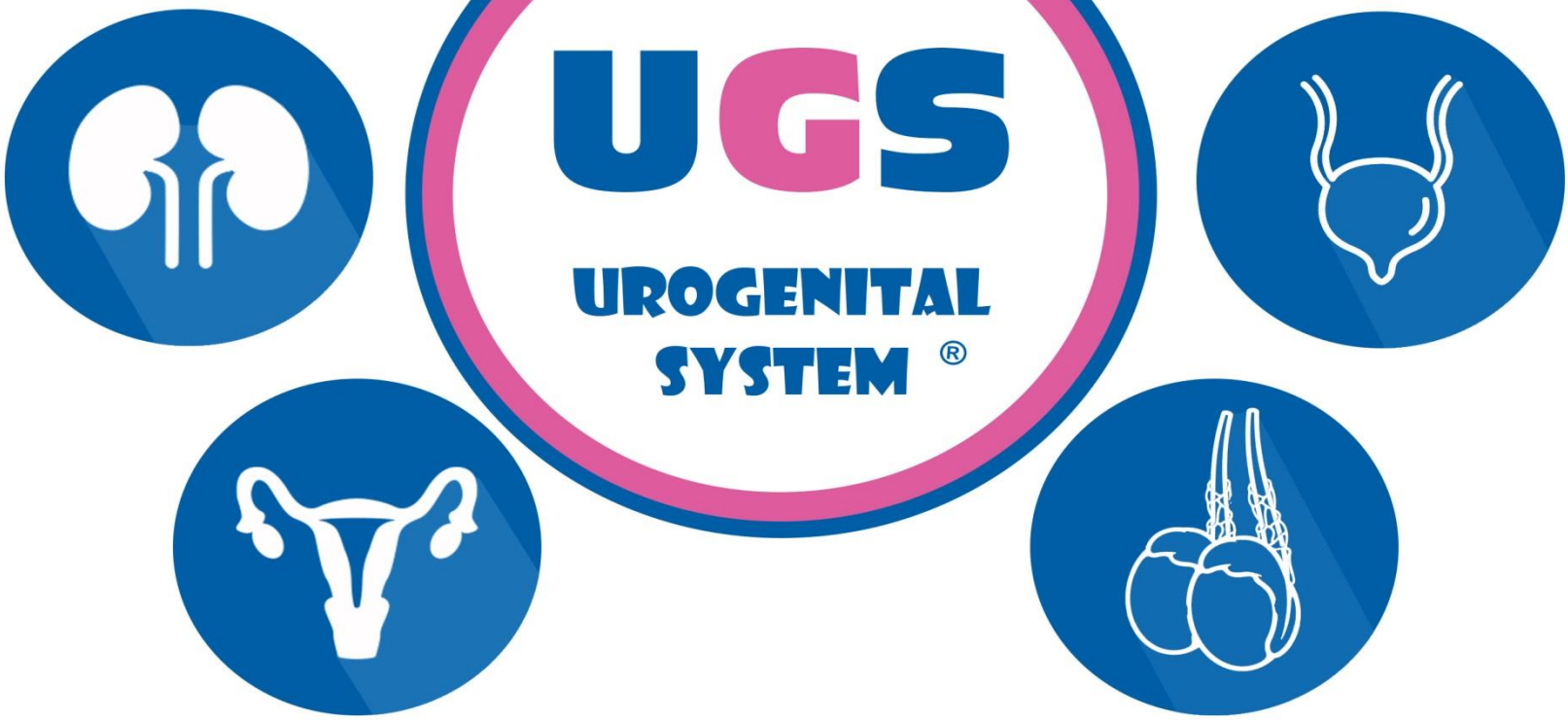


Sheets Pathology

Number: 2

Doctor: Mousa

Done By: Hala Abu Fares

Correction: Ghufran Touma

At the end of the previous sheet the various classifications of mammary carcinoma were briefly discussed which are:

