

Chapter 6
Pathology of Breast Carcinoma
and methods of analysis

Microscopic examination is the definitive means of evaluation of

breast disease. The ultimate method of treatment of the patients with breast carcinoma may be determined on the bases of the pathologic findings in the initial breast biopsy. The following sampling techniques are used singly or in combination:

1) Cytopuncture and Fine Needle Aspiration (FNA)

Cytopuncture or FNA may constitute the initial diagnostic procedure for palpable breast masses. This technique has been also used to evaluate non-palpable mammographically detected lesions under stereotactic or ultrasound guidance.

This method has two limitations: first its accuracy which depends upon the skill and experience of the personnel who perform the puncture, the radiologic guidance for the non palpable lesion, and also the microscopical analysis. Second, the inability to permit a reliable distinction between in situ and invasive ductal carcinoma except when the puncture concerns metastatic lymph nodes.

This technique is the simplest and the cheapest diagnostic method, only little material is required. It is immediately done and gives the possibility to have a nearly instant diagnosis. By being that easy to perform, this has allowed its integration to the consultations associating radiologist and clinicians to ensure a complete diagnosis in one visit. It equally allows a rapid evaluation of the efficacy of neo-adjuvant chemotherapy. This material guarantees the diagnosis of carcinoma, the evaluation of its type but also the measurement of its grade. The immunohistochemistry staining is possible thanks to the cytobloc techniques. The material, formed essentially of tumor elements, is especially adapted to the techniques of cytometry, molecular biology and even the microarray.

2) Core needle biopsies

The biopsied material has considerably progressed thanks to multiple technological improvements. First, the development of aspiration needles having variable calibers, starting from 18G, then the aspiration systems which guarantees the possibility to achieve multiple aspiration materials through only one entry site to the lesion and finally the instrument and technique of stereotactic detection or ultrasound allowing the precise millimetric targeting of non palpable lesions.

Today, it represents for most of the countries, where an organized mammographic screening was developed, the first diagnostic method thus allowing the surgical resections to be only limited to patients having malignant lesions (therapeutic surgery) or doubtful lesions (diagnostic surgery).

The handling of the specimens by the pathologist requires learning both for: their management that requires a severely strict protocol having multiple levels of cut sections and also for their microscopic analysis. The pathologist has a double role, performs the most precise microscopic diagnosis on the small size and fragmented material, then confirming the correct representation of the biopsy in relation to the doubtful image.

3) Incisional or excisional open biopsy

The pathologic evaluation of the primary excision specimen is a crucial component in the selection and implementation of breast conservative surgery. The following recommendations should be adopted for proper evaluation of the breast specimens:

- The specimen should be presented to the pathologist intact and carefully oriented by means of the suture tags or fixed to a support where the anatomical marks are indicated (Fig. 6.1).
- After measurement, it is inspected for gross margin involvement. If there is evidence that the specimen contains a grossly suspicious lesion that extends to the surface of the specimen, the surgeon, if still operating, is immediately notified about the precise location of the margin involved so that additional tissue can be excised. Prior to cutting the breast excisional biopsy, the surface should be blotted dry and then painted with marker (India ink), which will be visible on the permanent section.

The subsequent steps in processing will depend upon the nature of the specimen, whether it is obtained because of the presence of a palpable mass, and if carcinoma is suspected clinically or radiographically. For these specimens, the specimen should be cut in such a way as to permit examination of the resected margins on histologic sections. The steps of handling of the specimen are outlined in figure 7.1. Briefly, the tumor and the specimen are bisected transversely. The anteroposterior and mediolateral diameters of the tumor are measured. Aliquots of the tumor are systematically conserved in cryopreserved tumor bank when its size is sufficient. The standard method of sectioning varies, depending upon the size of excised specimen.

(A)



Coat surface with India ink



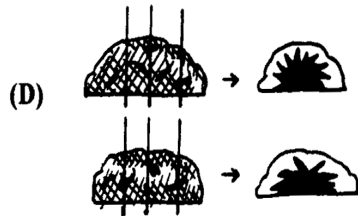
Blot Dry

(B)



Palpate for tumor & specimen transversely
 Bisect tumor & specimen diameters
 Obtain A-P, L-M partial SI measurement (a)
 Take blocks of L, M, A, P, margins and blocks of tumor

(C) *Fix remaining hemispheres 1-2 hours*



7 Place cut surface down
 Take sagittal blocks through superior and inferior portions
 Blocks viewed from side, each may be transected to give SA, SP, IA, IP margins.
 Measure SI diameter of tumor: $a+b+c$.

Figure 6.1.

For evaluating the margins of a breast excision specimen, the specimen is oriented, the margins are painted with India ink, and the specimen is sectioned in various planes (modified from Fisher B et al., 1986, 57: 1717-1724).

