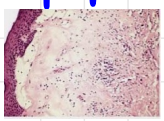
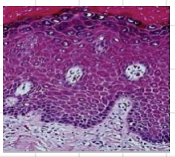
★Topic 1:- Vulvar diseases

- Vulvar diseases → Non-Neoplastic :- more common → Lichen sclerosus :- → skin
  - Lichen simplex chronicus → skin
  - condyloma accumulation :- HPV infection (warts)
- neoplastic :- Less common → Dysplasia (VIN)
  - Vulvar cancer :- Squamous cell carcinoma most common.

1. **Lichen sclerous :-** postmenopausal women, white plaque thined out skin (of valva)
   - micro :- thinning of epidermis, disapperance of rete pegs, hydrophopic degeneration of Basal cells sclerotic dermis (stroma).
   - pathogenisis :- uncertian, autoimmune, ↓estrogen
   - not pre-malignant by itself → differential dx.





2. **Lichen simplex chronicus :-** chronic (progressive Inflammation).
   - clinical term :- Leukoplakia (whitish plaques) on the valva.
   - micro :- epithial thickening (acanthosis) Hyperkeratosis, no atypia, mild-modrate dermis inflammation
   - no ↑ predisposition to cancer, maybe present at margin of adjacent cancer → DDx.

3. **condylomas (condyloma acuminatum, Angenital warts) :-** Low Risk HPV (6, 11)
   - Hallmark :- Koilocytosis (perinuclear cytoplasmic vaculoization + nuclear pleomorphism), abnormal shape of nucleus surrounded by Halo (by virus Replication) → Koliocyte (abnormal Keratinocyte)
   - not precarous by itself, won't lead to cancer & isn't a cancer.

- **Neoplastic vulvar diseases** → Vulvar intraepithial neoplasm (VIN) :- dysplasia by HPV.
  - mild → in situ → invasive (same morphology & etiology).
  - Invasive carcinoma :- Squamous cell carcinoma (most common).

- **HPV :-** STD
  - ↓ Risk types :- anogenital warts (condyloma) (6, 11)
  - ↑ Risk types :- intraepithial dysplasia & invasive cancers in all parts of genital tracts.
    - (16, 18, 45, 31) :- peak age of VIN 30y, cancer 45y → Latency period 15y.
  - 16 & 18 :- integrate into the host genome & express Large amount of viral proteins which block or inactivate tumor suppressor genes, Accumulation of mutations & DNA damge → malignancy.
    - E6 protein :- P53 gene.
    - E7 protein :- retinoblastoma gene.

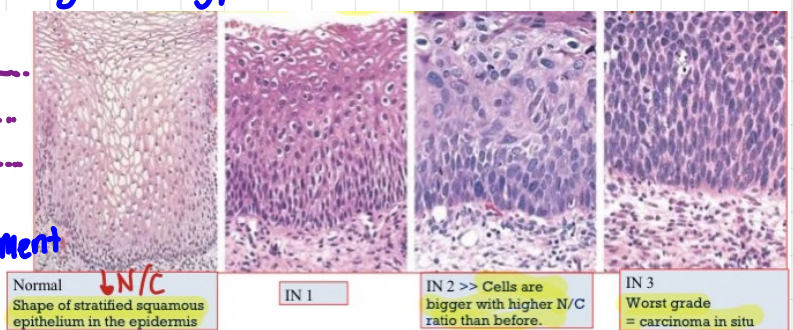
• HPV vaccine •

- **intraepithelial neoplasia (IN) concepts :-** ↑Risk HPV, graded depending on extent of epithial involvement
  - IN I :- mild dysplasia (Lower third of full epithial thickness).
  - IN II :- modrate dysplasia (up to ½ - ⅔ of full epithial thickness).
  - IN III :- severe dysplasia (full epithial thickness). equivalent to carcinoma in situ.
  - same concept & similar morphology to all lower genital tract organs.

