In the name of GOD
Tumor Markers
Cancer

Cancer is a relatively autonomous growth of tissue
Proliferation of normal cells regulated by:

- Oncogenes
- Tumor suppressor genes
  - BRCA1
  - BRCA2
BRCA1-BRCA2

- Naturally suppresses breast tumor
- Mutation in BRCA1 gene is seen in 50% of breast cancers
- Mutation in BRCA2 gene is seen in 70% of breast cancers in women and men
Adhesion Molecule

- Selectin E
- ICAM (Intercellular adhesion molecule)
- VCAM (vascular cell adhesion molecule)
Adhesion Molecule

- Cancer cells for invasion need these adhesion molecules
- Advance and end-stage of breast cancers is detected
- Poor prognosis
HIGH RATE CANCERS

- Lung
- Colon
- Rectal
- Breast
- Prostate
- Bladder
- Non Hodgkins
- Uterus
- Pharynx
- Oral Cavity
- Pancreas
- Leukemia
- melanoma
- Kidney
- Stomach
- Ovary
- Brain
- Nervous System
- Cervix
- Liver
- Larynx
- Thyroid Gland
- Multiple myeloma
- Esophagus
- Hodgkins
- Testis
Carcinogens

- Physical – Radiation
- Chemical – Polycyclic Hydrocarbon
- Biological – virus
The extent of the primary tumor:

- T0
- T1
- T2
- T3
- T4

Regional Lymph Node Metastasis:

- N0
- N1
- N2
- N3

The Presence Or Absence Of Distant Metastasis:

- M0
- M1
MORPHOLOGY

- Well differentiated
- Poorly differentiated
- Anaplastic (without form)
Tumor Markers

- Substance present in a tumor
- Substance produced by a tumor
- Substance produced by the host in response to a tumor
Classification of Tumor Markers

- Enzymes- LDH- PSA
- Isoenzymes
- Hormones- β HCG
- Oncofetal antigens- CEA-α FP
- Carbohydrate markers : mucin type
- Carbohydrate markers : blood group antigen type
- Proteins- CA-19-9 PANC'REASE-CA-125 OVARY-CA-15-3 BREAST
- Miscellaneous
- Oncogene products
- Tumor – suppressor gene
Potential Uses of Tumor Markers

- Screening in general populations - PSA
- Differential diagnosis in symptomatic individuals - CA-125
- Clinical staging of cancer - HER 2/neu-breast PR/ER
- Estimation of tumor volume
- Prognostic indicator of disease progression - Herceptin
- Evaluation of success of treatment - CEA-Colon
- Detection of recurrence of cancer
- Monitoring of responses to therapy
- Radioimmunolocalization of tumor masses
- Determination of direction for immunotherapy
Carcino embryonic antigen

Glycoprotein (mw~200 KD)

Produced normally at fetal age

Stops production before birth

Is not found in healthy individuals

Increase in heavy Smokers.
Increase specifically in colorectal Cancers along with increase in:
Transforming growth factor $\alpha$ (TGF $\alpha$)
Fibroblast growth Factor (FGF)

Uses for monitoring after surgery.
Increased in cancers of:

- pancreas
- gastrointestinal
- kidney
- Breast
- lung

Increased in non-Cancer disease of:

- ulcerative colitis.
- Inflammatory disease of pancreas
- Cirrhosis
- liver diseases (not cleared by liver)
Human chronic Gonadotropin
Glycoprotein
\( \alpha \) Chain and \( \beta \) chain
\( \alpha \) Chain similar to FSH, LH & TSH
\( \beta \) Chain is specific for each
produced by placenta trophoblast cells
free \( \alpha \) & free \( \beta \) also produced.
Increase seen in:

- pregnancy
- Neoplasm
- hydatiform mole
- Choriocarcinoma
- Embryonal cell carcinoma (ovary, Testis)
- Tratoma (Ecto, meso, endo)
- various cancers
- tumor of testes
HCG

- Urothelial cancer
  free $\beta$ and $\beta$ core

- Colorectal, endocrine cancer of pancreas

- Gastric, Pancreatic, Hepatic and ovary cancer HCG ($\alpha, \beta$)
α FP (α Feto protein)

- Glycoprotein - 590 A.A
- Produced by yolk sac, Gastrointestinal and liver of fetus.
- Major protein of fetal age
- Similar to Albumin
- Maximum increase in 12-14 wks of gestation (3 mg/ml)
- Decrease until one year after birth (1 ng/ml - adults level)
 increase $\alpha$ FP:

Cancer of:
- pancreas
- gut
- lung

Non malignant:
- Cirrhosis of liver
- Ataxia telangetastia
α FP

- increase α FP in pregnant woman:
  - open neural tubular defect
  - Abdominal wall defect
  - multiple fetus
  - fetal demise
  - fetomaternal bleeding
  - Incorrect estimate of gestational age
Decrease:

