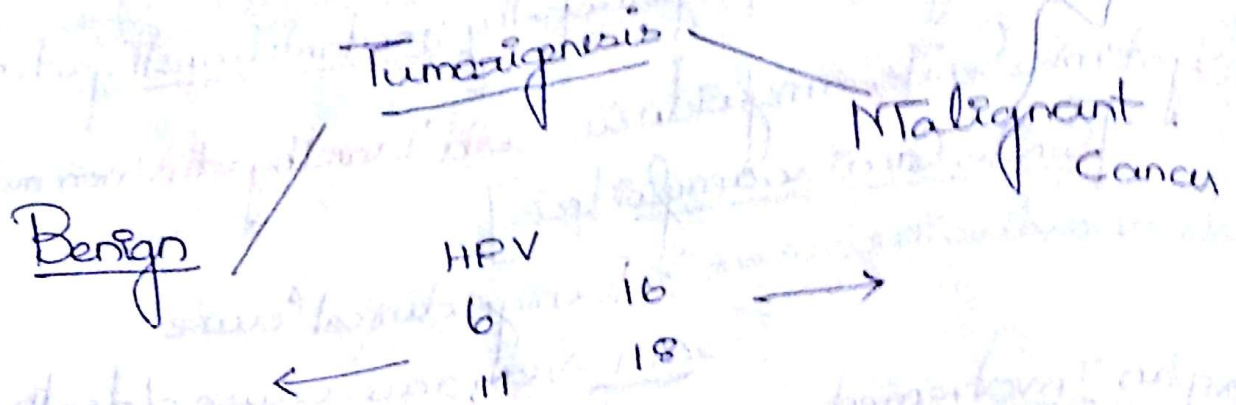




Characteristic -

1) Rate of growth - Monoclonal

Hematoma - Benign tumor
- clonal in origin
[abnormal tissue in
② anatomical site]

Hematoma } non-neoplastic
Choriostoma } polyclonal



2] Metastasis - Sure Sign of malignancy

exception -
RCC
Glioma

Metastasis ⊕
Carcinoma

pheochromocytoma
pituitary
Parathyroid

homets
Adenoma

Routes

Lymphatic

Hematogenous
Sarcoma

epithelial tumors

* Alveolar Rhabdomyosarcoma
except - RCC > HCC

→ Osteogenic Sarcoma

- Rhabdomyosarcoma

embryo
Pleomorph

Angioinvasive

Alveolar

* → Synovial Sarcoma

Metaplasia → Dysplasia → Anaplasia

Reversible

→ Partially Reversible

→ Completely Irreversible

Nuclear/cytoplasmic Ratio (N)

→ N/C Ratio - altered

N/C Ratio - 1

cell polarity - (N)

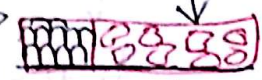
→ Lost-cell polarity

Anaplasia
Complete loss of differentiation

- Hallmark of malignancy

metastasis < Anaplasia

(normal arrangement over BNT)



Ca-In situ - Basement membrane Intact

$\frac{N}{C} - (N) - \frac{1}{4 \text{ to } 6 \text{ times}}$

Hallmark features of Cancer cells (8)

1) Protooncogene mutation → Oncogene

- 1) Self Sufficiency [don't require growth factor]
- 2) Resistant to growth inhibitory signals (Tumor Suppressors)
- 3) Evasion from apoptosis [$\uparrow$ Bcl-2 antiapoptotic expression]
- 4) Limitless Replicative potential (Telomerase)

5) Angiogenesis (m/c Cause - Hypoxia) - HIF 1 α gene → VEGF, bFGF
 without angiogenesis limit of growth 1-2mm
 ↓
 disorganized B.V

6) Metastasis - m/essential factor → Angiogenesis

Balance b/w
Metastatic gene $\uparrow\uparrow$
 → ezrin (RMTS)
 (first to discover)

Anti-metastatic gene $\downarrow\downarrow$

- i) NMT - 23.
- ii) miR - 22b, 335
- iii) KAI-1 - prostate Ca
- iv) KISS - melanoma

→ miR - 10b

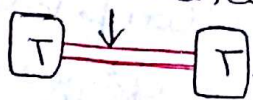
Snail, Twist → Breast Ca (lobular Ca)

Metastatic Cascade

EMTT - Epithelial mesenchymal Transition

- also associated with wound Healing & Repair.
Organ fibrosis.

e-cadherin [B/w normal/tumor cells]



↓ epithelial downregulation/e-cadherin

Tumour cells

1) Detachment.

