CHAPTER
18 Breast Cancer

GENERAL CONSIDERATIONS

Histology

The breast is a modified sweat gland, composed of about 15 lobes, each associated with a major lactiferous duct terminating in the nipple. The functional unit of breast is the terminal duct lobular unit (Fig 18-1), lined by two distinct cell types, an inner or luminal (columnar epithelium) and an outer basilar myoepithelium (cuboidal or spindle). Luminal cells are immunoreactive to cytokeratin 8 and 18, whereas, basilar cells are reactive to high molecular weight cytokeratin 5/6 (P 18-1). Basilar cells are also positive for myoepithelial markers (Actin, p63, S-100, CD-10 and calponin). Stem cells are also present in basal location, and function to renew both myoepithelial and epithelial cells. Stem cells are difficult to identify by routine histology, and, so far, have no specific diagnostic markers. With pregnancy, the terminal duct lobular units change to functioning acini.

Breast tissue has two distinct stromas, namely: (a) a loose myxoid intralobular specialized stroma which is responsive to estrogen and (b) an ordinary interlobular stroma, rich in collagen, which is not hormone responsive. Ductal epithelium and myoepithelium are enclosed by a basement membrane (positive for type IV Collagen and laminin) separating them from the stroma. Since lymphatics and blood vessels are only present in the stroma, invasion of basement membrane by carcinoma is an essential step for the development of lymph node or distant hematogenous metastases

Incidence

Breast cancer ranks as the first malignancy affecting females, contributing 30% of all female cancers. It affects 1 in 14 women during their lifetime. Breast cancer is second only to lung cancer as a cause of cancer death in females, almost one of every three affected women will die of the disease. It is most common in USA and least common in Japan. The median age is 50 years, and the majority of patients (67%) in the West are postmenopausal. Female to male incidence is 50:1.

Etiology

The following 10 risk factors are related to breast cancer, emphasizing hormonal, genetic, and dietary factors:

1. Nulliparity.
2. Age > 30 years at first pregnancy.
3. Early menarche.
4. Late menopause.
5. Family history (mother or sister).
6. Past history of breast cancer.
7. High socioeconomic status.
8. Atypical ductal or lobular hyperplasia.
9. Ionizing irradiation.
10. Alcohol, dietary fat and obesity.

Approximately 5% of breast cancer are hereditary, affecting first-degree relatives, developing at a younger age, with bilateral tendency. A list of these syndromes is presented in (Table 18-1). Klinefelter syndrome predisposes to breast cancer in males.

Table 18-1 Syndromes Associated with Hereditary Breast Carcinomas

Syndrome	Gene and (Cytoband)
Breast Cancer-1	BRCA1 (17 q 21)
Breast Cancer-2	BRCA2 (13q 12.3)
Li-Fraumeni	TP 53 (17 p 13.1)
Louis-Bar	ATM (11 q 22.3)
Cowden	PTEN (10 q 23.3)
Peutz - Jeghers	STK11 (19 p 13.3)
Lynch	MSH2 (2 p 22)

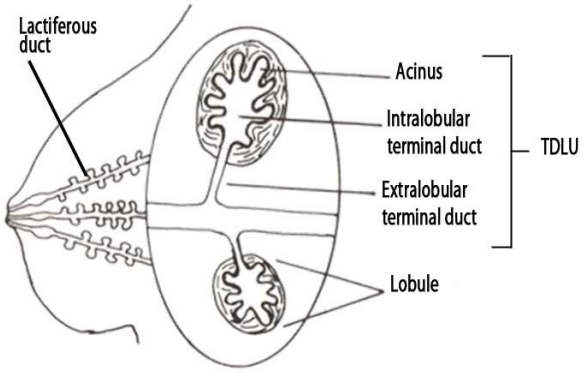

Fig 18-1 *Histology of normal mammary gland. The functional units are the terminal ductal lobular units (TDLU), which are arranged in lobules that drain in lactiferous ducts which open in the nipple.*

Mutations of tumor suppressor genes (BRCA – 1 and BRCA -2) are responsible for about 85% of hereditary breast cancer The protein product of these genes are responsible for repair of DNA double-strand breaks, hence, their mutation result in genomic instability. Females with such mutations have a lifetime risk of developing breast cancer of about 70% and ovarian cancer of about 30%. The management of patients with known BRCA mutation includes the following: (a) early age mammographic screening, (b) chemo-prevention by tamoxifen, and (c) prophylactic bilateral mastectomy and oophorectomy.

Li-Fraumeni hereditary syndrome is a germline mutation of TP53 tumor suppressor gene. Nearly all patients who survive childhood malignancy, will ultimately develop breast cancer in adulthood.

Atypical ductal and atypical lobular hyperplasia are the only precancerous lesions of fibrocystic disease. Patients with these lesions have a cancer risk of about 8% in 10 years (Dupont et al, 1993).

Molecular Oncogenesis

Breast carcinogenesis is not a unified stepwise genetic progression model (as colorectal carcinogenesis), but it is the result of accumulation of various genetic events that occur in a random order (a multihit random genetic progression model). For this reason, the profile of affected genes varies among different tumors. Cancer arises from adult stem cells (not mature cells). Cancer stem cells are pleuripotent and hence can differentiate along different cell lines according to the genes affected, giving rise to different histologic types of carcinomas.

The oncogenic mechanism is probably multifactorial, including the activation of oncogenes and the inactivation of tumor suppressor genes . This is accomplished by gene mutation or through epigenetic mechanisms, such as: cytosine methylation, chromatin remodeling or micro-RNA silencing of translation (chapter 6). The following are examples of genes involved in breast carcinogenesis:

1. Estrogen, a transcription factor: Estrogen plays a key role in breast carcinogenesis. By binding with its receptor (ER) and other associated proteins, it acts as a transcription factor for a variety of genes with proliferative function (C-myc, cyclin-D1, cyclin-E and cyclin-dependent kinase CDK-4), as well as, antiapoptotic function (BCL-2 and BAX), resulting in cell proliferation and survival.

2. TP53/BRCA and genomic instability: Inactivation of tumor suppressor genes is probably an early event. TP53 mutation is evident in 50% of cases and BRCA mutation in 5% of patients. There alterations are associated with deficiency of DNA repair with subsequent genomic instability.

3. RB, P16, PTEN and cell cycle control: RB and P16 are important of cell cycle at G1-S transition. RB is inactivated in 20% of breast cancer patients. PTEN is a phosphatase that inhibits the AKT/PI-3 signaling pathway. Inactivation of any of these control mechanisms will result in cell proliferation.

