Tumor markers

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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.”

*Oxford Concise Medical Dictionary*
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)
Incidence of malignancies

- Incidence of malignancies is very different worldwide

- In western industrialised nations, Ca bronchus is most common type in male and Ca breast in female

- Ca bronchus in women increasing, as is malignant melanoma in both sexes
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
Malignancies by type

- Lung: 27.1%
- Breast: 18.3%
- Stomach: 11.6%
- Prostate: 8.9%
- Ovary: 6.7%
- Colon: 7.4%
- Others: 20.0%
Tumor markers are:

- **Enzymes** – PSA - prostate specific antigen (serine protease), NSE (neurospecific isoenzyme of enolase), TK, LDH
- **Cytokeratiny** (rozpustné deriváty) – tkáňový polypeptidový antigen (TPA), fragment cytokeratinu 19 (CYFRA 21-1)
- **Hormones** - GH, prolactin, calcitonin, parathormon (PTH), gastrin, hCG
- **Imunoglobulines** – IgG, IgM, IgA, IgD, IgE, β₂-microglobulin
- **Glycoproteines, glycolipides a sacharides**
  - AFP, hCG, SCC, CA 19-9 (glykolipid), CA 125 (glykoprotein), CA 50 (glykolipid), CA 15-3 (sialomucin), CA 549, CA 72-4, CEA, Tg
EGTM Tumor Marker Recommendations

(EUROPEAN GROUP on TUMOUR MARKERS)

- Quality Requirements and Control
- Breast
- Gastrointestinal
- Germ Cell
- Gynecological
- Lung
- Prostate

http://egtm.web.med.uni-muenchen.de/index2.html
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. papilloma, hepatitis B, herpes or HIV virus

- Chemical factors (e.g. benzopyrene in tar, 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
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 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
**Tumour Markers**

- macromolecules whose appearance and changes in concentration are related to the genesis and growth of malignant tumours

- detected in concentrations exceeding those found in physiological conditions in serum, urine and other body fluids

- synthesised and excreted by tumour tissue or released on tumour disintegration
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 exist*
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
Positive Predictive Value of a Tumour Marker

The probability with which a tumour exists within a control group in the case of positive test results
Positive Predictive Value of a Tumour Marker

\[
\frac{\text{True positives}}{\text{True positives} + \text{False positives}}
\]
Negative Predictive Value of a Tumour Marker

The probability with which no tumour exists within a control group in the case of negative test results
Negative Predictive Value
of a Tumour Marker

True negatives

True negatives + False negatives
Specificity

The percentage of normal persons or persons with benign conditions for whom a negative result is obtained. The greater the specificity, the fewer the false-positives.
Specificity of a Tumour Marker

True negatives

True negatives + False positives
Sensitivity

- The percentage of test results which are correctly positive in the presence of a tumour. The greater the sensitivity, the fewer the false-negatives.
Sensitivity of a Tumour Marker

True positives

True positives + False negatives
Cut-off value

- The concentration of a tumour marker which differentiates healthy subjects from diseased subjects

- usually taken as the mean concentration of a control group plus 2 standard deviations (or the 95th percentile)

- control group could be healthy subjects or persons with benign disease

- target specificity should be 95% (5% false positives)
Cut-off value (PSA)

Healthy

100% specificity (no false positives)....
Cut-off value (PSA)

Healthy

Prostate cancer

But only 70% sensitivity (30% false negatives)!
Cut-off value (PSA)

100% sensitivity…..
(no false negatives)
Cut-off value (PSA)

Healthy

Prostate cancer

But only 70% specificity!
(30% false positives)
Cut-off value (PSA)

Healthy

Prostate cancer

At 4.0 ng/mL, 95% specificity and 95% sensitivity
CEA (Carcinoembryonic Antigen)

- Glycoprotein discovered in 1965
- MW 180,000, 40% protein, 60% carbohydrate
- an oncofetal protein, produced during embryonal and foetal development
- increased levels seen in primary colorectal cancer and GI, breast, lung, ovarian, prostatic, liver and pancreatic cancer
CEA

– Elevated levels seen in patients with non-malignant disease (especially elderly smokers), hepatitis, cirhosis, pankreatitis

– CEA levels not useful in screening the general population

– however, assay provides useful information regarding patient prognosis, recurrence of tumours after surgery and effectiveness of therapy
CEA

- Healthy non-smokers have CEA levels < 5 ug/L (smokers < 10 ug/L)
- Levels fall to normal (or near-normal) 6-8 weeks post-surgery
- Biological half-life 2-8 days
- A rise in CEA may be the first indication of disease recurrence or metastasis
- Serial CEA levels also useful in assessing the effectiveness of chemotherapy for colorectal cancer
AFP (Alphafetoprotein)

- A glycoprotein, MW 70,000, discovered in 1956 in foetal serum
- described as a tumour-associated protein in 1964
- synthesised in the liver and yolk sac of the foetus
- AFP is secreted into serum, reaching maximum levels at week 13 of pregnancy
AFP

– Useful in detecting and monitoring primary liver carcinoma

– Elevated levels seen in > 90% of affected patients

– Also useful assay for detection and prediction of germ cell tumours

– Direct relationship exists between AFP level and disease stage of non-seminomatous testicular carcinoma
AFP