2) Degradation of ECM. By.

proteases - i) plasmin

ii) MMP mmp2 mmp9 Better.

Break ECM & Synthesize BV

3) Attachment with ECM

① - integrin + ↑ Synthesis of ECM protein

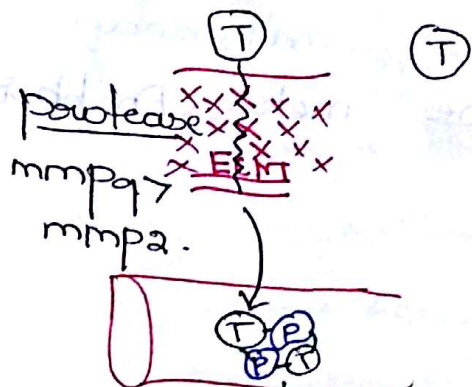
mesenchymal upregulation

[Collagen, Laminin, Vitronectin, Fibronectin]

4) Tumour emboli. in BV mostly associated

① cell + platelet

Organ.



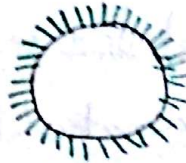
Detachment
Degradation
attachment



Antitumor cells - CD8, NK cells, Ntrophages

i) Ag - ve Tumor cells

ii) glycocalyx coating



iii) Ca cell $\leftarrow$ (CD8) - express FAS/FASL $\rightarrow$ undergo apoptosis

vii) Ca-metabolism - Aerobic glycolysis (Warburg effect)

Warburg $\rightarrow$ 1921

$\downarrow$
Nobel Prize - 1931

, Basis of PET Scan.

Gene Repair Defect - Chromosomal Instability Syndrome.

B - Bloom Syndrome

F - Fanconi-

A - Ataxia Telangiectasia

X - Xeroderma pigmentosa (nucleotide excision repair Defect)

Homologous DNA defect disorder.
AR

Lynch Syndrome $\rightarrow$ AD.

uv light
 $\downarrow$
Pyru
Skin

Pyrimidine
Dimers

$\rightarrow$ Repaired by excision $\rightarrow$ $\therefore$ accumulated in XP.

Skin Ca

Lynch Syndrome

(Spell checker)

microsatellite instability

Stomach

Colon

Chromothripsis - Dramatic Chromosomal
Catastrophy

Random damage of chromosome

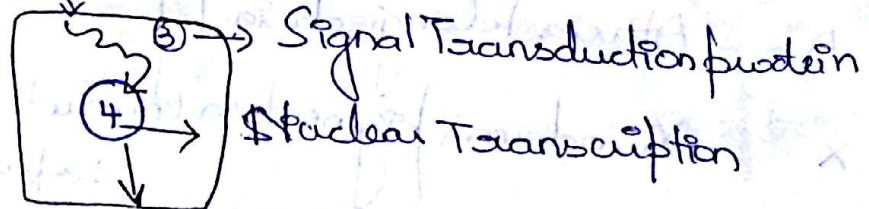
- activation of oncogenes
- inhibition of Tumor Suppressor

eg: Osteosarcoma, Glioma

Protooncogenes: Helps in normal proliferation & differentiation

1) growth factor

2) GF - R



⑤ Cyclin + Cyclin Dependent Kinase

Cell Cycle - $G_0 \rightarrow G_1 \rightarrow S \rightarrow G_2 \rightarrow M$

Any Protooncogene $\rightarrow$ oncogene - affect Cell Cycle

$\downarrow$
Tumorigenesis

- i) PDGIF
- ii) IGF
- iii) HGF
- iv) TGF- α (TGF- β - tumor suppressor gene)

2) Growth factor Receptor group

- i) ERBB-1: Adenocarcinoma of lung
- ii) ERBB-2 [Her-2/neu] - Breast Ca.
- iii) RET - Protooncogene - medullary Ca of thyroid.
- iv) C-KIT - GIST, melanoma, Seminoma, myeloid Cancers.