For small excisions specimen, the whole tissue is totally included. For larger specimens, a sampling is necessary. After inking the specimen, single incision is made through the center of the palpable mass where it most closely approaches the margin in this way, the size of the tumor and the relationship to the nearest margin can be quickly determined. The remaining margins can then be entirely removed from the specimen and submitted for permanent sections so that representative sections from each of the six surfaces of the specimen are submitted. Multiple sections can then be made through the remainder of the specimen at 3 to 5 mm intervals and several sections to the tumor and the adjacent parenchyma or fat should be submitted for microscopic evaluation. Segments of skin and muscle should be systematically sampled in order to demonstrate their relationship with the tumor.

For the specimen excised because of the presence of mammographic abnormality, in the absence of a palpable mass, the most frequent mammographic abnormalities promoting biopsy are microcalcifications, mass with or without associated microcalcifications, and focal asymmetry. These specimens are usually excised using the hook wire or needle localization technique. Specimen radiography is an essential component in the evaluation of these specimens in order to both, document the presence of the lesion detected by mammography or the clip and localize the suspicious area for histologic examination. The use of frozen sections is limited because many lesions have been previously evaluated by core needle biopsy and for the others; their small size renders difficult or even impossible the realization of a frozen section. After fixation, the entire specimen is submitted for permanent sections. The specimen can be cut perpendicular or parallel to its main axis in serial cut sections.

4) Mastectomy

The skin and the nipple are assessed, with sampling of any isolated cutaneous lesions. The tumor size is measured and any evidence of multicentricity is recorded. Adequate histologic sections should be obtained from the tumor mass, any other identified lesion, the nipple parallel and perpendicular to the axis of the main lactiferous ducts and systematically each quadrant.

5) Axillary lymph nodes

In mastectomy specimens, the axillary nodes are removed in contiguity with the breast tissue. In patients treated with breast conserving therapy, an axillary dissection usually comprises a specimen containing the lymph nodes which is

separate from the breast excision specimen and requires orientation by the surgeon. The number and size range of the lymph nodes should be recorded. After fixation, once lymph nodes have been grossly identified, they may be bisected or sectioned in slides of 1-1.5 mm and submitted in totality in separate cassettes (fig 7.2). The technique of analysis is critical and directly influences the number and size of metastases identified (fig 7.3). *This is crucial car avec la diminution de la taille tumorale induite par le dépistage de masse, parallèlement le nombre et la taille des métastases ganglionnaires diminuent. Lors de l'analyse microscopique, toute zone suspecte doit faire l'objet d'un immunomarquage pour distinguer les envahissements ganglionnaires minimes de lésions bénignes comme les inclusions glandulaires bénignes ou neuronaeviques. Les métastases des carcinomes lobulaires sont particulièrement difficiles à détecter, constituées de cellules isolées et régulières, s'insinuant entre les cellules lymphoïdes normales selon un mode réticulé. Les immunomarquages anti cytokératines réalisés systématiquement pour ce type histologique, identifient dans plus de 10% des cas des métastases non vues avec les colorations standard. Toutefois ceux-ci ne seraient pas associés à un pronostic péjoratif, à la différence des autres types de carcinomes notamment la forme canalaire.*

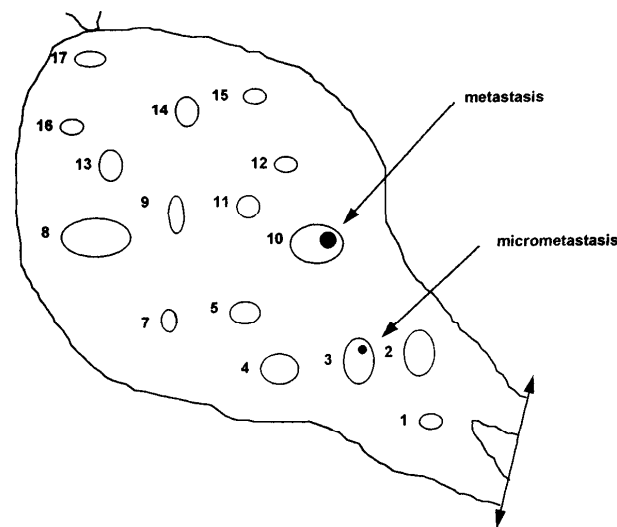


Figure 6.2: Macroscopic axillary lymph node dissection

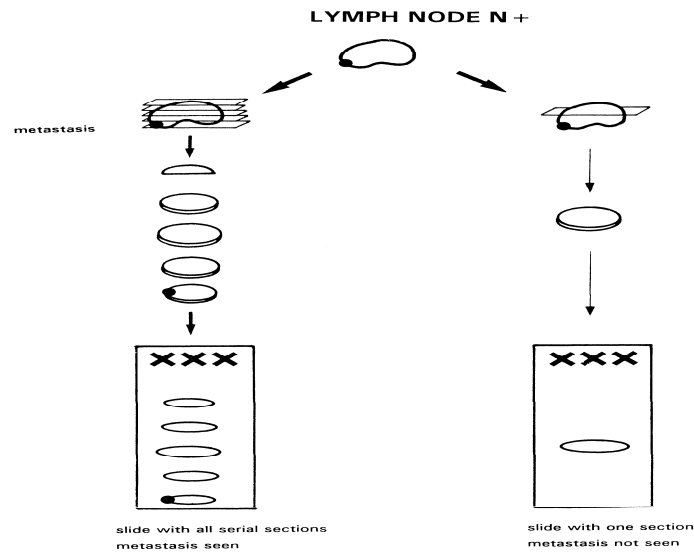


Figure 6.3 Macroscopical serial sectioning of lymph nodes

6) Sentinel lymph node biopsy

In this technique, the lymph node analysis is limited only to the lymph node (or nodes) draining the tumor area. These nodes are detected by injecting a dye or radioactive plotter in the peri tumorale zone, the injection is done in the subcutaneous layer facing the tumor or in peri-areolar region. The sentinel nodes are the first lymph node relay identified by these markers.