- Pure seminomas and dysgerminomas are always AFP-negative
- Pure yolk-sac tumours are always AFP-positive
- Also useful assay for detection of germ cell tumours
- AFP level, (together with hCG level), is established regimen for monitoring patients with non-seminomatous testicular carcinoma
AFP

- Growth rate of progressive cancer can be monitored by serially measuring serum AFP over time

- Biological half-life 2-8 days

- normal serum level < 8.1 ug/L
hCG

- sialoglycoprotein, subunits α a β
- α has the same structure like LH, FSH a TSH
- diagnosis and monitoring of germinal tumors especially of the testes or the ovaries.
- 70% sensitivity for non-seminomas, 97% in trophoblastic tumors
- normal serum level < 10 IU/l
- Biological half-life - 1-2 days
PSA

- glykoprotein, serine protease
- Therapy check and monitoring of patients with prostate carcinoma
- Due to its high sensivity, PSA can be use in primary diagnosis
- screening of symptomatic population
- ref.meze do 4 µg/l
- Biological half-life - 2 - 5 days
FPSA

- FPSA – non complexed form of PSA
- If level of PSA is between 3-20 µg/l
- Ratio FPSA/PSA – discrimination between cancer and benign prostatic hyperplasia
- Cut off 0.25
- As the ratio increases, probability of BPH increases
CA 19-9

– CA is an abbreviation of Carbohydrate Antigen

– CA 19-9 is an oligosaccharide present in serum as a high molecular weight mucin (MW >1 million). Derivate of the Lewis blood grouping system- people with blood group Le a-/b- don’t product it (7-10% of the population)

– is found in adult pancreas, liver, gallbladder and lung
CA 19-9

- is the primary marker in pancreatic carcinoma

- serum CA 19-9 levels correlate with tumour size

- CA 19-9 values above 1000 U/mL indicate metastasis into the lymph nodes

- can be used in monitoring of colorectal carcinoma, Ca stomach and Ca biliary tract
CA 19-9

- elevated CA 19-9 levels seen in benign conditions e.g. cholestasis, hepatitis, pancreatitis

- reference range 0 - 37 U/mL

- Biological half-life 7 h

- CA 19-9 has greater specificity than CEA for colorectal cancer

- CA 19-9 can be used to differentiate between carcinoma and benign intestinal disease.
CA 72-4

- Glycoprotein
- High specificity (about 100%), sensitivity higher than CEA and CA 19-9
- Monitoring of stomach cancer
- Useable for patients with blood group Le a-/b- instead of CA 19-9
- Reference range 4 kIU/l
CA 125

- CA 125 is a high MW, non-mucinoid glycoprotein secreted from the surface of ovarian cancer cells

- A normal CA 125 level does not exclude the possibility of an ovarian tumour

- this lack of specificity means that the CA 125 level should not be used as a diagnostic tool

- however there is a good correlation between CA 125 levels and clinical response
CA 125

- CA 125 is a good prognostic indicator and monitoring tool when used with other methods e.g. ultrasound

- Elevated CA 125 levels seen in benign conditions e.g. endometriosis, cirrhosis and pancreatitis

- Reference range 0 - 35 U/mL

- Biological half-life 2-6 days
CA 15-3

- CA15-3 (also known as MUC-1) is the marker of choice for breast cancer
- A glycoprotein of the mucin family, MW 300,000 to 500,000 daltons
- primarily released from breast carcinoma cells
- CA 15-3 is defined by its reaction with monoclonal antibodies (115 D8 and DF3)
CA 15-3

– CA15-3 is not sensitive or specific for screening, pre-op diagnosis or prognosis of breast cancer

– 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
CA 15-3

– Raised CA15-3 levels seen in bronchial, ovarian, pancreatic and colorectal cancer

– Raised CA15-3 levels also seen in cirrhosis and hepatitis as well as benign ovarian and lung disease

– No cross reactivity with unrelated serum proteins

– Reference range 0 -35 U/mL

– Biological half-life not yet known
SCC

The squamous cell carcinoma-associated antigen

Carcinoma of cervix, the lung, oesophagus and ENT region

Monitoring of therapy

Normal range > 2 µg/l

- 95% probability of NSCLC and 80% probability that it is a squamous carcinoma

Biological half-life - 20 minutes

SCC is present in saliva, sweat etc. Contamination!
The other tumor markers

- NSE – neuron specific enolase
- CYFRA 21-1
- TPA cytokeratiny 8, 18, 19
- TPS - cytokeratin 18
- TK - tymidinkinase
- β2-microglobulin
- Ferritin
Rare tumor markers

- **S100B** - protein from neural tissue, monitoring patients with malignant melanoma.
- **CA 549** - mucin - breast cancer
- **MCA** (mucin-like cancer associated antigen) metastatic breast cancer
Tumor markers

- Tumour markers may be helpful in differential diagnosis (e.g. in germ cell cancers where they may be different cell types) and especially where there are metastatic deposits but the primary site is unknown (e.g. NSE in lung cancer, CA15.3 in breast cancer).

- It is important to remember that no tumour marker is specific for malignancy (elevation may be due to other malignancy, or to benign disease), and that a "normal" tumour marker result never necessarily excludes malignancy or recurrence.