CD-117

3) Signal Transduction Protein

- a) RAS - m/c oncogene mutation in Human Cancer.

P53 $\rightarrow$ 50% Human Ca $\rightarrow$ 50%.

P53 $\rightarrow$ RAS

RAS - 20-30%.

Ca. Pancreas - m/c mutation. KRAS (60-70%) $\ll$ p-16 (95%)
m/c oncogene mutation - KRAS.

2) ABL

BCR-ABL
CML (good) ALL (poor)

$>60\%$ Skin Ca $\rightarrow$ BRAF

③ BRAF $\rightarrow >60\%$ Skin Ca (melanoma)

$>90\%$ Human Ca $\rightarrow$ BRAF

↳ Langerhan Cell Histiocytosis (monoclonal)

1) JAK - 2 - Polycythemia vera

NOTCH - T-cell leukemia

4) Nuclear Transcription Factor -

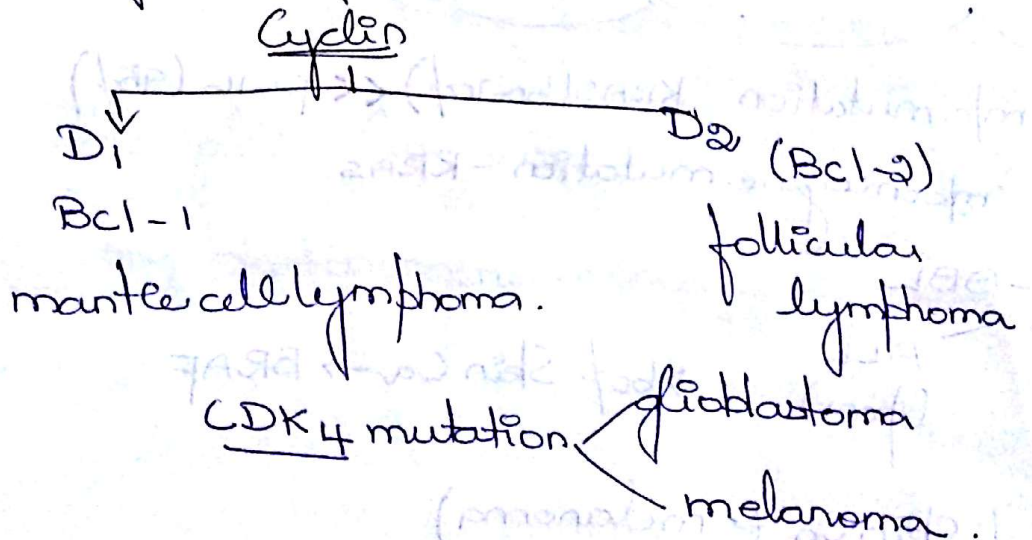
Myc; Fos; Jun

↓
n-myc amplification

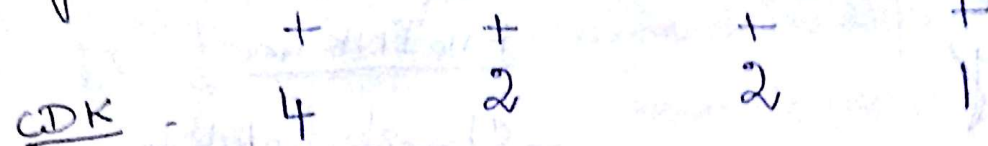
↓
neuroblastoma (Bad)
medulloblastoma

C-myc - Burkitt's lymphoma
Translocation

5) Cyclin + Cyclin Dependent Kinase -



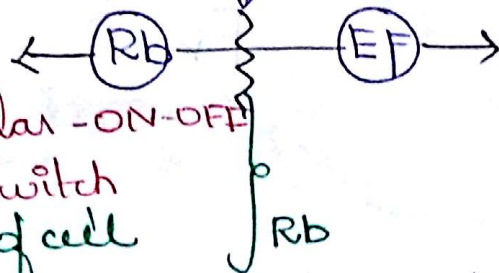
Cyclin



[OFF] $\rightarrow$ Rb + EF-2 (inactive) [EF-elongation factor]

