

Cancer Biochemistry and Tumour makers

James Pethick

Clinical Scientist

Sandwell and West Birmingham Hospitals

KNOWLEDGE

- Understand the different types of tumour and the disorders in biochemistry they can cause.
- Understand the staging of tumour growth and the implications for the patient biochemically.
- Understand the appropriate use of tumour markers in screening, diagnosis and monitoring malignant disease.
- Be aware of the criteria for the ideal tumour marker.
- Be aware of clinical sensitivity and specificity of methods, problems with cross reactivity and prozone effects.
- Understand the possible biochemical consequences of tumour growth such as ectopic hormone production.
- Be aware of the roles of faecal occult blood, PSA, CEA, CA125, CA153, CA19-9, AFP, HCG, HIAA, catecholamines and metadrenalines and how these assays maybe performed.
- Understand the sample requirements for tumour marker measurement and possible interferences or cross reactions.

COMPETENCE

- You must be able to:
- Explain the physiological significance of tumour marker measurements.
- Give examples of routinely used tumour markers and how they are used appropriately.
- Locate information for sample requirements for tumour marker tests and be able to give advice to clinicians regarding sample types.
- Explain the methodological techniques used to measure tumour markers and how different methods and standards used may alter results obtained.

UK CANCER STATISTICS



Cases

356,860



New cases of cancer,
2014, UK

Deaths

163,444



Deaths from cancer,
2014, UK

Survival

50%



Survive cancer for 10
or more years, 2010-
11, England and
Wales

Prevention

42%



Preventable cases of
cancer, UK

Diagnoses per day?
Males?
Females
Biggest risk?
Highest incidence?

980, 1 every 2 minutes
181,000
176,000
Age
+85 years

1 in 2 people born after 1960 will be diagnosed
with some form of cancer during their lifetime
4 in 10 cancer cases are linked to lifestyle factors
Smoking is the largest single preventable cause of
cancer each year in the UK

There are over 200 types of cancer but Breast, Lung, Prostate and Bowel cancer account for 53% of all cancers in the UK

BREAST CANCER



The most common cancer in the UK and accounts for 15% of all new cases per year
 Almost half breast cancer cases are diagnosed in women over 65 years
 There were 390 new cases of breast cancer in males in 2014
 Breast cancer is less common in women who live in deprived areas and is more common in White females than Asian or Black females



- Mother died of ovarian cancer
- BRCA1 is a tumour suppressor gene – it fixes damaged DNA
- There are >1800 known mutations in BRCA1 – cause truncation of BRCA1 protein
- BRCA1 mutations inherited and cancers cluster within families
- BRCA1 mutation severely increases your risk of developing breast and ovarian cancer
- If worried your GP can refer you to genetics for predictive genetic testing

