



Tumor Marker, in a Journey of Cancer Management: Advantages and Limitations

Presenters -

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Clinical scenario

Case scenario-1

A 61 year old man with a known H/O Chronic Hepatitis C and long-standing liver cirrhosis presents with progressive weight loss, anorexia, and dull right upper quadrant pain. On examination, he has mild hepatomegaly and ascites.

- Ultrasound reveals a focal liver lesion suspicious for malignancy.
- Tumor marker-
- Serum Alpha-fetoprotein is within normal limits- 8 ng/ml (<10-20 ng/ml)
- PIVKA-II is markedly elevated- 125 mAU/ml (0-40 mAU/ml)
- What's your diagnosis?

Case scenario 1:

Provisional diagnosis:

1. Cirrhosis
2. Hepatocellular Carcinoma

Case scenario 1:

- CT guided FNAC of liver: Trabecular pattern, sheets and cluster of cells, increased nuclear-cytoplasm ratio.

Diagnosis:

1. Hepatocellular carcinoma

- **Message:** Tumor marker tests often cannot diagnose cancer on their own; this case are typically confirmed with a FNAC and biopsy.

Case scenario-2

A 54 year old woman presents with progressive abdominal distension and weight loss for 4 months. On examination, she has ascites, a palpable irregular pelvic-abdominal mass and mild hepatomegaly

- CT abdomen reveals a complex bilateral adnexal mass, ascites with omental thickening, and multiple small lesions in the liver
- Tumor marker panel-
- **CA-125- markedly elevated- 750 U/ml (<35 U/ml)**
- AFP-normal- 6 ng/ml (<10 ng/ml)
- **CA 19-9- mildly elevated- 80 U/ml (<37 U/ml)**

- **What's your diagnosis?**

Case scenario-2

Provisional diagnosis:

1. Ovarian carcinoma
2. Metastatic hepatocellular carcinoma

Case scenario-2

- CT guided FNAC of liver
- Oophorectomy done followed by histopathology

Diagnosis:
Serous cyst adenocarcinoma with
hepatic metastasis

- **Message:** Tumor marker tests often cannot diagnose cancer on their own; this case are typically confirmed with a FNAC and biopsy and tumor marker can also detect metastasis along with imaging.

Case scenario-3

- A 57-year-old man altered bowel habit, anorexia, weakness, weight loss and melena. The Carcinoembryonic Antigen (CEA) was elevated. In colonoscopic biopsy, diagnosed as adenocarcinoma of the colon and underwent right hemicolectomy. CEA declined to within normal range after surgery.
- Six months later, he presents with vague, dull abdominal pain and mild weight loss.
- On investigation:
 - Serum **CEA is significantly elevated- 150 ng/ml (\leq 2.5-3.0 ng/ml)**
 - **CT scan of the abdomen reveals multiple hypodense lesions in the liver.**
- **What's your diagnosis?**

Case scenario-3

- Colonoscopic biopsy followed by histopathology done

Diagnosis:

Recurrent colon carcinoma with
liver metastasis

- **Message:** Tumor marker helps in diagnosis to possibility of recurrence and treatment response.

Case scenario-4

A 28-year-old woman presents with a 7-week history of amenorrhea. She reports mild lower abdominal discomfort and intermittent spotting for the past few days. The pregnancy test is positive, the ultrasound shows no intrauterine gestation.

- Tumor marker: \uparrow β -hCG - 1,500 mIU/L
- Laparoscopic surgery done followed by histopathological examination
- After 4 weeks of surgery β -hCG declined to within normal range (>5mIU/L)

- **What is your most likely diagnosis?**

Case scenario-4

Provisional Diagnosis:

1. Ectopic pregnancy
2. Ovarian tumor

Case scenario-4

- Laparoscopic surgery done followed by histopathological examination
- After 4 weeks of surgery β -hCG declined to within normal range (>5mIU/L)

Diagnosis:

- Ectopic pregnancy

Note: Tumor marker can be raised in non neoplastic condition as well.



