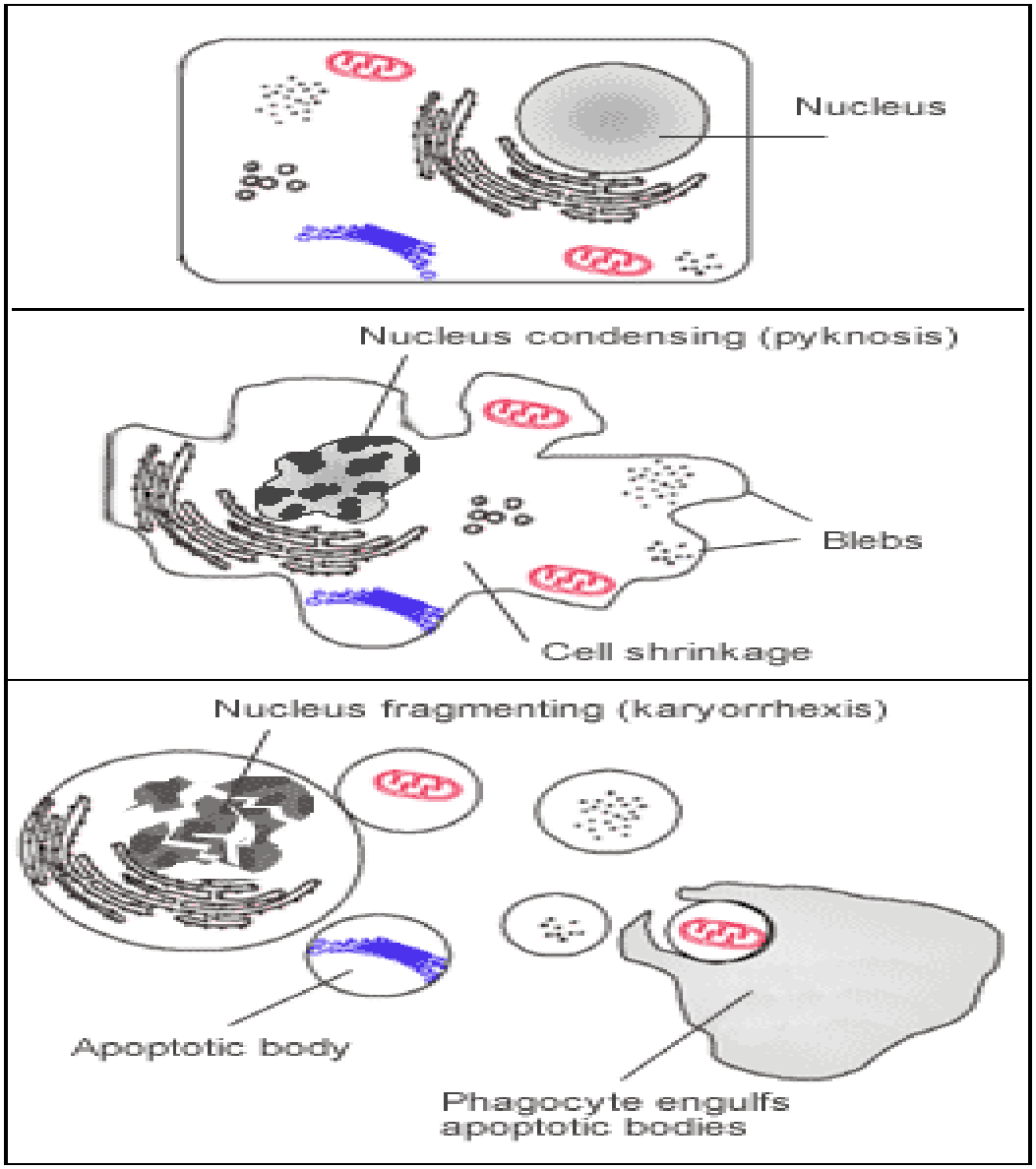

Nucleus
Nucleus condensing (pyknosis)
Blebs
Cell shrinkage
Nucleus fragmenting (karyorrhexis)
Apoptotic body
Phagocyte engulfs
apoptotic bodies

Diagnostic IHC markers:

The diversity of IHC markers used in diagnostic surgical pathology
is substantial. Many clinical laboratories will have menus of over 200 antibodies used as diagnostic, prognostic and predictive biomarkers. Examples of some commonly used markers include:

Cytokeratins: used for identification of carcinomas but may also be expressed in some sarcomas.