- Dysplasia :- ↑ N/c Ratio, nuclear enlargment, hyperchromasia & abnormal nuclear membrane (shape)

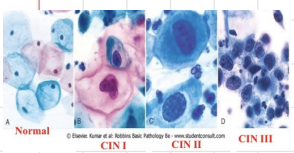
- Vulvar dysplasia (V) → VIN1 ...
- Vaginal dysplasia (Va) → VaIN1 ...
- cervical dysplasia (C) → CIN1 ...

- Course :- genetic, immuno, environment (smoking, new HPV).



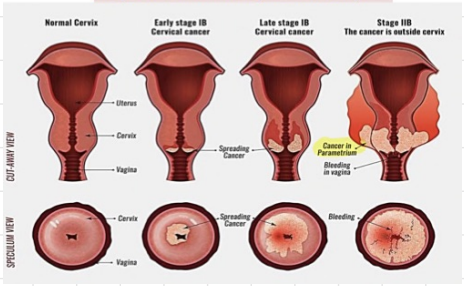
Vulvar Squamous cell carcinoma SCC
there are two biologic forms:

1- Basaloid or poorly differentiated SCC	2- Well-differentiated SCC
❖ most common (90%)	❖ Less common
❖ relatively younger	❖ older women (60-70s).
❖ HPV-related (16,18)	❖ Not HPV-related
❖ HPV lesions also in vagina and cervix.	❖ Maybe found adjacent to lichen simplex or sclerosus
❖ Poorly differentiated cells	❖ well to moderately differentiated cells
Responds better to treatment.	



- cervical carcinoma:- used to be the most frequent cancer in women.
  - papanicolaou (Pap) cervical smear :- screening test for HPV of uterine cervix , useful test(↓99%).
    swab is taking from transition zone of cervix (squamous+endocervix)
  - most common type:- SCC (75%) :- peak 45y , 15y after CIN.
  - other types:- adenocarcinoma & adenosquamous (20%) . neuroendocrine (<5%).
  - clincal Aspects
    - CIN :- tx by Laser or cone biopsy
    - invasive cancer:- surgical excision
    - 5-years survival ↓ with ↑ stage:-
      - pre-invasive (CIN):- 100%
      - stage I :- 90%.
      - stage II :- 82%.
      - stage III :- 35%.
      - stage IV :- 10%
  - Radiotherapy & chemotherapy in advanced stages.

Cervical cancer stage is one of the most important prognostic factors
Helps determine mortality and morbidity.



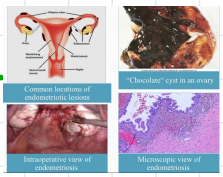
★ Topic 2 :- Uterine pathology

- **Endometritis:-** inflammation of the endometrium, acute or chronic.
  - causes:- infection (PID), miscarriage or dilivery, intrauterine device (IUCD)
  - signs & symptoms:- fever, abdominal pain, menstural abnormalities, infiltrity & ectopic presrency (danger table)
  - Rx:- removal of cause, antibiotics, D&C

cancers are monoclonal proliferation, so it's not a cancer.

- **Adenomyosis:-** endometrial stroma, glands or Both embedded in myometrium
  - morph:- thick uterine wall, enlarged uterus.
  - Derived from:- stratum basalis → no clinical Bleeding.
  - Signs & symptoms:- menorrhagia (menstrual Bleeding), dysmenorrhea (painful). due to enlarged uterus, uterine contractions are exaggerated.

- **Endomertriosis:-** endometrial glands & stroma outside the uterus (not cancer), 10 % in reproductive.
  - signs & symptoms:- infertility, ectopic presrency, dysmenorrhea, pelvic pain, pelvic mass filled with Blood (chocolate cyst), functionalis endometrium → cyclic Bleeding.
    - multifocal in pelvic:- m.c ovaries, Douglas, Ligaments, tubes, rectovaginal septum.
    - sometimes distant site:- umbilicus, LN, Lungs.
  - pathogenesis (theroies)
    - Regurgitation theory (most accepted):- menstrual backflow through tubes & implantation.
    - Metaplastic theory:- Endometrial differentiation of coelomic epithelium.
    - Vascular/Lymphatic dissemination:- extrapelvic or intranodal implants.
    - Extrauterine stem/progenitor cell:- stem from BM → endometrial tissue (distant).
  - consequences:- fibrosis, sealing of tubal fimbriated ends & distortion of the ovaries.
  - Dx (2 of 3):- 1) endometrial glands 2) endometrial stroma 3) Hemosidrin pigment.