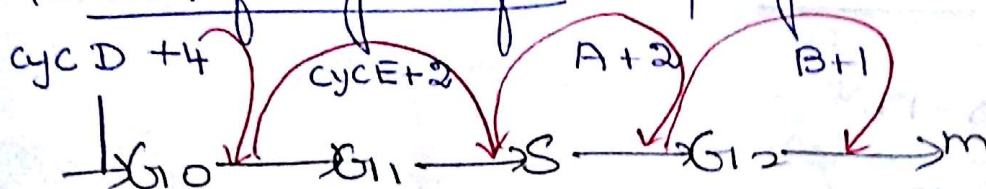
D + 4 $\rightarrow$ O₂ phosphorylation

$\uparrow$ ATP



Rb- allows
 $G_1 \rightarrow S$

Removal of elongation factor - progression of cell cycle



mid G₁ phase - Cyclin - D Synthesis

Check point - G₁ S

error before DNA
replication

G₂ M

after DNA
replication errors

Cyclin A $\ll$ Cyclin B

Cp. kip family

(Cp-way)

- Non specific inhibitor

P21, P27, P57

P53 - induce → p21
[indirect cell cycle inhibitor]
G1-S → G2-M

PI3K/AKT

- Specific inhibitor

Cyclin D + K4
K6

P15

P16

P18

P19

Tumor Suppressor Gene

BRCA-1 : Ch-17

BRCA-2 → Ch-13

male Breast Ca { BRCA 2 & BRCA1
Ovarian tumor }

BRCA-1 medullary Breast Ca.

↓

Triple negative [ER-ve, PR-ve, Her-2-ve]

BRCA-2 = ER+, PR+ve, Her-2-ve

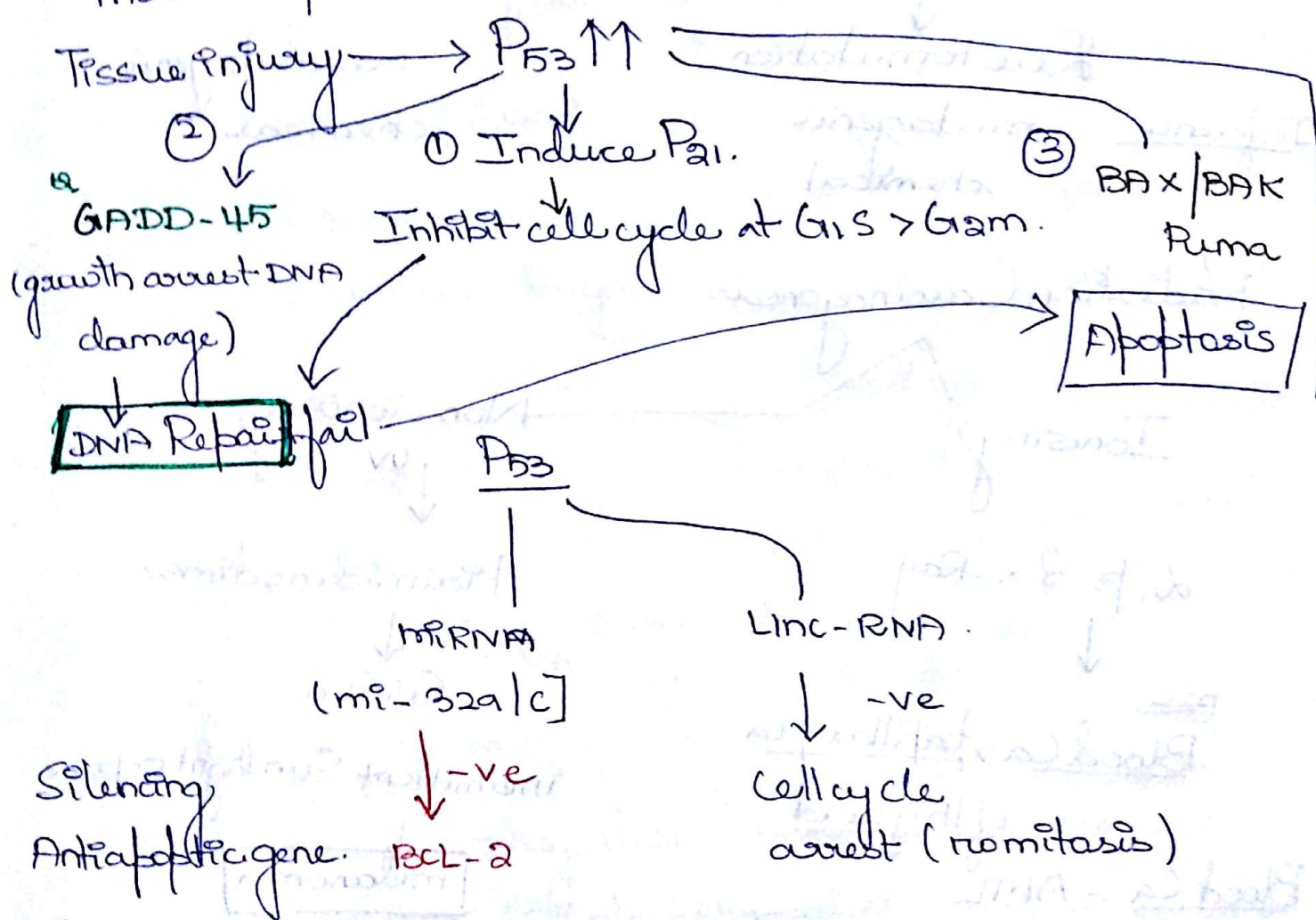
P53: Ch-Hp molecular weight - 53 kDalton