CD15 and CD30: used for Hodgkin's disease

Alpha fetoprotein: for yolk sac (A membrane outside the human embryo that is connected by a tube (the yolk stalk) though the umbilical opening to the embryo's midgut). tumors and hepatocellular carcinoma

CD117 : for gastrointestinal

stromal tumors **(GIST)** and mast cell tumors

- **CD10** : for renal cell carcinoma and acute lymphoblastic leukemia
- Prostate specific antigen **(PSA):** for prostate cancer
- estrogens and progesterone receptor **(ER & PR)** staining are used both diagnostically (breast and gyn tumors) as well as prognostic in breast cancer and predictive of response to therapy (estrogen receptor)
- Identification of B-cell lymphomas using **CD20**
- Identification of T-cell lymphomas using **CD30**

Tumor markers

Dr. Rasha Zahran

A tumor marker

is a biomarker found in blood, urine, or body tissues that can be elevated by the presence of one or more types of cancer. There are many different tumor markers, each indicative of a particular disease process, and they are used in oncology to help detect the presence of cancer. An elevated level of a tumor marker can indicate cancer; however, there can also be other causes of the elevation (false positive values).

Tumor markers can be produced directly by the tumor or by non-tumor cells as a response to the presence of a tumor.

Definitions

- ***Carcinoma***
  - ***"Cancer that arises from the epithelium, the tissue that lines the internal organs of the body."***
- ***Sarcoma***

  Any cancer of connective tissue, e.g. muscle, fat, bone, lymphatic vessels."
- ***Therefore the main difference between the two types of cancer is their place of origin.***
- ***Carcinomas originate in epithelial tissue; Sarcomas originate in connective tissue.***

- **Cancer occurs** after a single cell in a tissue is progressively genetically damaged to produce cells with uncontrolled proliferation. This uncontrolled proliferation by mitosis produces a primary heterogeneic tumour. The cells which constitute the tumor eventually undergo metaplasia, followed by dysplasia then anaplasia, resulting in a malignant phenotype. This malignancy allows for invasion into the circulation, followed by invasion to a second site for tumorigenesis.

Mortality rates

- Mortality increasing since 1900 (4% in 1909, 20% in 1990)
- Deaths from malignant tumours second only to cardiovascular disease as most common cause of death
- Rise partly due to increased life expectancy as incidence of cancer increases with age (10-fold higher incidence at 70 years than 25 years)