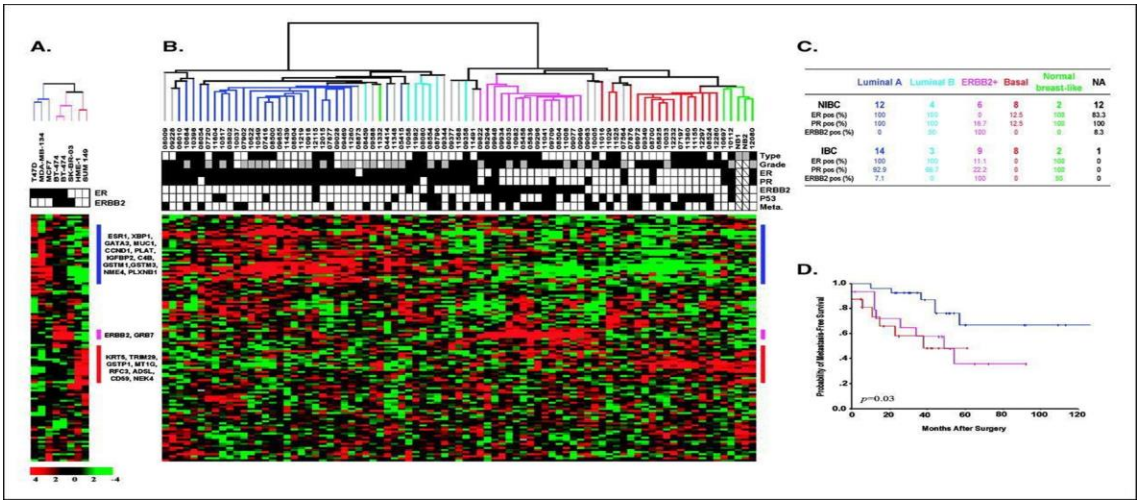
- *Histological appearance under the microscope:*
  - ✓ *Ductal & lobular*
- *Receptor status:*
  - ✓ *Estrogen receptor (ER) positive and HER2 negative*
  - ✓ *HER2 positive (ER positive or negative)*
  - ✓ *Triple negative (ER, HER2, and progesterone receptor (PR) negative)*
- *DNA-based classification:*
  - ✓ *When specific DNA mutations or gene expression profiles are identified in the cancer cells this may guide the selection of treatments.*

The gene profile classification categories mammary carcinomas into three categories;

✓ *LUMINAL A*	✓ *LOWER GRADE, ER +VE, HER-2-* ✓ *NEU -VE*
✓ *LUMINAL B*	✓ *HIGHER GRADE, ER+VE, HER-2-* ✓ *NEU +VE*
✓ *HER-2-* ✓ *ENRICHED*	✓ *HER-2-NEU +VE, ER-VE*
✓ *BASAL-LIKE*	✓ *HER-2-NEU -VE, ER-VE*

The genetic profile technique is not frequently used in Jordan as it is still new and expensive so it is not part of the routine cancer classification methods.

As you can see in the following diagram this is what a particular breasts cancer genetic profile looks like, each pixel represents one gene and its amino acid sequence.



Actually all three methods are used in combination to describe any mammary carcinoma , please refer to the table below for detailed information.

TABLE 19.7 Summary of the Major Biologic Types of Breast Cancer

Feature	ER Positive/HER2 Negative	HER2 Positive (ER Positive or Negative)	Triple Negative (ER, PR, and HER2 Negative)
Overall frequency	50%–65%	20%	15%
Typical patient groups	Older women; men; cancers detected by screening; germline *BRCA2* mutation carriers	Young women; germline *TP53* mutation carriers	Young women; germline *BRCA1* mutation carriers
Ethnicity			
European/American	70%	18%	12%
African/American	52%	22%	26%
Hispanic	60%	24%	16%
Asian/Pacific Islander	63%	26%	11%
Grade	Mainly grade 1 and 2	Mainly grade 2 and 3	Mainly grade 3
Complete response to chemotherapy	Low grade (<10%), higher grade (10%)	ER positive (15%), ER negative (>30%)	30%
Timing of relapse	May be late (>10 years after diagnosis)	Usually short (<10 years after diagnosis)	Usually short (<8 years after diagnosis)
Metastatic sites	Bone (70%), viscera (25%), brain (<10%)	Bone (70%), viscera (45%), brain (30%)	Bone (40%), viscera (35%), brain (25%)
Similar group defined by mRNA profiling	Luminal A (low grade), luminal B (high grade)	Luminal B (ER positive), HER2-enriched (ER negative)	Basal-like
Common special histologic types	Lobular, tubular, mucinous, papillary	Apocrine, micropapillary	Carcinoma with medullary features
Common somatic mutations	*PIK3CA* (40%), *TP53* (26%)	*TP53* (75%), *PIK3CA* (40%)	*TP53* (85%)

PIK3CA encodes phosphoinositide 3-kinase (PI3K).

Each column represents one of the three receptor based / hormonal classifications and details about each type is provided.