www.FirstRanker.com

www.FirstRanker.com

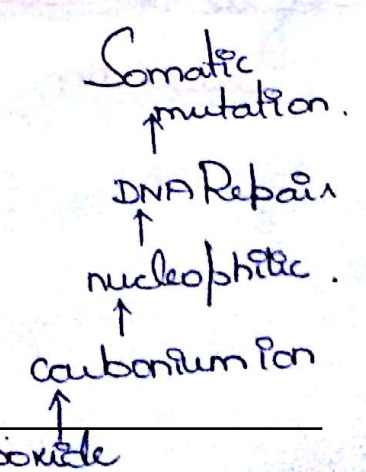
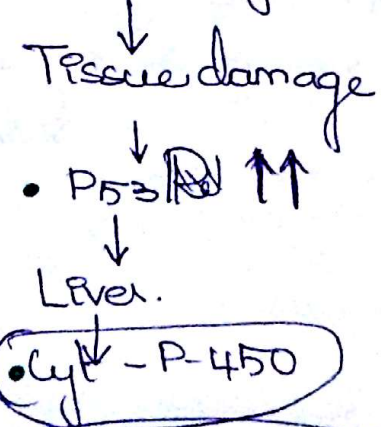
Li-Fraumeni Syndrome → multiple Ca.

guardian of genome
molecular policeman



Carcinogenesis

1) Chemical Carcinogenesis - Benzopyrene



Benzopyrene
www.FirstRanker.com

Salmonella typhimurium

Chemical + (normal Histidine negative)

Histidine +ve

Histidine -ve

Due to mutation

Inference - mutagenic chemical

non mutagenic chemical

Radiation Carcinogenesis

Tonising

Non-Tonising

α, β, γ X-Ray

Pyrimidine dimers

Blood Ca $\rightarrow$ papillary Ca
of thyroid

Skin Ca.

Blood Ca - AMTL
 $\rightarrow$ ALL.

