Tumor Markers

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CANCER IS:

- a broad term used to describe so many diseases.
- the second leading cause of death.
- the uncontrolled growth of cells that can develop into a solid mass or tumor & spread to other areas of the body .

CANCER IS:

- The formation (tumorigenesis) & spreading (metastasis) of tumors are caused by a complex combination of inherited and acquired genetic mutations .
- During tumorigenesis, these mutations include activation of growth factors e.g. Epidermal Growth Factor (EGF) & oncogenes (e.g. K-ras), in combination with inhibition of apoptosis, tumor suppressor, and cell cycle regulation genes

COMMON CANCER TERMS

Angiogenesis	Development of new blood vessels to supply oxygen and nutrients to cells
Apoptosis	Programmed cell death
Cell cycle	Phases of cell activity divided into G, S, and M (growth, DNA synthesis, and mitosis, respectively)
Oncogene	Encodes a protein that, when mutated, promotes uncontrolled cell growth
Tumor suppressor gene	Encodes a protein involved in protecting cells from unregulated growth

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."

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.
- Incidence of cancer increases with age (10-fold higher incidence at 70 years than 25 years).

Cancer severity is generally classified by a combination of several factors.

Depending on the type of cancer, these factors include:

- Tumor size
- Histology
- Regional lymph node involvement
- The presence of metastasis

For most solid tumors (e.g., breast , lung , kidney), cancer is broadly classified (using roman numerals I-IV) into 4 stages:

- stage I: Localized primary tumor
- Stage IV: Metastasis of tumor to distant tissues

CANCER CELLS

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

CAUSES OF CANCER :

-Tumours are 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. papilloma, hepatitis B, herpes .

- ***Chemical factors :***(e.g . benzopyrene in tar, N-nitroso compounds in cigarette smoke, aflatoxins in Aspergillus mould)
- ***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.

CLINICAL ASPECTS

- Early diagnosis is difficult as the carcinoma is usually asymptomatic.
- Most diagnostic procedures (e.g. X-ray, CT, mammography, isotope scanning) only detect tumour at 1-2 cm size .
- at this time, tumour already consists of *>1 billion cells.*

THERAPEUTIC ASPECTS

- Surgery
- Radiotherapy
- Chemotherapy
- Hormone treatment
- Immunotherapy

THERAPEUTIC ASPECTS

- Therapy is 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

WHAT ARE TUMOR MARKERS?

Tumor markers are produced by cancer cells or by other cells of the body in response to cancer or certain benign (noncancerous)conditions.

Most tumor markers are made by normal cells as well as by cancer cells ; however, they are produced at much higher levels in cancerous conditions.

DEFINITION

Tumor markers are a group of proteins, hormones, enzymes, receptors, and other cellular products that are overexpressed (produced in higher than normal amounts) by malignant cells.

-Tumor markers are usually normal cellular constituents that are present at normal or very low levels in the blood of healthy persons.

- If the substance in question is produced by the tumor, its levels will be increased either in the blood or in the tissue of origin.

TUMOUR MARKERS

- Macromolecules whose appearance and changes in concentration are related to the genesis and growth of malignant tumours.
- detected in serum, urine and other body fluids in concentrations exceeding those found in physiological conditions.
- synthesised and excreted by tumour tissue or released on tumour disintegration.

-These substances can be found in the blood, urine, stool, tumor tissue, or other tissues or body fluids of some patients with cancer.

-Most tumor markers are proteins. However, more recently, patterns of gene expression and changes to DNA have also begun to be used as tumor markers.

A perfect tumor marker would be one that could be used as a cancer screening blood test for all people.

-The tumor marker would only be found in people with cancer.

-It would tell doctors the type of cancer, how much cancer there is, and which treatment would work best.

-At this time there are ***no*** tumor marker tests that work like this.

Thus far, more than 20 different tumor markers have been characterized and are in clinical use. Some are associated with only one type of cancer, whereas others are associated with two or more cancer types.

There is no "universal" tumor marker that can detect any type of cancer .They are used in oncology* only to help detect the presence of cancer.

There are some limitations to the use of tumor markers:

1- Sometimes, noncancerous conditions can cause the levels of certain tumor markers to increase:

For example, the level of the tumor marker CA 125 can be high in women with gynecologic conditions other than ovarian cancer .

2- In addition, not everyone with a particular type of cancer will have a higher level of a tumor marker associated with that cancer.

3-The levels of these markers tend to get higher than normal only when there's a large amount of cancer present.

4- Moreover, tumor markers have not been identified for every type of cancer.