4. HER-2 and tyrosine kinase signaling: The oncogene HER-2/neu is a member of epidermal growth factor receptors family which can activate tyrosine kinase and this triggers the activation of two important signal transduction pathways namely: RAS/MAPK cell proliferation pathway and PI-3K/AKT cell proliferation and survival pathway. HER-2 overexpression is observed in about 20% of cases of breast cancer as a result of mutation.

5. Invasion-related genes: Loss of adhesion molecules E-cadherin and expression of collagenase leads to cell dissociation and invasion of basement membrane respectively. This is an early event leading to the conversion of carcinoma in situ into an invasive carcinoma.

6. Metastasis-related genes: Loss of metastasis suppressor gene (nm-23) and expression of vascular endothelial growth factor (VEGF) and Notch-1 are probably late events that lead to metastases.

Macroscopy

The outer breast hemisphere is more commonly affected (60%) than the inner hemisphere (20%) with about one half of cases arising in the upper outer quadrant (Fig 18-2). Bilaterality is observed in 4% of invasive duct carcinoma and 25% in invasive lobular carcinoma, often at different time intervals (metachronous). The gross appearance varies according to the histologic type and will be presented in the next section. In regard to tumor size, a *microcarcinoma* refers to an invasive carcinoma less than 1 mm, whereas, a *minimally invasive* carcinoma is 2-10 mm in size. The frequency of multiple tumors is 13% if careful study by whole organ serial sections is made. The multiple tumors include both invasive and noninvasive carcinomas. Two types of multiple tumors are recognized, namely: *multicentric and multifocal* (Fig 18-3).

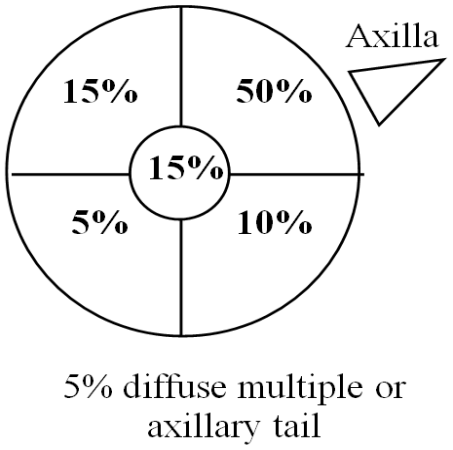

Fig 18-2 *Sites of origin of carcinoma in breast. The upper outer quadrant is the most common site (50%). In 5% of cases the tumors may be diffuse, multiple or arise from axillary tail of breast.*

Mammography

Mammography is a useful tool in both detection of breast carcinoma by screening population, and diagnosis of palpable tumors. Small impalpable tumors (1-2 mm) can be localized by guide-wire to the surgeon. Moreover, radiography of surgical specimens or paraffin blocks will assure that the tumor mass has been included in the excised specimen. The characteristic mammographic features of an invasive carcinoma is an irregular tentacular (stellate) mass lesion and associated micro-calcification (P 18-2). Mammographic lesions are reported following BIRADS categories (Table 18-2). Three mammographic patterns of carcinoma in situ are recognized, namely: microfocal, tumor-forming and diffuse (Fig 18-4). This anatomic distribution determines the extent of surgery (mastectomy for the diffuse pattern and conservation surgery for the other two patterns). Mammography is usually combined with other techniques, such as sonography and MRI. Ultrasound is particularly useful to identify tumors in a fibrotic breast, small tumors (<5 mm) and distinguish solid from cystic lesions. MRI is useful to detect tumor recurrence after conservation surgery, tumors in women with implants and evaluation of axillary lymph nodes.

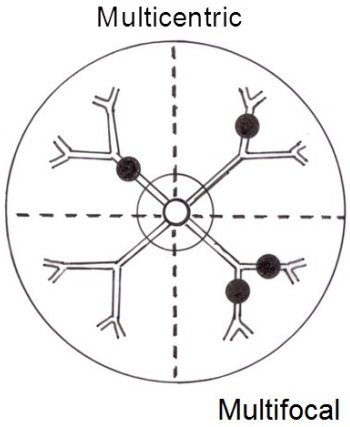

Fig 18-3 *The two types of multiple tumors. Multicentric represent two distinctive clones, affecting two different ducts which and are widely apart, whereas, multifocal tumors arise from a single clone and duct and hence are close to each other (distance < 0.5 cm) in a single breast quadrant.*

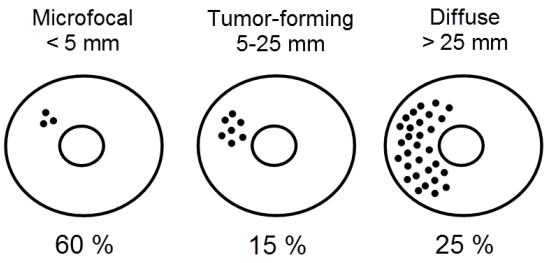

Fig 18-4 *Mamographic growth pattern of breast CIS*

Histopathology

Breast carcinoma includes a heterogeneous group of malignant tumors of variable natural history. It is customary to divide them into noninvasive (favorable) and invasive categories. (Table 18-3).

Table 18-2 BIRADS Categories of Mammographic Lesions and Corresponding Risk of Malignancy

Category	Risk %
1. No Findings	0
2. Benign findings	0
3. Probably benign findings	< 2
4. Probably malignant findings	30
5. Highly suspect findings	95

Abbreviations: BIRADS Breast Imaging Reporting of Data System, BIRADS 6 Malignancy is verified histologically prior to radiology.

Table 18-3 Histologic Classification of Breast Cancer

Non Invasive (5%)*	
DCIS	4%
LCIS	1%
Invasive (95%)	
Duct carcinoma (NOS)	70%
Lobular carcinoma	10%
Special types	9%
Tubular, Cribriform	
Adenoid cystic, Tubulolobular	
Mucinous, Papillary	
Secretory carcinoma	
Medullary	5%
Rare unfavorable	1%
Micropapillary, Metaplastic,	
Sarcomatoid, Clear cell type,	
Pleomorphic lobular	

*Recent frequency in western series is 22% in hospital series and 40% in mammography detected cases.