The detection of metastasis in the sentinel lymph node, even minimal, leads to a complementary axillary dissection. On the other hand, in case of absence of metastasis in the sentinel node, the risk of finding metastasis in the remaining axillary dissection is so minimal that no excision is done.

These sentinel nodes, requires a rigorous and extensive examination to be perfectly representative of the of the remaining axillary dissection state. Their size, number and color are registered and the suspected zones are systematically looked for.

They are immediately examined, by opposition, and / or by cryostat cut sections with the possibility of immunohistochemical examination thanks to the presence of rapid analysis kit.

Then, they are totally included in separated cassettes and examined on staged cut section levels stained by immunohistochemistry. As required for their identification, their management by the pathologist also requires learning.

7) Frozen section

Despite the obvious limitations, frozen section diagnosis remains to be the most useful tool in the evaluation of breast lesions and sentinel lymph nodes. The clinical data, gross morphology, specimen consistency and mammographic findings, if available, should be taken into consideration. False negative results may be encountered with sampling error or when dealing with a well differentiated tubular carcinoma. False positive results may be obtained in lesions exhibiting sclerosing adenosis and like lesions. In frozen sections of lymph nodes, the largest and firmest nodes should be selected for sampling. Diagnostic difficulties arise in the setting of small intrasinusoidal-subcapsular micrometastases, or nodal deposits of infiltrating lobular carcinoma with pseudoreticular forms.

8) Investigational Tools

As an adjuvant to routine histopathologic examination of breast tumors, additional investigational tools can help improve the evaluation. These tools include immunohistochemistry, cytogenetics and molecular biopsy tests.

Many protein products can be detected by immunohistochemistry, some including estrogen and progesterone receptors, HER-2/Neu oncogene done on a routine basis; other like p53 tumor suppressor gene, proliferation markers, angiogenesis, apoptosis, basal and luminal cytokeratins, EGFR etc. as a complement or for research purpose. Their application should be perfectly controlled and in the frame of using automation, calibrated internal and external control, as part of the quality assurance in order to ensure constant precision and reproducibility. Different European organisations suggest a quality control program.

Molecular biology methods have been developed and adapted in order to be able on fixed and embedded tissues. Fluorescent in situ hybridization (FISH) technique is today the gold standard method for the determination of amplification of her2 gene. Research of deletion and mutation of different genes such as EGFR, K-ras are

possible by PCR and more recently prognostic and predictive molecular signature determined by microarray has been developed.

Proliferative disease and in situ carcinoma

Lobular neoplasia

- lobular carcinoma in situ

Intraductal proliferative lesion

- usual ductal hyperplasia
- flat epithelial atypia
- atypical ductal hyperplasia
- ductal carcinoma in situ

Intraductal papillary neoplasms

- central papilloma
- peripheral papilloma
- atypical papilloma
- intraductal papillary carcinoma
- intracystic papillary carcinoma

Table 6.1.

Simplified WHO Histologic Classification of epithelial proliferation

1- Lobular Neoplasia

This type of lesion occurs during a woman's period of sexual activity, that is to say while the lobules are fully active, and disappears after the menopause. Its incidence represents about 1 to 4% of breast carcinoma. Lobular neoplasia is nearly always diagnosed by incidental microscopic discovery on surgical specimen of patients with microcalcifications or other abnormal radiographic images connected with benign pathology. Microscopically, there is a proliferation of globular cells, which are of the same shape and a little bigger than the neighboring cells, which have slightly bigger nuclei and slightly more irregular chromatin, with vacuolised cytoplasm in places. They fill in the center of terminal ectasic ducts and are able to propagate between the layers of neighboring extralobular ducts in a "Paget" spreading way. The absence of expression of E-Cadherin facilitates their

recognition. About 80% of lesions are multifocal and multicentric and 30% bilateral. Despite their name, they finally represent risk lesions as about 20% of patients treated by lumpectomy alone develop an infiltrating carcinoma after 10 to 25 years.

According to the intensity of the proliferation and the cytology 3 different groups are distinguished:

Atypical lobular hyperplasia

This lesion (Page) is characterized with small and irregular cells which incompletely filled in the acini, or involved less than half the acini of a lobule. The relative risk is estimated about 4 times the risk of the general population. This lesion could be more associated with an homolateral rather than a bilateral risk of cancer.