For example ;

- *the most prevalent type of mammary carcinoma(two third of the cases) is the Estrogen receptor (ER) positive and HER2 negative type, in fact most breast cancers in men are of this type.*
- *It is usually a low grade carcinoma and responds well to Tamoxifen treatment,*
- *it also occurs in older patients.*
- *As for the histological appurtenance -notice how these two classifications are combined together - they are usually either lobular, tubular, mucinous or papillary; which all reflect low grade toumors especially both lobular and tubular histological types* ***-well differentiated-*** *…*
- *on the genetic basis it is usually Luminal A or B type which have better prognosis than Basal - like.*
- *Mostly metastasize to bone*

As for the triple negative type;

- it has the **worst** prognosis among all other types as it occurs in younger ages-not that young it still occurs in old age groups but compared to the other two it starts earlier-
- it is ER –ve so it does not respond well to Tamoxifen treatment –anti ER treatment-
- On the genetic bases it is usually **a basal- like (basal cell layer)** cancer which again has a worse prognosis than Luminal A and B.
- It has BRCA1 and BRCA2 mutations

Finally the HER2 positive (ER positive or negative) falls in the middle between these two extremes.

- ✓ It should be mentioned that all three types typically metastasize in bone.
- ✓ Once again please look at the table for more detailed information.

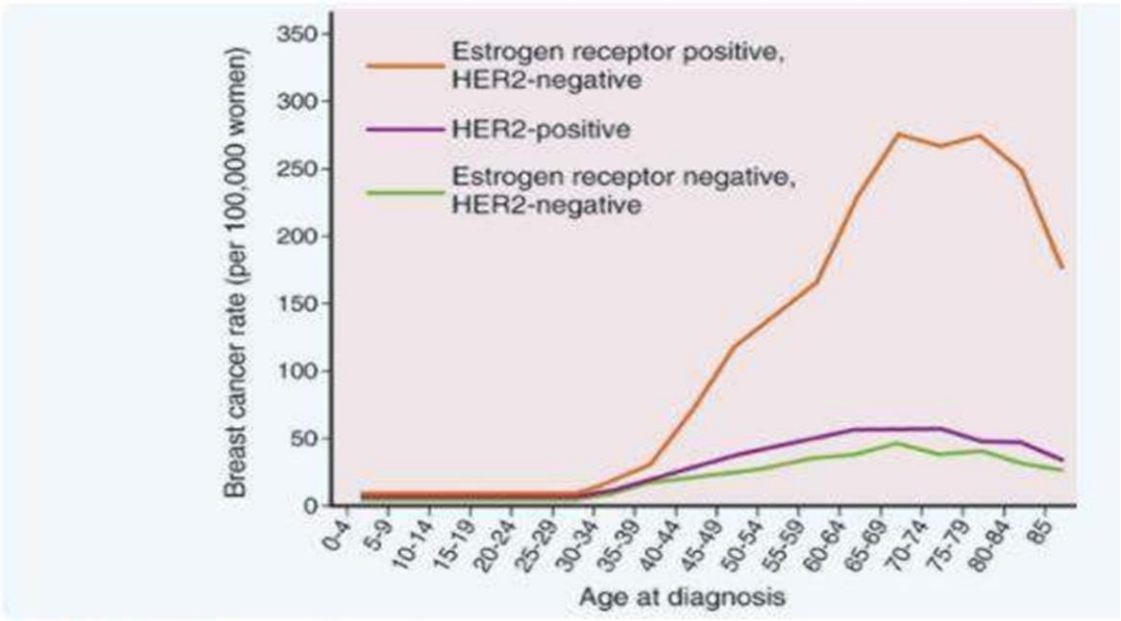


FIG. 19.26 Age and the incidence of breast cancer subtypes.

In this graph you can clearly see the pattern and prevalence of each category of mammary carcinoma, so the ER positive her neu –ve type is the most prevalent than the others and you can notice that all three occur usually in older age groups.