NONINVASIVE CARCINOMA (CIS)

Ductal Carcinoma in Situ (DCIS)

In the past, duct carcinoma in situ (DCIS) was a rare tumor (<1%), but, at present it represents about 22% of newly diagnosed cases and 40% of mammography-detected cases (Silberman, 2010). Most of the detected cases (95%) were nonpalpable and 80% showed microcalcification by mammography. Patients with a diagnosis of DCIS may have an associated invasive carcinoma in about 12% of cases, and if DCIS is left untreated, 30% of patients develop invasive carcinoma, generally within 10 years. In the past, mastectomy was the treatment of choice, but at present 72% of patients are treated with breast conservation.

Histologically, DCIS was originally classified into comedo and non-comedo types (Table 18-4) according to the architectural pattern (Lennington, 1994). The comedo carcinoma (P 18-3 and P 18-4) is the most common (40%) and most aggressive. The non-comedo (low grade) includes 4 subtypes, namely: solid, cribriform, papillary and micropapillary (P 18-5, P 18-6 and P 18-7).

In 1995, the Van Nuys group of University of Southern California introduced a new pathologic classification of three groups (Silberman, 2010) by considering nuclear grade as a better biologic predictor than architecture (Fig 18-5). In the high-risk (group 3), tumor cells have large nuclei, prominent nucleoli and generally show necrosis.

Table 18-4 Classification of DCIS of Breast

	Comedo	Non-Comedo
Nuclei	Large	Small
DNA content	Aneuploid	Diploid
Necrosis	Present	Absent
S-phase fraction	High	Low
HER-2 positive	77%	15%
Recurrence after local Excision (5 years)	20%	5%

(Lennington, 1994)

The necessity of postoperative radiotherapy for DCIS depends on several factors such as: tumor size, status of surgical margin, histologic grade and age of the patient (Table 18-5). These parameters are an integral part of Van Nuys prognostic index (VNPI). The current treatment guidelines after conservation surgery are as follows: patients with low index (4-6) there is no need of postoperative radiotherapy, intermediate index (7-9) needs radiotherapy, and high index (10-12) needs mastectomy (Table 18-6).

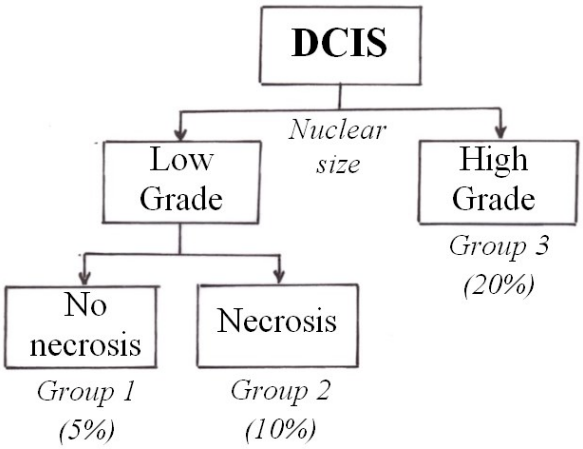

Fig 18-5 *The Van Nuys biologic classification of ductal carcinoma in situ (DCIS) of breast. It is based on nuclear size and necrosis and stratifies the cases into three groups with increasing malignancy. Percentages represent rates of local recurrence after conservation surgery.*

Table 18-5 The Van Nuys Prognostic Index (VNPI) Scoring System for Intraductal Breast Carcinoma

Parameter	Score		
	1	2	3
Tumor size (mm)	≤ 15	16-40	≥ 41
Margin (mm)	≥ 10	1-9	< 1
Pathologic Grade	1	2	3
Age	≥ 61	40-60	≤ 39

(Silberman, 2010)

Table 18-6 The Van Nuys Prognostic Index (VNPI) Categories as a Guideline For Postoperative Radiotherapy

VNPI	Total Score	Radiotherapy
Low	4-6	Unnecessary
Intermediate	7-9	Indicated
High	10-12	Ineffective

(Silberman, 2010)

Paget Disease

Most cases of Paget disease (70%) are typical intraduct carcinomas involving the main excretory ducts with infiltration of the epidermis of nipple and areola (P 18-8 and P 18-9). This subset of Paget disease is associated with excellent prognosis. But if the ductal component is invasive to the stroma (30%), the carcinoma will behave as conventional invasive duct carcinoma.

Lobular Carcinoma in Situ (LCIS)

LCIS is an incidental and uncommon lesion (1 % of breast biopsies). It is often multicentric (50%) and bilateral (40%). Histologically, the acini of the lobular unit are distended by uniform cells with obliteration of the lumen (P 18-10). Lobular carcinoma may extend to proximal ducts in pagetoid fashion. LCIS has low risk to progress into an invasive carcinoma, with an annual cumulative risk of 1% only, hence, prophylactic mastectomy is not justified. The developing invasive tumors are commonly ductal rather than lobular carcinomas.

Differential Diagnosis

Ductal carcinoma in situ (DCIS)

1. Usual ductal hyperplasia (UDH): The nuclei are small and normochromatic, lack of necrosis, cells are polymorphic (two cell types, epithelial and myoepilhelial, CK8/18+ and CK5/6+), apocrine metaplasia may be present, a streaming pattern (nuclei parallel to the lumen and overlapping each other) and ductal spaces variable in size and shape.

Conversely, DCIS is composed of only one cell type (luminal phenotype CK8/18+, CK5/6-), the nuclei may be small or large, non-overlapping, hyperchromatic may be arranged perpendicular to gland lumen or at random and ductal spaces are sharply-demarkated and regular in shape and size.

2. Atypical ductal hyperplasia (ADH): This problematic lesion shows some but not the full picture of DCIS (P 18-11). The diagnostic criteria

are not precisely defined, but, helpful features include the following: (a) Cytologic features of CIS is present (hyperchromatic nuclei) but architectural pattern is lacking (gland lumens, variable in size and shape (b) Cytologic criteria of CIS are of limited extent (< 2 mm or involving only one or two ducts), (c) a mixture of benign and malignant cells and (d) Columnar cell change.

In practice, there is a great risk of underestimating the dangers of ADH. Thus, 50% of atypical ductal hyperplasia diagnosed on core biopsy were upgraded to DCIS or invasive carcinoma after excision biopsy. Moreover, the biology of ADH is closely similar to that of low grade DCIS, with about 8% risk of progression to invasive carcinoma if left untreated. For these reasons, lumpectomy is advisable for ADH, combined with careful follow up to ovoid missing more serious tumors.