Down SX

Fetal triomy 18 or 21.
CA 15-3 (cancer Antigen)

- mucin like
- Present on glandular cells e.g breast.
- Increase in Adenocarcinoma of:

  breast (30% of local, 75% of advanced and metastatic cancer)
CA 15-3 (cancer Antigen)

- large intestine
- lung
- ovary
- pancreas

Increase in (Non malignant):
- chronic hepatitis
- liver cirrhosis
- sarcoidosis
- TB
- Lupus
- Smoking
CA 27.29

- Mucin like
- more sensitive than CA 15-3 in breast cancer
- CA 15-3 and CA 27.29 is ordered for monitoring and recurrance of breast cancer.
Glycoprotein- mucin like (exudate) increased in 80% of non-mucinous ovarian carcinoma.

Increased in ovarian cancer:
- clear cell carcinoma
- endometrioid carcinoma
- serous – Transudate
80-85% ovarian cancer patients have CA-125 ≥35 u/ml.

Monitoring uterus tumors increased in more than 60% of patients with uterus tumors.

Sensitivity- 23.2% in early phase.
CA -125

Increase in cancer of:

- endometrium
- Cervix
- fallopian tube
- pancreas
- breast
- lung
- large intestine
CA -125

*moderate increase in*:

- pregnancy
- Endometriosis
- Pelvic inflammation
- uterus fibrosis
- non – Hodgkin lymphoma
- liver cirrhosis
- menstrual hemorrhage
Human Epididimys gene Product (HE4)

- Increase in ovarian cancer
  - Serous
  - Endometriose
- Positive in 88% of ovarian malignancy
- Positive in only 5% of benign ovarian diseases
HE4

- HE4 and CA125 are measured together
  - Sensitivity: 68.3%
  - Specificity: 98%
- Used for monitoring of Patients with metastatic cancer to epithelium of ovary after therapy.
ROMA-A Risk of Ovarian Malignancy Algorithm

- Classifies patients as being at low or high risk for malignant disease
- Calculates a risk of finding ovarian cancer during surgery
ROMA-A Risk of Ovarian Malignancy Algorithm

- CA-125
- HE4
  HE4 begins to climb before CA-125 increases
Set specificity - 75%
For epithelial ovarian cancer and low malignant potential tumors of the assay - sensitivity - 89%
For all patients (pre and post menopausal)
NPV - 94%
ROMA-A Risk of Ovarian Malignancy Algorithm

- Premenopausal women:
  ROMA value: ≥13.1% High risk
  ROMA value: ≤13.1% Low risk

- Postmenopausal women:
  ROMA value: ≥27.7% high risk
  ROMA value: ≤27.7% low risk
  of finding epithelial ovarian cancer
Glycoprotein – mucin like
Produced by Adenocarcinoma cells
Carcinoembryonic protein

found in epithelium of fetus increase in various cancer.
Increase in tumors of:

Colorectal
Gastric monitoring and recurrence of
Gastric tumor after surgery
CA 19-9

Carbohydrate for Antigenic site on mucin like molecule

Antigenic site

sialylated lacto-N- fucopentose II

Sugar compound
Increase in Cancer of:
- Pancreas
- Colorectal
- Gastric

Related to Blood group Louis
- Le + phenotype
- Le (a⁺ b⁻)
- Le (a⁻ b⁺)
Increase in:

- obstructive Jaundice
- pancreatic inflammation
- gall stone
- Cystic fibrosis
CA 50

- Like CA 19-9.

- Antigenic site like CA 19-9 except lacking Fucose (sugar)

- Complementary of CA 19-9 for Dx of tumor of pancrease
CA 19-5

- Like CA 19-9.
- Combined increase of CA 19-5 with CA 50 seen in cancer of:
  - Large intestine
  - Pancreas
  - Hepatocellular carcinoma
- Increase in:
  - Benign liver disease
  - Obstructive jaundice
Kallikrein

- Belongs to Serpins enzymes
- located on chromosome 19
- 15 different enzymes are recognized
- KLK3 or PSA – in prostate
- hk2 80% similar to hk3 and increase in prostate cancer with metastasis to lymph node
Kallikrein

- Increase Kallikrein is seen in tumors of Prostate, Breast, Ovary, Testes.
- Human Kallikrein (hk6) – Cancer of ovary for Dx, prognosis and monitoring.
- Increase hk10 in cytosole seen in: Cancer of ovary, Cancer of breast.
One chain Glycoprotein with 7% Carbohydrate
Serpins enzymes group
Kallikrein family
Found in normal, benign and malignant prostate tissue
produced for liquidification of Semen.
Property like chemotrypsin and trypsin
Increase in:
acute urinary retention
prostatitis
PSA