These are the reasons why, today, tumor markers are used mainly in patients who have already been diagnosed with cancer to watch their response to treatment or look for the return of cancer after treatment

HOW ARE TUMOR MARKERS USED IN CANCER CARE ?

1- SCREENING FOR THE PRESENCE OF DISEASE:

Screening refers to looking for cancer in people who have no symptoms of the disease.

Early detection is finding cancer at an early stage, when it's less likely to have spread and is easier to treat.

Tumor markers were first developed to screen for cancer without symptoms – but very few markers have been shown to be helpful in this way.

Tumour markers is not, in routine clinical practice, used to screen for malignancy, however this might be in theory.

The exception to this rule is the screening of specific high risk populations.

For example, the hormone calcitonin, which is increased in patients with medullary carcinoma of thyroid, may be used to screen close relatives.

2- DIAGNOSIS:

Markers alone are rarely used to establish a diagnosis.

Their detection in blood when there is clinical evidence of the tumour as well as radiological and, perhaps, biopsy evidence, will often confirm the diagnosis.

- Alpha fetoprotein (AFP) is a tumor marker that may be used to help diagnose cancer.
- The level of AFP can go up with some liver diseases, but when it reaches a certain high level in someone with a liver tumor, doctors can be fairly sure that the tumor is liver cancer (a biopsy will still be needed).

3- MONITORING TREATMENT:

Treatment monitoring is the area in which most tumour markers have found a useful role.

The decline in concentration of the tumour marker is an indication of the success of the treatment, whether that be surgery, chemotherapy, radiotherapy, or a combination of these.

Tumor markers is measured periodically during cancer therapy :

-A decrease in the level of a tumor marker or a return to the marker's normal level may indicate that the cancer is responding to treatment, whereas

-No change or an increase may indicate that the cancer is not responding.

If a tumor marker is available for a certain type of cancer, the level of the marker may be able to be used to see if the treatment is working, instead of doing other tests like x-rays, CT scans, or bone scans.

If the marker level goes up, then the cancer is not responding and the treatment may need to be changed. (One ***exception*** is if the cancer is very sensitive to a certain chemotherapy treatment. In this case, the chemotherapy can cause many cancer cells to die and release large amounts of the marker into the blood, which will cause the level of the tumor marker to rise for a short time.)

4- PROGNOSIS:

Prognosis: ***A prediction of the probable course and outcome of a disease and the likelihood of recovery from a disease***

To be of value in prognosis, the concentration of the tumour marker should correlate with tumour mass.

Tumor markers help :

a) **to show how aggressive a particular cancer is**

b) **how it can respond to a particular drug.**

In testicular cancer , high levels of AFP(Alpha-fetoprotein) predicts a more aggressive cancer and requires more aggressive treatment to start with.

5: LOOKING FOR RECURRENT CANCER

- Tumor markers are also used to look for cancer that might have come back (recurred) after treatment.
- Even when a patient has had successful treatment, it is often valuable to continue to monitor the marker long after the levels have appeared to stabilize. An increase indicates recurrence of the malignancy. Detection of increasing marker concentration allows second-line therapy to be instituted promptly.

IDEAL TUMOUR MARKER SHOULD BE :

- Highly sensitive i.e. detectable when only a few cancer cells are present
- Highly specific i.e. not detectable in benign disease and healthy subjects
- Specific to a particular organ

WHEN TO DETERMINE TUMOUR MARKERS:

1- Before surgery or any kind of treatment.

2- After surgery , during treatment and after treatment (once in 3 to 6 months period in 1st second yr then once yearly)

3- In case of suspected relapse or disease progression.

4- Before introducing a new treatment.

5- 3 weeks after introducing new ttt.

6- 2 to 3 weeks after determining raised concentration of the marker.

TYPES OF TUMOR MARKERS

- Tumor markers are produced either directly by the tumor or as an effect of the tumor on healthy tissue (host).
- Tumor markers are diverse molecules such as:
  - Oncofetal antigens
  - Hormones
  - Enzymes
  - Serum proteins
  - Metabolites
  - Receptors

TUMOUR MARKERS FALL INTO ONE OF SEVERAL GROUPS:

- Oncofetal antigens e.g. carcinoembryonic antigen (CEA) , AFP.
- Hormones e.g. human chorionic gonadotrophin (HCG) , GH, prolactin, calcitonin, parathormone (PTH).
- Enzymes e.g. prostatic acid phosphatase , NSE (neurospecific isoenzyme of enolase), TK (thymidine kinase), LDH
- Special proteins e.g.Ferritin , B2 miccoglobulin.