Lobular Carcinoma in Situ (LCIS)

1. Atypical lobular hyperplasia (ALH): This lesion differs from lobular carcinoma by the following three features (a) the terminal duct lobular units are filled, but not distended, by the hyperplastic epithelium, (b) some residual lumens are evident in most ducts and (c) no associated carcerization of large ducts.

2. Cancerization of lobules by invasive duct carcinoma. This is distinguished from lobular carcinoma in situ by large size of malignant cells, pleomorphic shape and E-Cadherin positivity.

INVASIVE CARCINOMAS

1. Invasive duct carcinoma (IDC) is the most common (70%) and rather aggressive tumor. Grossly, it appears as a firm (scirrhous) tumor, whitish gray in color with irregular stellate shape (P 18-12). Histologically, it is composed of a pleomorphic cell population with central nuclei and evidence of ductal differentiation (P 18-13). It is usually graded into 3 grades according to: tubule formation, anaplasia and mitosis (Lakhani et al, 2012). The relative frequency of grades in Western series is: Grade I (18%), Grade II (37%) and Grade III (45%). Lymphatic invasion by tumor is found in 10% of node negative patients and is a prediction of recurrence and metastatic spread. Invasive duct carcinoma associated with extensive intraduct component (CIS), comprising at least 25% of tumor area, is associated with high risk of local recurrence (24% in 5 years) after conservation surgery especially in premenopausal women. This combination is encountered in about 15% of IDC either within the tumor or in adjacent breast tissue, and in spite of recurrence, may offer a better long-term survival.

2. Invasive lobular carcinoma (ILC) constitutes 10% of breast carcinomas and is characterized by the high risk of bilaterality (25%) and equals in aggression to IDC. Grossly, it presents as an indistinct mass with fine multifocal areas of induration (P 18-14). ILC is classified into classical (75%) and variant subtypes, including: solid, alveolar, pleomorphic and mixed. The cells of lobular carcinoma are small, uniform, with eccentric nuclei and scanty vacuolated cytoplasm. The classic type shows a characteristic single cell pattern of invasion (Indian file) or concentric pattern of invasion around ducts and vessels (targetoid pattern) (P 18-15). A mixed lobular-ductal carcinoma is encountered in about 5% of cases of breast cancer, and are best classified according to the predominant cell component.

3. Special types: the following 7 subtypes of invasive breast carcinomas are associated with a favorable prognosis provided they represent >90% of tumor area (Table 18-3). They are usually not graded.

a. Tubular carcinoma: It is composed of oval tubules with pointed ends (tear drop), and dense stroma (P 18-16).

b. Cribriform carcinoma: It is composed of solid groups with multiple glandular lumens.

c. Mucinous carcinoma: is characterized by abundant secretion of mucin in the stroma (P 18-17).

d. Papillary carcinoma: may be macropapillary, intraductal or intrcystic (P 18-18).

e. Adenoid cystic: The solid areas of tumor contain cylinders filled with stromal material (P 18-19).

f. Tubulolobular carcinoma: It is a mixed tumor of tubular carcinoma and classic lobular carcinoma with immunophenotypic features of both.

g. Secretory juvenile carcinoma: A rare carcinoma (0.2%) affecting children. Histologically it shows secretory product in the cytoplasm and ductal lumen. The prognosis is most favorable.

Medullary Carcinoma

This subtype contributes about 5% of all breast cancers and is particularly common in patients with BRCA-1 mutation. It was previously classified as a

favorable carcinoma, but at present considered of intermediate malignancy (10-year survival about 70%). The WHO classification (Tavassoli and Devilee, 2003) lists five criteria that must be fulfilled for the diagnosis: (a) solid or syncytial architecture (b) absent ductal structures (c) dense lymphoplasmacytic infiltrate in the stroma, (d) nuclear pleomorphism and active mitosis and (e) circumscribed tumor margin (P 18-20). In the past, medullary carcinoma lacking lymphocytic infiltrate in the stroma were called atypical medullary (P 18-21). Such tumors, in view of their aggressive behavior, should be classified as grade 3 invasive duct carcinoma.

Unfavorable Histologic Types

1. Micropapillary carcinoma: It comprises about 2% of all invasive breast carcinoma. Histologically, it shows small nests of malignant cells within well-defined empty spaces representing retraction artifacts (P 18-22 A)

2. Metaplastic carcinoma: It comprises about 1% of all invasive carcinomas. It is a duct carcinoma which may exhibit squamous metaplasia (P 18-22 B) or mesenchymal differentiation (vimentin positive spindle cells, osseous or cartilaginous cells). Tumors which show both epithelial and mesenclymal differentiation are considered *carcinosarcomas.*

3. Undifferentiated sarcomatoid carcinoma: It is compased of cytokeration (CK+) spindle cells.

4. Clear cell carcinoma.

5. Pleomorphic lobular carcinoma.

Differential Diagnosis

1. Sclerosing lesions: Sclerosing adenosis (P 18-23) and radial scar (P 18-24) may simulate malignancy due to irregularity of glands and associated fibrosis but these lesions are distinguished from invasive duct carcinoma by the presence of myoepithelial cells well-demonstrated by markers (S-100). Radial scars are small (<10 mm) impalpable stellate lesions usually detected by mammography and can not be distinguished from carcinoma by mammography or grossly. It is noteworthy that about 8% of radial scars are associated with carcinoma in situ or invasive carcinoma in the breast.

2. Microglandular adenosis:: This lesion lacks myoepithelial cell and may show pseudoinvasion, but, it is characterized by very small size of ducts and uniform small (bland) nuclei (P 18-25).

3. Tubular adenoma: This is distinguished from carcinoma by its well-defined margins, preserved lobular pattern and intact myoepithelium (P 18-26).

4. Benign papillary lesion: Intraduct papillomas (P 18-27) and healing retroareolar duct papilloma (P 18-28) may be misdiagnosed as papillary carcinoma. However, benign papillary lesions have intact myoepithelial cells.

IMMUNOHISTOCHEMISTRY

Diagnostic Markers

1. E-Cadherin : help to distinguish lobular carcinoma (E-cadherin-ve) from duct carcinoma (E-Cadherin + ve)

2. Cytokeratins: This can help to identify luminal type of carcinomas (CK-7, CK-8, CK-18. and CK-19 positive) from basal cell type carcinomas (CK5/6, CK -14 and CK-17 positive).

3. Myoepithelial markers: help to distinguish benign sclerosing and papillary lesions (positive) from malignant tumors (negative).