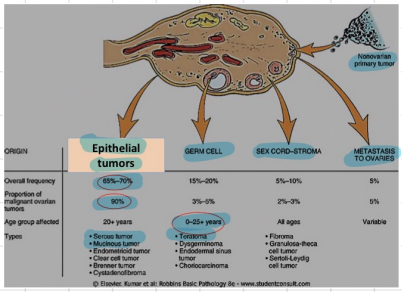


- **Endometrial hyperplasia:-** testrogen relative to progestin → exaggerated proliferation → may cancer.
  - Risk factors:- obesity, DM, HTN, infertility, testrogen replacment, Estrogen-secreting ovarian tumors.
  - Severity Based on:- architectural crowding & cytologic atypia → typica & Atypical (20% cancer risk).

- **Tumors of Endometrium**
  - Benign endometrial polyps:- sessile or pedunculated, no Risk of cancer, dilated glands + small muscular arteries + fibrotic stroma.
  - **Endometrial carcinoma:-** most common cancer in female genital tract, 50-60y
    - I (endometrioid):- perimenopausal women with estrogen excess (most common)
      - similar to endometrium, precancerous lesion = Atypical endometrial hyperplasia (same risk factors)
      - mutation in DNA mismatch repair gene & PTEN., prognosis depends on stage.
    - II (serous):- older women with endometrial atrophy, no Relation with Hyperplasia or hormones.
      - mutation in P53 tumor suppressor gene (all or none), poor prognosis depends on stage (peritoneal cytology.)

- **Tumors of the myometrium**
  - Lieomyoma/fibroids:- Benign tumor of SM, most common (30-50%), Estrogen-dependent (shrink after menopause, circumscribed, firm grey-white masses with whorled cut surface
    - Locations:- intramural, submucosal, subserosal
    - cllinically:- Hemorrage, cystic change or clacification, Asymptomatic, menorrhagia, dragging sense, anemia
    - never transform into sarcoma & multiple lesions doesn't ↑ risk of malignancy.
  - Lieomyosarcoma:- malignant counterpart of Leiomyoma, not from preexisting Lieomyomas. Hemorrhagic necrotic, infiltrative borders.
    - Dx:- Coagulative necrosis, cytologic Atypia & mitotic activity.
    - Recurrence & metastasis is common, 5y surival rate 40%.

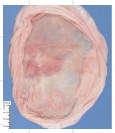
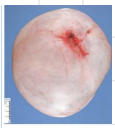
★ Topic 3:- Ovarian & Fallopian tube pathology.



- Ovarian neoplastic Diseases:- 5th most cancer & cancer death in womens.
  - primary:- epithelium, germ cells, sex cord/stromal cells
  - secondary:- metastatic malignancies.
  - Risk factors:- nulliparity, family history (10%), OCPs → ↓ Risk.

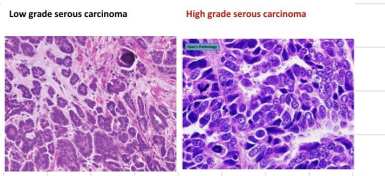
1 Epithial ovarian Neoplasm:- majority, 90%, previously → coelomic epi:, Recent → fimbrited end & epi cyst
- pathogenises
  - sporadic:- BRCA 1 & 2, P53, HER2/NEU over expression, K-RAS (mucinous)
  - familial:- BRCA1 & 2 (& Breast).
- Types:- serous, mucinous, Endometrioid, clear cell, Brenner (all types ⇄ Benign, borderline, malignant).