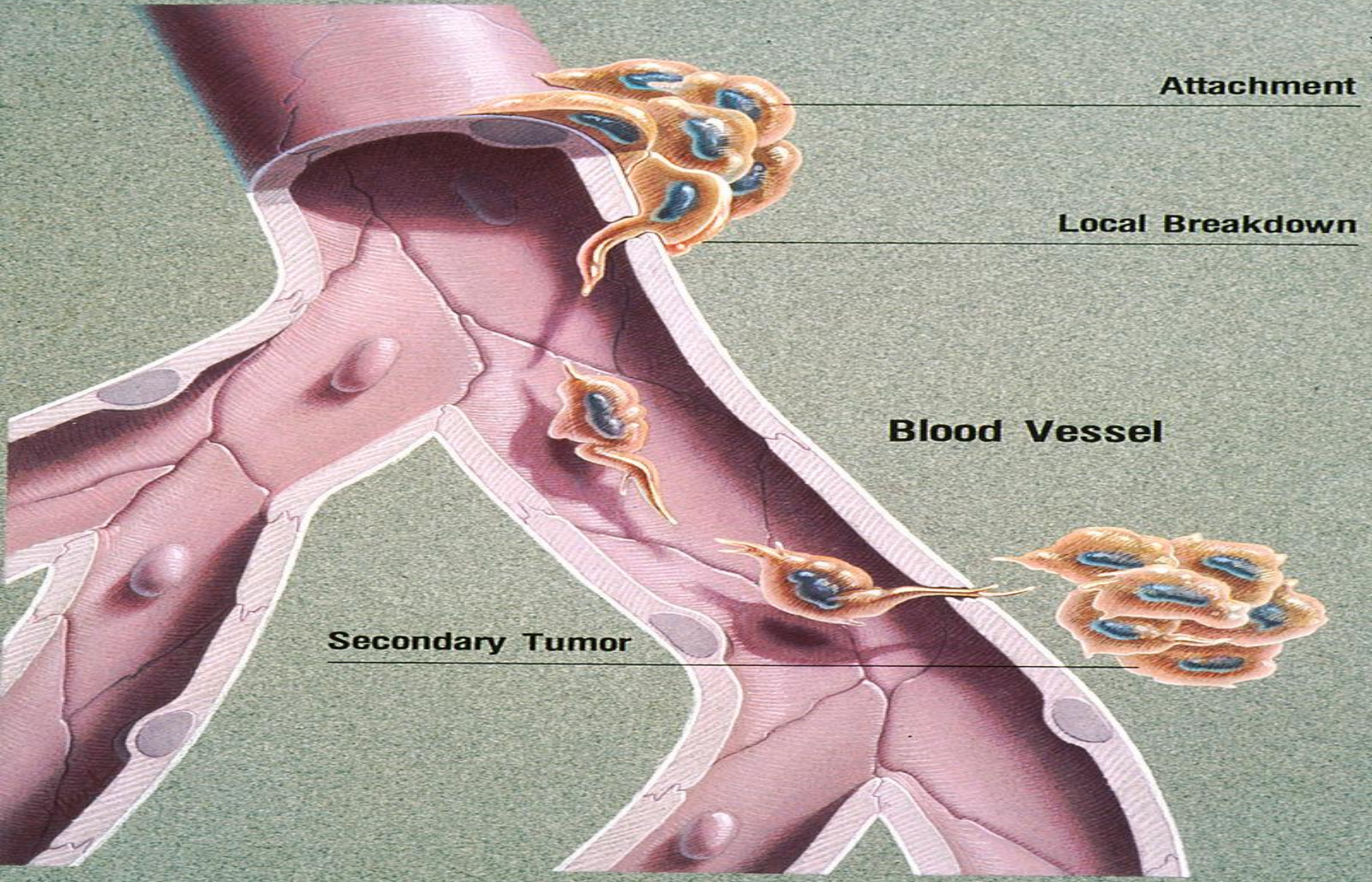
Cancer cells

- are not subject to regulatory system of cell growth
- infiltrate adjacent tissue (in contrast to benign tumours)
- form ***metastases*** due to lymphogenic or haematogenic spread

Metastasis

- Metastasis is the spread of a cancer or other disease from one organ or part of the body to another without being directly connected with it. The new occurrences of disease thus generated are referred to as metastases

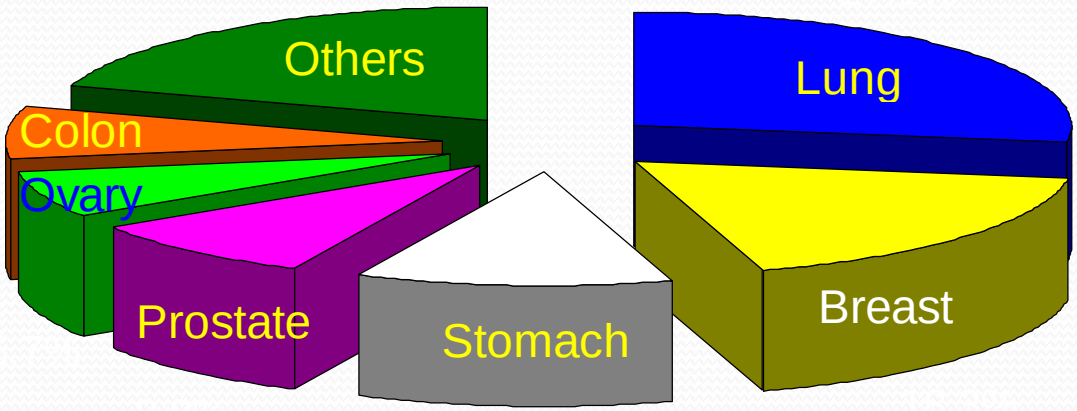
How Cancer Spreads



"How Cancer Spreads"

- "How Cancer Spreads" explains the process of metastasis. Once metastatic cells are attached to the basement membrane (a physical barrier that seperates tissue components), they break through with the help of an enzyme called type IV collagenase. Cancer cells then move through the blood stream enabling them to spread to other parts of the body. This new tumor is known as a metastatic (or secondary) tumor. A secondary tumor may form at another site in the body.