Objectives

- ❖ Definition and types
- ❖ Characteristics of an ideal tumor marker
- ❖ Sampling
- ❖ Molecular basis
- ❖ Common tumor markers & importance
- ❖ Take away message.

Definition

Tumor markers are biological substances (proteins, genes, or metabolites) produced by cancer cells or the body in response to cancer.

Characteristics of an Ideal Tumor Marker

Characteristics	Remarks
Highly Sensitive	Non detectable in physiological or benign Disease states.
Highly Specific	Detectable only in one tumor type.
Long Lead Time	Sufficient time for natural course of disease.
Levels Correlates with tumor burden	Has prognostic & predictive utility.
Short half life	Frequent serial monitoring of marker level after 5-6 half lives.
Simple & Cheap test	Applicability as screening test.

Sampling

These markers are detected in blood, tissues, or body fluids for screening, diagnosis, monitoring, and prognosis.

Samples we use -

- ❖ Blood/ Serum.
- ❖ Urine.
- ❖ Tissue biopsy.

Blood/ Serum

- ❖ Blood is typically drawn via standard venipuncture (5-10 ml).
- ❖ Drawn blood collected into specific tubes (red/Yellow top).
- ❖ EDTA is used as anticoagulants.
- ❖ Refrigerated at 4-8°C during transport.
- ❖ For extended storage it should be typically frozen at -20°C.

Urine

Urine tumor markers are substances released by the cancer cells into urine.

Important tumor markers we use here -

- ❖ NMP22 (Nuclear matrix protein 22).
- ❖ BTA (Bladder tumor antigen).

Other methods -

- ❖ FISH (urovysion).
- ❖ Cytology.



Tissue biopsy

- ❖ A biopsy specimen serves as a critical, definitive source for identifying tumor marker, specifically protein expression, gene mutation or rearrangement within cancer cells.
- ❖ Tissue biopsies allow pathologist to analyze tumor heterogeneity and determine specific biomarkers for targeted therapies.
- ❖ i.e. - Formalin fixed breast tissue for breast carcinoma we do.
 - HER2 (Human Epidermal Growth Factor Receptor 2)
 - EGFR (Epidermal Growth factor receptor)
 - BRCA1/ BRCA2

Molecular Basis

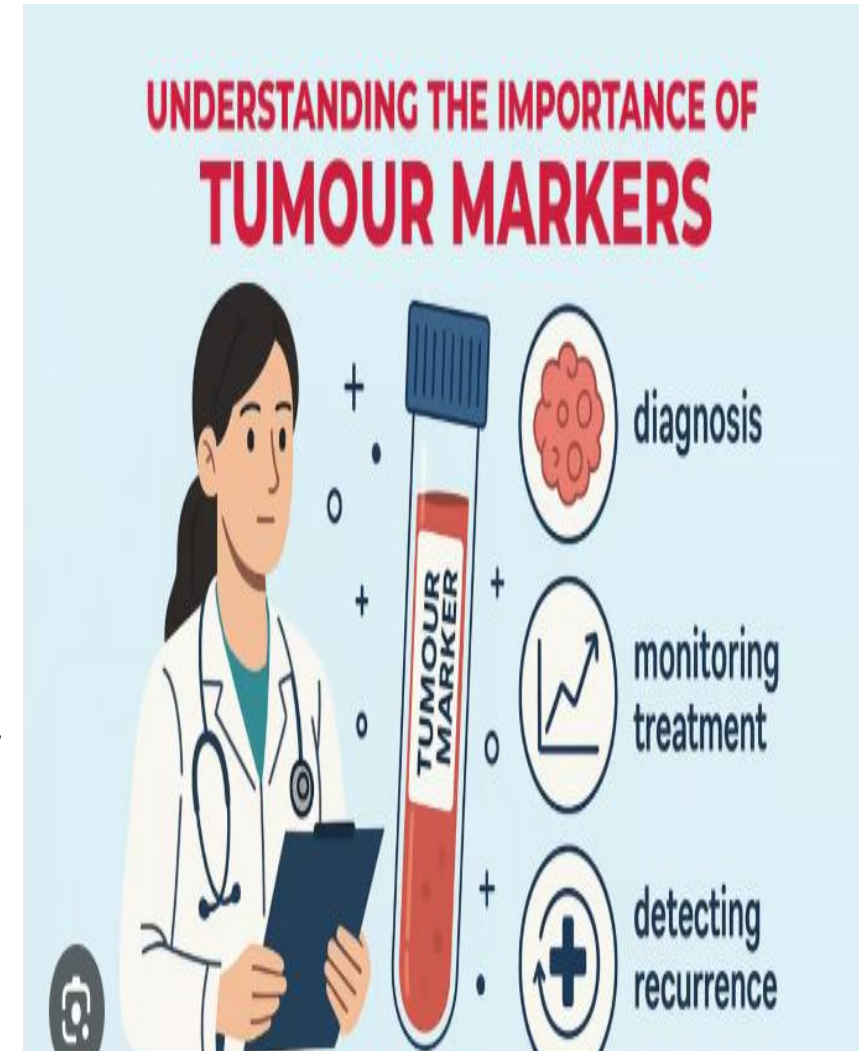
Their molecular basis lies in genetic alterations -