Lobular in situ carcinoma

The cells are more homogeneous and completely filled the lumen of the majority of acini of lobules in at least a minimum of 2 lobules.

Despite the term of carcinoma, this lesion is only associated with a high risk of cancer. After conservative surgery, about 20% of the patients developed homo or contralateral carcinoma. LCIS's multifocality is brought to light by all authors, and is estimated at 50 to 70% depending on the series

Pleomorphic lobular in situ carcinoma or LIN3

This recently variant of LCIS associates LCIS with specific features

- large distension of the lumen
- presence of comedonecrosis sometimes calcified
- neoplastic cells with large and irregular nuclei

These features might be isolated or more often associated. This variant of LCIS is considered more aggressive, with 20 to 60% of microinvasive areas and unlike the classic LCIS is generally treated by complete surgical excision.

2- Ductal Carcinomas In-Situ (DCIS)

Until the 1980's, this type of cancer was detected either by bleeding of the nipple or a mastocic lump in the breast in which DCIS was discovered, or by Paget's nipple disease. In even rarer cases, a focus of microcalcifications was found accidentally. Today, it is the opposite, for the majority of DCIS's are discovered due to an isolated cluster of microcalcifications. In microscopic terms, DCIS corresponds to a proliferation of cells, which vary in shape and size. These cells

proliferate within the lumina of the ducts and do not go beyond the myoepithelial border, which can be proven by appropriate immuno-staining. At the center of certain formations, necrotic areas form with some calcareous degeneration as in comedo-carcinoma. They are characterized by “stick-like” radiological images. Many microscopic forms of DCIS have been reported, both architectural (massive, comedomatous, papillary, cribriform, clinging ...), and cytologic (with big, small, apocrine or clear cells ...).

Until 1970, mostly comedomatous forms were discovered due to bleeding and/or tumoral masses and the treatment chosen for breast cancers in general, and in situ forms in particular, was mainly surgical, by mastectomy according to Patey or Halsted due to widespread diffusion to the mammary gland. But the development of screening campaigns has gradually brought about patients being operated on due to radiological signs alone, without any clinical symptoms. These infraclinical forms are the subject of this chapter, and the proportion of in situ carcinomas is increasing more and more, parallel to a decrease in size.

At the same time, came the idea of women, with early cancers, keeping their breast. This brought about a revision of therapeutic protocol. Moreover, after proving that small infiltrating carcinomas could benefit from “conservative” treatment, it seemed unethical that women with carcinomas with even better prognoses “intraductal forms” should continue to undergo mammary amputation. The first studies carried out confirmed the validity of conservative treatment but also observed a high number of relapses, linked to different factors like the size of the carcinoma and its histologic shape. Consequently, from 1988 onwards when EORTC held an initial consensus meeting, the separation of DCIS into 2 different types was recommended: the large cell type, or “comedomatous”, and the small cell type or “non-comedomatous”. This distinction was made from biological and evolutive characteristics: in fact the comedomatous type is pejorative, as shown by the over-expression of C-erb B-2, which is much higher (77%) than in the non-comedomatous type (15%).

Thereafter, another classification was suggested which put forward 3 groups divided up according to nuclear features and the architectural pattern (polarization of cells): the well differentiated type, clinging; the intermediate type, and the poorly differentiated comedo type. Finally in 1995, another classification divided into 3 groups came about, “Van Nuys classification”, based on nuclear grade and necrosis (fig). It was separated into: group 1, with neither high nuclear grade nor necrosis; group 2, without high nuclear grade but with comedomatous necrosis; and

group 3 with high nuclear grade, whatever its architectural shape. This classification is based on a prognostic report study, which confirms the wisdom of certain radical treatment of comedomatous types.

Differential diagnosis of DCIS is difficult, from atypical hyperplasia to one hand to invasive carcinoma. *L'identification d'une assise de cellules myoépithéliales par immunohistochimie (smooth muscle actine, p63...) facilite le diagnostic de micro infiltration. Par contre malgré les espoirs placés dans l'immunohistochimie, comme l'identification de cytokératines de différents poids moléculaire, pour aider la distinction entre lésions proliférante, atypique et in situ, il n'existe pas à ce jour de marqueurs utiles en cas de difficulté diagnostique.*

Clinically, and in relation to infiltrating carcinomas, average age is variable, sometimes significantly younger (50 vs. 54), which gives value to the idea of a “continuum” between in-situ and infiltrating carcinoma, and sometimes non-different if there is a high proportion of comedomatous forms in the group studied. Moreover, asymptomatic forms “T0” are ten times more numerous than in general breast cancers (55 vs. 5%).