4. CD-34 endothelial marker: This can help to distinguish angioinvasion (positive) from retraction artifacts around invasive carcinomas (negative).

Predictive and Prognostic Markers

A *predictive marker* is that which predicts the response of a given tumor to a specific therapy, hence, can help to select a given patient to an appropriate treatment. Conversely, a *prognostic marker* foretells the outcome of therapy as measured by survival. Hormone receptors studies (ER and PR), HER-2/neu and Ki-67 proliferation index have both predictive and prognostic value.

Estrogen (ER) and Progesterone Receptors (PR)

Immunohistochemistry is the standard method for determining ER and PR status of the tumor. Estrogen receptors exist in two isoforms: α and β, and current testing is performed on the ERα receptor only (P 18-29). Immunoreactivity is usually reported according to the percentage of stained nuclei, as well as, the intensity of staining, and a wide range of cutoffs (5% or 10%) have been employed in the past by different laboratories. Recently (ASCO, 2010) it is recommended to report hormone receptor evaluation as either positive or negative. Nuclear staining greater than 1% is considered positive. By applying this cutoff value, 75% of breast carcinomas express ER and 40% express PR.

The predictive value of hormone receptor expression is strong, but, the prognostic value is rather modest. Thus, the response rate to antiestrogen

therapy (Tamoxifen) is 80% when both ER and PR are positive, 40% when either is positive and only 10% when both receptors are negative. It is noteworthy that the favorable prognosis of patients with ER-positive tumors is lost after 10 years.

HER-2 Receptor

The oncogene human epidermal growth factor receptor 2 (HER-2) is amplified in 15-20% of breast carcinomas. HER-2 overexpression is associated with a more aggressive tumor phenotype, but more responsive to monoclonal targeted therapy (Herceptin). Currently, two methods are available to determine HER-2, namely: immunohistochemistry (IHC) as well as fluorescence in situ hybridization (FISH) and (CISH).

1. HER-2 immunohistochemistry: This is a semiquantitative method that identifies HER-2 receptors on cell surface using a 4 grade system: 0, 1+, 2+ and 3+ (P 18-30). Grade 0 and 1+ are considered negative, Grade 2 considered equivocal or inconclusive and Grade 3 (staining of >10% of cells) is regarded as over-expression or positive

2. HER-2 (FISH) analysis: This is a quantitative method measuring the number of copies of HER-2 gene present in each tumor cell. FISH result is considered positive if more than 6 gene copies are observed per nucleus, or a FISH ratio (gene signals to chromosome 17 signals) of more than 2.2. FISH method is more reproducible, but, time consuming and expensive. It is recommended to confirm equivocal results by immunohistochemistry (Grade. 2+ cases). At NCI Pathology Registry, HER-2 positive cases (scores 2 and 3) constituted 45% of cases (Mokhtar et al, 2007).

Patients with HER-2 positive tumors will benefit from adjuvant targeted therapy (Herceptin). This humanized anti-HER-2 monoclonal antibody reduces recurrence by 40% and mortality by 30%.

Ki-67 (MIB1)

This cell proliferation marker is expressed during all active phases of cell cycle. Its overexpression correlates with poor prognosis, but favorable response to chemotherapy. The optimal cutoff value of Ki-67 index for breast carcinoma is 15% labeled nuclei. Ki-67 analysis is valuable in a selected group breast cancer (Hormone receptors positive/HER-2 negative) to select these patients for specific adjuvant therapy (Table 18-7).

MOLECULAR CLASSIFICATION

This was first introduced by Perou et al (2000) and is based on the determination of gene expression profile of hormone receptors and HER-2, using microarray technology. This system classified breast carcinomas into four molecular subtypes, hence, it is useful to guide therapy (Table 18-7). However, this molecular classification has its limitations and

Table 18-7 Molecular Classification of Breast Carcinoma

Feature	Luminal A (50%)	Luminal B (20%)	HER-2+ (15%)	Basal-like 15%)
ER/PR	Positive	Positive	Mostly Negative	Negative
HER-2	Negative	Amplified in some*	Amplified	Negative
Other markers Positivity	CK 8/18	CK 8/18	Androgen receptor	CK 5/6 EGFR,Vimentin C-Kit
Proliferation rate (Ki 67 index)	Low	Intermediate	High	Very high
Recommended therapy	Hormonal	Hormonal and Chemotherapy	Herceptin and chemotherapy	Chemotherapy
Prognosis	Favorable	Unfavorable	Poor	Worst

(Perou et al, 2000) * Recently subclassified into two groups (Vodue et al., 2010) Positivity criteria: Hormone receptors >1% labeled cells, HER-2 score 3 and Ki-67 index >14%

drawbacks. Thus, some breast carcinomas do not fit into these subgroups. Moreover, the test is highly expensive and these molecular subgroups could be identified by less expensive routine methods such as (a) Immunohistochemistry and FISH for hormone receptors and HER-2, and (b) CK 5/6, EGFR, vimentin and C-Kit for basaloid carcinoma.

Modes of Spread

1. Local Spread

This is most marked in invasive lobular carcinoma which spreads >2 cm of its gross margin in 11% of cases. Nipple invasion occurs in 23-31% of retro-areolar carcinomas. In locally-advanced tumors, the skin or chest wall are infiltrated.

2. Lymphatic Spread

The regional lymph nodes of breast include 3 groups, namely: the axillary nodes, supraclavicular nodes and internal mammary group. About 97% of lymphatic flow drains into the axillary nodes (only 3% to internal mammary nodes).

The axillary lymph nodes are classified surgically into three levels in relation to pectoralis minor (Fig 18-7) and anatomically into 9 groups (Table 18-10 and P 18-31). The frequency of lymph node metastases is about 40-50% in western series, but a higher figure was reported in Egyptian patients, of 70.6% (Nouh et al, 2004). Level I group of lymph nodes contains most of the nodes of axilla and hence most of metastatic cancer burden. However, skip metastases may occur (Negative level I nodes and positive levels II or III) and the reported frequency was 3.7% in western series (Veronesi et al, 1989) and 8.4% in Egyptian series (Khafagy et al, 2011).