Malignancies by type



Causes of cancer (1)

- **tumours not attributable to a single cause**
- **factors involved can be biological, chemical, physical, or age-related**
- **biological factors can be genetically linked or virus linked** e.g. hepatitis B

– **chemical factors** (e.g N-nitroso compounds in cigarette smoke,, aflatoxins in Aspergillus mould)

Causes of cancer (2)

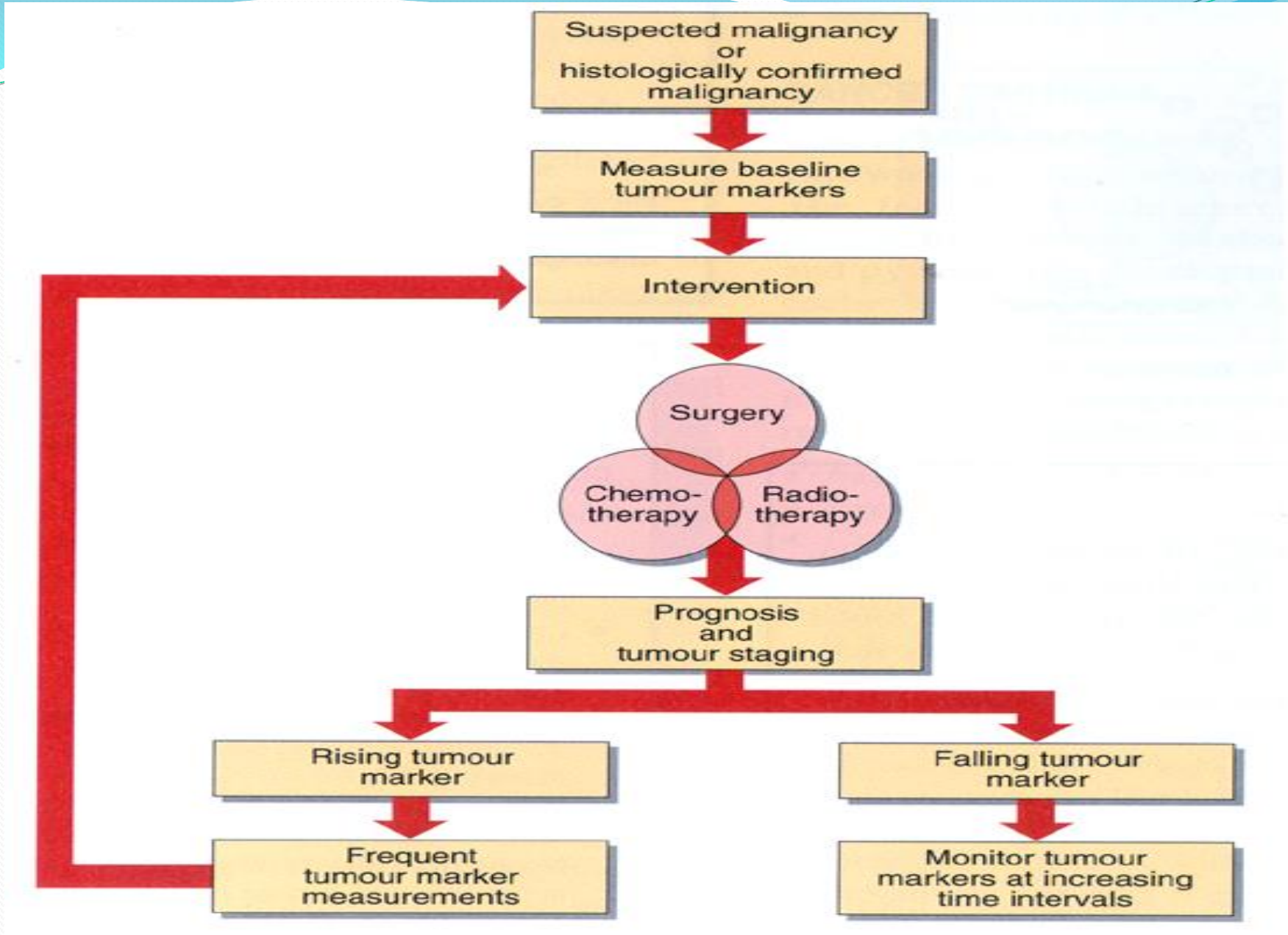
- physical factors (e.g UV, γ, x-rays)
- age-related; increasing errors in DNA transcription and translation occur with ageing
- immune system defects can predispose individuals to cancer