The risk factors;

- *Age and gender*
- *Family history*
- *Geography (diet, late pregnancy, breast feeding)*
- *Race and ethnicity (ER+ve European; worse cancers in Hispanic and AA and at younger age)*
- *Reproductive hx. (early menarche, nulliparity, no breast feeding, older age at pregnancy)…more Estrogenic effect*
- *Ionizing radiation at younger age*
- *Other factors: post M obesity, HRT, Mammographic density, alcohol consumption*

- ✓ *Environmental factors; for example Japanese people have lower prevalence of breast cancer than Americans –ethnicity- however when someone from Japan lives in America for a long time the risk of having cancer increase so there must be an environmental basis to the development of breast cancer.*

Pathogenesis of breast cancer;

- *Most ER positive carcinomas have BRCA2 mutations, this pathway further involves mutation in chromosome 1 and 16, With time the accumulation of mutations results in Atypical ductal hyperplasia which was discussed in the previous sheet , and it increases the incidence of caner by 15 percent , then with further additional mutation that are acquired with time to both tumor suppressor genes and proto-oncogenes the DCIS occurs and finally invasive carcinoma is established which is usually in this scenario of the luminal A type .*
- *As for the ER-ve type which has the worst prognosis, it usually involves germ line mutations in BRCA1 in addition to multiple mutations in tumor suppressor genes . Typically they are triple –ve (-er-ve , pr-ve and her-ve-)and the setup is usually basil-like .*
- *Some tumours are ER positive but have HER2 receptor amplification which is part of the EGFR genes which HER2enriched.*
- *Notes worth mentioning;*

- *Her2-ve tumors do not respond to herceptin - anti her 2 treatment -*
- *Er –ve does not respond to tamoxiphen*

This is why we have to understand and know the pathogenesis and the molecular basis of each caner in order to be able effectively target and treat various tumors.

<u>Diagnosis of mammary carcinoma;</u>

*The **diagnosis** of the patient till now depends **on microscopic examination**-on histological basis- even in countries like the US which have the access to genetic profiling techniques, microscopic examination remains vital for diagnosis.*

Under the microscope there are various morphological types of the breast cancer ;

Breast cancers are classified according to whether they have or have not penetrated the limiting basement membrane: Those that remain within this boundary are termed in situ carcinomas, and those that have spread beyond it are designated invasive or infiltrating carcinomas.

.

NON –INVASIVE CARCINOMA	***INVASIVE CARCINOMA***
Ductal carcinoma in situ (DCIS) ***Lobular carcinoma in situ (LCIS)***	***Invasive ductal carcinoma (IDC) 70-80%*** ***Invasive lobular carcinoma (ILC) 10-15%*** ***Medullary carcinoma 5%*** ***Colloid (mucinous carcinoma) 5%*** ***Tubular carcinoma 5%*** ***Other types***

Notes on the previous table

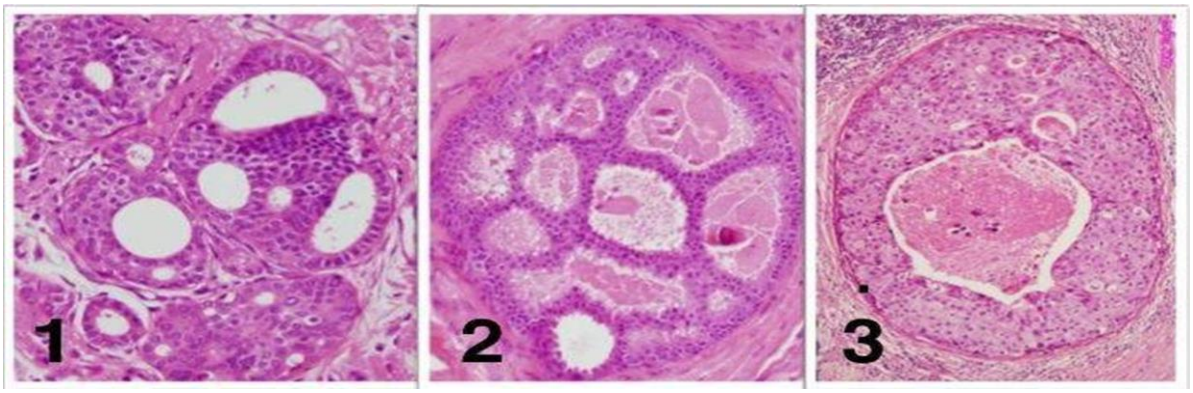
Invasive lobular carcinoma *is usually;*

- *lower grade than the ductal invasive carcinoma*
- *ER positive and her2 neu –ve ,*
- *has a tendency to be multicentric and bilateral , no small masses of cancer cells are formed , thus treatment is usually by bilateral mastectomy .*

Medullary carcinoma *is a special type of cancer that involves a mass associated with inflammation , usually triple –ve and basil- like*

Colloid carcinoma *90 percent produce mucin, and responds well to treatment*

Tubular carcinoma*, usually grade 1 cancer and is well differentiated*



A Special type of DCIS ; Comedo carcinoma –picture 2-, which is still a DCIS but the nuclear grade is high and there is extensive central necrosis.