Table 18-8 The Three Levels of Axillary Lymph Nodes and their Corresponding Anatomic Nodal Groups

Surgical Level	Anatomic group
Level I	Pectoral (anterior) Subscapular (posterior)
Level II	Central Rotter (interpectoral)
Level III	Apical Subclavicular

N.B. Surgical levels are preferable

Two special modes of lymphatic spread need emphasis in view of their clinical importance, namely: (a) *inflammatory carcinoma*: This is the result of wide spread invasion of dermal lymphatics associated with inflammation and edema (P 18-32). This may be misdiagnosed as a skin disease (erysipelas), and (b) *Lymphovascular invasion* of lymphatics in the stroma of tumors (P 18-33). This feature is considered a high risk factor in node-negative patients which adversely affects prognosis.

The sentinel node: It is defined as the first lymph node in axilla which receives metastases, usually located by the surgeon after dye or radioactive injection in the tumor. If sentinel node is proved to be negative for metastases other axillary nodes are also invariably negative, hence, the patient can be spared axillary lymphadenectomy.

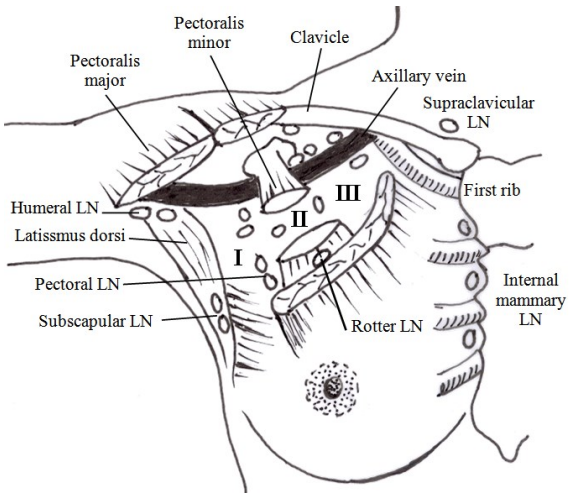

Fig 18-7 *The regional lymph nodes of breast includes: supraclavicular and internal mammary groups. Surgeons classify axillary lymph nodes into three levels (I, II, and III) according to the relation to pectoralis minor, whereas, anatomists classify them into several groups according to their location, most of them are not removed by the standard operation.*

3. Hematogenous Spread

Distant metastases are evident in about 10% of patients at initial presentation, and will ultimately kill 50% of patients with breast carcinoma. Common sites of metastases include: the bone, lung, pleura, liver, adrenal, ovary and brain.

4. Intraepithelial spread

This involve the epidermis of nipple (Paget disease) or affect large breast ducts or lobules (cancerization).

5. Implantation

This results from contamination of surgical wound of previous operation resulting in multiple local recurrences (seeding)

Theories of Spread

Three main theories were proposed:

1. Local disease model (Halsted, 1895): Breast cancer is considered a local disease, with axillary lymph nodes acting as a barrier of spread. Radical surgery will cure the patient.

2. Systemic model (Fisher, 1979): Breast cancer is considered a systemic disease from the start. Lymph nodes are inefficient barriers of systemic spread and may even act as a source of distant disease. Chemotherapy is essential to cure the patient.

3. An eclectic model (Hellman, 1994): This postulates that both previous models are operable in breast cancer spread. Thus, the disease is local at its initial phases, but ultimately progresses to a systemic disease at its late phases, hence, the importance of early detection and multimodality therapy.

Staging

Two classifications are available for staging, the *TNM* (Tables 18-9 and Table 18-10) and the SEER systems. The latter is based only on anatomic extent of the disease rather than tumor size. The *SEER system* classifies breast carcinoma into the following 4 groups: Stage 0 carcinoma in situ (CIS), stage I localized, tumor confined to breast, stage II regional spread by direct extension (skin, muscle or chest wall) or axillary or internal mammary lymph nodes, and stage III distant structures are involved e.g. contralateral breast, supraclavicular, or axillary nodes and distant metastases.

Table 18-9 Pathologic TNM Staging of Breast Carcinoma

Tumor (T)
- T0 No evidence of primary tumor
- TIS Carcinoma in situ
- T1 Tumor ≤ 2 cm (mi= <1 mm, a =1-5 mm, b =5-9 mm, c =9-20 mm)
- T2 Tumor 2-5 cm
- T3 Tumor > 5 cm
- T4 Extension to chest wall or skin, a=chest wall, b= skin nodules or ulceration c=both a and b, and d= inflammatory breast carcinoma

Regional lymph nodes (N)
- N0 No metastases
- N1 Metastases in 1-3 ipsilateral axillary (N1 mi = micrometastases)
- N2 Metastases in 4-9 axillary nodes
- N3 (a) >10 axillary nodes
  (b) metastases in internal mammary nodes
  (c) metastases in supraclavicular lymph nodes

Metastases (M)
- N0 No distant metastases
- M1 Distant metastases

(Lakhani et al, 2012)

Table 18-10 Descriptive Staging of Breast

Stage	Feature
0	Noninvasive ductal or lobular Carcinoma (DCIS, LCIS)
I	Small organ confined tumor <2 cm
II	Moderate size tumor (2-5) ± limited node involvement (1-3+ nodes)
III	Locally advanced: large tumors (> 5 cm) skin or chest invasion, massive axillary node affection (>3) or matted nodes, spread to ipsilateral internal mammary or supraclavicular, inflammatory breast cancer
IV	Distant metastases (nodal or organs)

Prognosis

The 10-year overall survival of breast carcinoma is still no more than 50%. There are two biological types of breast cancer, an indolent type (60% of cases) with an annual mortality of only 2.5%, and an aggressive type (40%) with an annual mortality of 25%. The current availability of effective chemotherapy for the worst prognostic groups have made prognostic factors mandatory to help select those patients who will actually benefit from such treatment (risk- adapted therapy).

The currently available *prognostic factors* in breast cancer are classified into established and potential prognostic factors (Table 18-11). Established factors are in current clinical use, but, the potential factors are still under investigation.

Table 18-11 Prognostic Factors in Breast Carcinoma

Established factors
Stage, lymph node metastases,
Tumor size, grade,
Nottingham prognostic index
Tumor type,
HER-2 amplification, Age
Angioinvasion (Selected patients)
Ki 67 (Selected patients)
Potential Factors
Growth fraction, ploidy,
Microarray gene expression
Invasion associated markers
Metastases associated markers
TP 53, Rb inactivation

Established Prognostic Factors

1. Tumor stage: the stage of the tumor is the most important prognostic indicator (Table 18-12). Thus, the overall 5-year survival for TNM stage I is 80%, for stage II 75%, for stage III 46%, and for stage IV only 13%.