- a. Mutations- EGFR, BRCA1/BRCA2.
- b. Amplifications- HER2
- c. Translocations- Philadelphia Chromosome in CML
- d. Epigenetic modifications- GSTP1 (Glutathione S-transferase P1)

These cause overexpression or inappropriate expression of molecules.

IMPORTANCE

- ❖ **Diagnostic support along with image and biopsy-** eg. High level of serum AFP (>400 ng/dl) predicts HCC.
- ❖ **Treatment monitoring-** To see the treatment response to tumor marker. eg. HCG in incomplete abortion/ trophoblastic tumor.
- ❖ **Recurrence prediction-** After surgery if it rises usually Indicates Recurrence.
- ❖ **Screening and early detection-** Used as frequently with imaging to detect HCC in high risk patient.



Tumor markers	Tumor type
Hormones	
HCG	Trophoblastic tumor Non seminomatous testicular tumor
Calcitonin	Medullary carcinoma of thyroid
Catecholamine	Pheochromocytoma
Oncofetal Antigen	
α FP	HCC Non seminomatous germ cell tumor
CEA	Carcinoma colon, pancreas, stomach, lung, heart
Lineage specific protein	
Ig	Multiple myeloma
PSA & prostate specific membrane Antigen	Prostate cancer

Tumor markers	Tumor type
Mucins & other glycoproteins	
CA- 125	Ovarian cancer
CA- 19-9	Carcinoma colon, Pancreatic carcinoma
CA- 15.3	Breast cancer
New molecular marker	
p53, APC, RAS mutations in stool and serum	Colon cancer
p53 and RAS mutations in stool and serum	Pancreatic cancer
p53 and RAS mutations in sputum and serum	Lung cancer
p53 mutations in urine	Bladder cancer