LUNG CANCER

Cases

46,403

New cases of lung cancer, 2014, UK

Deaths

35,895

Deaths from lung cancer, 2014, UK

Survival

5%

Survive lung cancer for 10 or more years, 2010-11, England and Wales

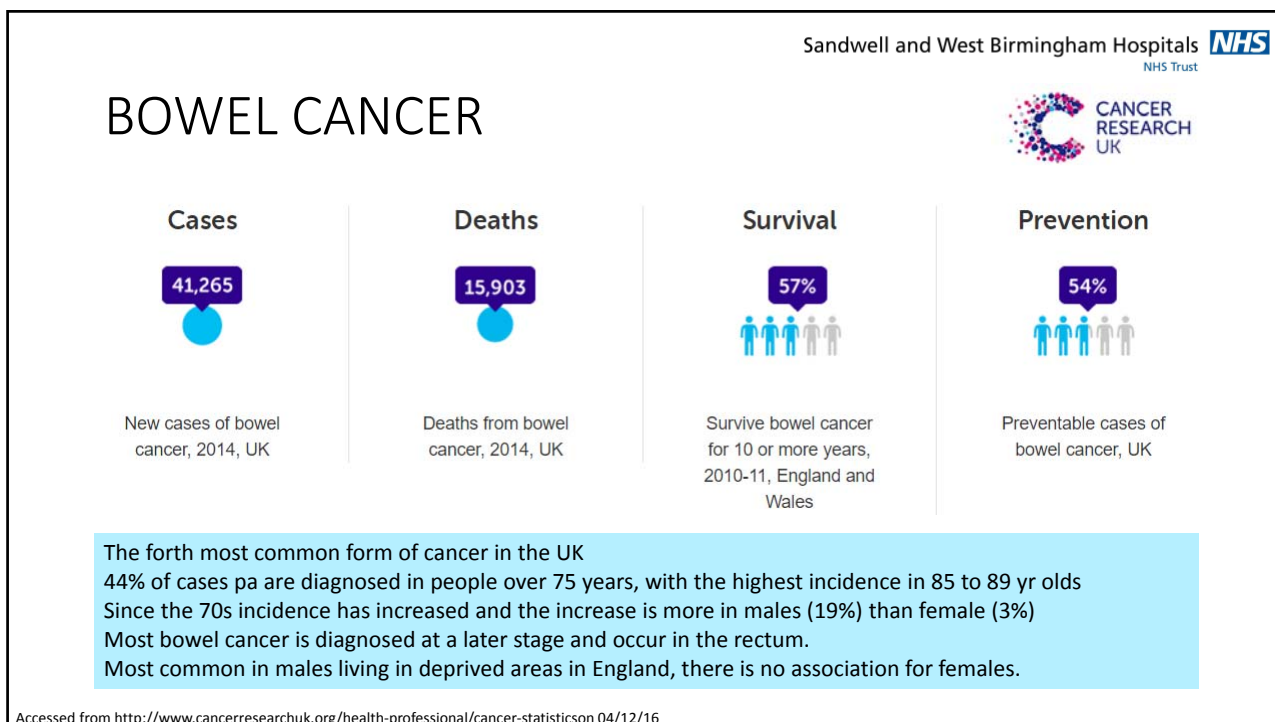
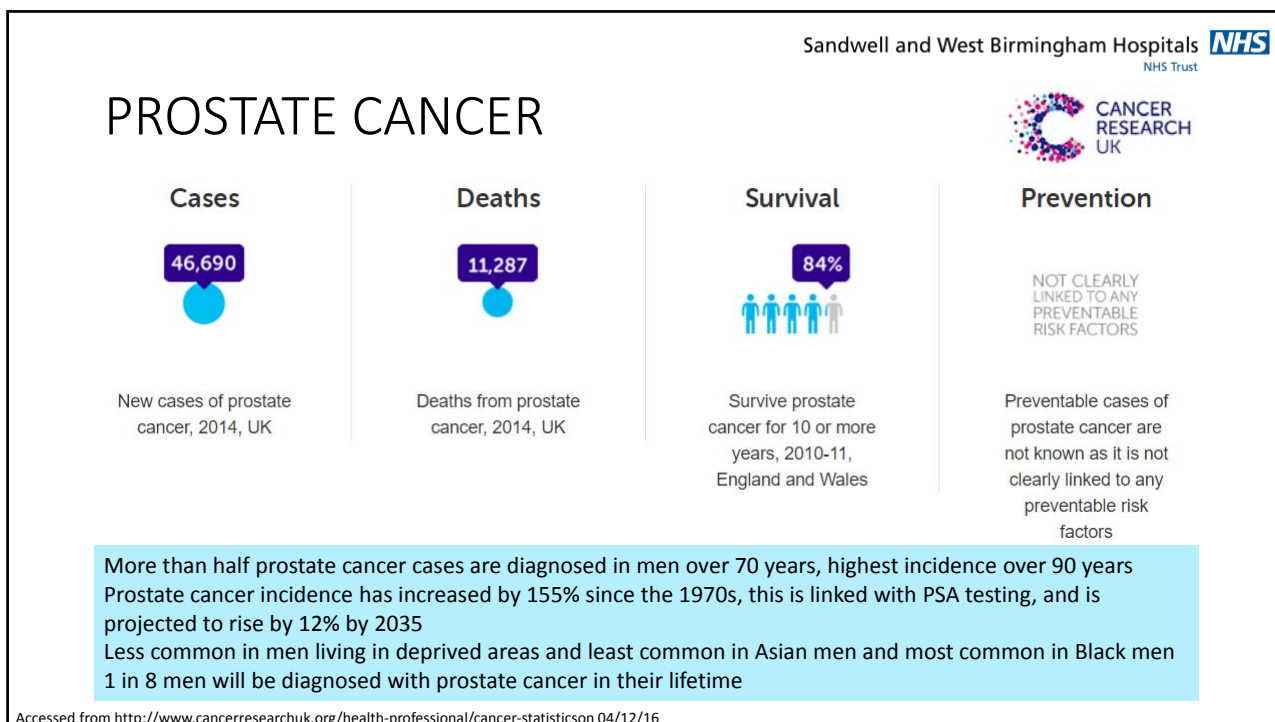
Prevention