Intermittent Sunlight exposure
 $\downarrow$
melanoma

$\rightarrow$ CMTL

CLL is not associated with
radiation

→ Microbe 1st established → *Helicobacter pylori* gastric adenocarcinoma > NHL

m/c NHL lymphoma of stomach - DLBCL > MALToma

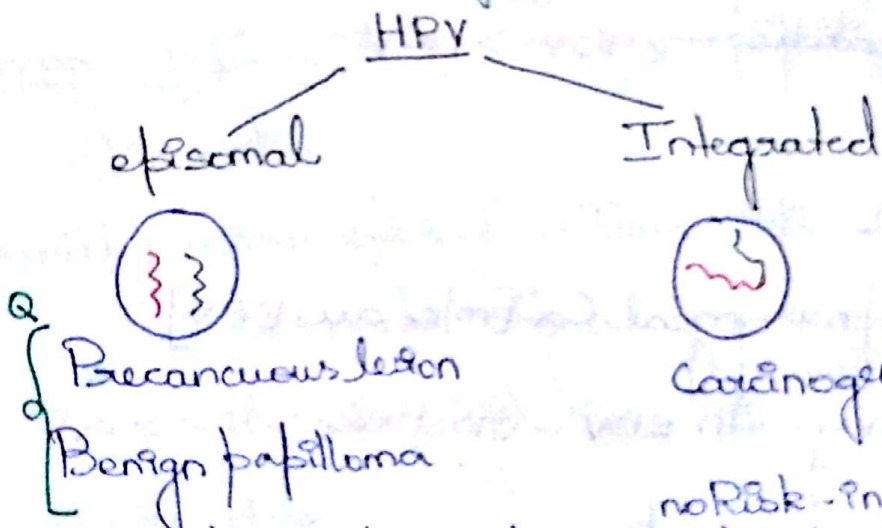
NTALT - m/c site **ileum** (Peyer's patches)

MTALToma - m/c site - **stomach**

→ HPV - 6, 11 - Papilloma 16, 18 - Carcinoma

E₆ → inactivate P₅₃

E₇ → inactivate Rb gene



HPV → Risk for esophageal SCC - **only in endemic regions**

Leukoplakia - Risk of esophageal SCC

Vit - A, Zn, Se - protective

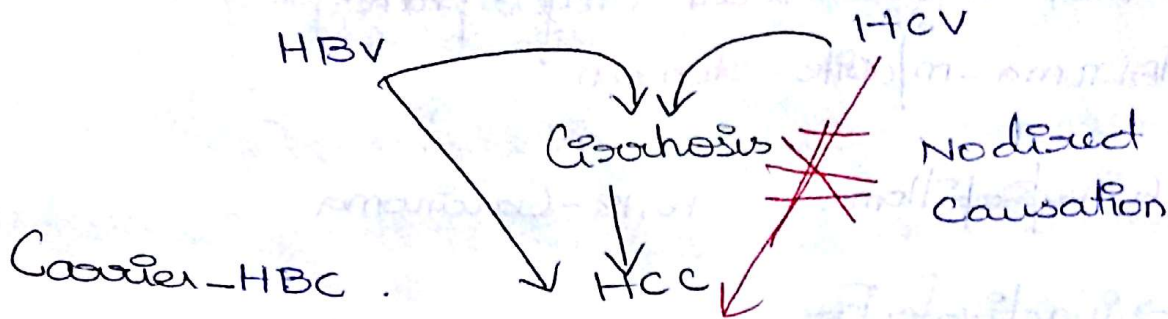
HBV
↓
DNA
Nuclear
damage
↓
10 years

HCC
HBV > HCV

HCV → 21-30 yrs

HBV can also cause HCC directly, even without undergoing Cirrhosis

But HCV do not cause direct HCC



Chronicity, Cirrhosis → HCV

Transfusion Hepatitis → HBV > HCV

→ EBV:

HL
NHL

Nasopharyngeal Ca [m/c w/ EBV]

m/c malignancy with EBV - Gastric adenocarcinoma

Tumor diagnosis approach -

i) Tumor markers - Never confirm diagnosis

Uses - prognosis,

Response to Rx

→ may correlate to size of tumor.

eg:- α -HCG - not a marker.

↓
FSH | LH | TSH

β -HCG → Chorio Carcinoma.

↓
variant

Embryonal variant - α -FP; Neurotension marker

→ α -FP - Non Seminomatous; max elevation yolk Sac tumor/ended
Seminomatous - LDH, PLAP 15% - arise from Syncytiotrophoblast
15% - β -HCG.

yolk Sac tumor - α FP, α -1 antitrypsin.