In Radiology – mammogram- of pure type of DCIS, only abnormal calcifications are usually seen and no definite mass is identified.

As for Lobular carcinoma in situ ; it consists of smaller cells , lower grade, and a higher nuclear to cytoplasm ratio , it is also not easy to detect it with radiology.

Invasive Carcinoma ;

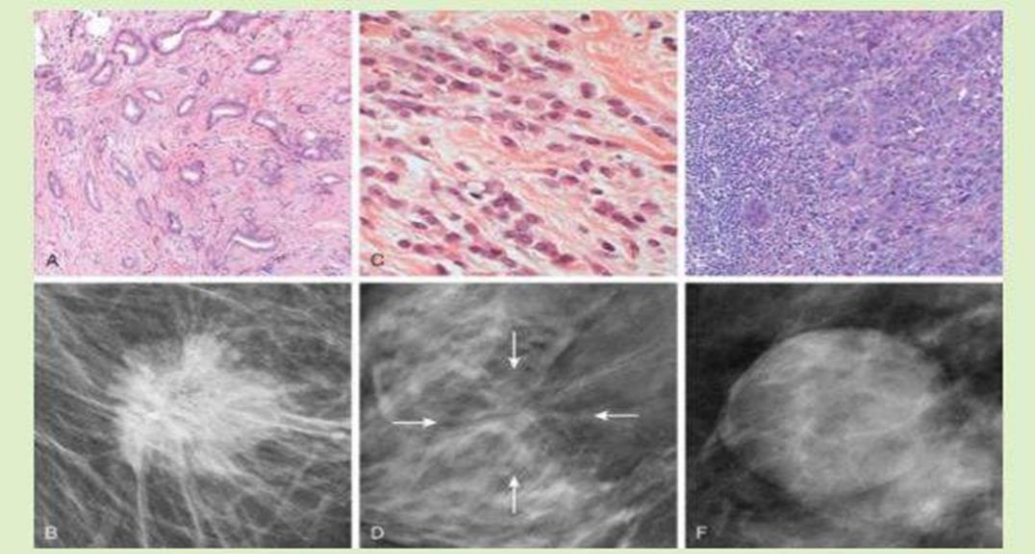


FIG. 19.29 Growth patterns of invasive breast carcinomas. (A) Most grow as tub…

- *(A) is a well differentiated tubular type of carcinoma*
- *(C lobular invasive, single cells infiltrating, giving an Indian firing appearance . (بتبشه صف العسكر)*
- ***3rd picture ; Medullary carcinoma which consists of 'ugly' looking cells but has a well circumscribed mass in radiological examination in contrast to lobular carcinoma.***
- *Also tubular invasive carcinoma is well identified in mammograms.*

Paget disease of the nipple;

It is a disease in which Cancer cells go to the epidermis, it is distinguished clinically by ;

- *destruction of the nipple ,*
- *crusty nipple ,*
- *Itching.*
- ✓ *Almost always there is underlying carcinoma , this is opposite to Paget disease of vulva- discussed later-*
- ✓ *If we have mammary carcinoma in addition to Paget disease of the nipple the prognosis will be worse.*