- Found in two forms in blood.
  1. Bound – with $\alpha_1$ antichemotrypsin and $\alpha_2$ macroglobulin
  2. Free - Small amount
- Labs determination is based on free form and bound to $\alpha_2$ macroglobulin
- Long $\frac{1}{2}$ life – takes 2-3 wks after biopsy, sonography and surgery levels return to normal
<table>
<thead>
<tr>
<th>Age (year)</th>
<th>PSA level μg/l</th>
</tr>
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<tbody>
<tr>
<td>40-49</td>
<td>0-2.5</td>
</tr>
<tr>
<td>50-59</td>
<td>0-3.5</td>
</tr>
<tr>
<td>60-69</td>
<td>0-4.5</td>
</tr>
<tr>
<td>70-79</td>
<td>0-6.5</td>
</tr>
</tbody>
</table>
Daily activity is needed
18% decrease at rest for 24 hrs

- more than 0.75 μg/L/y good indication of prostatic cancer
- PSA > 50 μg/L metastase to capsule
- PSA <20 μg/L No bone metastase
For monitoring after therapy

- therapy
  - prostatectomy
  - anti Androgenic drug

After surgery (PSA determination)
- 1st year - every 3 months
- 2nd year - every 4 months
- After 2nd year - every 6 months
PSA

- Specificity - 50% for prostate cancer
- Sensitivity - 80% for prostate cancer
- in prostate cancer
  - Increase complex PSA
  - Decrease free PSA – Less than 6%
  - More than 23% increased in FPSA is BPH
Free PSA

- break down above 4°C
- Less than 3hrs after specimen collection
  PSA should be analyzed or store at –70°C

- PSA density > 0.15 seen is prostate cancer.
Calcitonin

- Produced by C- cells of thyroid (Para follicular cells)

- Increase in:
  - C- cells hyperplasia
  - Modularly thyroid carcinoma (Malignant and metastatic)

- Can be Produced ectopically in Bronchogenic carcinoma
Medullary thyroid cell carcinoma

- 75-80% sporadic - more in female
- 20-25% - genetic (more in male)
MEN

Multiple Endocrine Neoplasm

MEN I – PTH, adenoma of hypophysis ZE Sx

MEN II - PCC, thyroid Carcinoma. PTH

MEN III - PCC, thyroid Carcinoma, mucosa neurosa
Chromogranin A

- Soluble protein from chromaffin granules
- Produced along with catecholamines from adrenal medulla
- Produced also from sympathetic nerves and other Neuroendocrine


Chromogranin A

- Increase in:
  - Pheochromocytoma
  - medullary cell carcinoma of thyroid
  - small cell carcinoma of lung

- Increase also in cancers of:
  - Prostate
  - Pancreas
  - Breast
  - Large intestine
  - Ovary
Cytokeratin 19 fragment or cyfра 21-1

- Found on simple epithelium and malignancy of them
- Increase in:
  - Breast cancer
  - Squamous cell carcinoma of Lung
  - Tumor of Non small cells of lung (increase volume, increase cyfра 21-1)
  - Metastatic squamous cells of head and neck
- Normal in non malignant diseases of lung
  - Pneumoconiosis (dust disease)
  - Lung obstruction
Para thyroid Hormone Related peptide (PTH-RP)

- Increase in squamous cell carcinoma of:
  - Kidney
  - Ovary
  - Bladder
- Has Amino Acids sequence similar to PTH
- Activates PTH receptors (increase calcium)
Para thyroid Hormone Related peptide (PTH-RP)

- Differentiates malignancy from benign disease of:
  - primary hyperparathyroidism
  - Sarcoidosis
  - V-D intoxication
- Renal insufficiency
  - Increase PTH-RP without increase in calcium levels or having cancer
HER2/neu (C-erb B-2)

**HER-** Human epidermal growth factor

**Neu-** neuro glioblastoma cell line

**Erb B-2-** avian Erthroblastosis oncogen B

- Membranous protein
- Tyrosine kinase property
- Similar to epidermal growth factor receptors
HER2/neu (C-erb B-2)

- Increase in tumors of:
  - Breast
  - Lung
  - Colon
  - Ovary

- Measured P105 (the outer layer cell shed off of this protein) by ELISA
HER2

- Used mainly for breast cancer

Prognosis

Volume of tumor

Grade of tumor

Metastasis to Lymph node

Recurrence of disease

- Located on long arm of ch. 17.
**HER2**

- Seen in 25-30% of breast cancer with poor prognosis
- *Transtuzumab* or *Herceptin* (monocolonal Ab against *HER2* for treatment)
- *Herceptin* also used for treatment of tumors with *HER2*
  - Ovary
  - Prostate
  - Gastric
  - Bronchial
Nuclear matrix protein (NMP)

