
In the name of God

HISTOPATHOLOGY of Therapy for Breast Carcinoma

FAKHRJOU. A
PROFESSOR OF PATHOLOGY
TABRIZ UNIVERSITY OF MEDICAL SIENCES
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Therapy for Breast Carcinoma

Therapy for breast carcinoma includes surgery, radiation therapy, hormonal therapy, chemotherapy, and targeted therapy, depending on the type and extent of the disease.

Surgical therapy:

Radical mastectomy, now includes a wide variety of options, such as partial mastectomy (lumpectomy, segmentectomy, or quadrantectomy, i.e., breast-conserving surgeries) and total (simple) mastectomy.

The procedure selected is influenced by many factors, including:

tumor stage, patient preference and breast size, the surgeon's practice, whether or not reconstructive surgery is available, and geographic region.

Radiation therapy is often employed as a postoperative adjunct (especially in more limited operations), as well as for control of locally recurrent disease.

Endocrine therapy is the standard of care for all patients with ER-positive breast cancer. At present, administration of a selective estrogen receptor modulator (SERM, e.g., tamoxifen) or an aromatase inhibitor in postmenopausal women (e.g., anastrazole) is the standard of care for early-stage, hormone receptor–positive breast carcinoma, usually combined with irradiation, with or without adjuvant chemotherapy, depending on the patient's age and other parameters. Hormonal therapy, which had historically included the options of bilateral oophorectomy, adrenalectomy, and hypophysectomy, is now largely dependent on the aforementioned antiestrogen drugs.

Microscopic evaluation of all surgical margins

In breast-conserving surgery and of the deep margin in mastectomy is critical to determining the need for additional surgery and/or radiation therapy. Anything else should be reported as a negative margin and the distance in millimeters reported. Distant metastases is related to the amount of carcinoma near the margins.

Margin width is also a factor influencing recurrence among

women with DCIS, particularly among those who forgo radiationtherapy. A recent meta-analysis indicates that a 2-mm margin is desirable for patients with DCIS.

There is no requirement to report the margin status for classical LCIS, though reporting of margin status is recommended for the variant forms of LCIS, such as pleomorphic LCIS.

Genetic Predisposition

Approximately 5%–10% of all breast cancers are familial. Two high-penetrance susceptibility genes which, when affected

by germline mutations, are associated with a high lifetime risk for

development of breast cancer, as well as some other cancers, in

particular ovarian cancer.

Originally, mutations in these genes were thought to be responsible for a high proportion of familial breast carcinomas, but they are now found to be responsible for only about 16% of them.

These are *BRCA1* and *BRCA2*

Mutations of these genes have been estimated that the risk for breast carcinoma among carriers is up to 70%–80% by the age of 70 years. The finding of a positive test for the mutation can lead to an agonizing decision on the part of the affected individual.

the main choices being close follow-up or bilateral prophylactic mastectomy.

Both *BRCA1* and *BRCA2* are essential for accurate repair of DNA double-strand breaks through homologous recombination. Loss of such function in the associated cancers has been exploited to develop novel therapies—for example, poly-adenosine diphosphate (ADP)-ribose polymerase (PARP) inhibitors which block repair of DNA damage via alternate pathways in tumor cells deficient in DNA repair through homologous recombination—a process that has been referred to as “synthetic lethality.

Analysis of breast carcinomas developing in carriers of *BRCA1* mutations has shown a higher percentage of tumors with the basal-like gene expression profile and that tend to be high grade, mitotically very active, with a syncytial growth pattern, pushing margins, confluent necrosis, negativity for hormone receptors and HER2 (“triple negative”), and associated with *TP53* mutation.

On the other hand, *BRCA2*-associated cancers are a heterogeneous group without specific morphology or phenotype and are commonly positive for hormone receptors.

In addition to *BRCA1* and *BRCA2*, several other genes (e.g., *CHEK2*, *CDH1*, *RAD50*, and *PALB2*) confer a low to moderate increased risk for the development of breast cancer. Hereditary breast cancer can also occur in the setting of multiple cancer syndromes, such as Lynch syndrome (e.g., *MLH1*), Li–Fraumeni syndrome *(TP53)*, ataxia–telangiectasia syndrome *(ATM)*, and Cowden syndrome *(PTEN)*.

Molecular Studies have shown clonality in the epithelial and metaplastic elements, For example, low-grade adenosquamous carcinoma has been found to frequently have *PIK3CA* mutations while they lack the *TP53* mutations commonly identified in other MC. *TP53* mutations have been found across non-metaplastic triple-negative breast cancer (TNBC) and MC other than low-grade adenosquamous carcinoma. *TERT* promoter mutations were identified more commonly in spindle cell carcinoma and squamous cell carcinoma but were not found in those cases with chondroid differentiation.

WNT pathway mutations have been found more commonly in MC than in non-metaplastic TNBC. From these studies, it appears that metaplastic carcinoma is distinct from TNBC and that different metaplastic morphologies may have differing genetic alterations.

Phyllodes

MED12 are present in about 70–80 % of phyllodes tumors. Some studies show a similar frequency in all grades, but others found a lower frequency in malignant phyllodes tumors. MED12 mutations are also common in fibroadenomas, particularly those with an intracanalicular growth pattern. The MED12 mutations in both (0–7 %).

Lobular Carcinoma

There was no specific genomic pattern that distinguished PALCIS from PLCIS and/or classical LCIS. However, some molecular changes occurred or were more prevalent in PALCIS, including amplifi cation of 17q11.2–17q12 (HER2 gene region), amplification of 11q13.3 (cyclin D1 gene region), gain of 16p, and losses of 3q, 11q, 13q, and 17p.

Effects of Therapy on the Tumor and on Normal Breast

Radiation therapy:

In the neoplastic breast;

Bizarre nuclear changes, formation of giant tumor cells, naked nuclei, and abnormal mitotic figures. Mucinous changes and Extensive tumor necrosis may develop, which can become surrounded by a thick fibrous wall.

In the non-neoplastic breast;

Atypia of epithelial cells in the terminal ductules.

Lobular sclerosis.

Atrophy.

(These postradiation changes can persist for years)

Endocrine therapy

1/ Prominent stromal fibrosis and hyalinization.