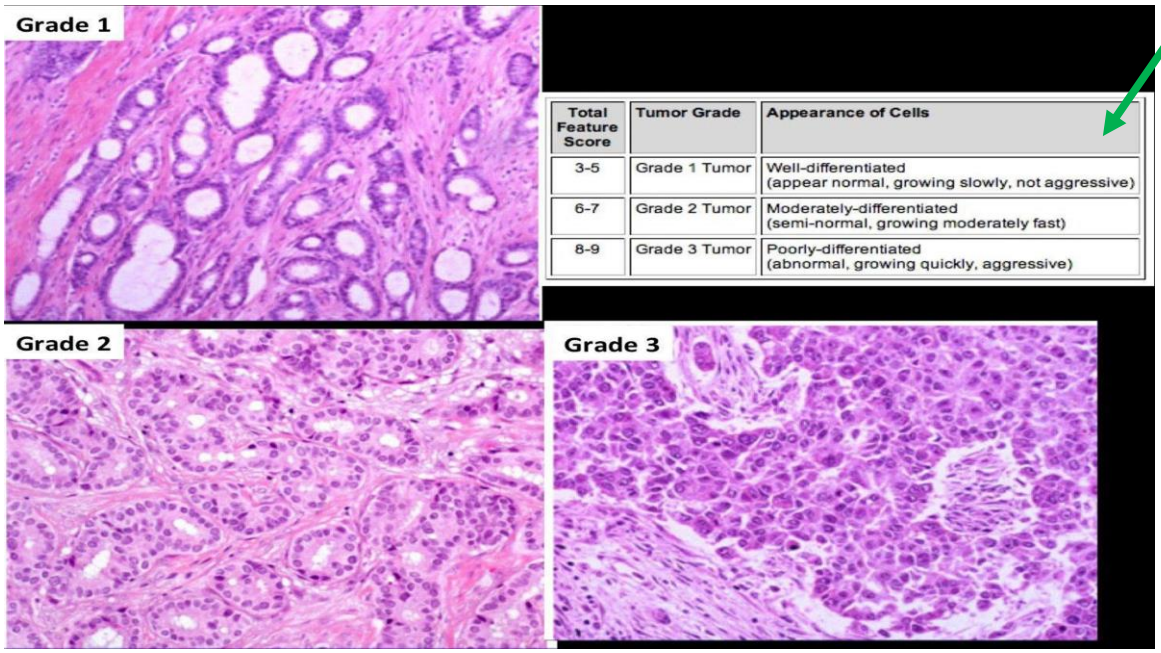
The best things early detection, stage 1 and 2 not 3 and 4.

Grading of mammary carcinoma;

Grading is done by pathologists, after diagnosis of the tumor type ; Histological Grading depends on ;

- ✓ *The number of tubules –differentiated glands- ; there are three levels 1 is lowest and 3 is the highest.*
- ✓ *Nuclear grade; there are three levels 1 is lowest and 3 is the highest.*
- ✓ *Mitotic activity; there are three levels 1 is lowest and 3 is the highest.*

So let's assume that the level of tubules was 3 and the nuclear grade as well as the mitotic activity were also a level 3 then the total grade –see table- is 9 -3plus 3 plus 3-



Clinical features;

- *Unscreened: palpable mass, 2-3 cm, 50% spread to regional lymph nodes*
- *Screened; 60% of cancer discovered before symptoms; 20% are in situ carcinomas.*
- *IC in screened are 1-2 cm, 15% spread to LN at time of dx.*
- *"Interval cancers": palpable discovered between screening intervals (high grade)*
- *Behavior depends on: Molecular, morphological and* ***stage- most important****- of cancer at time of dx*

Staging of mammary carcinoma;

Staging depends on TNM classification technique;

Were T ; size of the tumor

N ; no. of lymph nodes involved

M; the presence of metastasis

Table 1: Breast Cancer T, N, and M Categories

Primary Tumor (T):

TX: Primary tumor cannot be assessed
T0: No evidence of primary tumor
Tis: Carcinoma in situ (DCIS, LCIS, or Paget's disease of the nipple with no tumor mass)
T1: Tumor is ≤2 cm
T2: Tumor is >2 cm but <5 cm
T3: Tumor is >5 cm
T4: Tumor of any size growing into the chest wall or skin

Lymph Node Status (N):

NX: Nearby lymph nodes cannot be assessed
N0: Cancer has not spread to nearby lymph nodes
N1: Cancer has spread to 1 to 3 axillary lymph nodes, and/or tiny amounts of cancer are found in internal mammary lymph nodes on sentinel lymph node biopsy
N2: Cancer has spread to 4 to 9 axillary lymph nodes under the arm, or cancer has enlarged the internal mammary lymph nodes
N3: One of the following applies:
- Cancer has spread to 10 or more axillary lymph nodes
- Cancer has spread to the lymph nodes under the clavicle
- Cancer has spread to the lymph nodes above the clavicle
- Cancer involves axillary lymph nodes and has enlarged the internal mammary lymph nodes
- Cancer involves 4 or more axillary lymph nodes, and tiny amounts of cancer are found in internal mammary lymph nodes on sentinel lymph node biopsy

Metastases (M):

MX: Presence of distant metastases cannot be assessed
M0: No distant spread
M1: Spread to distant organs is present

DCIS: ductal carcinoma in situ; LCIS: lobular carcinoma in situ.
Source: References 6, 12, 21.