89%

Preventable cases of lung cancer, UK



The third most common cancer in the UK and accounts for 13% of all new cases per year. Lung cancer incidence has been decreasing since the 1970s, this includes an increased incidence in females. Lung cancer is more common in people living in deprived areas and is more common in males than females and White people compared to Asian or Black people. The biggest cancer related cause of death in males and survival has not shown much improvement in the last 40 years. Diagnosed at an early stage 1/3 people survive for 5 or more years, but often diagnosed at a late stage.



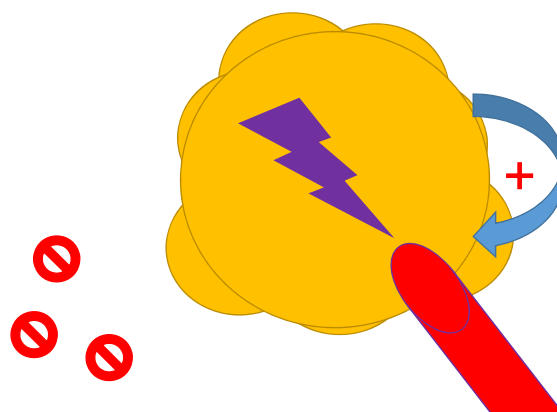
CANCER CATEGORIES

- Classified depending on the tissue from which they arise:
 - **Carcinomas** arise from epithelial cells and are by far the most common
 - **Sarcomas** are cancers that begin in connective tissue such as bone, cartilage, fat, muscle and blood vessels
 - **Leukaemias** start in blood forming tissue such as bone marrow and result in production of large numbers of abnormal blood cells to be produced and enter circulation
 - **Lymphoma** and myeloma are cancers of the immune system
 - **Central nervous system** tumours arise from tissues in the brain and spinal cord

CANCER: A disease of uncontrolled cell growth

Pathogenesis of cancer is driven by genetic changes, mostly acquired, but some are hereditary causing a predisposition to developing cancer

1. Autonomy of growth signals
2. Insensitivity to growth inhibitory signals
3. Evasion of programmed cell death
4. Unlimited replication potential
5. Angiogenesis
6. Invasion and metastasis



CANCER: A disease of uncontrolled cell growth

- Cancer cells reproduce in defiance of normal restraints on cell growth and division and invade and colonise other territories usually reserved for other cell types
- A cell that grows and proliferates out of control gives rise to a tumour – ‘*neoplasm*’
 - Benign
 - Malignant
 - Pre-malignant

A tumour is considered a cancer only if it is **malignant** – when its cells have acquired the ability to invade other tissues

Tumour cells that invade other tissues are called **metastases** – Generally it is the metastases that kill cancer patients