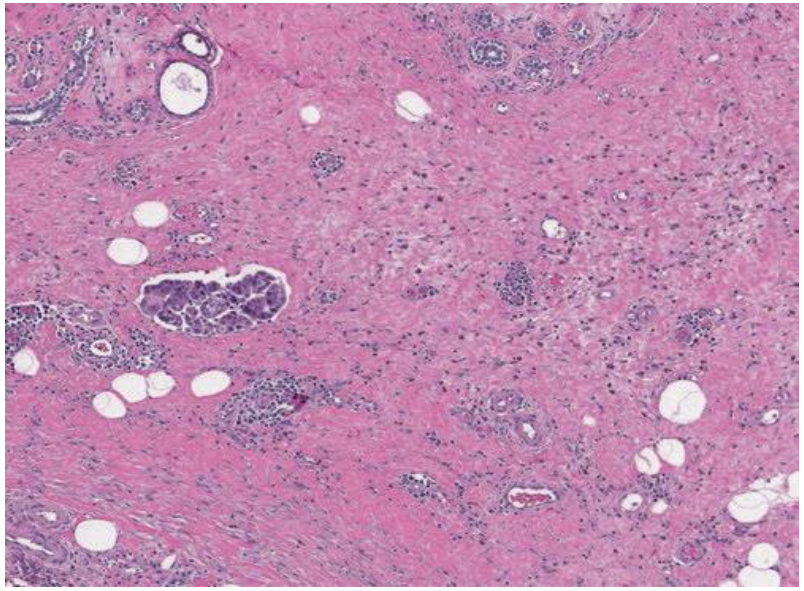
2/ Increase in the amount of elastic tissue.

3/ Degenerative changes in the tumor cells and eventual necrosis. These changes may occur both in the primary tumor and in the metastases.

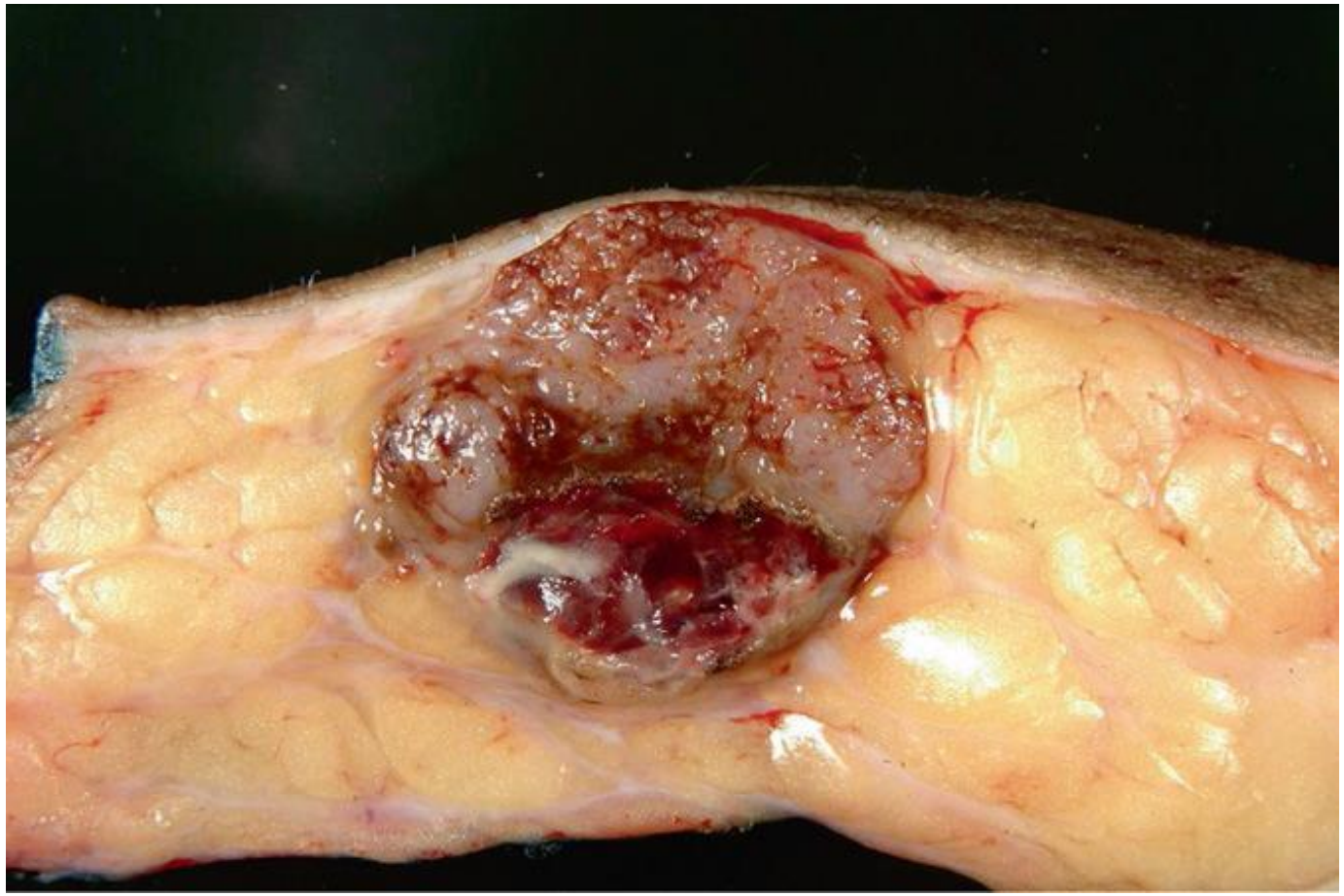
Chemotherapy can also induce striking morphologic changes in

the tumor cells, including such a degree of vacuolization as to simulate histiocytes. It also results in atrophy of the TDLU, with occasional atypia of the normal epithelial cells. In most instances, treatment with neoadjuvant chemotherapy does not affect the histologic grading of the carcinoma; however, in some cases.