- Receptors e.g. estrogen receptors, progesterone recpetors, Her-2 .
- Imunoglobulines – IgG, IgM, IgA, IgD, IgE.

- Antigens :glycoproteins, glycolipids

  CA 125, CA 15- 3,CA 72-4 ,PSA (glyoprotein), SCCA,CA 19-9 (glycolipid).

1-ONCOFETAL PROTEINS

They are antigens that are normally produced during the embryonic development.

Their production is limited or completely absent in adults.

Increased levels in adults result from reactivation of certain genes that control cellular growth and involved in malignant process

1-CEA (Carcinoembryonic Antigen)

- **One of the first known TM**
- **Produced during embryonal and foetal development.**
- **Glycoprotein, 40% protein, 60% carbohydrate.**
- During development: it is produced in epithelial cells of **GIT, liver and pancreas**

CEA

- It is important for follow-up patients in colorectal cancer:
  a) High level is present in 65% of all patients
  b) High level is present in 100% of patients with metastatic disease.

- Serial CEA levels is useful in assessing the effectiveness of chemotherapy for colorectal cancer.

- It can also be used as a follow-up marker for other malignancies:
  Breast, ovarian, lung and liver cancer.

CEA

- Elevated levels seen in patients with non-malignant disease (especially elderly smokers), hepatitis, cirhosis, pancreatitis, bronchitis.

- Serum concentrations 4-10 ng/ml : patients with benign, malignant diseases and in heavy smokers.

- Serum concentrations > 10 ng/ml : malignant diseases

2- Alpha-fetoprotein

- It is a glycoprotein.
- It is produced during embryonic development in epithelial cells of GIT and liver.
- In healthy adults, AFP can be found in very minute concentrations.
- Elevated AFP levels (more than 10 ng/ml) is found in : viral hepatitis, liver cirrhosis, pancreatic cancer, lung cancer.

AFP

- Useful in detecting and monitoring primary liver carcinoma :

-elevated levels seen in > 90% of affected patients

-AFP levels above 1200ng /ml confirm primary liver cancer.

- AFP levels is high in testicular and ovarian cancer.

HORMONES

Quantitative or qualitative alterations of the synthesis and hormone secretion can indicate malignancies and work as a TM.

-*Quantitative alteration*:

tumor develops in tissue of endocrine glands; increasing or decreasing hormonal secretion.

-*Qualitative alteration*:

Malignant cells of some organs (lungs, breasts, CNS, ovaries) start producing hormones (Ectopic hormone production).

1-HCG –HUMAN CHORIONIC GONADOTROPIN

-It is a carcinoplacental antigen (proteins synthesised in the placenta during pregnancy)

-Elevated serum levels can be found:

a) Female patients with germ tumors of ovaries

b) Male patients with germ tumors of testicles

-It has a short half-life (36- 48 hrs) : used follow- up treatment

-βHCG is used in combination with AFP for monitoring patients with germ tumours.

-Increased levels of βHCG can be found in patients with : breasts, lung, liver or colorectal cancer

2- CALCITONIN

-Hormone produced by parafollicular C cells of thyroid gland.

-It helps regulate blood Calcium levels.

-Cancer of parafollicular C cells is known as medullary thyroid carcinoma (MTC): increased levels of calcitonin.

-It is one of rare TM that helps in detecting early cancer.

-MTC is inherited so calcitonin is used in screening family members who are at risk.

Enzymes

Certain enzymes are produced more intensely in case of malignancy:

1- Prostatic acid phosphatase (PAP):

It is produced by normal prostatic tissue

Increased levels above 3 ng/ml is seem in patients with prostatic cancer.

2- Alkaline phosphatase:

It exists in different isoforms synthesized in the liver, bones and placenta.

Elevated serum concentrations indicate malignant diesease usually in metastatic stage in liver/bones/ primary bone tumours (osteocarcinoma).

3-Lactate dehydrogenase:

It is present in different organisms and different tissues.

It catalyses interconversion between lactate and pyruvate and NADH- NAD interconversion.

It is used as follow-up in lymphoma patients.

4-Thymidine kinase:

leukemia, lymphoma, brain tumors.

5-Neuron specific enolase:

in tumors of neuroectodermal or neuroendocrinal differentiation .

SPECIAL PROTEINS

1- Feritin

It binds iron for detoxification, found in liver, spleen and bone marrow.

Increased serum conc is found in acute leukemia, lymphoma, lung and liver prostatic cancer.

2- Thyroglobulin

It is responsible for production and storage of thyroxine.

Increased serum levels can be found in thyroid carcinoma.