Organ Based Tumor Markers

Tumor Markers



Common Tumor Markers and Their Uses

PSA



Prostate cancer monitoring

Elevated in benign monitoring

CEA



Colorectal cancer monitoring

Elevated in smokers, benign conditions

CA-125



Ovarian cancer monitoring

Elevated during menstruation, pregnancy

CA 19-9



Pancreatic cancer monitoring

Elevated in non-cancerous bile issues

AFP

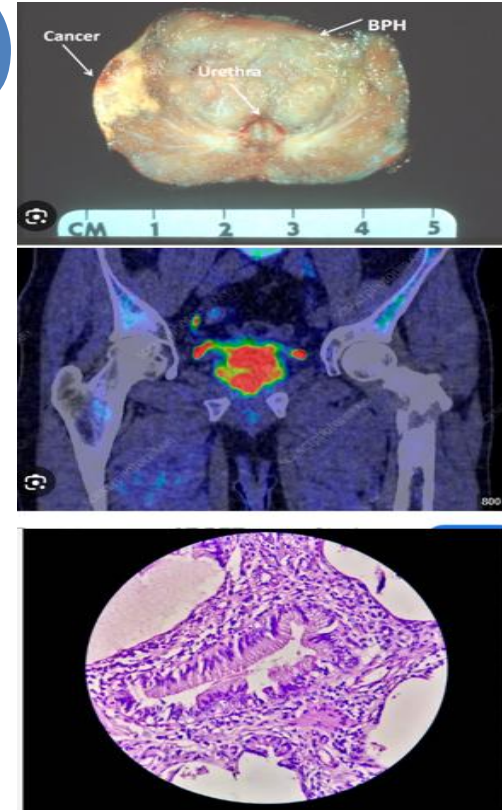


Liver/ testicular cancer

Elevated in hepatitis, cirrhosis

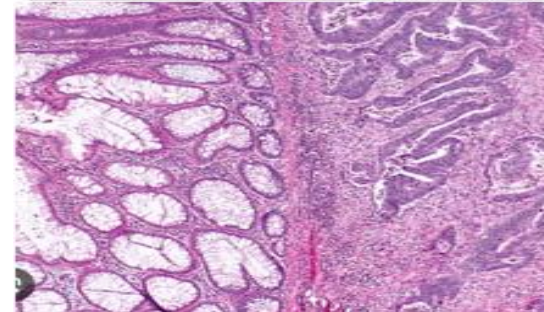
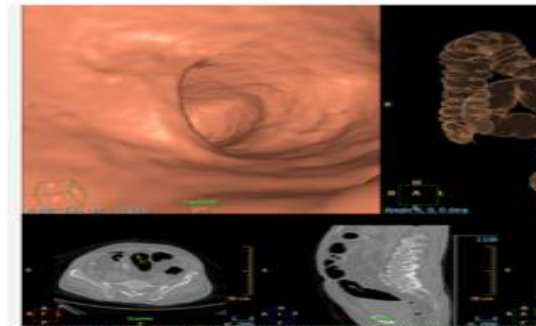
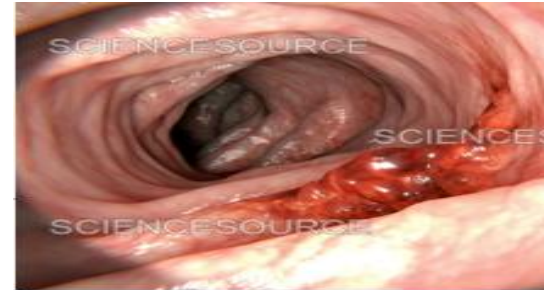
PSA (Prostate-Specific Antigen)

- ❖ **Primary Applications:** Prostate Cancer Metastasis.
- ❖ **Utility:** Used to monitor for recurrence and distant metastasis (Bone/Lymph Nodes).
- ❖ **Normal Level:** 4.0 ng/mL or lower.
Significant level for cancer is >20 ng/ml.
- ❖ **Limitations:** The test can produce false positives in - smokers (>5 fold), Prostatitis (>10 fold), increasing age (>3 fold), Recent activity like intense exercise or any urinary procedure within 24 hours (>3 fold) etc.
- ❖ Highly sensitive- 88%-94%, But low specificity- 14%-26%.



CEA (Carcinoembryonic Antigen)

- ❖ **Primary Applications:** Colorectal Cancer, Breast Cancer, Lung Cancer.
- ❖ **Utility:** Elevated in 50-70% of colorectal cancer patients.
Elevated in 60%-65% of Luminal breast cancer cases.
- ❖ **Normal Level:** 3 ng/mL or lower.
Significant level for cancer is >10 ng/ml.
- ❖ **Limitations:** The test can produce false positives in -
Smokers, hepatitis, cirrhosis, peptic ulcer disease, pancreatitis.
- ❖ Highly sensitive- 70%-80%, Also highly specific- 70%-94%.