TUMOUR STAGING

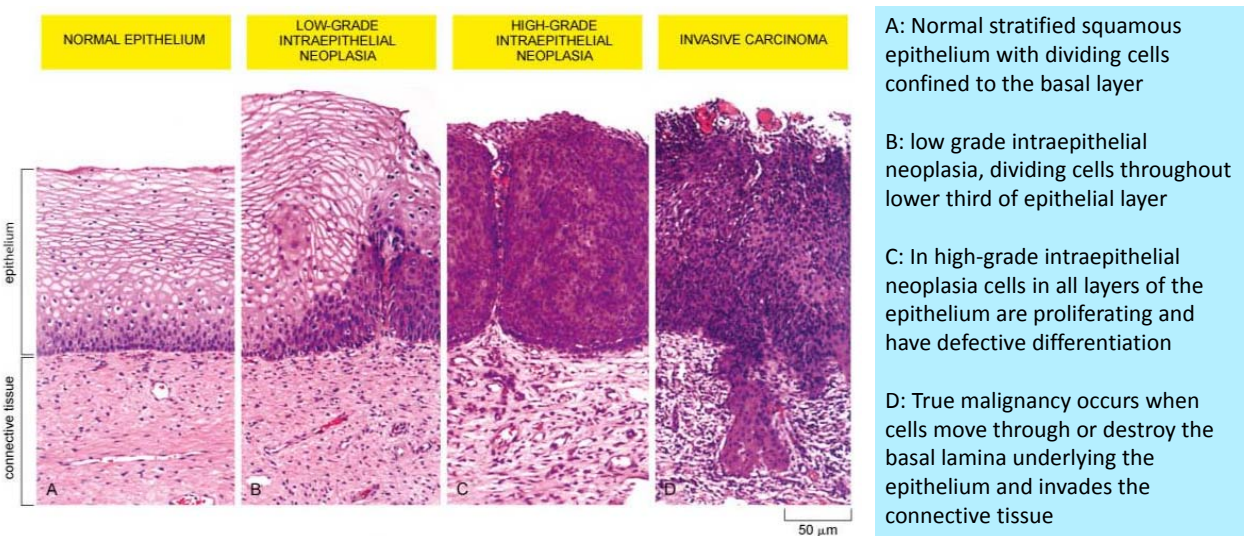


Image from Alberts et al. The Molecular Biology of The Cell 5th Ed. Image 20-9. Accessed from <http://slideplayer.com/slide/5742475/> on 04/12/2016

TUMOUR PROGRESSION

Successive cycles of random inherited change followed by natural selection.

At each cycle cells develop genetic or epigenetic changes giving them selective advantage over other cells.

The environment within a tumour is hostile to cells with low oxygen, scarce nutrients, and natural barriers to growth presented by surrounding cells.

Oxygen and nutrients do not become limiting until the lesion is 1-2mm in diameter so cells in the core of the tumour must acquire additional changes to continue to grow.

Proliferation of each clone hastens the occurrence of the next step of tumour progression by increasing the size of the cell population at risk of undergoing additional mutations.

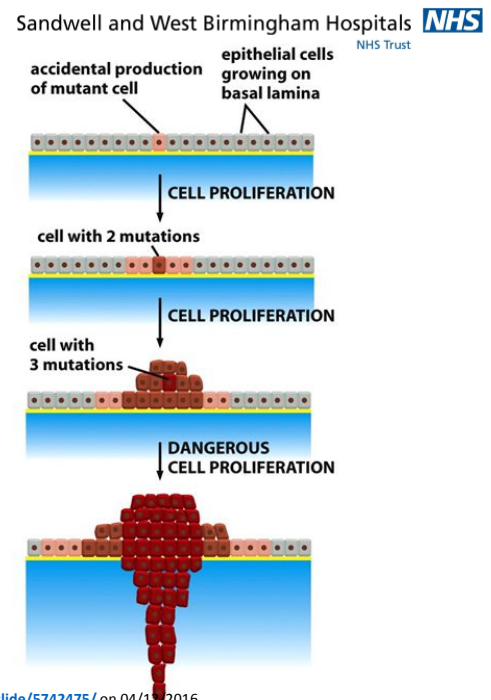


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Sandwell and West Birmingham Hospitals **NHS**
NHS Trust

TUMOUR STAGING: Classification

Most solid tumours are staged using the TNM system

- T – the extent of the tumour
- N – the extent of spread to lymph nodes
- M – the presence of metastases

Tx	Primary tumour could not be assessed
T0	No evidence of primary tumour
T_{is}	Carcinoma <i>in situ</i>
T1-4	Size and/or extent of primary tumour 1= small tumour with minimal invasion 4= large tumour with extensive invasion
Nx	Nodes cannot be assessed
N0	No node involvement
N1-3	Regional node metastases
M0	No distant spread
M1	Distant metastases

CANCER SIGNS AND SYMPTOMS

Local effects

- Depends on the tumour
 - Lung – blockage of bronchus – cough and pneumonia
 - Esophageal – narrowing of esophagus – painful/difficult to swallow
 - Colorectal – narrowing of the bowel – change in bowel habits
 - Local bleeding – rectal, coughing up blood, vaginal bleeding, blood in urine

Systemic effects

- Unexpected weight loss
- Unexplained fever
- Fatigue
- Back pain

METABOLIC CONSEQUENCES OF CANCER

- During tumour growth the nutritional and metabolic state of the host changes in favour of the neoplasm
- Metabolic changes can result directly from the presence of the tumour or secondary to secretory products of the tumour, these are known as paraneoplastic syndromes