Therapeutic aspects

- surgery
  - radiotherapy
  - chemotherapy
- hormone treatment
- immunotherapy

Therapeutic aspects

- therapy chosen according to tumour type, tumour extension, tumour mass and clinical condition of patient
- surgery and radiotherapy are options for locally-limited tumours
- a combination of different approaches is often necessary


Suspected malignancy or histologically confirmed malignancy
Measure baseline tumour markers
Intervention
Surgery
Chemo-therapy
Radio-therapy
Prognosis and tumour staging
Rising tumour marker
Falling tumour marker
Frequent tumour marker measurements
Monitor tumour markers at increasing time intervals

Ideal Tumour Marker should be….

- **Highly specific :**

  i.e. not detectable in benign disease and healthy subjects

- **Highly sensitive:**

  i.e. detectable when only a few cancer cells are present

- **Specific to a particular organ**

Ideal Tumour Marker should ….

- Correlate with the tumour stage or tumour mass
- correlate with the prognosis
- have a reliable prediction value
- ***but ideal tumour marker doesn ´t exists***

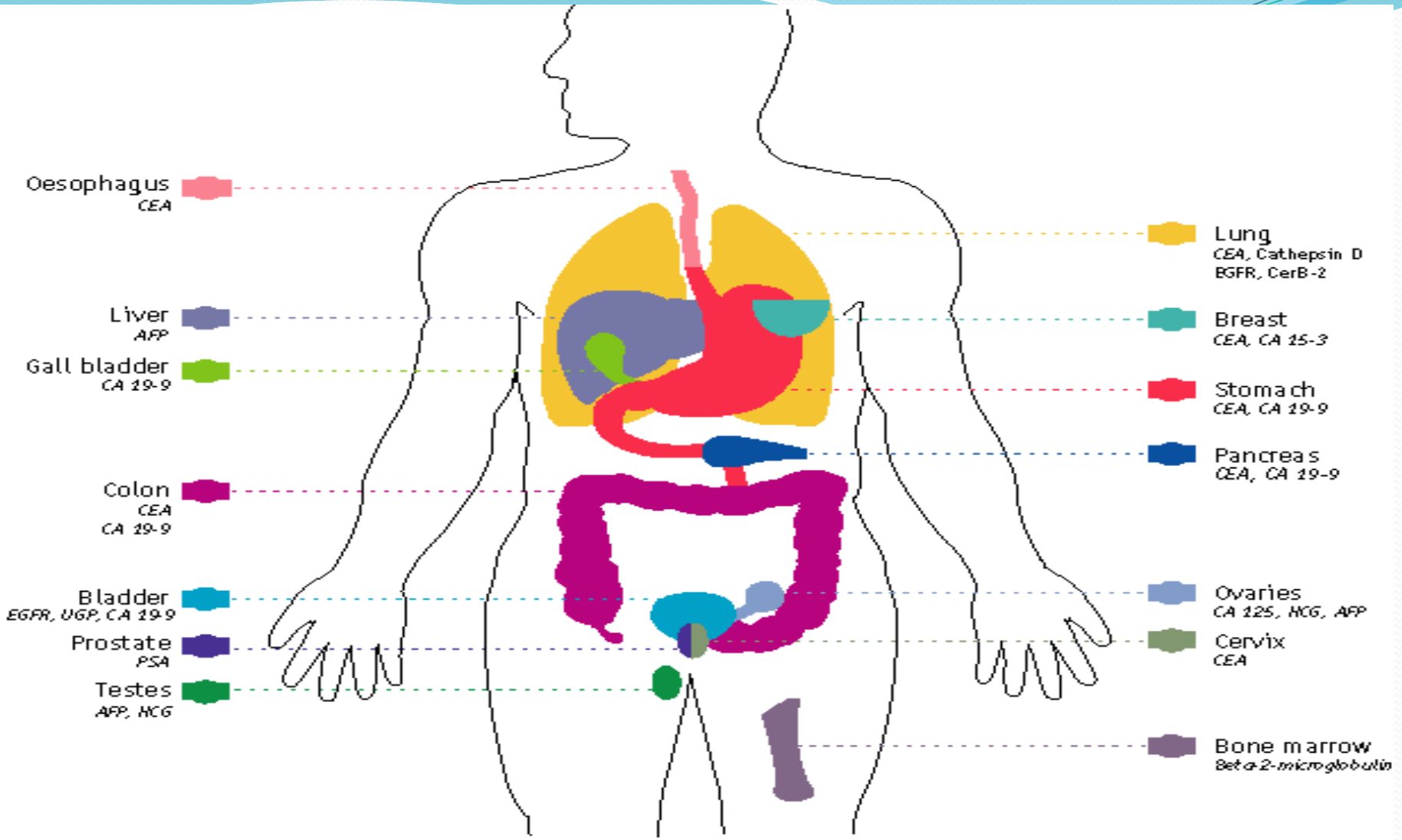
Current Tumour Markers…

- PSA and AFP are organ-specific markers (almost!)
- Many markers show a correlation with tumour stage, ***but ranges for certain stages are very wide and can overlap***
- Prognostic value is obtained from some markers e.g pre-op CEA in colorectal cancer and pre-op CA 125 in ovarian cancer

Tumor markers are:

- **Enzymes –PSA** - prostate specific antigen (serine protease), **NSE** (neurospecific isoenzyme of enolase), **TK** (thymidine kinase), **LDH**
- **Hormones** - GH, prolactin, calcitonin, parathormon (PTH), gastrin, hCG
- **Imunoglobulines** – IgG, IgM, IgA, IgD, IgE, β_2-microglobulin
- **Glycoproteines, glycolipides**

  AFP, hCG, SCC,CA 19-9 (glykolipid), CA 125 (glykoprotein), CA 50 (glykolipid), CA 15-3 (sialomucin), CA 549, CA 72-4, CEA


Oesophagus
CEA
Liver
AFP
Gall bladder
CA 19-9
Colon
CEA
CA 19-9
Bladder
EGFR, UGP, CA 19-9