- One of oncoprotein targets is to invade nuclear proteins
- NMP is seen with tumors of Bladder, Breast, Bone, Prostate, Colon
- Transitional cells of bladder is detected always with NMP22
  - 10-20X more in malignant cells Compare to normal cells
$\beta_2$ microglobulin

- Seen on the surface of most nucleated cells

- Increase in:
  - CLL
  - Non-Hodgkin Lymphoma (multiple myeloma)

  seen in 75% patients with mm

- B-Cell Lymphoma
P53

- Nuclear Phosphoprotein
- Regulate Negative cell growth
- Suppresses tumor
- Stimulates gene expression to suppress growth and proliferation
- Guardian of genome
Point mutation or deletion of P53 (Ch.17) causes in 50% of tumors such as:

- Liver
- Breast
- Lung
- Large intestine
- Bladder, and...

- **P53 Antibody** against mutant P53 Ag is seen in 10-35% of cancers
  
  - specially breast cancer: increase Ki-67 Ag
deletion of ER
Transforming Growth factor &

\[ \alpha \beta \]

\text{TGF} \beta

Protein

\text{TGF} \beta \ 1 \ - \ \beta \ 5

- \text{Increase in hepatocellular carcinoma}

- \text{TGF} \beta \ 2 \ - \ \text{invasive cancer of bladder where as} \ \text{NMP22 increases in invasive and noninvasive cancer of bladder}
Transforming Growth factor &

TGFα increases in cancers of:

- breast (100%)
- Lung
- Stomach
- Intestine
- Liver
- Hepato cellular carcinoma (early detection)
P21

- Protein
- Related to G protein of membrane
- Product of RAS gene
- Expression or mutation of P21 seen in tumors of:
  - Breast
  - Colon
  - Liver
  - Prostate
  - Lung
Colon cancer

- OB
- Mutant protein in controlling cell cycle
  - K- RAS
  - Mutant P53
  - Gene product of APC
    - (Adenomatous polyposis)
  - BAT – 26
Heat shock protein (HSP)

- A group of proteins produced at the time of heat and other stresses
- Stable cell proteins in unfavorable situations
- HSP 27 increases in cancer of:
  - Breast
  - Endometrium
  - Leukemia
Heat shock protein (HSP)

HSP 70 also in:

- Breast
- Endometrium
- Osteosarcoma

Kidney (with metastasis, poor prognosis and Resistance to therapy)

- HSP 60 and HSP 90 also detected in:
  - Breast
  - Lung
  - Lymphoma
  - Hodgkin
Urokinase- plasminogen activator (UPA)

- Urokinase activates plasminogen
- Plasminogen converts to plasmin
- Plasmin destroys extra cellular matrix and releases growth factors
- Used for prognosis of breast cancer
Urokinase- plasminogen activator ( UPA)

- PAI ( Plasminogen Activator inhibitor)
- PAI -1, PAI -2
- Inhibits urokinase
S-100 proteins

- S-100 protein groups bound to Calcium
- S-100 A4 seen in cancer of
  - Breast
  - Esophagus
  - Squamous cell carcinoma
  - stomach
- Protein S-100 $\beta$ used as:
  - diagnosis of melanoma
  - metastasis of melanoma
Anti Cyclic citrullinated peptide (anti CCP)

- Citrulline is an Amino Acid
- *Is not used as a codan in DNA synthesis*
- Some protein have Citrulline in their structure
- *Arginine is converted to citrulline by peptidyl arginine deimmanse*
Proteins Contain Citrulline in their structures:

- Myeline
- Filaggrin
- Histone
- Fibrin, Vimentin - in process of Apoptosis or inflammation

Anti CCP seen in

- 80% of Rheumatoid Arthritis
- Sensitivity – 70%
- Specificity – 98%
Anti perinuclear factor (APF) Anti RA 33

Increase in Rheumatoid Arthritis
Thyroid

- Graves- LATS. Hyperthyroidism
- Hashimoto’s thyroiditis- hypothyroidism
- HLA- B8 seen in both diseases
- Auto Antibodies:
  - Anti Tg (anti thyroglobulin)
  - Anti TPO (anti thyroperoxidase) microsomal Antibody
  - Anti TSH- R
Diabetes type 1

- **Auto Antibodies:**
  - ICA (Islet cell Auto Antibody)
  - GAD (Glutamic Acid Decarboxylase)
  - IAA (Insulin Auto Antibody)
  - Protein tyrosine phosphatase (IA – 2)
Gluten Sensitive entropathy
Celiac disease

Auto Antibodies:

- Anti TTG (anti tissue transglutaminase)
- IgA – anti endomysial
- Anti Gliadin
- Anti Reticulin
Thank you