METABOLIC CONSEQUENCES OF CANCER

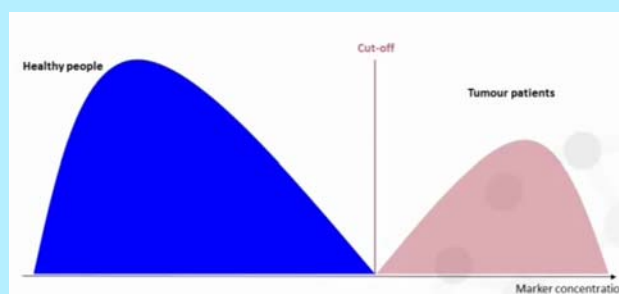
- **Marked derangements of carbohydrate metabolism are a feature of malignancy**
 - Impaired glucose tolerance, hyper/hypoglycaemia, lactic acidosis, increased glucose turnover and increased transport of glucose into tumour cells.
- **Abnormal lipid metabolism is a feature of some malignancies**
 - Some tumours utilise lipids in preference to glucose and promote the mobilisation of fatty acids from fat stores
- **Muscle wasting is due to increased protein catabolism**
 - Proteolysis is driven in response to cytokines

PARANEOPLASTIC SYNDROMES

- **NEUROLOGICAL PARANEOPLASTIC SYNDROME**
 - Autoimmune basis, immune response directed against cancer antigens that cross react with components of the nervous system
- **HUMORAL PARANEOPLASTIC SYNDROME**
 - Arises from secretion of substances from the tumour
 - ACTH, particularly associated with small cell carcinoma of the bronchus, resulting in corticosteroid excess – Cushing's syndrome
 - PTHrP, hypercalcaemia is a common complication of malignancy. PTHrP has N-terminal homology with PTH and is typically secreted by numerous cancer types.
- **OTHER PARANEOPLASTIC SYNDROMES**
 - Haematological sequelae – anaemia is the most common haematological abnormality encountered in malignancy, there are various causes: ACD, folate deficiency or autoimmune

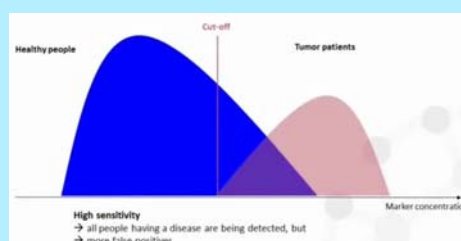
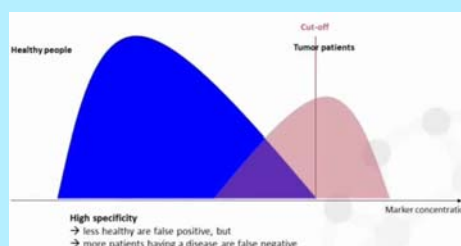
THE IDEAL TUMOUR MARKER

- Specific and sensitive for a specific cancer type
- Not present in other conditions
- Concentration relates to tumour volume
- Condition must be treatable
- Cheap, quick and reliable assay

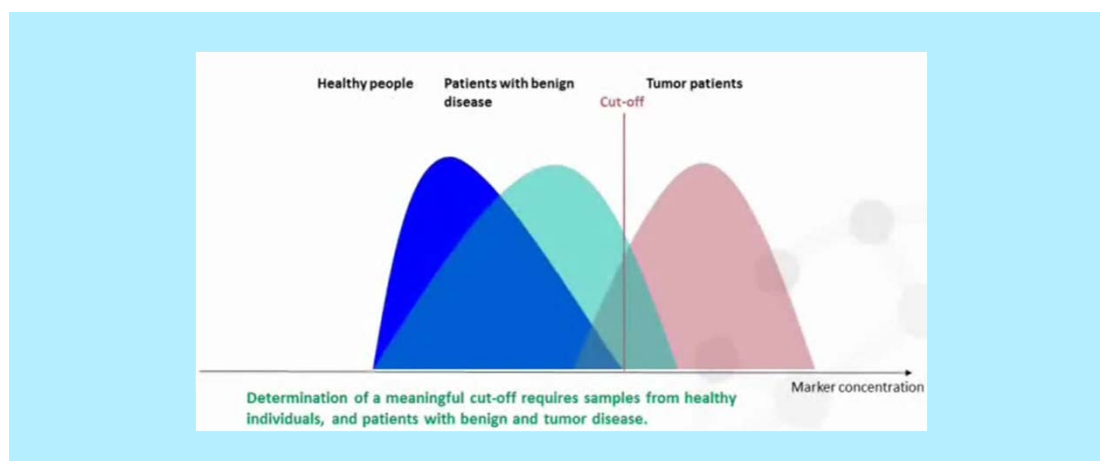


ANALYTICAL CHARACTERISTICS

- **SPECIFICITY**
 - The proportion of people who are known to not have a disease who will test negative for
- **SENSITIVITY**
 - The proportion of people who do have a disease and test positive for it