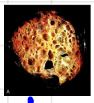
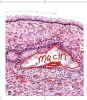
I) Serous tumors:- Most frequent & most common malignant (60%).
- genitics
  - Borderline & ↓grade carcinoma:- BRAF & K-RAS.
  - ↑ Grade carcinoma:- P53 & BRCA1
- Benign (60%) Cystic, Large, filled with serous good prognosis, Serous cystadenoma

  - single Layer of columnar epi ± cilia.
  - psammoma bodies:- Laminated calcified concretion, tip of papillae, in all serous tumors.
- Borderline:- (15%) complex architecture, mild cytologic atypia, no stromal invasion, may have peritoneal implants (metastasis), recure or → carcinoma, intermediate prognosis.
- malignant (25%)

low-grade serous carcinoma:	high-grade serous carcinoma:
- arise from borderline lesions	- develop rapidly
- progress slowly to become invasive carcinoma	- many arise form fallopian tube via serous tubal intraepithelial carcinoma, rather than ovarian coelomic epithelium.
- Differentiated morphology	- mutations in TP53
- mutations in KRAS BRAF	• Anaplasia of cells and invasion of the stroma.
	• prognosis poor, depends on stage at the time of diagnosis.



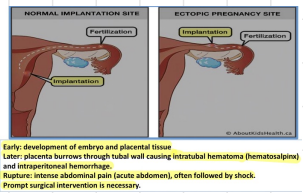



II) Mucinous ovarian tumors:- mucin-Secreting cells, 80% benign, 10% borderline, 10% malignant (cystadanocarcinoma). Large & multilocular, no psammoma boides, Stage → prognosis.

2 Germ cell tumors
- Types:- dysgerminoma (oogonia), Embryonal, yolk sac, choriocarcinoma, Tetroma (most com

I) Benign (mature) cystic teratoma:- totipotential germ cell from mature tissues of all three germ cell layer 15-20% ovarain, incidentally, 90% uniLateral, immature is rare, torsion (10% - 15%) → Abdominal pain.

- Clinical correlation for all ovarian tumors:- Abd.pain, gastrointestinal compliants, Urinary frequency
  - Ascites:- fibroma & malignant serous.
  - functioning ovarian tumors:- Estrogen & androgen.
  - Tx:- Surgery + chemo + Radio
  - outcome:- not good, no screening method, malignancy → Late

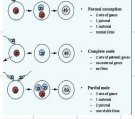


Early: development of embryo and placental tissue
Later: placenta burrows through tubal wall causing intratubal hematoma (hematosalpinx) and intraperitoneal hemorrhage.
Rupture: intense abdominal pain (acute abdomen), often followed by shock.
Prompt surgical intervention is necessary.

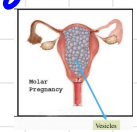
★ Ectopic presrency:- implantation of fertilized ovum outside uterus, 90% in fallopian tube
- predisposing factors:- tubal obstruction (50%), PID, tumors, endometriosis, IUCD. 50% → no factor.

★ Tubal malignancies:- most common is serous (origin of ↑grade)
- serous tubal intraepithial carcinoma (STIC):- fimbriated end, TP53 (90%), ↑ with BRCA → spread to omentum & peritoneal cavity at the time of presentation.

★Topic 4:- Trophoblastic diseases



- **hydatidiform mole**:- abnormal gestational processes, result from abnormal fertilization.
  - complete mole:- empty egg + 2 spermatozoa/diploid sperm → diploid paternal gene
    no embryogenisis = never contains fetal parts (46 xx or 46xy).
  - partial mole:- normal egg +2 spermatozoa/diploid sperm → Triploid.
    early embryo formation & may contantain fetal part, chorionic villi, (69, xxy).



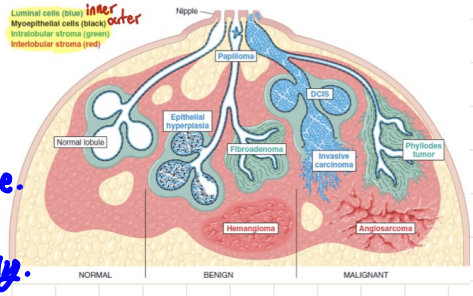
  - morphology:- snow storm, dilated chronic villi (grapelike), covered by atypical chorionic epi.