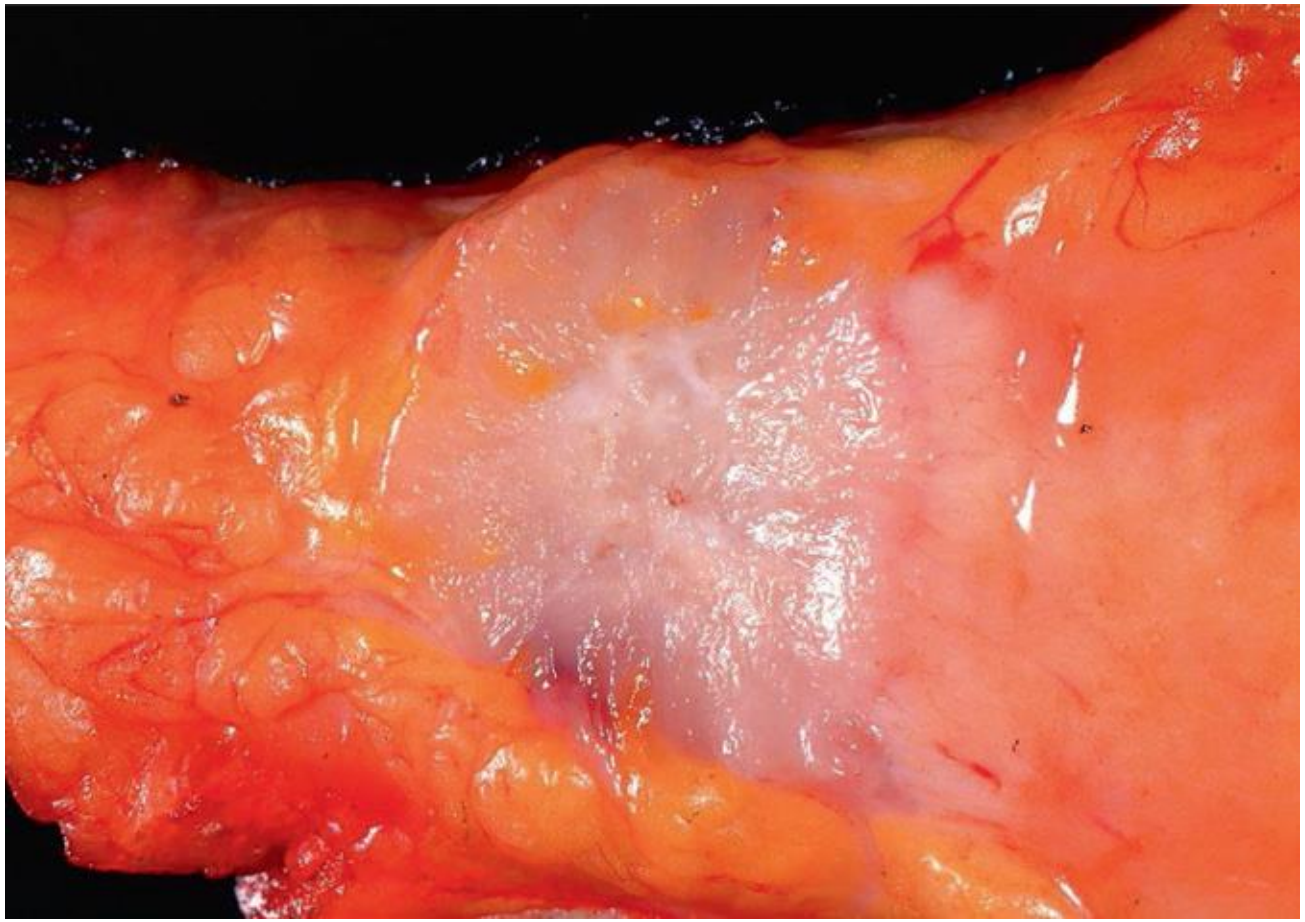
The tumor may appear to be higher grade (due to greater nuclear pleomorphism) or even lower grade (due to the identification of fewer mitoses). The microscopic features of the treated tumor correlate poorly with patient outcome. In some cases the residual tumor is present exclusively or predominantly as lymphatic emboli, a prognostically unfavorable feature.