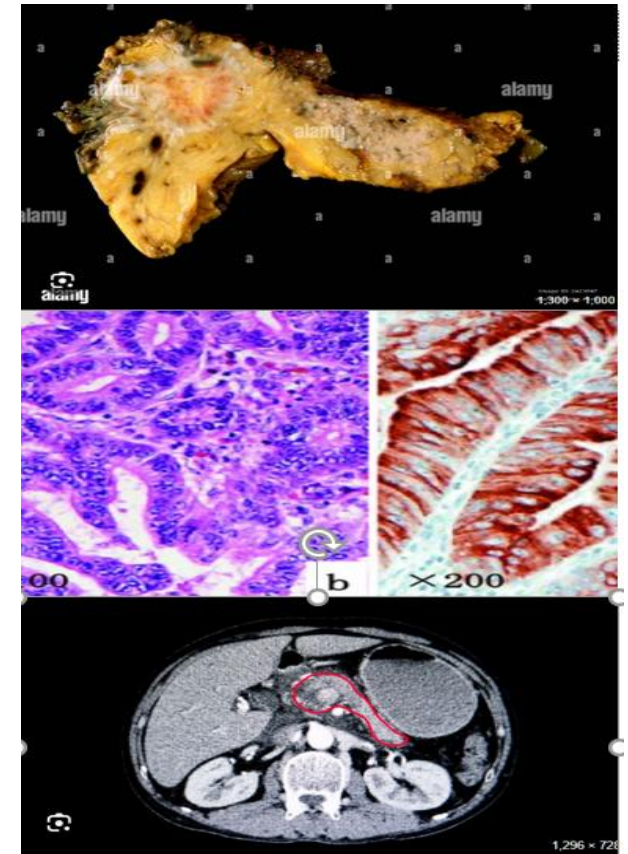
CA 125 (Cancer Antigen 125)

- ❖ **Primary Applications:** Ovarian Cancer, Breast Cancer (Metastatic).
- ❖ **Utility:** Used often in combination with CA 15.3, to identify metastasis to the peritoneum, liver, or lung in ovarian cancers. Elevated in approximately 50% of metastatic breast cancer cases.
- ❖ **Normal Level:** 35 U/mL or lower.
Significant level for cancer is >50 ng/ml in early stage.
- ❖ **Limitations:** The test can produce false positives in - Endometriosis, fibroid uterus, pelvic inflammatory diseases, pregnancy etc.
- ❖ **Highly sensitive- 75%-90%, Also very highly specific- 95%-98%.**



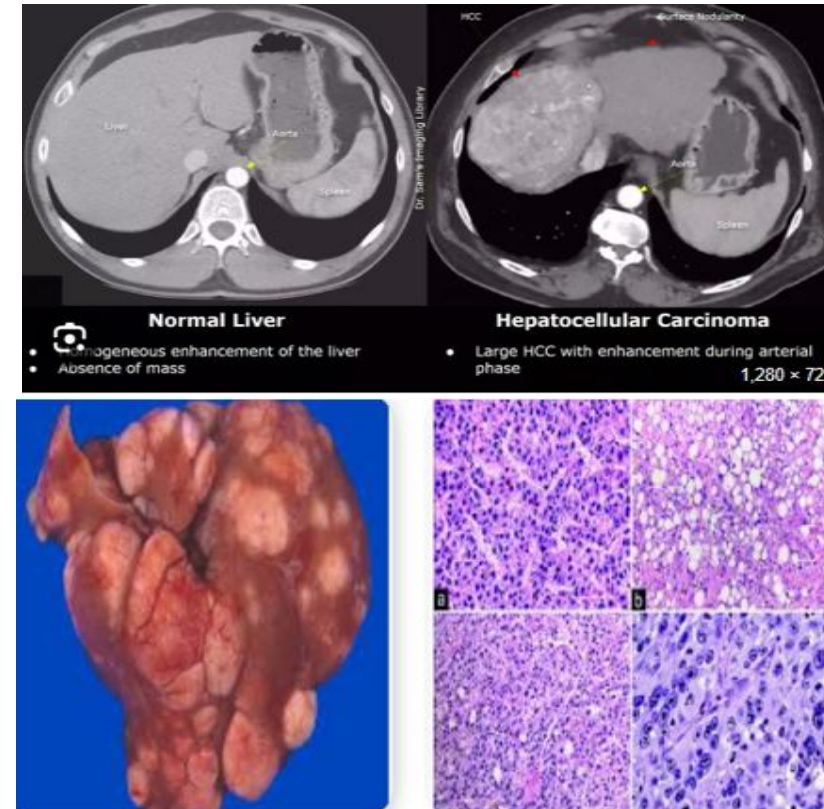
CA 19-9 (Carbohydrate Antigen 19-9)