Tissue-bound receptors:

1- Epidermal growth factor receptor [EGFR (Her-1)]

It is a family of receptors that help regulate cell growth, division and death.

Normal epithelial cells contain two copies of EGFR gene and produce low levels of EGFR.

In different cancers:

1- Amplification (many copies of the gene produced)

2- Over-expression (increased protein production)

Tumour have increased EGFR, grow more aggressively and induces metastasis and become more resistant to chemotherapies

CLINICAL USES

It is used to guide treatment and determine prognosis in case of positive EGFR in solid tumours such as : lung, head and neck, colon pancreas and breast.

***Methods of determination*:**

1- Measuring amount of EGFR protein

2- Measuring genetic level of genetic amplification.

Sample of cancer tissue is obtained by biopsy.

2-HER-2/NEU

1- **Oncogenic growth factor receptor.**

2- **It is the same family as EGFR but evaluate different types of cancers.**

3- **It is associated with breast cancer and used to:**

determine ttt options such as drugs that can block this protein and reduce cancer growth e.g Herceptin (Trastuzumab).

4- **It is measured in tissues (protein or gene)**

5- **Increased levels of HER-2/neu indicate aggressive tumour and poor prognosis.**

3-ESTROGEN RECEPTOR (ER)

-Measurement of estrogen receptor used to evaluate breast cancers.

-It gives an indication of prognosis and responsiveness to therapy.

4-Progesterone Receptor (PR)

It is important prognostic marker in breast cancer and receptor expression.

TUMOUR-ASSOCIATED ANTIGENS

This is a group of markers that comprises various membrane structures of tumour cells.

Specific monoclonal antibodies against these antigens can be developed to detect tumours markers.

These markers are more specific to the type of malignancy and their serum concentrations reflects more accurately the growth or regression of tumour cells

1- CARCINOMIC ANTIGEN 15-3 (CA 15-3)

- **It is a glycoprotein of the mucin family, released from breast carcinoma cells**
- **Elevated serum levels > 30 U/ml can be found in patients with: breast cancer, lung, prostatic, ovarian, cervical and gastrointestinal cancer.**
- **CA15-3 (also known as MUC-1) is the marker of choice for breast cancer.**
- **It is not specific but is a good indicator for ttt of breast cancer.**

CA 15-3

- It has clinical utility in following the clinical course of breast cancer, detecting metastases and monitoring response to therapy
- Rising CA15-3 levels indicate disease recurrence

2-CARCINOMIC ANTIGEN 125 (CA-125)

-CA 125 is a glycoprotein secreted from the surface of ovarian cancer cells

-Reference range 0 -35 U/mL

-Elevated levels above 35 U/ml is doing in patients with ovarian cancer , prostatic cancer.

-It is the most reliable TM for follow-up in patients with ovarian cancer.

CA 125

- A normal CA 125 level does not exclude the possibility of an ovarian tumour.
- however there is a good correlation between CA 125 levels and clinical response
- CA 125 is a good prognostic indicator and monitoring tool when used with other methods e.g. ultrasound.

3-PROSTATE SPECIFIC ANTIGEN (PSA)

-It is a glycoprotein isolated from tissue of prostate and sperm.

This marker is specific to prostatic cancer:

a) It is used for follow-up of prostatic cancer patients.
b) It is used for screening of prostatic cancer for males over 50 yrs old.
c) Due to its high sensivity, PSA can be use in primary diagnosis
d) Determination of different forms of PSA (total, bound and free) is useful in identifying patients with benign or malignant prostatic tumors.

4-Squamous cell carcinoma (SCC) antigen:

-It is used to identify cervical cancer.

-It helps in staging the cancer and determine response to ttt.

5-Bladder Tumour antigen (BTA)

-It is present in urine of patients with bladder cancer.

-Cytoscopy is still recommended for diagnosis and follow-up of bladder cancer.

GENES

1- BRCA1

Breast cancer 1, is a human gene that belongs to class of genes Tumor Suppressor Genes.

BRCA1 :

1- regulates cycle of cell division by preventing growth of cells that line milk ducts in the breast.

2- BRCA1 proteins are involved in repair of DNA damage by radiation or other exposure to stabilise humane genome.

3- BRCA1 protein regulates activity of other genes and important in embryo development.

4- BRCA1 protein interacts with other proteins (tumour suppressors and regulators) of cell division cycle.

BRCA1 and breast cancer:

1- **Variation in BRCA1 gene lead to increased risk in breast cancer.**

2-Mutated BRCA1 gene that makes the protein non-functional as it is unable to fix mutations in other genes.