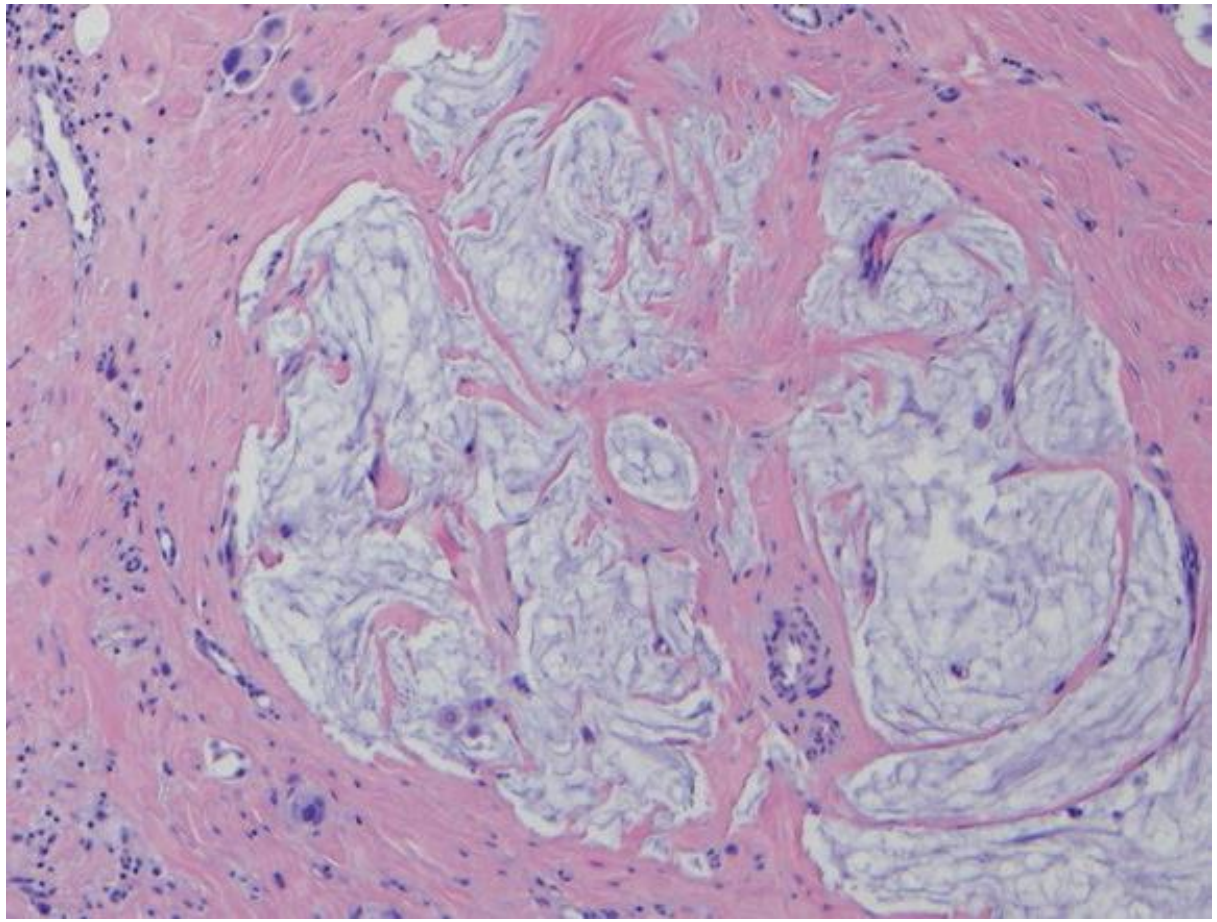
Necrosis after neoadjuvant



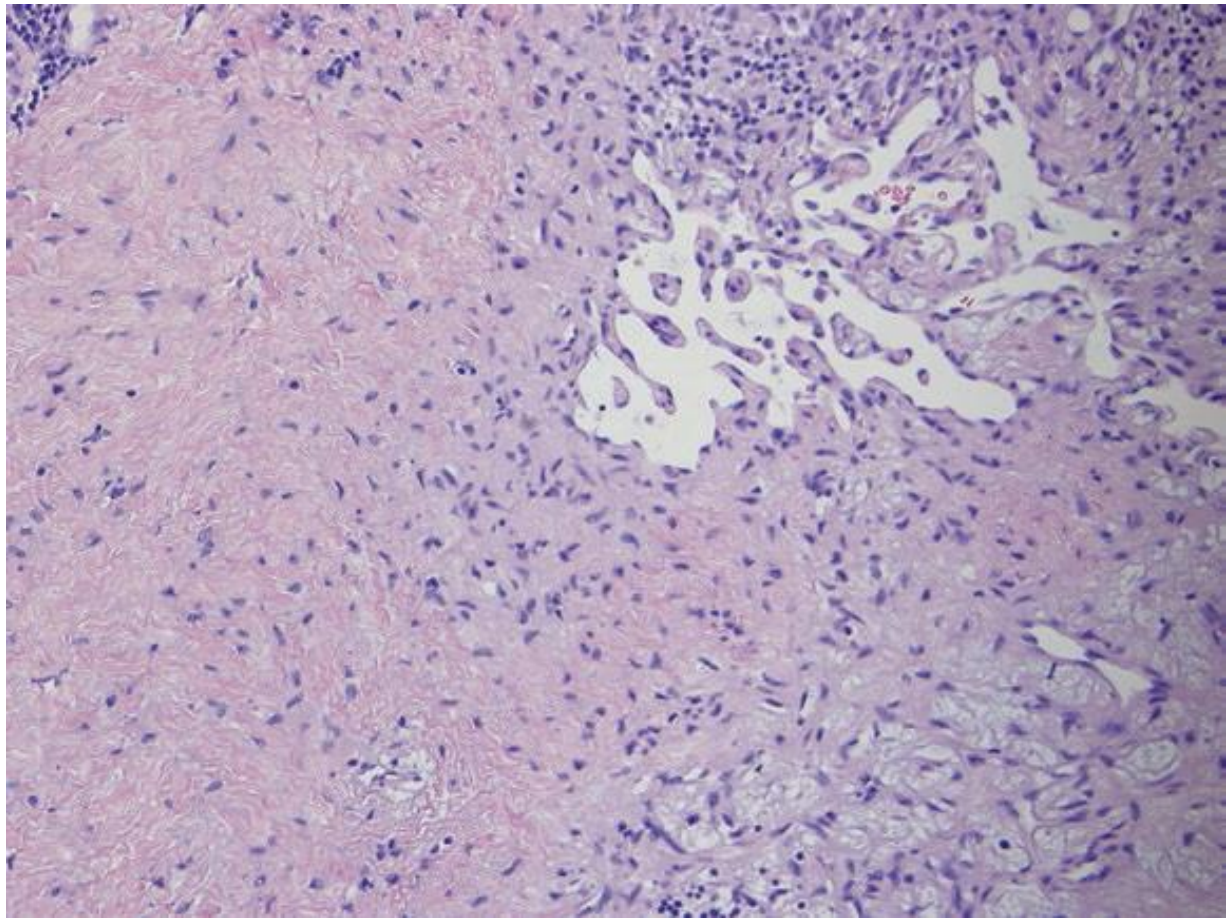
Fibrosis after neoadjuvant



Mucinous changes after neoadjuvant



Epithelial Atypia after neoadjuvant



Histologic Evaluation of Lymph Nodes After Neoadjuvant Therapy

Neoadjuvant therapy affects nodal metastases in a similar manner as the primary tumour. Lymph node metastases may completely disappear after therapy and may show a partial response or complete.

Similar to non-treated breast cancer, the number of positive lymph nodes after therapy is one of the most important prognostic parameters.

Classification of neoadjuvant-treated breast cancers

There are a variety of classification schemes in use to score the degree of tumor response with the 2 best known being the Residual Cancer Burden score and the Miller-Payne grade.

Residual Cancer Burden (RCB) CATEGORY DEFINITION

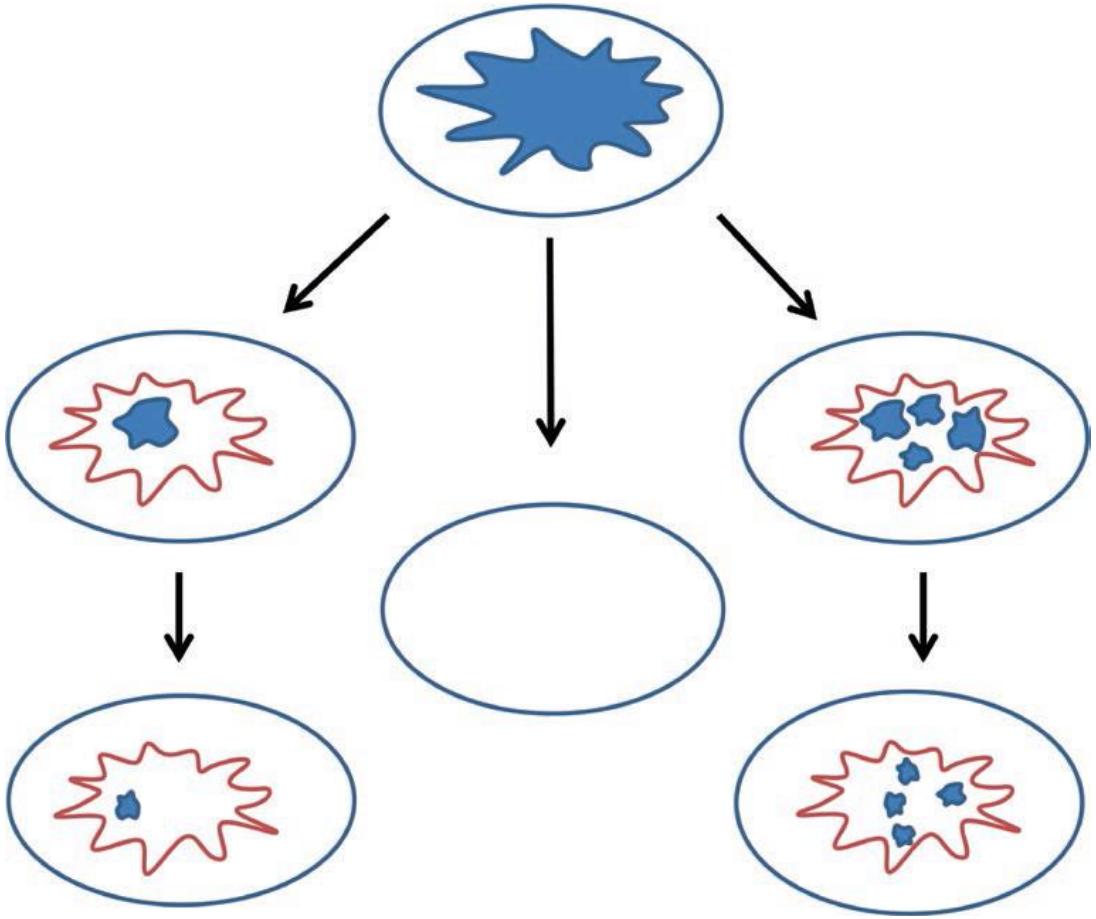
RCB-0 (PCR) No carcinoma in breast or lymph nodes

RCB-I Partial response(mild)

RCB-II Partial response(moderate)