2. Lymph node metastases in western series varies between 25% (USA) and 40% (France). Patients with positive axillary nodes have a 70% chance of ultimate relapse and fatal outcome. Accordingly, positive axillary lymph nodes is an indication of adjuvant chemotherapy. The prognosis is also affected by the number of positive nodes, with 10-year survival of 76% for negative nodes, 36% for 1-3 positive nodes and only 14% for 4 or more positive lymph nodes (Fisher, 1975).

3. Tumor size is an independent prognostic factor, evident in both LN-negative and LN-positive patients (Table 18-13). Thus, in node negative cases, the prognosis is adversely affected with in-crease in tumor size (the 10-year survival is 82% for tumors <2 cm, 65% tumors 2-5 cm and 44% for tumors >5 cm (Schottenfeld, 1976). About 30% of patients with negative nodes will die of metastases, hence, the need of identification and chemotherapy for that subset.

4. Tumor grade: This is also an independent prognostic factor. The 10-year survival is 90% for grade 1 tumors, 60% for grade 2 and 40% for grade 3.

Table 18-12 Prognosis in relation to stage of breast carcinoma

Stage	T	N	M	% 5-Year Survival
0	CIS	- ve	-ve	99
I	<5 m	- ve	- ve	98
	5-20 mm	- ve	- ve	87
II	2-5 cm	0-3	- ve	75
II	>5 cm	>3	- ve	46
V	Any size	any	+ ve	13

Table 18-13 The 5-year Survival and Tumor Size and Lymph Node Status

Lymph Nodes	Tumor Size (cm)	
	< 1	> 5
Negative	100%	81%
Positive	93%	63%

5. Nottingham Prognostic Index (NPI): This combines 3 factors: tumor size, grade and lymph node status. The index is the sum of these 3 separate scores: tumor size score (obtained by multiplying tumor size in cm by 0.2), Grade score (score 1 for grade 1, score 2 for grade 2 and score 3 for grade 3) and lymph node score (score 1 for negative node metastases, score 2 for 1-3 positive nodes and score 3 for more than 3 positive nodes. Originally NPI used to divide patients into 3 prognostic groups only (good, intermediate and poor prognostic groups). However, recently (Garden et al 2007) several confirmatory studies have led to a refined NPI with five categories (Table 18-16). Patients with score <3.4 have more then 90% 10-year survival.

6. Histologic type: Breast carcinomas are classified according to the survival of patients into: five groups (Table 18-17). The special types of invasive carcinomas include seven histologic subtypes (Fig 18-6). In a special type, the histologic features must be present homogeneously in more than 90% of tumor area. In the variant type, the special features are present in 75-90% of the tumor. In the nonspecial type (NST) tumor, the special features are less than 75% of the tumor and these are considered conventional invasive duct carcinoma not associated with any survival advantage (Fig 18-6).

7. HER-2 amplification: HER-2 over-expression is associated with unfavorable prognosis, and calls for adjuvant chemotherapy. It is a more important risk factor compared to hormone receptors.

Table 18-14 Updated Nottingham Prognostic Index (NPI) and 10-y Survival

Prognostic group	Index value	Survival%
Excellent	≤ 2.4	98
Good	≤ 3.4	90
Moderate I	≤ 4.4	83
Moderate II	< 5.4	75
Poor	> 5.4	47

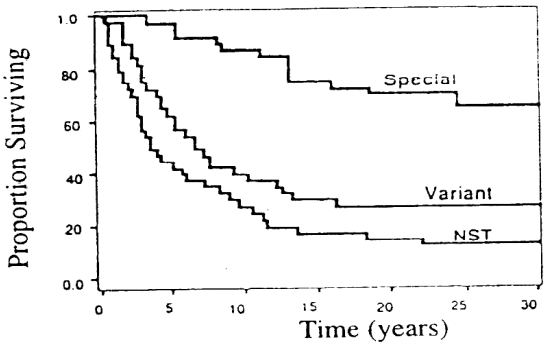

Fig 18-6 *Breast cancer histologic subgroups and survival. Three main subgroups are recognized with increasing malignancy, according to the frequency of favorable histology in tumor area. Special type favorable histology >90%, variant favorable histology 75-90%, NST conventional IDC (Dixon, 1985).*

Table 18-15 Prognosis of Breast Carcinoma in Relation to Histologic Type

Categories	Subtypes	10-year Survival %
Excellent	Noninvasive carcinomas	99
Favorable	Special types (Tubular, tubulo- lobular, cribriform, mucinous, papillary, adenoid cystic and secretory)	80-90
Intermediate	Classic lobular, medullary, mixed types	60-80
Poor	Invasive duct carcinoma (NST)	30-50
Worst	Micropapillary, metaplastic, sarcomatoid, clear cell type and pleomorphic lobular	10-30

8. Age: prognosis is unfavorable in young patients.

9. Angioinvasion: Histologic study of tumor stroma for evidence of lymphangioinvasion by carcinoma is an important prognostic factor in selected patients, namely: lymph node negative cases. Patients with angio-invasion will benefit from chemotherapy.

10. Ki-67 proliferation index: This is a useful risk factor in selected patients, namely: HER-2 negative cases. Ki-67 index value (>14%) will help to stratify patients to specific adjuvant therapies.

Potential Prognostic Factors

1. Growth fraction of tumor cells and ploidy analysis, determined by flow cytometry.

2. Microarray gene expression profile (breast cancer bioclassifiers) are under trial to predict prognosis but their routine use is not generally accepted.

3. Invasion associated markers (e.g. E-cadherin, cathepsin D, urokinase plasminogen activator and type IV collagenase).

4. Metastases-associated markers (e.g. loss of metastases suppressor gene nm23, exper-ession of angiogenic factors such as VEGF microvessel density and study of or lymph nodes).

5. Inactivation of tumor suppressor genes (e.g. p53 and Rb).

Prevention

Primary prevention: Chemoprevention in high-risk women (Tamoxifen).

Secondary prevention (early detection) by (a) monthly breast self examination from age 20 years, (b) annual periodic physical examination from age 40 years, and (c) annual mammography after the age of 50 years. But, if there is a family history of breast cancer, mammograms may be started at an earlier age. The early treat-ment of breast cancer following discovery by routine mammography ultimately decreases mor-tality by about 30% in the screened populations.