CD30+ve, C-KIT-ve: embryonal Ca.

NT melanoma - m/Sensitive - S-100; m/Specific HMB-45.

→ Vimentin.

→ mitf-1 (microphthalmia Transcription factor-1)
↓
Choroidal melanoma.

Cytokeratin - for epithelial cancers.

Ca15 → Breast Ca

Ca19.9 → pancreas, Colon

Ca125 - Ovarian tumor (not used for Screening)

↓
→ only for prognosis.

II FNAC: Size: 22G - 27G.

CI: 1) Patient's consent.

2) Bleeding Diathesis

3) H/o anaphylaxis

4) Testicular malignancy

→ To rule out infatality

→ Follicular adenoma vs Follicular Carcinoma - FNAC not useful.

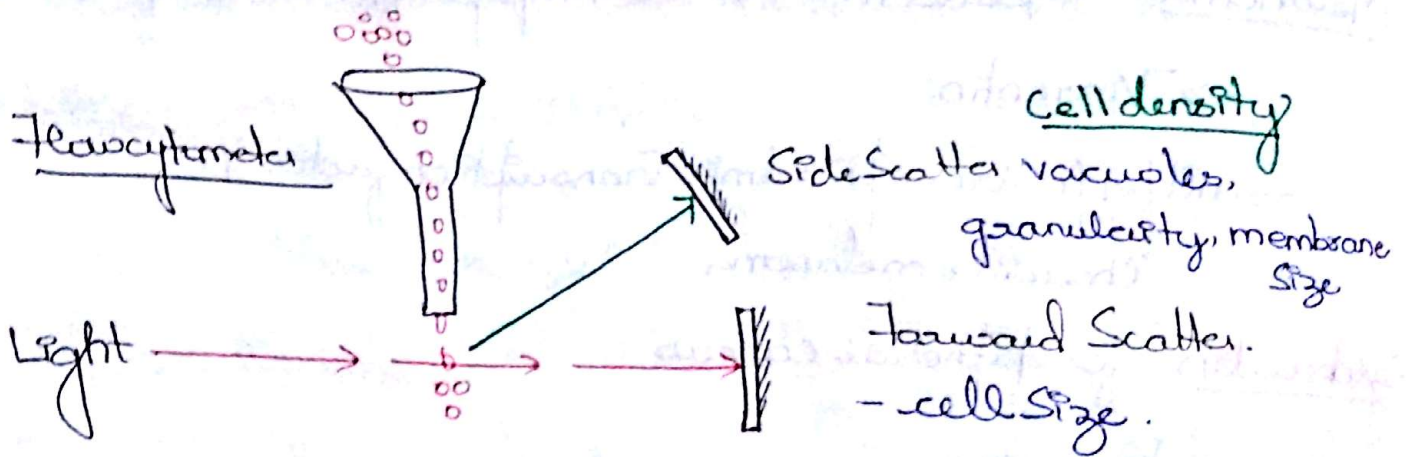
Confirm - only by tissue Biopsy

III Immunophenotyping - Study of CD markers.

Flow cytometry - ideal for lymphocytosis.

→ Simultaneous provide Immunophenotyping

∴ IOC → CLL, ANTL.



IV Immunohistochemistry - IHC

Artificial Cloned Ab → Tumor Ag - complex under microscope.

Basis - Intermediate filament

1) Cytokeratin (epithelial tumors)

→ Carcinoma (any Carcinoma)

2) Vimentin - Connective tissue

melanoma, Sarcoma

RNTS

RNTS myogenin > myo D-1 > Desmin.

4) Neurofilament -

a) Neuroendocrine tumor [NET]

→ Carcinoid

→ Pheochromocytoma / Paraganglioma

→ Small cell Ca of lung.

→ Neuroblastoma.

b) Neuronal tumor of Brain.

→ ganglioglioma

→ gangliocytoma

→ Neurocytoma.

5) Glial Fibrillary Acidic Protein - GFAP

→ Glial tumor of brain - Astrocytoma.

↓
Oligodendroglioma
ependymoma.