RCB-III Chemoresistant

Patterns of response to neoadjuvant therapy



Histologic Categorisation of Response to Therapy

A number of different classification systems to categorise response to neoadjuvant systemic therapies have been proposed

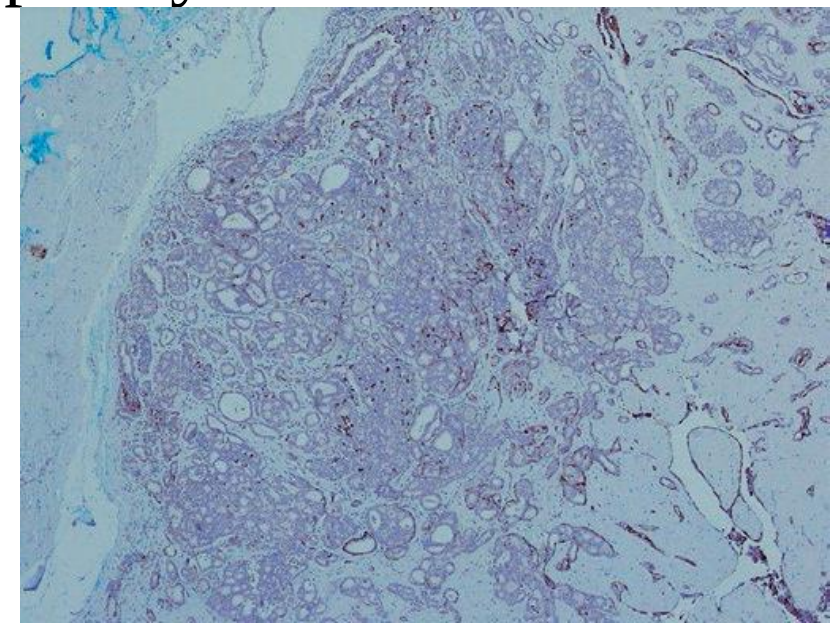
All of these systems recognise two categories:

1/ Complete pathologic response

2/ No response to therapy.

Solid Papillary Carcinoma

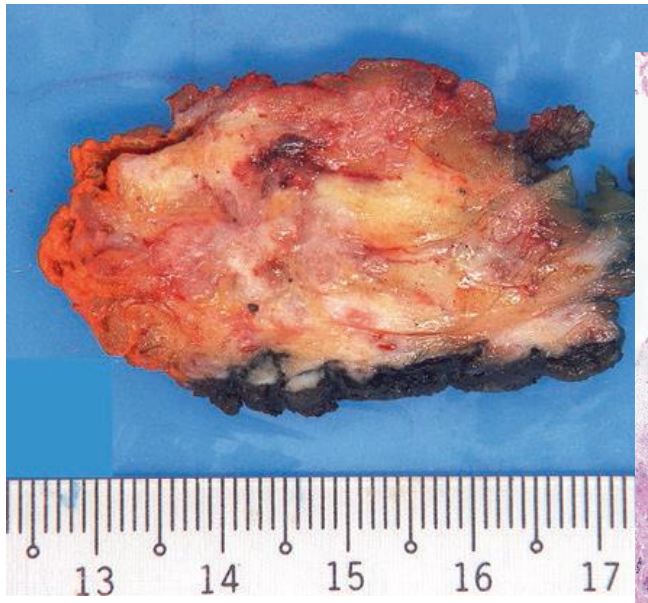
This is a malignant tumour consisting of multinodular, expansile solid epithelial masses whose underlying papillary architecture is subtlety reflected by fine delicate vessels coursing through the cellular islands. Myoepithelial cells may be present, attenuated, or completely absent around fibrotic tissue.

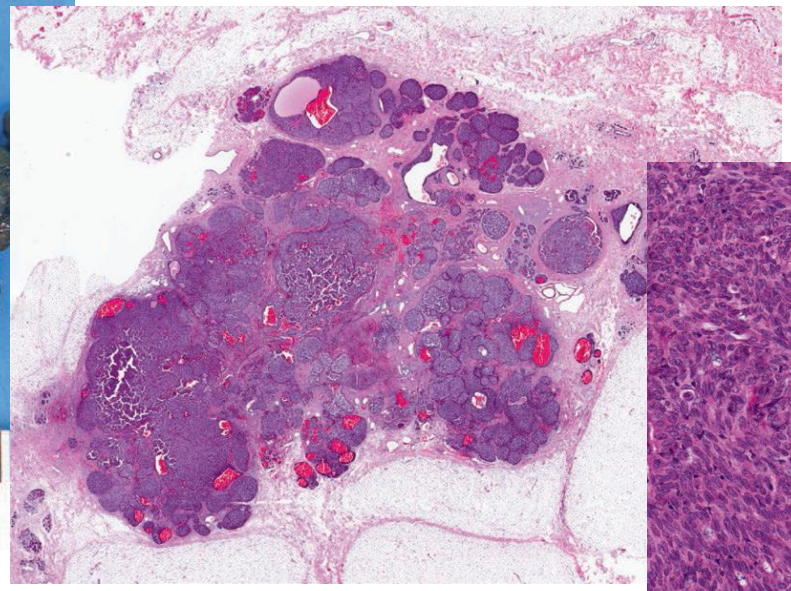


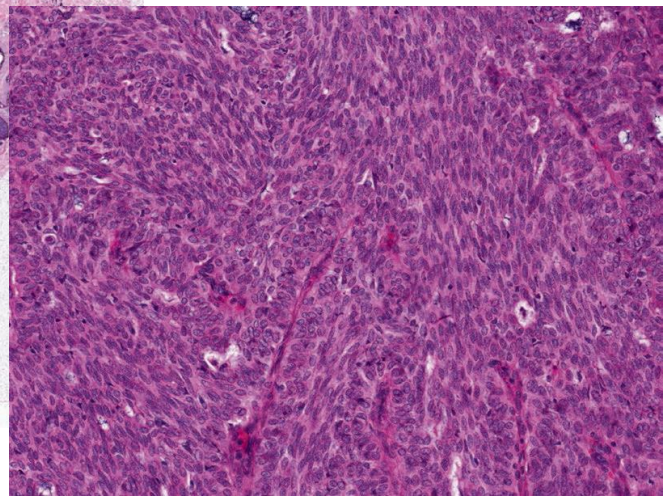
Pathologic Features

Macroscopic Pathology

Solid papillary carcinoma appears grossly as multinodular lobulated soft-to-firm masses. Tumours with mucin production may show a glistening cut surface .