Notes;

- *Triple negative and her2 positive breast cancer metastasize to brain and viscera and this is bad news since usually this is considered stage 3 and 4*
- *ER positive usually metastasize to the bone and this take approximately 10-15 years from the time of diagnosis.*

Stage	Definition
Stage 0 is carcinoma *in situ*	Tumors that have not grown beyond their site of origin and invaded the neighboring tissue. They include: - ductal carcinoma *in situ* - lobular carcinoma *in situ*
Stage 1	Tumor size <2 cm, metastases to other organs and tissues not available
Stage 2a	Tumor <2 cm in cross-section with involvement of the lymph node or tumor from 2 to 5 cm without involvement of the axillary lymph nodes
Stage 2b	Tumor more than 5 cm in cross-section (the result of axillary lymph node research is negative for cancer cells) or tumor from 2 to 5 cm in diameter with the involvement of axillary lymph nodes
Stage 3a	Also called local spread of *breast cancer*: tumor more than 5 cm with spread to axillary lymph nodes or tumor of any size with metastases in axillary lymph nodes, which are knitted to each other or with the surrounding tissues
Stage 3b	Tumor of any size with metastases into the skin, chest wall or internal lymph nodes of the mammary gland (located below the breast inside of the chest)
Stage 3c	Tumor of any size with a more widespread metastases and involvement of more lymph nodes
Stage 4	Defined as the presence of tumors (regardless of the sizes), spread to parts of the body that are located far removed from the chest (bones, lungs, liver, brain or distant lymph nodes)

When breast cancer spreads to adjacent lymph nodes one of which are the axillary lymph nodes one solution would be the removal of such nodes however this can be of inconvenience for the patient as it can cause complications so as physicians it is advised to remove the nodes only if we are sure that the cancer reached the nodes.

Thus Before examining the axillary lymph node surgeons examine a type of lymph nodes known as sentinel lymph nodes, during the surgery they insert a blue dye specific to the tumor and follow the path that the dye takes, the blue colored lymph node will be the sentinel lymph , then they provide a sample to the pathology team for further examination, if negative they stop the surgery and avoid removing the axillary lymph nodes.

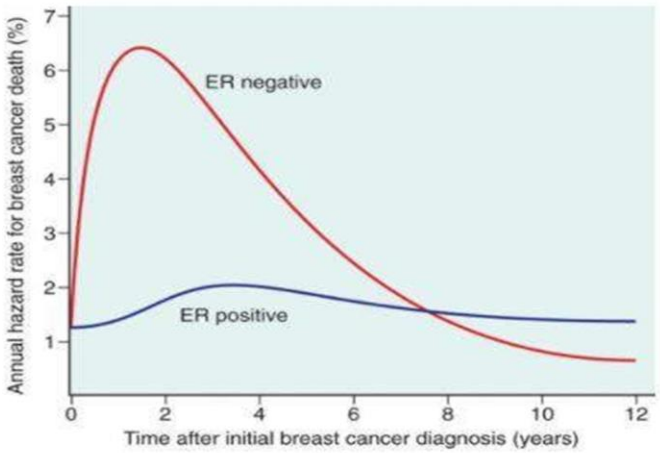


FIG. 19.31 Time to recurrence of breast cancers. The hazard ratio reflects the risk of re...

- *Er –ve cancers are more aggressive so the recurrence is usually 2-3 years after the initial diagnosis(early) opposed to ER positive tumors.*

TABLE 19.8 Targeted Treatment of Breast Cancer

Target	Treatment	Assay	Comments
ER	Estrogen deprivation (oophorectomy, aromatase inhibitors) Blockage of ER (tamoxifen)	IHC for nuclear ER	Effective cytostatic (but not cytotoxic) therapy for ER-positive cancer
HER2	Antibodies to HER2 Cytotoxic therapy linked to HER2 antibody Tyrosine kinase inhibitors	IHC for membrane HER2 ISH for HER2 gene amplification	Effective for HER2-positive cancers
Susceptibility to DNA damage resulting from BRCA 1 and BRCA2 mutations that cause defects in HRR	Chemotherapy with agents causing DNA damage that requires HRR (e.g., platinum agents) Inhibition of alternative DNA repair pathway (poly-ADP ribose polymerase or PARP inhibitors)	Sequencing of *BRCA1* and *BRCA2*	May be effective for carcinomas arising in patients with germline *BRCA1* or *2* mutations or cancers with somatic loss of BRCA function
PI3K/AKT pathway	Inhibition of proteins in the pathway	Activating mutations or pathway activation—not yet validated	>80% of breast cancers have alterations in this pathway Effectiveness of treatment not yet demonstrated
Immune checkpoint proteins	Blocking antibodies to PD-L1, PD-1, and other immune checkpoint proteins	IHC for immune checkpoint proteins—not yet validated	Under investigation in patients with triple-negative breast cancer

ER, Estrogen receptor; *HRR*, homologous recombination repair; *IHC*, immunohistochemistry; *ISH*, in situ hybridization.