Feature	Complete Mole	Partial Mole
Karyotype	46,XX (46,XY)	Triploid (69,XXY)
Villous edema	All villi	Some villi
Trophoblast proliferation	Diffuse; circumferential	Focal; slight
Atypia	Often present	Absent
Serum hCG	Elevated	Less elevated
hCG in tissue	++++	+
Behavior	2% choriocarcinoma	Rare choriocarcinoma

  - incidence:- 1/2000, Asian, Before meternal age 20 & after 40, ↑HCG & abs of fetal parts.
  - prognosis → complete:- 80-90% → no recurrance, 10% → invasive mole (myometrium), 2% → choriocarcinoma
    partial:- Better prognosis, ↓Risk of choriocarcinoma.

- **Chorriocarcinoma**:- agressive malignant tumor arise from gestational chroionic epi or gonads.
  - 1/30.000, Asia & Africa, <20, >40, 50% → complete mole, 25% → abortion, rest → normal.
  - clinically:- Blody, Brownish discharge & ↑HCG, Hemorrhagic, necrosis mases in myometrium
    chrionic villi are not formed; tumors is composed of anaplastic cytotrophoblast & syncitiotrophb
  - prognosis:- → Blood → Lung (50%), vagina, Brain, Liver, Kidney, uncommon lymphatic, good chemo.

★Topic 5:- Breast cancer



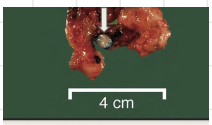
- Regardless of symptoms → The cause is benign in >90% of cases
  - Likelihood of malignancy increases with age.
  - (nipple discharge & palpable masses).
  - 45% have symptoms, other 55% by screening.

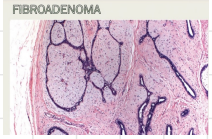
- Mammographic screening:-
  - detect early, nonpalpable asymptomatic breast cancer Before metastasis ≈1cm (15% to LN) (s→ 2-3cm)
  - The sensitivity & specificity ↑ with age :- ↑fibrous in ↓age (radiodence) → fatty adipose in ↑age (Radiolucent)
  - From 45-55 yearly mammograms, <40 & >55 if they choose.

- clinical presentations
  - pain (mastalgia or mastodynia) :- most common, 90% Benign (↑with age→malignancy). Related to menses (cyclic edema & swelling). Localized due to ruptured cyst or physical trauma.
  - inflammation :- Rare, causes edema & erythema, caused by Infection (Breastfeeding), mimic of inflammatory Breast cancer (→obstruction of LN → edema).
  - Nipple discharge
    - N :- Small quantity & bilateral
    - milky (galactorrhea) :- ↑prolactin (adenoma, ↑T3, OCPs, tricyclic Antidepressant, methyldopa).
    - Bloody or serous :- Large duct papilloma, pregnency (Rapid growth & Remodeling).
    - Spontaneous, unilateral, bloody discharge → ↑concern for malignancy.
  - palpable masses (2-3cm) :- 95% Benign, Requires evalation (cysts, fibroadenoma, invasive carcinoma).
  - Gynecomastia (males) :- ↑stroma & epithial cells, imbalance between estrogen & androgen.

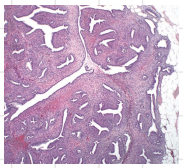
- Stromal neoplasms
  - Intralobular :- fibroadenoma & phyllodes. Biphasic (stromal → Cf → epithial cells)
  - InterLobular :- monophasic
    - other sites :- Lipomas & angiosarcoma (only malignant)
    - Breast :- pseudoangiomatous stromal hyperplasia & myofibroblastoma

1. Fibroadenoma :- most common benign, 20-30, discrete, solitary, movable (1-10cm)
   - estrogen activity :- enlarge in late cycle & pregnency, regress & calcify after menopause.