This high multifocality is often underlined in old series which mainly reported comedomatous DCIS: it reached nearly 80% in an IGR study. More recently following the work of R. Holland in correlation with radiologists, there appeared a distinction between multicentricity which, is rare and characterized by the presence of multiple neoplastic areas, at a distance from the initial tumor and independent of it; and multifocality, which is more frequent, and corresponds to areas in direct liaison with the tumor, less than 2 cm from it in 40% of cases, and more than 2% from it in 10% of cases, suggesting a segmentary distribution or a gradual invasion (Table 15.3), which reinforces the development of conservative surgery. These observations contrast with the usual absence of axillary node invasion at this stage. As far as evolution is concerned, relapse rate is, on the one hand, connected to histologic classification, which is based on nuclear size and the presence of necrosis, as shown in the majority of recent studies, and on the other hand, to the quality of resection. *Les rechutes se font pour moitié sous forme infiltrante et pour moitié reste in situ. Elles comportent les mêmes caractéristiques moléculaires. Ceci souligne l'importance du choix initial de traitement local et la difficulté à trouver un consensus pour sélectionner les patientes pouvant bénéficier d'une résection chirurgicale sans radiothérapie associée, qui représentent de 5% à 30% des patientes selon les pays.*

In conclusion, the pathologist in direct liaison with the radiologist and the surgeon, play a capital role both in the diagnosis of DCIS, distinguishing it from atypical hyperplasia or micro-invasive carcinomas, as well as in treatment, by giving details of its boundary of the specimen. However, in reality it is very difficult, even impossible, in spite of the claims of certain authors, to evaluate the size of these DCIS, even if the tumor foci are placed as precisely as possible on the glass slides. The pathologist's role is to broaden the field, using new techniques offered by modern biology, and to attempt to forecast the forms, which stay local and may benefit from "conservative" treatment, and those which will become multifocal and/or multicentric and which justify mastectomy. Thus, individual treatment of each patient will be better programmed through communal decision.

3- Histologic classification of invasive breast carcinomas

Epithelial tumors

- invasive ductal carcinoma, not otherwise specified
- invasive lobular carcinoma
- tubular carcinoma
- invasive cribriform carcinoma
- medullary carcinoma
- mucinous carcinoma
- neuroendocrine tumours
- invasive papillary carcinoma
- invasive micropapillary carcinoma
- apocrine carcinoma
- metaplastic carcinoma
- lipid-rich carcinoma
- secretory carcinoma
- oncocytic carcinoma
- adenoid cystic carcinoma
- acinic cell carcinoma
- glycogen-rich clear cell carcinoma
- sebaceous carcinoma
- inflammatory carcinoma

Table 6.1.

Simplified WHO Histologic Classification of breast carcinoma

Invasive Duct Carcinoma (NOS)

This represents the most frequently encountered histologic type of breast carcinoma. Grossly, the tumor appears either well circumscribed, stellate, or shows a combination of both. The stellate variant is associated with extensive fibrosis (scirrhous carcinoma). The size of the tumor is variable and its assessment constitutes an important prognostic parameter. Microscopically, the tumor is characterized by the presence of irregular or rounded solid clusters of tumor admixed with single cells and cords of tumor cells. Based on the degree of tubule formation, nuclear appearance and mitotic activity, the tumor should be graded. In some tumors, an in-situ ductal carcinoma may be found; alternatively both ductal and lobular types of in-situ carcinoma may be present.

Infiltrative Duct Carcinoma with Extensive In-situ Component

This variant has been defined as invasive tumor in which 25% of the overall area involved by the invasive carcinoma is composed of intraductal carcinoma. The presence of abundant intraductal carcinoma within the tumor was associated with a tendency to have in-situ component beyond the tumor margin and multicentric carcinoma. However the risk of local relapse as other tumor type is directly dependant of the status of the resection margins.

Microinvasive Carcinoma

These are tumors that are predominantly intraductal but focally the tumor cells have barely broken through the basement membrane, invading the stroma immediately adjacent to the defective portion of the duct wall but measuring less than 1mm.

Infiltrating Carcinoma Presenting as an Axillary Mass

Breast carcinoma may present as axillary mass in the absence of a clinically detectable breast tumor. It is possible that some of these tumors actually arise from either the axillary tail of the breast, accessory breast tissue in the axilla, or heterotopic breast tissue in an axillary lymph node.

Invasive Lobular Carcinoma

The tumor tends to present either as an irregular infiltrating or well circumscribed, indurated mass. Originally the invasive lobular carcinoma is characterized by a linear growth pattern of small cells in "Indian file" of one cell width. Subsequently, additional patterns of invasive lobular carcinoma were defined including: solid pattern, alveolar pattern, and a mixed group composed of an admixture of one or more of these patterns. Another pattern designated tubulo-lobular has been described. In this variant, tubules formations are arranged along with cords of cells

arranged in “Indian files”. Cytologic variants such as apocrine, histiocytoid and pleomorphic have been also described. This latter form differs from the classic type by its aggressiveness. Infiltrating lobular carcinoma can closely simulate a lymphoma. Immunostains for cytokeratin and leucocyte common antigen (LCA) are helpful in establishing the nature of the neoplastic cells. E cadherin, a membranous antigen which expression is typically absent in lobular carcinoma is helpful for the recognition of these rare variants.