BREAST CANCER IN EGYPT

At NCI Pathology Cancer Registry, breast cancer is the foremost oncologic problem, contributing 20% of all cancers and 43% of female cancers (Mokhtar et al, 2007). The median age is 46 years, one decade younger than the corresponding age in Western countries. In Egyptian patients 60.5% of patients are premenopausal (age 50 years and younger). The female to male ratio is 44:1.

Breast cancer in Egyptian patients is biologically more aggressive disease than that encountered in the West. This is explained partly by the predominance of premenopausal patients, and partly by the late presentation of patients at an advanced stage. Moreover, inflammatory type of breast cancer is relatively more frequent. Thus, in NCI series, clinical (T) categories were as follows: Tl (1.2%), T2 (30%), T3 (26.4%), and T4 (42.4%). The mean tumor diameter is 4.5 cm at NCI, versus, 2.9 cm in private patients. The frequency of axillary lymph node metastases varied between 71% and 75% at NCI (Nouh et al, 2004/Mokhtar, 1991), versus, 63% in private patients. The number of positive nodes was (1-3) in 23%, (4-10) in 22% and more than 10 in 17% of patients.

The relative frequency of histologic types in private pathologic material was: noninvasive carcinoma (2%), invasive duct carcinoma (81%), invasive lobular carcinoma (7%), favorable special types including medullary carcinoma (9%) and rare unfavorable histology (1%). At NCI Pathology Registry, the profile of histologic types were: 2% noninvasive carcinomas, 83% invasive duct carcinoma, 6% lobular carcinoma, 3% mixed ductal-lobular carcinoma, 4% special favorable subtypes, 1% unfavorable subtypes and 1% sarcomas (Mokhtar et al, 2007). The profile of hormone receptors as determined by immunohistochemistry was positive in 58% and HER-2 positive (Scores 2 and 3) in 45% (Mokhtar et al 2007).

In a surgical NCI series, the 5-year survival was found to be 55.7% and the cure rate (disease free survival DFS) was 42.8% (Omar, 1988). In another radiotherapy series from NCI, the 5-year overall survival and DFS were 68% and 33% respectively (El-Mongy, 1998). In the latter series, it was possible to stratify patients according to a modified prognostic index (Brown, 1993) into two groups: PI <3.2 with overall 5-year survival of 11% and PI >3.2 with 55% survival rate.

BREAST SARCOMAS

Phyllodes Tumor

Muller in 1838 introduced the term cytosarcoma phyllodes to describe a fibroepithelial tumor characterized grossly by leaf-like projections into cystic spaces and histologically by a neoplastic stroma and benign epithelium. At present, the term phyllodes tumor is preferable, since many cases are not malignant. Phyllodes tumor arises from the specialized stroma around the ducts and usually occur in women between the 30 and 70 years of age, with a median age of 50 years. The tumor is rare, contributing only 0.4% of malignant breast tumor at NCI Pathology Registry (Mokhtar et al, 2007).

The WHO classified phyllodes tumors into: benign, borderline and malignant, with relative frequencies of 65%, 20% and 15% respectively (Lakhani et al, 2012). An alternative classification scheme (Koerner, 2009) is to consider benign phyllodes tumors as fibroadenomas (P 18-34) and call the other two potentially aggressive tumors as low-grade (P 18-35) and high-grade (P 18-36) phyllodes tumors (Table 18-16).

In contradistinction of fibroadenoma, phyllodes tumor show gross slit-like spaces (P 18-37), but such feature is absent in recurrent tumors (P 18-38). Phyllodes tumors show variable stroma to epithelial ratio in different parts of the tumor, but, in fibroadenoma this ratio is constant. In phyllodes tumor, the stroma is neoplastic but the epithelial component is not. However, stromal cells of tumor secrete growth factors which may cause focal epithelial hyperplasia.

Differential Diagnosis

Phyllodes tumor must be distinguished from other *spindle cell lesions* of breast (Table 18-17). Immunohistochemistry plays a major role in the differential diagnosis (Table 18-18).

Table 18-17 Spindle Cell Lesions of The Breast (P18-39 to 18-41)

Benign
Reactive spindle cell nodule
Nodular fasciitis
Pseudoangiomatous stromal hyperplasia
Myofibroblastoma
Myoepitheliosis
Adenomyoepitheliosis
Locally-Recurrent
Fibromatosis
Periductal stromal sarcoma
Malignant
High-grade phyllodes tumor
Metaplastic carcinoma
Sarcomatoid carcinoma
Malignant myoepithelioma
Spindle cell sarcoma (Fibro, MFH and Rhabdo)

Table 18-16 Diagnostic Features of Fibroepithelial Tumors of Breast

Feature	Fibroadenoma	Phyllodes Tumor	
		Low-grade	High-grade
Slits and Cysts	Absent	Present	Present
Margin	Pushing	Pushing	Infiltrative
Stromal cellularity	Mild	Moderate	Marked
Stromal/epithelial ratio	Constant	Variable	Variable
Nuclear atypia	Absent	Mild	Marked
Ki 67 index	< 2%	2-5%	>5%
Immunohistochemistry	Negative	CD 34, β catenin	P 53, CD 117
Biologic behavior	Benign	Local recurrence	Recurrence and Metastases*

*Risk of local recurrence 20%, lymph node metastases 5% and distant metastases 8%

Table 18-17 Differential Diagnosis of Spindle cell lesions of Breast by Immuno-histochemistry

	CK	B-Catenin	CD34	PR	Actin
Nodular fasciitis	-	-	-	-	-
Pseudoangiomatous stromal hyperplasia	-	-	+	+	-
Myofibroblastoma	-	-	+	+	-
Myoepithelioma	+	-	-	-	+
Fibromatosis	-	+	-	-	-
Phyllodes tumor	-	-	+	-	-
Sarcomatoid carcinoma	+	-	-	-	-

(Loffe and Silverberg, 2009)

Other sarcomas

Sarcomas which are not uncommon in breast fall in 3 main groups:

1. Soft tissue sarcomas arising in breast stromal e.g. angiosarcoma (P 18-42), liposarcoma (P 18-43) and extraskeletal osteosarcama.

2. Iatrogenic sarcomas, including (a) postmas-ectomy lymphangiosarcoma (Stewart-Treves tumor) complicating chronic lymph-edema, and (b) post-radiation sarcomas including hemangioendothelioma and malignant fibrous histiocytoma (MFH).

3. Primary extranodal lymphoma, usually MALT related, B-phenotype non-Hodgkin lymphoma.

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