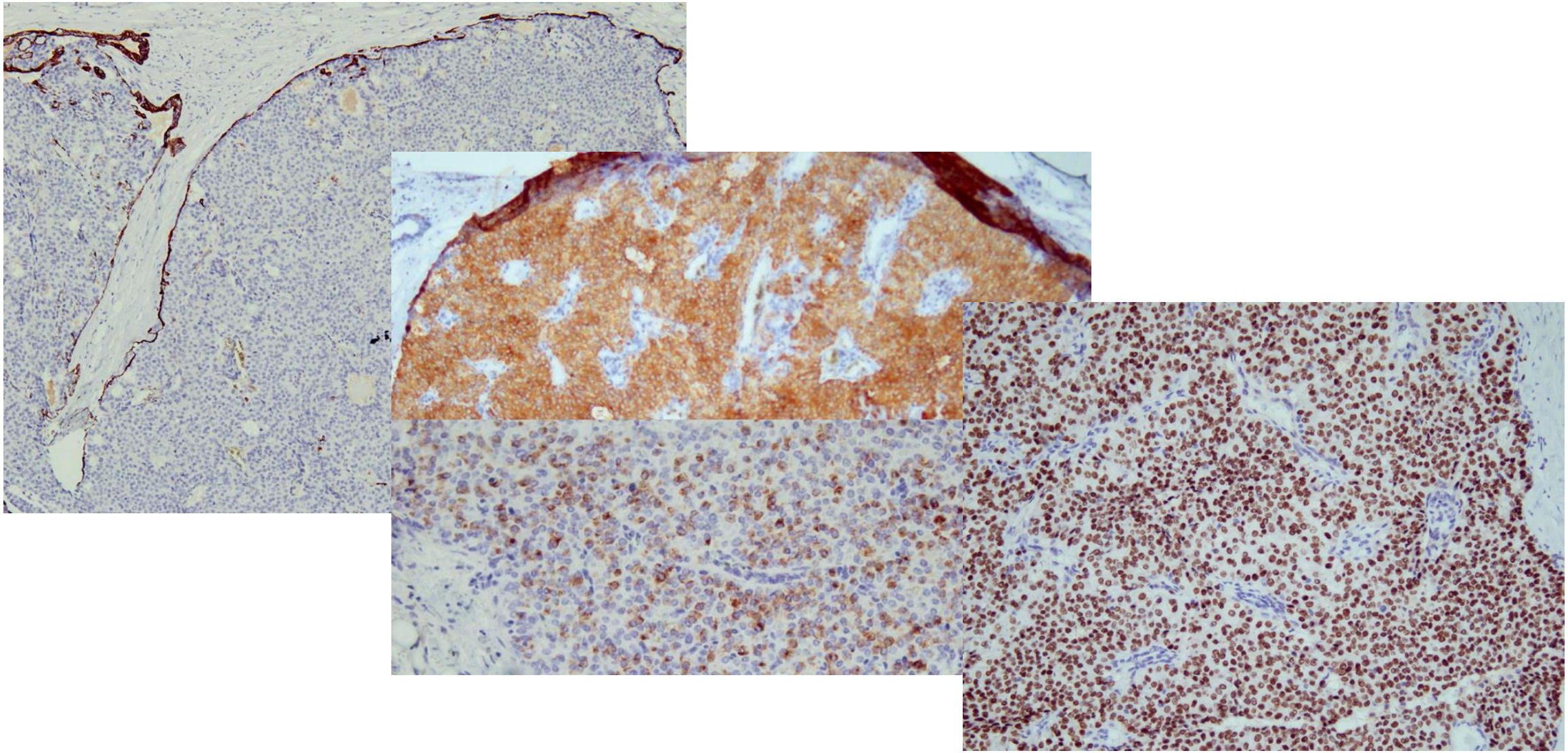
Prognosis and Therapy Considerations

Solid papillary carcinoma without areas of conventional

invasive carcinoma is currently staged and managed as non-invasive

disease (Tis), despite occasional absence of myoepithelial cells and rare reports of metastases to axillary lymph nodes .Prognosis after excision is generally favourable.

The presence of a solid papillary carcinoma pattern is associated with favourable clinicopathological parameters when evaluated among breast cancers with neuroendocrine differentiation.



Encapsulated Papillary Carcinoma

Macroscopic Pathology:

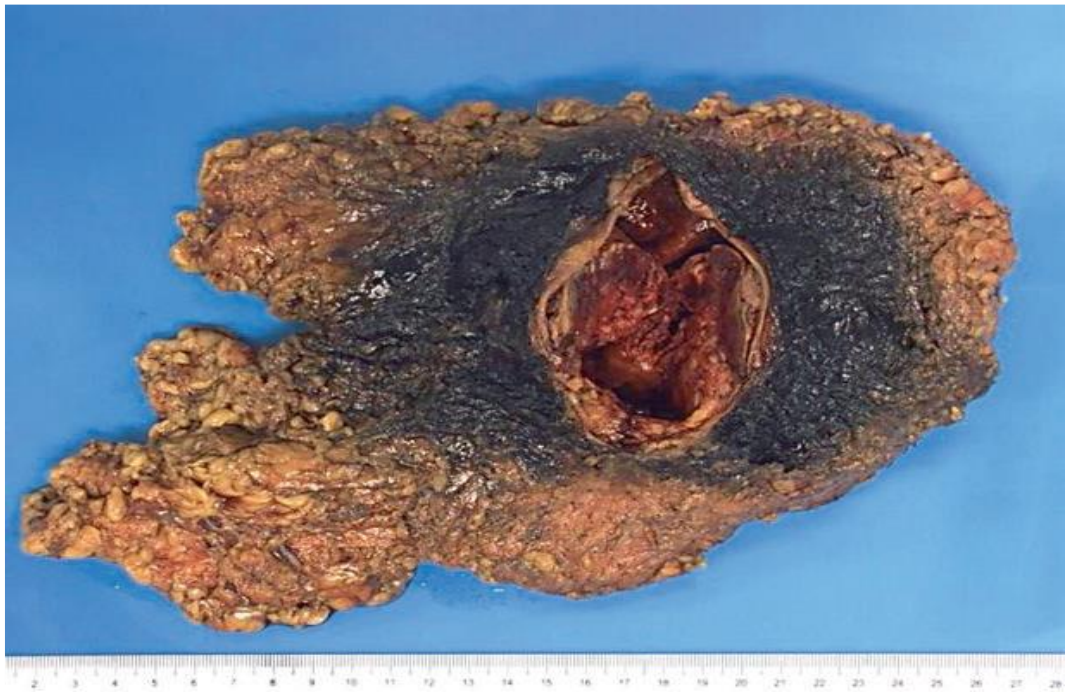
Encapsulated papillary carcinoma appears grossly as a circumscribed solid or solid–cystic mass. It may occur as a mural fleshy nodule within a dilated cystic space.

Microscopic Pathology:

The malignant papillae of both papillary DCIS and the encapsulated papillary carcinoma are similar. However, the encapsulated papillary carcinoma usually shows mass like distension of the duct surrounded by a fibrous wall, while papillary DCIS extends along the duct without excessive distension. Apart from absent-to-diminished myoepithelial cells within the papillae, myoepithelial cells are also nearly always absent at the periphery of the encapsulated papillary carcinoma, but present in papillary DCIS.

An encapsulated papillary carcinoma is a malignant papillary tumour that forms a circumscribed mass with a fibrous capsule.