Tubular Carcinoma

A distinctive variant of mammary carcinoma characterized by proliferation of angulated tubules separated from each other by a reactive fibroblastic stroma. The tubules display open lumens and are lined by a single layer of epithelial cells. A minimum of 75% of the lesion should display this morphology in order to call this tumor a tubular carcinoma. When such arrangement is present as a minor component the tumor is referred to as a mixed tubular carcinoma. The recognition of tubular carcinoma is important because of its good prognosis and the rarity of axillary node metastases. Tubular carcinoma can be mistaken for sclerosing adenosis, microglandular adenosis and radial scar.

Invasive cribriform carcinoma

This rare type grows mainly in a cribriform pattern similar to that seen in intraductal carcinoma but without any myo-epithelial cells. A minor tubular component is frequently seen. This form is associated to an excellent prognosis. Immunohistochemistry is important to distinguish it from an adenoid cystic carcinoma and intraductal carcinoma.

Medullary Carcinoma

Medullary carcinomas are distinctive tumors with pushing expansile margins. Occasionally, they may appear encapsulated. The tumors have fleshy soft consistency and composed of a syncytium of anastomosing cords and sheets of tumor cells separated by loose connective tissue. The tumor cells are round with abundant cytoplasm, round vesicular nuclei, containing one or more prominent nucleoli. Mitosis is common. Squamous metaplasia and atypical tumor giant cells have been noted in some of these tumors. Typically, the tumor cells in medullary carcinoma are accompanied by moderate to pronounced lympho-plasmocytic infiltrate in the supporting and surrounding stroma. Microglandular or tubular formations are absent. The constant lymphocytic reaction seen in medullary carcinoma may be linked to the favorable prognosis of medullary carcinoma and low frequency of nodal metastasis. This form is rare since strict histologic criteria

have been used to its identification. It is frequently observed in predisposed patients for breast carcinoma with BRCA1 germ line mutation.

Mucinous Carcinoma

In this form, the uniform tumor cells are accompanied by large amounts of extracellular mucin lakes. Pure and mixed variants of mucinous carcinoma have been recognized. An infiltrating duct carcinoma is the most common associated tumor in the mixed tumors. It is important to differentiate the pure form from the mixed type because of the favorable prognosis of the former.

Neuroendocrine Tumours

These are mammary carcinomas that display any growth patterns similar to those of carcinoid tumors that occur in other organs. They express neuroendocrine markers in more than 50% of the cell population. Hormonal receptors are frequently identified. If neuroendocrine markers are frequently found in other breast carcinomas, they are limited to scattered cells. This group comprises different subtypes, solid neuroendocrine carcinoma, atypical carcinoid, oat cell carcinomas and large cell neuroendocrine.

Invasive papillary carcinoma

This tumor is generally well delineated, frequently cystic and associated with hemorrhage. Myoepithelial cells are completely absent. It is now considered that many of the intra cystic carcinoma published may represent invasive papillary carcinoma. As they share an excellent prognosis, they have been called also papillary encapsulated carcinoma.

Invasive micropapillary carcinoma

This newly identified form of carcinoma is characterized by the presence of small clusters of tumours cells lying in clear stromal spaces mimicking vascular channels. This is an aggressive form, with frequent and numerous axillary lymph node metastases and poor prognosis. It may be pure or associated with a ductal component.

Metaplastic Carcinoma

Several metaplastic forms may be encountered in this category. Pure squamous or epidermoid carcinoma is rare, a more common presentation being foci of squamous differentiation in vicinity of necrotic areas in other histologic patterns of tumor. Spindle cell differentiation and metaplasia such as cartilagenous or osseous metaplasia are rare in pure form.

Adenoid Cystic Carcinoma

In this histologic subtype, a cribriform pattern is seen with rounded hyaline spaces enclosed in between cellular masses. It associated two cell components one expressing cytokeratin the other actin. Perineural invasion is a peculiar feature to this pattern of growth. Generally, this type of neoplasm exhibits a slow rate of growth and a favorable prognostic outcome.

Lipid Rich Carcinoma

This histologic variant has a particularly unfavorable prognosis. Large tumor cells exhibit lipid material, best demonstrated in frozen tissue material

Juvenile (Secretory) Carcinoma

It occurs primarily in children and adolescents. This neoplastic variant is highly differentiated exhibiting excessive PAS positive secretory products.

Inflammatory Carcinoma

This type of breast carcinoma has been given a variety of terms such as mastitis carcinoma, carcinoma mastitoides, or acute mammary carcinoma. It is considered as the most malignant type of breast carcinomas, and of high proliferative activity (PEV 3). It represents 1% to 2% of breast carcinoma in Western literature, however, in Egypt, North Africa and Tunisia such mammary carcinoma is not uncommon. Characteristically, the skin of the breast is reddened, warm, edematous and thickened. During early stage, an underlying breast mass may not be palpable, and this may cause an erroneous diagnosis of inflammatory non-neoplastic process. Histologically, the skin dermis is filled with many lymphatic tumor cell emboli. Blocking of lymphatics causes skin edema.