2. Phyllodes tumor :- ↓common, not from preexisting fibroadenoma, 6th decade.
   - Leaf like cleft & slit :- nodules of proliferating stroma covered by epithelium.
   - classification
     - Benign (60-75%) :- rare recurrance & no metastasize.
     - Borderline (15-26%) :- Higher risk of Local recurrant, ↓Risk of metastasis.
     - malignant (8-20%) :- 30% recurrence, 9% distant metastasis.



- Benign epithial lesions
  - nonproliferative changes (fibrocystic) :- 0% → cancer, most common, 1) cyst (mc) :- apocrine metaplasia → Rupture
    2) fibrosis 3) Adenosis :- ↑n of acine/lobule.
  - proliferative without atypia :- polyclonal hyperplasia, x1.5-2 → ↑Risk of cancer, not true precursors.
    - epithial hyperplasia :-
    - sclerosing adenosis :-
    - complex sclerosing lesion :-
    - papilloma :-
  - proliferative with atypia (precancers) :- monoclonal x4-5 → cancer in Both breast.
    - atypical Lobular hyperplasia (ALH) :- resembles Lobular carcinoma in situ (LCIS).
    - atypical ductal hyperplasia (ADH) :- resembles ductal carcinoma in situ (DCIS).
    - having some but not all, histological features that are require to dx → carcinoma in situ.

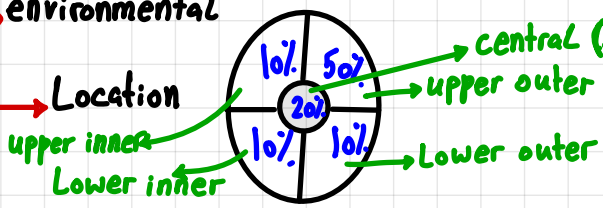
★Topic 6 :- Breast cancer - 2

- **Epideminology** → most common non-skin malignancy of women.
  - 2nd most common of cancer death on women (1st → Lung carcinoma).
  - ↑incidence & mortality:- ↑screening & ↓use of hormonal replacment therapy.

- **Risk factors** → Age:- ↑After 30, 75% >5oyrs.
  - Gender:- 1% men.
  - Family history:- multiple affected first-degree relatives → early-onset breast cancer.
  - Geographic factor:- ↑Amirica & Erope (diet, reproductive patterns, Breastfeeding practies & adoption).
  - Race/Ethnicity:- ↑Europen descent, Hispanic & African American → younger age & ↑aggressive.
  - Reproductive history:- ↑estrogen exposure (nullipaty, no Breastfeeding, first pregrency >35yrs).
  - Ionizing Radiation:- chest Radiation (young age only <3oyrs).
  - others:- postmenopausal obesity or hormone replacment, alcohol, mammographic density.

- **pathogenesis** → genitics :- 1) BRCA1&2 (>55%) 2) HER_2 amplification. 3) TP53 ; PTEN.
  - Hormonal :- Estrogen Related.
  - environmental

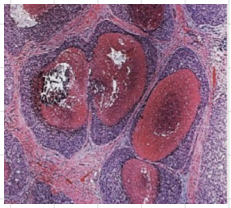
- **morphology** → Location



- 4% have Bilateral primary tumors or sequential Lesions in same breast.

1 Noninvasive :- confined by BM & don't invade into stroma or lymphovascular channels.

- Lobular carcinoma in situ (LCIS)
  - malignant clonal proliferation of cells within lobules & ducts.
  - cell grow in discohesive fashion (acquired Loss of tumor supressive adhesion protein E-cadherin).
  - Lobular → proliferation takes an apperance resembling Lobules.
- Ductal carcinoma in-situ (DCIS)
  - malignant clonal proliferation of epithelial cells within ducts & Lobules.
  - wide variety of histologic apperance:- Solid, comedo, cibriform, papillary, micropapillary.