IN REALITY



Appropriate use of Tumour Markers

- Normal levels do not exclude the presence of a tumour
- High levels are not necessarily diagnostic
- Different assays are not always comparable
- “Shotgun” requesting is not appropriate!
 - Should be used in conjunction with imaging and histological investigations
- Most useful for monitoring of treatment and detecting relapse


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Tumour Marker	Relevant cancer	Use	Associated cancer	Associated benign condition
Alpha-fetoprotein (α FP)	Germ cell/testicular Hepatocellular	Diagnosis, Prognosis, monitoring treatment and detecting recurrence	Colorectal; gastric; hepatobiliary; lung	Cirrhosis; pregnancy; neural tube defects
Calcitonin	Medullary thyroid	Diagnosis, monitoring treatment and detecting recurrence	None known	C-cell hyperplasia
Cancer Antigen (CA) 125	Ovarian	Diagnosis, Prognosis, monitoring treatment and detecting recurrence	Breast; cervical; endometrial; hepatocellular; lung; non-Hodgkin's lymphoma; pancreatic	Many liver disease; cystic fibrosis; pancreatitis; urinary retention; diabetes
CA 19.9	Pancreatic	Diagnosis, Prognosis, monitoring treatment and detecting recurrence	Colorectal; gastric; hepatocellular; oesophageal; ovarian	Acute cholangitis; cholestasis; pancreatitis; diabetes; IBS; jaundice
CA15.3	Breast	Monitoring treatment and detecting recurrence	Hepatocellular; pancreatic	Cirrhosis; benign breast disease; in normal health
Carcinoembryogenic antigen (CEA)	Colorectal	Prognosis, monitoring treatment and detecting recurrence	Breast; gastric; lung; oesophageal; pancreatic	Smoking; chronic liver disease; chronic kidney disease; jaundice
Human chorionic gonadotrophin (β -HCG)	Germ cell/testicular Gestational trophoblastic	Diagnosis; prognosis, monitoring treatment and detecting recurrence	Lung	Pregnancy
Paraproteins	B cell proliferative disorder (myeloma)	Diagnosis, monitoring treatment and detecting recurrence	None known	None known
Prostate Specific Antigen (PSA)	Prostate		Prostatic hyperplasia	
Thyroglobulin	Thyroid (follicular/papillary)	Monitoring treatment and detecting recurrence	None known	None known

Table from Murray Longmore, Ian Wilkinson, Andrew Baldwin, and Elizabeth Wallin, Oxford Handbook of Clinical Medicine, 9th Ed, p534-535

Tumour Markers: PSA

BACKGROUND

- Single chain glycoprotein of 237 aa, molecular weight ~30KDa
- A serine protease produced in glandular epithelium and is involved in lysis of seminal coagulum
- PSA is specific to the prostate – not detected in most females or males without prostate tissue
- Can be elevated when BMI<25, in Black Africans, prostatitis and UTI
- Should be measured in conjunction with DRE or ultrasound for detection of prostate cancer

ANALYSIS

- Total PSA
- Free and complexed PSA measured by sandwich CMIA
- Reference ranges:
 - Up to 49yrs: 0-2.5ug/L
 - 50-59yrs: 0-3.5ug/L
 - 60-69yrs: 0-4.5ug/L
 - >70yrs: 0-6.5ug/L

Tumour Markers: CEA

BACKGROUND

- Glycoprotein ~200KDa usually associated with embryonic development
- Can be raised in 30-50% of CRC patients at the time of diagnosis
- Can also be raised in liver and/or kidney disease as well as other malignancies
- Cannot be used diagnose, but is useful for monitoring and prognosis

ANALYSIS

- Two-step immunoassay using chemiluminescent micro-particle immunoassay
- Reference range:
 - 0-5µg/L
- Specimens with concentration >1500µg/L require dilution

Tumour Markers: CA125

BACKGROUND

- High molecular weight glycoproteins with heterogenous size and charge
- Menstruation, T1+2 of pregnancy, ascites, pleural effusion and adenocarcinomas all raise CA125
- Single measurements lack sensitivity and specificity
- NICE CG122: persistent symptoms >12 times per month plus CA125 >URL, refer for further investigation.