Clinical Versus Pathologic Definition

The criteria for clinical diagnosis of inflammatory carcinoma include diffuse erythemaedema extending to greater than two thirds of the breast, "peau d'orange", tenderness, engorgement, and diffuse breast involvement. The pathologic diagnosis requires the presence of tumor emboli in the dermal lymphatics, in addition to the presence of invasive carcinoma with spontaneous necrotic foci. In majority of cases, the clinical picture and the pathologic picture of dermal lymphatic involvement coincide. However, all patients with the clinical disease have demonstrable dermal lymphatic involvement, and there are also cases with dermal lymphatic involvement but without the clinical inflammatory features. It was found that clinically occult inflammatory carcinoma i.e. patients without clinical signs of inflammatory carcinoma but with tumor emboli in the dermal lymphatics followed

rapidly deteriorating clinical course, and wide spread metastases similar to clinically diagnosed inflammatory carcinoma. Furthermore, clinically diagnosed inflammatory carcinoma without demonstrable dermal lymphatic invasion, behave aggressively. Therefore, the use of the term “inflammatory carcinoma” is justified with either the clinical or the pathologic features.

Pronostic classification

Histologic SBR Grade

Tumor grading regardless of the system used has prognostic importance in breast cancer. Grading systems have been developed based on nuclear features, architectural pattern, mitotic rate or combinations of these features. Its use, initially restricted to the sole invasive ductal carcinoma, now has been extended to every subtype of invasive carcinoma except the medullary carcinoma. The chief difficulty with any of these grading systems is their subjective nature and the resultant poor reproducibility among pathologists, one approach is to use a uniform grading system with distinct criteria that are easy to reproduce among observers (Table 7.2.). For instance, the mitotic count is evaluated on ten consecutive high power fields and adjust according to the microscopic field area (table 7.3.). Studies have indicated that proliferation is the most important prognostic compound of this system. Other investigators have combined morphologic grade with other features, including tumor size and nodal status to calculate a prognostic index that appears to be highly predictive of clinical course.

Axillary Lymph Node examination

Involvement of axillary lymph nodes by metastases in patients with cancer breast is one of the important markers of prognosis. Pathologic examination of the axillary nodes in patients with breast cancer is required in order to assess prognosis and determine the need for adjuvant therapy. For sentinel lymph node, serial sectioning and the use of immunohistochemical staining is mandatory to ensure the predictive value for the involvement of the other axillary lymph nodes. One consequence of this method is to increase the detection metastases, in particular those of limited size (micrometastases) whose prognostic value is still under discussion. UICC has modified its classification of these small metastases, based on their size, in order to be able in the future to determine their prognostic value.

Features	Score
Tubule formation Majority of tumor (>75%)	1

Moderate degree (10-75%)	2
Little or none (<10%)	3
Nuclear pleomorphism	
Small, regular uniform cells	1
Moderate increase in size and variability	2
Marked variation	3
Mitotic counts	
Dependent on microscopic field area	1-3

3~5 points: Grade I, well differentiated
 6-7 points: Grade II, moderately differentiated
 8-9 points: Grade III, poorly differentiated

Table 6.2. Summary of Semiquantitative Method for Assessing Histologic Grade in Breast Carcinoma

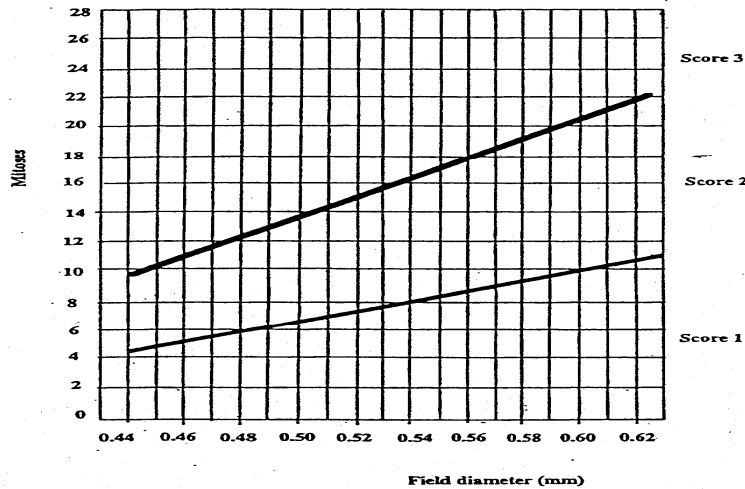


Figure 6.1 Value of the mitotic count according to the microscopic field area

pN0	absence of lymph node metastasis with a routine analysis
pN0 i-	absence of lymph node metastasis with a special analysis
pN0 i+	presence of a metastasis measuring less than 0,2mm

pNmi	presence of a metastasis measuring between 0,2mm and 2mm
pN1a	presence of a metastasis measuring more than 2mm

Table 6.4. UICC classification for the limited metastatic involvement of lymph nodes

New classifications

The recent development of molecular biology techniques, in particular the microarray techniques which allows the simultaneous analysis of thousands of genes, has considerably modified our cancer knowledge. One of the first consequences was grouping of infiltrating carcinomas according to their genetic expression similarity (unsupervised analysis) in so called molecular sub types. Five main groups have thus been individualized, **Luminal A** and **B** associated to hormonal receptor related and luminal type cytokeratin expression genes, **basal** related to basal type cytokeratin and absence of genes related to Her2, **Her 2** associated to the genes of the amplicon of this part of the chromosome 17 and **normal** type characterized by normal mammary tissue expression genes.