Notes on the previous table ;

- *The various assay techniques for the identification of the tumour markers are shown in the table above, one if which is IHC(Immunohistochemistry).*
- *For Equivocal cases of her2 we do a better test which is known as ISH(In situ hybridization)*
- *The other tumor markers are not frequently identified for targeted therapy*
- *Nonetheless We also test for brca1 and brca2 but sometimes we can deduce the required information from the general morphology of the tumor and thus there is no need to specifically test for these tumor markers.*
- *Thus we mainly look at ER and HER 2*

Final notes;

- *Staging is very important for prognosis*
- *Untreated females die within 3-4 years so we must have periodic screening and if diagnosed we must initiate treatment promptly.*
- *80% of women who receive optimal treatment survive*
- *Early detection and easy access to optimal care are key factors*

The end of Breast cancer

Female genital tract pathology

The female genital tract consists of ;

- *Vulva*
- *Vagina*
- *Fallopian tube*
- *Cervix*
- *Ovaries*

Diseases of the Vulva;

The Vulva ; as we took in our anatomy lectures is part of the female external genitalia and is a Continuation of skin so it is covered by squamous epithelium .

- *Most diseases are inflammatory; tumors are very rare.*
- *Uncomfortable and annoying rather than serious*

Vulvitis:

- *Dermatitis, contact and allergic*
- *Infections: STDs such as HPV , most common cause of stds , males carry it and infect females (condyloma Accuminatum infection of vulva & VIN(vulvar intra epithelial neoplasia)); HSV, N. Gonorrhoea, Treponema pallidum. Candida (not STD) especially in diabetics and in people who take a lot of antibiotics*
- *Infection may obstruct glands and cause Bartholin cyst, may become large and painful and may form Bartholin cyst abscess which requires drainage and surgery*

Other non-neoplastic diseases of the VULVA;

LICHEN CHRNICUS	LICHEN SIMPLEX CHRONICUS
• Leukoplakia "white plaque" • Postmenopausal & prepuberty • Etiology: ?T cell, ? Autoimmune • 1-5% of symptomatic LS may develop HPV –ve SQ.C Carcinoma • Atrophic epithelium	• Leukoplakia "white plaque" • Chronic irritation, pruritis due to other inflammatory dermatoses • No increased risk for cancer • Hyperplastic epithelium

- *Both have white plaque formation we have to distinguish between them under the microscope since one of them increases the risk of squamous cell carcinoma of the vulva and the other does not.*

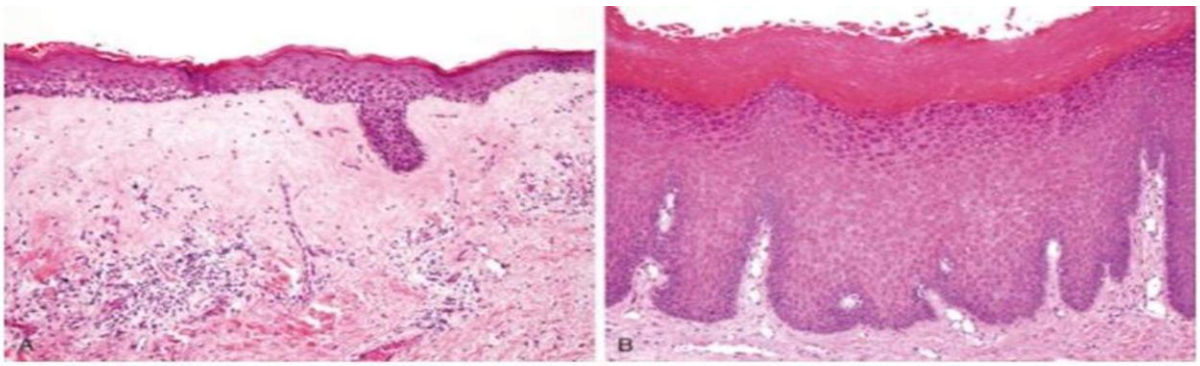


FIG. 19.1 Nonneoplastic vulvar epithelial disorders. (A) Lichen sclerosus. There is mark...

- *As you can see the lichens cholocus have atrophic epithelium and sclerosis-superficial dermal sclerosis -so it is sometimes called lichen cholochus sclerosis.*
- *The other one is clearly hyperplastic and thickened.*

Good luck