Myoepithelial cells are invariably absent in the fibrous wall. It is also referred to as encysted papillary carcinoma.



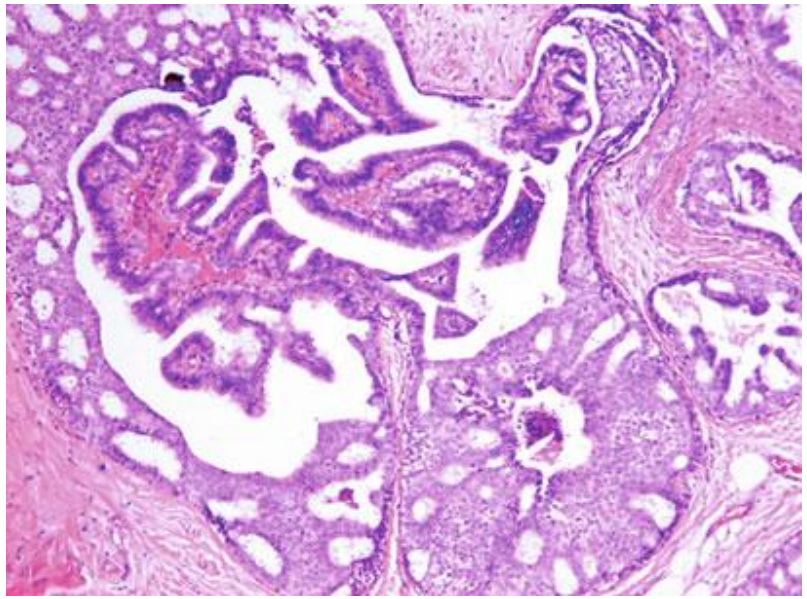
Ductal Carcinoma In Situ

Despite the name, most DCIS is generally considered to arise from the junction of the terminal duct and the lobular units. Typically, however, it then extends within the duct system.

Interestingly, unlike some other precursor lesions at other sites, DCIS is in the vast majority of cases, a unicentric proliferation of epithelial cells within a single duct system.

DICS should not be misinterpreted as multifocal because it is not seen contiguously in two-dimensional histological sections and it is important that pathologists understand the breast duct distribution and anatomy.

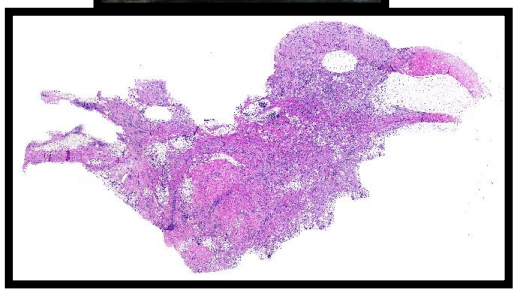
Low-grade ductal carcinoma within a Papilloma.
An architecturally atypical (largely cribriform) low-grade epithelial proliferation is seen contained within this expanded space. Centrally, wide fibrovascular cores with overlying columnar-shaped epithelium are seen as part of the pre-existing papilloma. The extent of the atypical proliferation was more than 3 mm, and this was therefore regarded as low-grade DCIS in a papilloma