Prostate
PSA
Testes
AFP, HCG
Lung
CEA, Cathepsin D
EGFR, CerB-2
Breast
CEA, CA 15-3
Stomach
CEA, CA 19-9
Pancreas
CEA, CA 19-9
Ovaries
CA 125, HCG, AFP
Cervix
CEA
Bone marrow
Beta-2-microglobulin

tumor marker assays help in the staging and treatment of the cancer, they are usually not definitive diagnostic tests. The diagnosis is mostly confirmed by biopsy.

Classification:

On the basis of their chemical nature tumor markers can be proteins, conjugated proteins, peptides or carbohydrates. Proteins or conjugated proteins may be enzymes, hormones or fragments of proteins.

Uses:

Tumor markers may be used for the following purposes:
-Screening for common cancers on a population basis. Screening for specific cancer types or locations requires a level of specificity and sensitivity that has so far only been reached by Example: elevated prostate specific antigen suggests that is used in some countries to screen for prostate cancer.

-Monitoring of cancer survivors after treatment, detection of recurrent disease.
-Diagnosis of specific tumor types, particularly in certain brain tumors and other instances where biopsy is not feasible.
-Confirmation of diagnosis to verify the characteristics such as size and aggressiveness of a tumor and thereby to help in the evaluation of a suitable treatment protocol.

-Staging: some tumor markers are included in the staging procedures for some tumor localizations.
- Prognosis to plan the treatment when used pre-treatment and to help the patient to plan his future when used after the operation of cure.
-To verify the effect of treatment to change the treatment if ineffective.

Techniques:

Tumor markers can be determined in serum or rarely in urine or other body fluids, often by immunoassay but other techniques such as enzyme activity determination are sometimes used. Microscopic visualization in tissue by immunohistochemistry does not give quantitative results . For many assays, different assay techniques are available. enzyme activity or amount of substance.