ANALYSIS

- Two step immunoassay
- Monoclonal antibody coated paramagnetic particles added with sample
- After incubation acridinium-labelled conjugate added
- Reference range:
 - >35KU/L

Tumour Markers: CA153

- CA15-3 offers very little value for early detection of symptomatic or asymptomatic breast cancer and screening should be performed using mammography. NICE recommends MRI scanning in high risk individuals such as those with family history in a close relative or individuals with BRCA1 and BRCA2 mutations.
- Most useful following treatment.

Tumour Markers: CA19-9

BACKGROUND

- CA19-9 is a sensitive and specific marker for non-endocrine pancreatic cancer
- CA19-9 is raised in most malignant pancreatic cancers
- Better diagnostic sensitivity when combined with imaging
- Most useful for monitoring disease recurrence – better prognosis if normalises

ANALYSIS

- Two step immunoassay using a reactive monoclonal antibody and acridinium labelled conjugate.
- Reference range:
 - 0-37KU/L

Tumour Markers: AFP

- 70KDa glycoprotein
- Normally produced by the foetal liver and yolk sac during gestation
- Elevated levels are measured in pregnant women and neonates
- Most frequently elevated in adults with hepatocellular carcinoma or germ cell cancers, but can be raised in non-malignant conditions
- Used clinically with HCG to monitor non-seminomatous germ cells tumours
- Diagnostic aid for hepatocellular carcinoma

Tumour Markers: HCG

- Elevated hCG concentrations not associated with pregnancy are found in patients with other diseases such as tumours of the germ cells, ovaries, bladder, pancreas, stomach, lungs, and liver
- HCG also serves as a marker for gestational trophoblastic neoplasia, which can develop following normal or molar pregnancy and should be considered in women with persistent vaginal bleeding post birth
- It is a useful tumour marker with sensitivity and specificity around 99% for choriocarcinoma
- Not useful for screening general population, but should be measured in males with suspicious testicular lumps or malignancy of unknown origin

Tumour Markers: HIAA

- 24 hour urine collection used to measure 5-HIAA, the primary metabolite of serotonin
- Serotonin produced by GI tract to regulate intestinal movement or CNS to regulate mood, appetite and circadian rhythm
- Carcinoid tumours are slow growing masses typically of GI tract
 - Can grow large enough to block GI tract
 - Some spread to other sites in the body, mainly the liver
 - This usually results in carcinoid syndrome
- Significantly increased 5-HIAA in 24 hr urine is highly suggestive of carcinoid, but diagnosis should not be made without locating tumour

CANCER SCREENING

- <https://www.gov.uk/topic/population-screening-programmes>
- NHS Bowel Cancer Screening Programme
- NHS Breast Screening Programme
- NHS Cervical Screening Programme
- PSA screening is not reliable – men over 50 can ask for the test if they wish

PRINCIPLES OF SCREENING

- Condition is an important health problem
- Natural history well understood
- Recognisable at an early stage
- Treatment is better at an early stage
- Suitable test exists
- Acceptable test exists
- Adequate facilities exist to cope with abnormalities detected
- Screening is done at repeated intervals when the onset is insidious
- The chance of harm is less than the chance of benefit
- The cost is balanced against benefit

BOWEL CANCER SCREENING PROGRAMME

- In England: men and women aged 60 to 74 every two years
- Test for faecal occult blood
- Guaiac FOB detects all blood within the GI tract, sensitive, but not very specific
- Immunochemical method FIT uses Ab to detect only human blood
- Subjects with positive screen result are referred for colonoscopy



CONCLUSION

- Half of us will be diagnosed with cancer at some point in our lives, however, more people are surviving cancer than at any point previously
- People can have a genetic predisposition to cancer
- TMs should be specific and sensitive for a specific cancer type
- TMs are most useful for monitoring of treatment and detecting relapse
- Normal levels do not necessarily exclude tumours
- Widespread population screening is not always appropriate

The future?



Hyperlink to: <https://www.youtube.com/watch?v=Eci1cHf1e5E>