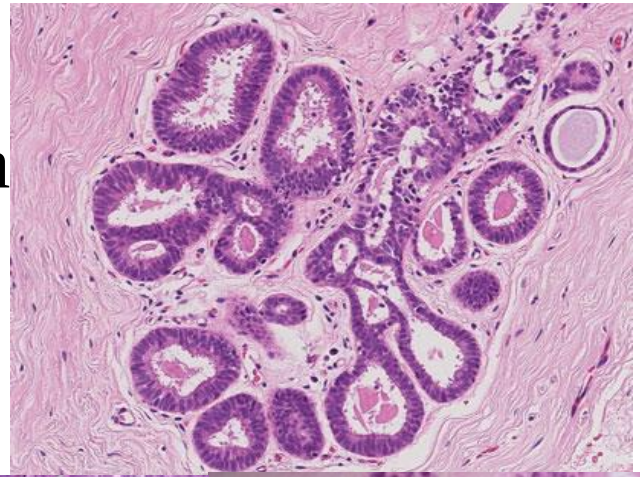


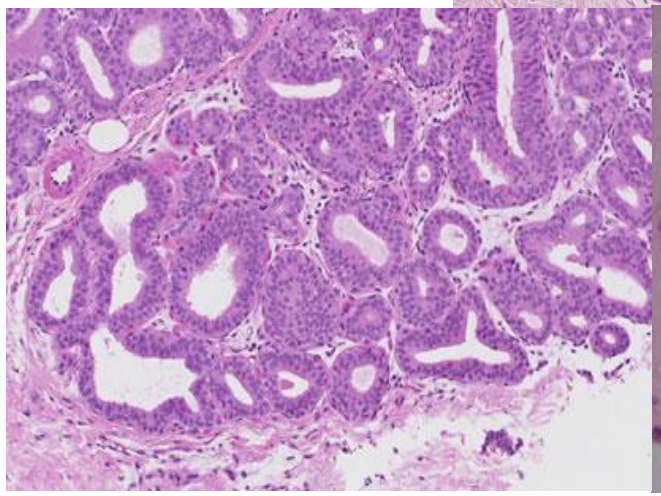
Columnar Cell Lesions

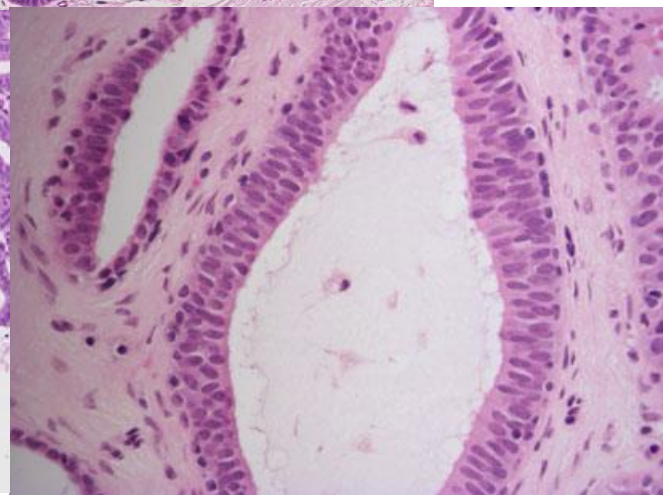
Columnar cell change

- Columnar Cell Hyperplasia
- Flat Epithelial Atypia

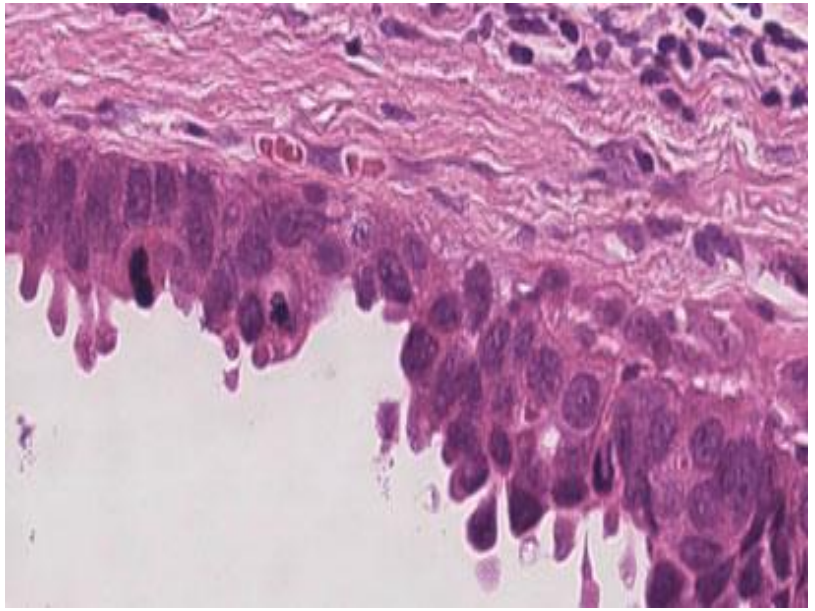






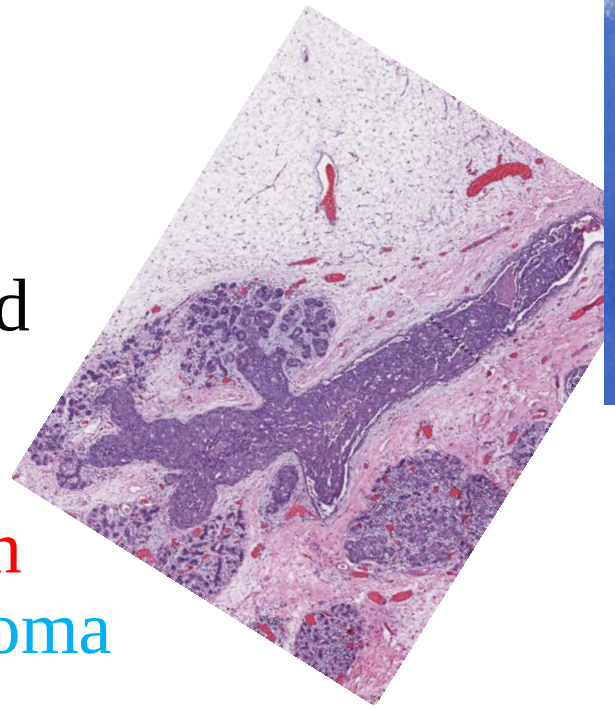


Flat Epithelial Atypia



If low-grade cytological atypia is seen lining the terminal duct lobular unit, the lesion is classified as flat epithelial atypia (FEA). On low power the terminal duct lobular unit may appear darker than other adjacent units, and there is sometimes an associated mild to moderate lymphoid cell population in the stroma. The cells in this process are cytologically akin to those of low-grade DCIS but are present in a fl at layer (one or more) lining mildly dilated acini.

ADH and DCIS with low nuclear grade and cribriform or micropapillary architectureoften arise in the background of CCH with atypia.
Tubular Carcinoma
and Columnar Cell lesions are also often associated with classical lobular Carcinoma insitu or Atypical Lobular Hyperplasia.



This Complex has been reffered to as the “ROSEN TRIAD”

Molecular Classification of Breast Carcinoma

Luminal breast cancers are enriched for ER-positive tumors divided into two subgroups based on the expression of proliferation- related genes

1/ Luminal A tumors are typically low grade with an excellent prognosis, characterized by ER and PR positivity and HER2 negativity,

with high expression of ER-related genes and low expression of proliferation-related genes.

2/ Luminal B tumors are higher grade, have a worse prognosis, and may be PR and ER negative and or HER2 positive with high expression of proliferation- related genes.

ER-negative tumors comprise biologically distinct entities with different drivers that can be divided into 3 main groups:

- HER2 enriched
- Basal-like
- Normal-like

Triple-Negative Breast Carcinoma

Triple-negative breast cancers have been subdivided into seven subgroups with different molecular drivers, variable clinical outcomes, and response to neoadjuvant chemotherapy. The groups include:

1/ The luminal androgen receptor group is characterized by high expression of androgen receptor and hormonally regulated pathways with similarities to the molecular apocrine group of breast cancers. They have a good prognosis and show a lower pathological complete response (PCR) rate following neoadjuvant chemotherapy (10 %), more akin to ER-positive tumors, and may potentially respond to antiandrogenic agents or PI3K inhibitors.

There are 2 basal-like subgroups:

2/ Enriched for genes involved in proliferation, DNA damage response (BL1) .

3/ Growth factor receptor signaling pathways (BL2).

The BL1 group shows high PCR rates following neoadjuvant chemotherapy (52 %), while the BL2 group shows poor response.

4/ The immune modulatory group is enriched for genes involved in immune cell processes such as B- and T-cell receptor signaling, cytokine signaling, and antigen presentation and shows overlap with the gene profile of medullary like cancers.

5/ Mesenchymal (M)

6/ Mesenchymal and Mesenchymal stem-like (MSL) groups show enrichment for genes involved in cell motility, cell differentiation,

growth signaling pathways, and extracellular matrix interactions. The MSL group shows low expression of proliferation- related genes and high expression of genes associated with stem cells lesions are most often missense mutations affecting codon 44. This suggests a biological continuum between these lesions similar to the histological continuum. Mutations in the TERT promotor are present in 50–60 % of phyllodes tumors and are much less common in fibroadenomas.

7/ Mesenchymal stem-like (MSL)

The last two groups were associated with worse 5-year distant metastasis-free survival (DMFS) consistent with upregulation of pathways involved in motility and metastasis.

The M group showed the poorest DMFS and overall survival (OS) following neoadjuvant chemotherapy.

Mutations are present in the stroma of these lesions and not in the adjacent breast tissue, so they are somatic mutations of the stroma. Mutations in known cancer driver genes such as TP53, RB1, NF1, ERBB4, and EGFR appear to be restricted to malignant and borderline phyllodes tumorsThese include LOH in 52 % of the cases at the p53 locus, 18 % at the ESR locus, 19–24 % at the HER2 locus, and 27–32 % at the BRCA1 locus and amplifi cations of c-myc and HER2 genes. These changes support the contention that PLCIS is related to classical LCIS, but probably represents an aggressive form of the disease.

Retesting of Tumor Markers Postneoadjuvant Therapy

Reassessment of hormone receptors and HER2 status post-neoadjuvant therapy is currently not routine in many centers. Several studies have compared ER, PR, and HER2 status pre- and post-neoadjuvant chemotherapy, and two metaanalyses of published series have reported discordance for ER in 13 and 18 %, PR in 32 and 26 %, and HER2 in 9 and 6 % of cases.


Together
We can find a cure
DR. FAKHRJOU


THANK YOU
DR. TAKHRJOU