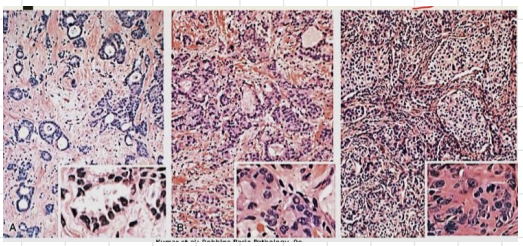


2 invasive (infiltrating) Breast cancer

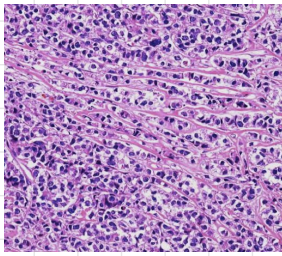
- classification (Receptors):- Estrogen (ER), progesterone (PR), Human epidermal growth factor 2R (HER_2/neu).
  - ER positive (HER_2 nigative) :- 6o%
  - HER_2 positive (EP positive or negative) :- 2o%
  - Triple nigative 1o%

I) invasive ductal carcinoma :- 7o-8o%,

- other name :- non otherwise specifed.
- precancerous Lesion :- DCIS.
- clinically :- mammographic density or Hard, palpalbe irregular mass.
- Receptor profile :- ER, PR ⊕ , HER_2 ⊖

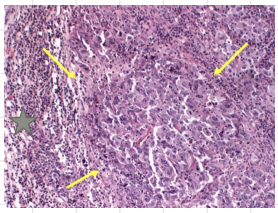


II) invasive Lobular carcinoma:- 10-15%.



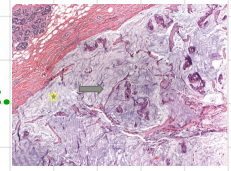
- precancerous Lesion:- 2/3 LCIS.
- clinically:- multicentric & bilateral (10-20%), palpable masses or mammographic densities.
- Histo:- cell invade stroma individually & often aligned in single-file.
- receptor profile:- ER, PR ⊕ , HER_2 rare or ⊖.

III) carcinoma with medullary features:- 5%



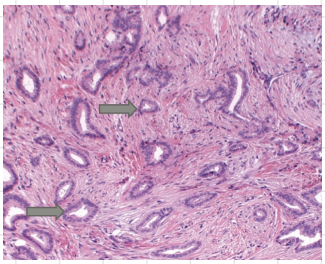
- micro:- Large anaplastic cells + pushing, well-circumscribed border + pronouced Lymphocytic infiltrate.
- no precancerous Lesion
- ↑frequency in women with BRCA1 mutations.
- receptor profile:- Triple nigative.

IV) colloid (mucinous) carcinoma :- Rare.



- Grossly:- soft & gelatinous.
- micro:- abundant quantities of extracellular mucin → dissects into stroma.
- receptor profile:- ER ⊕ , HER2 ⊖.

V) Tubular carcinoma:- <5%



- clinically:- irregular mammographic densities
- micro:- well formed tubules + ↓grade nuclei
- Lymph node metasteses:- Rare
- prognosis:- excellent.
- Recepto profile:- ER ⊞ , HER_2 ⊖.

- **features of invasive cancers.**
  - fixation:- adherent to the pectoral muscles or deep fascia of chest wall.
  - Retraction/dimpling:- of skin or nipple, adherence to overlying skin.
  - peau d'orange (orange peel):- involvement of Lymphatic pathway → Lymphedema & skin become thickened & exaggereted around Hair follicles.

- **Spread of Breast cancer**
  - through Lymphatics & hematogenous channels.
  - to Bone, Lung, skeleton, Liver, adrenal → Brain, spleen & pituitary.
  - metastases may appear many years after therapeutic control of primary Lesion.

- **Screening**
  - mammographic
  - MRI.

- **prognosis**
  - Tumor stage
    - invasive or in situ.
    - tumor size.
    - LN involved & it's number.
    - Distant metastases.
  - Histologic grade
  - Histologic type of carcinoma.
  - Lymphovascular invasion.
  - estrogen/progesterone receptor expression.
  - overexpression of HER_2 :- to predict response to a monoclonal antibody Herceptin against gene product.