This causes an increased risk of ovarian, prostate and colon cancer.

BRCA2

Human gene belongs to tumor suppressor genes.

Different structures, but similar functions to BRCA1:

1- Repair DNA damage.

2- Regulate activity of other genes and in embryo development.

BRCA2 and Cancer:

1- Variations in BRCA2 gene increases risk for breast cancer

2- About 450 mutations found in BRCA2 genes were associated with cancer

3-Mutations resulting in non-functional proteins result in increased risk to:

ovarian risk (especially in central region of the gene)Prostate cancer, pancreatic cancer.

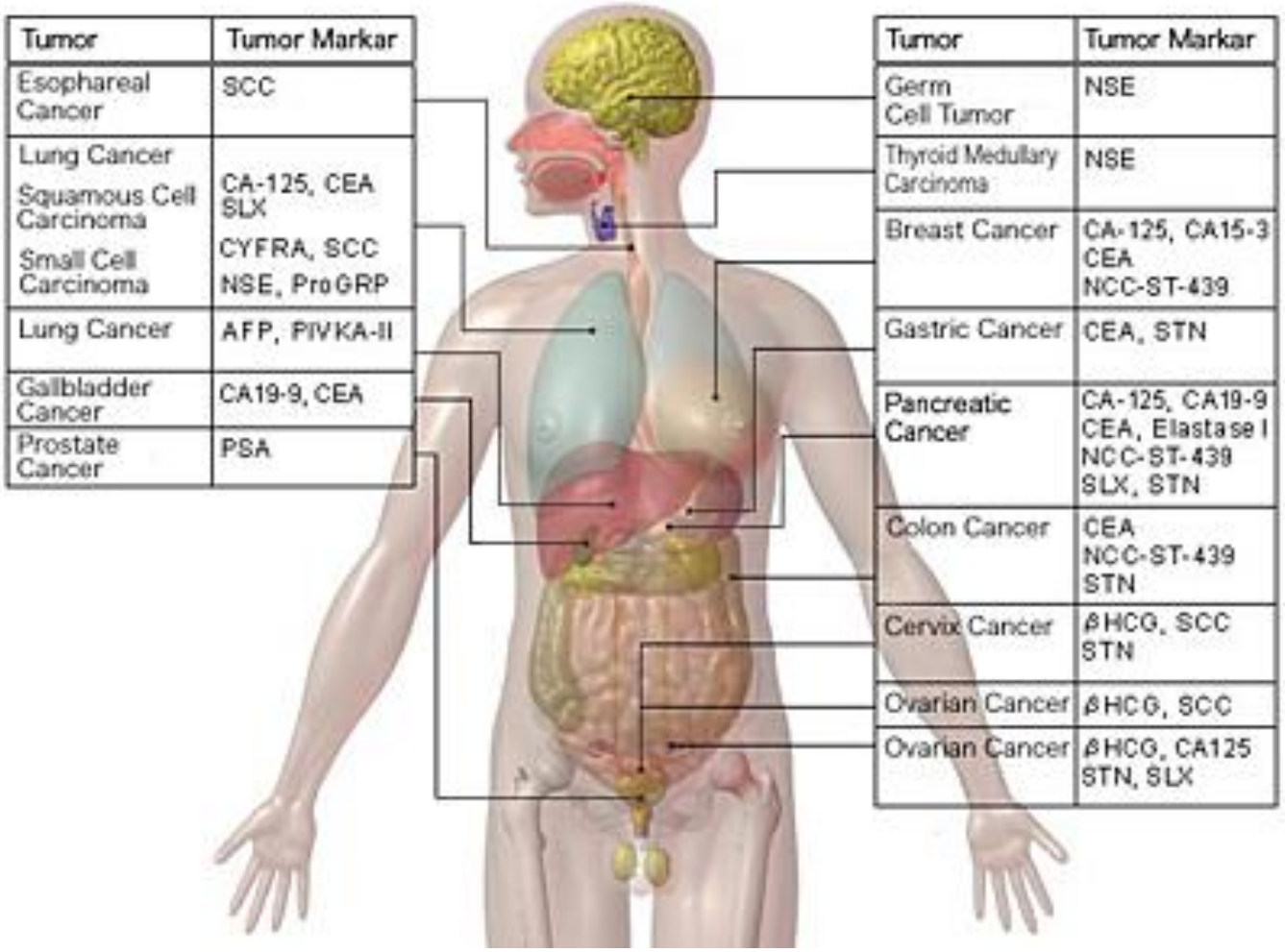

Figure indicates some of tumor markers' sites in the human body