- ❖ **Primary Applications:** Pancreatic and gastric cancer metastasis.
- ❖ **Utility:** Used to monitor for recurrence and distant metastasis, often spreading to the liver or peritoneum.
- ❖ **Normal Level:** 37 U/mL or lower.
Significant level for cancer is >100 U/ml.
- ❖ **Limitations:** The test can produce false positives in - Gallstones, cirrhosis, liver diseases, pancreatitis etc.
- ❖ **Highly sensitive- 70%-90%, also highly specific- 80%-90%.**



AFP (Alpha-fetoprotein) in HCC

- ❖ **Primary Applications:** Hepatocellular Carcinoma.
- ❖ **Utility:** Strongly associated with metastatic spread or incomplete removal of the primary tumor.
- ❖ **Normal Level:** 15-20 ng/mL or lower.
Significant level for cancer is $>200 \mu\text{g} /\text{L}$.
- ❖ **Limitations:** The test can produce false positives in - Cirrhosis, chronic hepatitis, pregnancy etc.
- ❖ **Sensitivity - 40%-65%, Also high specificity - 80%-94%.**



AFP (Alpha-fetoprotein) in ovarian cancer

- **Germ Cell Tumors:** It is a highly reliable marker for ovarian yolk sac tumor and malignant mixed germ cell tumors.
- **Epithelial Ovarian Cancer:** Some epithelial ovarian cancers can produce AFP, with very aggressive course and poor prognosis.
- **Correlation:** Elevated AFP is usually accompanied by elevated CA-125, which acts as a guide for therapeutic response.
- **Half-life:** Serum half-life of AFP is approximately 5 to 7 days, which is important for evaluating the effectiveness of treatment.

Some other important tumor markers

- ❖ Calcitonin - for medullary carcinoma of thyroid gland.
- ❖ CA 15.3 - for breast carcinoma.
- ❖ Human chorionic gonadotropin - for trophoblastic carcinoma.
- ❖ Catecholamine - for Pheochromocytoma.
- ❖ Immunoglobins - for multiple myeloma.

Tumor markers in metastatic cancer

- ❖ Brain: Breast carcinomas (CA 15.3)
- ❖ Liver: Colorectal carcinomas (CEA)
- ❖ Lung: Choriocarcinomas (Beta-HCG)
- ❖ Bone: Prostate carcinoma (PSA)

Commonest recurrent carcinomas

- ❖ Ovarian carcinomas
- ❖ Urothelial/ Transitional cell carcinoma of urinary bladder
- ❖ Triple negative breast carcinomas
- ❖ Pancreatic adenocarcinoma
- ❖ Skin Cancers like SCC and BCC
- ❖ Colorectal carcinoma
- ❖ Small cell carcinoma of lung.

Take away Message

1. Tumor markers alone aren't diagnostic but it can diagnose cancer along with image studies and biopsy.
2. It is done as screening, staging, treatment monitoring, metastatic, residual & recurrent cancer.
3. Tumor markers has limitations like false negative (low sensitivity), false positive.

This is why tumor markers can not replace tools like biopsies or CT scans, Which provide a direct look at the diseases, rather these markers can complement those investigations for diagnosis.



**THANK
YOU**