Their evolution as well as their aggression and their response to treatment could have been different but with some restrictions related to weak stability of this classification; each new incorporated case modifies the distribution of each of the designated class, also by the selected statistical algorithm and the number of selected class. Different groups have tried to characterize these different groups using immune-histo-chemistry.

Morphologic changes induced by radiation and chemotherapy

Since radiation therapy is being used with increasing frequency as part of the conservative treatment option in the management of women with stage I and II breast carcinoma, it is important to become familiar with morphologic and functional alterations induced by this modality. Familiarity with the range of morphologic alterations induced by radiotherapy will prevent misinterpretation of these changes as atypical or malignant.

One significant change that could result in diagnostic problems that deserve practical attention is the development of epithelial cells with enlarged hyperchromatic nuclei, inconspicuous nuclei, and cytoplasmic vacuolization in the terminal duct lobular unit as well as in areas of adenosis. These changes are not related to age, interval between termination of radiotherapy and the subsequent biopsy, or the usual dosage of radiation. Similar changes may also affect the

epithelial cells in larger ducts, but less frequently. Variable degrees of lobular sclerosis may also occur. The radiation induced atypia differs from carcinoma involving the lobules by the absence of epithelial hyperplasia, mitotic activity, and luminal necrosis. Furthermore, the cytoplasmic vacuolization and a history of prior radiotherapy should serve as additional clues.

Similar epithelial changes have also been observed secondary to chemotherapy. An increase in nuclear size, pleomorphism, vacuolization, and chromatin clumping in residual tumor cells has been described after chemotherapy. Chemotherapy may induce nodular fibrosis and areas of fibrohistiocytic proliferation in both the breast as well as in axillary lymph nodes. Chemotherapy does not induce the vascular and stromal changes. Preoperative chemotherapy can abolish the tumor leaving no evidence of residual malignancy in the specimen.

Name:		No:	
Breast:	1) Left	2) Right	
Specimen:	1) Excisional (for palpable mass)	2) Mammographic Loc.	
	3) Incisional (includes core needle and FNA)	5) Mastectomy	6) Chest wall
	4) Re-excisional		
Specimen Size:			
Tumor			

Size(s):			
Tumor Type	1) DCIS 2) LCIS 3) Infiltrating ductal (NOS) 4) Infiltrating lobular	5) Mixed NOS/ILC 6) Tubular 7) Mucinous 8) Medullary	9) Papillary 10) Cribriform 11) Other. (specify)
Grade of invasion:			
	1) I	2) II	3) III
Gross margin:	1) Free (specify distance)	2) Focal	3) Inevaluable
Margins invasive (specify type of margin evaluation)			
	1) Free (specify distance)	2) Focal	3) Inevaluable
Margins DCIS (specify type of margin evaluation)			
	1) Free (specify distance)	2) Focal	3) Inevaluable
DCIS nuclear morphology			
	1) High grade	2) Intermediate grade	3) Low grade
DCIS patterns (specify all that apply)			
	1) Large areas of central necrosis (comedo) 2) Small areas of central necrosis 3) Cribriform	4) Solid 5) Micropapillary 6) Papillary	
Calcification in situ:			
	1) Absent 4) In LCIS 6) Focal in benign breast tissue	2) Prominent in DCIS 5) Prominent in benign breast tissue	3) Local in DCIS
Peritumoral lymphatic invasion:			
	1) Absent	2) Present	3) Dermal
Peritumoral vascular invasion:			
	1) Absent	2) Present	

Extent DCIS within invasive tumor:		
1) Absent	2) Slight	3) Moderate-Marked
4) Tumor primarily DCIS with focal invasion		
Extent DCIS adjacent to invasive tumor:		
1) Absent	2) Slight	3) Moderate-Marked
EIC status:		
1) EIC negative	2) EIC positive	3) EIC intermediate
Note: If a tumor is primarily DCIS with focal invasion or has a moderate or marked amount of DCIS within the infiltrating tumor and in the -adjacent tissue it is EIC positive		
Skin:		
1) Not sampled	2) Free	3) Invasive
4) Dermal lymphatic		
Nipple:		
1) Not sampled	2) Free	3) Invasive
4) Dermal lymphatic		
5) DCIS		
6) Paget's		
Muscle:		
1) Not sampled	2) Free	3) Involved
Mastectomy tumor location:		
1) Central	2) UOQ	3) UIQ
4) LOQ		
5) LIQ		
6) Axillary tail		
Multiple areas involved:		
1) Central	2) UOQ	3) UIQ
4) LOQ		
5) LIQ		
6) Axillary tail		
7) Only one area involved		
Lymph nodes (number of involved nodes in relation to total number examined):		
Total	Level II	
Level I	Other (specify)	
Level III		
Extranodal extension		
	1) Absent	2) Present

