REVIEW ARTICLE

Changing Paradigms in Breast Carcinoma: A Review

Shameem Shariff

ABSTRACT

The journey of breast cancer a common malignancy the world over, is long drawn with several ups and downs finally resulting in patterns of management and therapy amounting to an attempt at breast conservation. Impressive advances have been made in the past 50 years in an effort to prevent, treat and cure breast cancer. Some of the major milestones include methods of screening modalities, newer classifications and a shift from mastectomy to breast conservation therapy. At most oncology centers the first line triple approach has come to mean tissue core biopsy instead of fine needle aspiration cytology, as the histological grade and receptor status can be easily defined and is closer to results obtained at resection. Imaging modalities like mammography have unmasked lesions whose biological behavior and association with cancer is not well defined - columnar cell hyperplasia, columnar cell change, flat atypia as well as complex sclerosing lesions. Reporting these on core biopsy pose a dilemma to, not only the pathologist, but also the treating physicians. Newer concepts like the molecular classification of breast carcinoma have overshadowed the conventional specific and not specific type. This encompasses the estrogen receptor (ER) positive and the ER-negative groups. Among the ER-positive are the luminal Types A and B with fairly good prognosis. Among the ER-negative group are the ones, which are Her2 neu positive and negative ones. The last group is the normal breast type, which is yet to be recognized as a specific entity. Such categories result in specific gene signatures of good prognostic and poor prognostic variants and response to targeted therapy.

KEY WORDS: Breast cancer, core biopsy, molecular classification

Introduction

Carcinoma breast is one of the most common malignancies affecting women in both the western world as well as in the subcontinent of India. In spite of all advanced modalities of therapy, the incidence seems to be on the rise. It becomes the responsibility of all treating physicians and reporting pathologists to keep abreast with knowledge of the changing patterns in this neoplasm. Advances in technology have resulted in the emergence of recording changes in cancer cell at a molecular level. This reflection in breast pathology has culminated in the emergence of newer techniques, terminologies and basis for a new classification, which might revolutionize not only the response to therapy, but prognosticate the behavior of the various types of breast carcinoma. This review aims at a visit into the changing trends in the pathology and diagnosis of breast neoplasia starting from screening to defining the molecular classification and prognostic parameters.

Breast cancer is one of the leading causes of cancer-related death in women worldwide. In the mid-eighteenth century Henri Francois Le Dran proposed that breast cancer originated as a localized disease that spread via the lymphatics to the general circulation. According to Donegran,[1] Le Dran's recognition of the dominant course of breast cancer progression was pivotal and established the idea that surgery, if performed early, offered the potential to cure breast cancer.

The journey of breast cancer since then has been long drawn with several ups and downs finally resulting in patterns of management and therapy amounting to an attempt at breast conservation. Impressive advances have been made in the past 50 years in an effort to prevent, treat and cure breast cancer. Some of the major milestones include screening modalities, a shift from mastectomy to breast conservation therapy, advances in chemotherapy for primary disease, anti-estrogenic therapy for progression of breast cancer and target therapy at the molecular level.

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The following review will analyse some of these aspects.

Pathologists form an important part in contributing information to therapeutic decisions. The complex multifactorial description of breast pathology now considered to be standard practice has resulted in the expansion of the report from a brief descriptive statement to a catalogue of data, which runs several lines. This has resulted in an active participation by the pathologists toward diagnosis and the awareness how various components of their report are relevant to treatment decisions.

Triple Assessment: Changing Picture

- The accepted management of a lesion discovered in the breast by any means is the "triple approach technique."
- Several studies have shown that a combination of clinical examination, imaging (mammography or ultrasound) and fine needle aspiration cytology (FNAC) or core biopsy will give an accurate diagnosis on the breast lesion.
- The triple approach is considered +ve if any one of these investigative modalities is positive.
- In 99.6% of cancers it is +ve; in <1% of cancers it is –ve.

Minimally invasive breast biopsies as a prong in triple assessment

These are sampling of breast tissue using non-surgical techniques; i.e., using a needle and are:

1. Fine-needle aspiration (FNA): 20-25 gauge needles
2. Core needle biopsy: 8-18 gauge (usually 14 gauge is preferred)
3. Vacuum assisted cores.

To use FNAC or core biopsy in diagnosing breast lesions is a dilemma for most clinicians, surgeons and probably even pathologists. Samples obtained by any of these methods are evaluated by pathologists and classified histologically with the primary goal of determining whether the lesion is benign or malignant. Evidence-based literature discussing which of these two modalities is preferable in breast lesion diagnosis is sparse, and there is no consensus among different specialized breast cancer centers. Each method has its advantages and disadvantages.[2-4]

Fine-needle aspiration cytology

- This technique is ideal for the investigation of breast disease and is one of the elements of the triple approaches
- The principle of FNAC - a representative sample of cells is aspirated from a lesion, and the nature of the lesion is diagnosed from these cells
- Routine practice uses the following major diagnostic categories when reporting a FNAC of a breast lesion:
  Non-diagnostic: (Category 1)
  Benign: (Category 2)
  Atypical/equivocal: (Category 3)
  Suspicious: (Category 4)
  Malignant: (Category 5)

(National Health Service Breast Screening Program guidelines for cytology practice)[5]

- The importance of FNAC, as it emerged as a diagnostic tool, was that in several Institutions, particularly in Europe, FNAC largely replaced excisional biopsy for the evaluation of mammographic abnormalities
- In the US, the acceptance of this procedure was slower possibly due to the fact.
  a. It requires a skilled cytopathologist
  b. The variability in the reported accuracy of the procedure
  c. The high rates of insufficient sampling, and the medicolegal environment.

Advantages of FNAC

- It is inexpensive and quick to perform
- The results can be made available rapidly, enabling a 1-stop diagnostic result in clinics
- Excellent results with FNA and triple assessment are reported in the literature
- In general, FNAC is more suitable for patients on anticoagulants and for lesions close to the skin, chest wall, vessels and implants or for very small lesions and those that are deep-seated and difficult to reach
- This approach has an accuracy of over 90% for palpable breast lesions when all 3 components are concordant for benign or malignant disease
- A most useful function of FNAC is to confirm that a lesion is malignant. However, this has to be correlated with clinical and radiological findings
- Reliable (if positive) for palpable lumps; Unreliable if negative - may need an additional biopsy.

Limitations of FNAC

- In non-palpable lumps less reliable; image-guided core biopsy is recommended
- In as many as 40% of cases, the findings are not concordant, in particular in non-palpable lesions
- For non-palpable lesions, the insufficient sample rate for FNA averages 34%
- Differentiation between *in-situ* and invasive carcinoma cannot be made out
- Grading on FNA may not be accurate
- Immune-histochemistry (IHC) - estrogen receptor (ER) and progesterone receptor (PR) and Her-2 neu, though may be performed on FNA are not cost effective
- The category of C3 is a definite grey zone area - includes sclerosing lesions, radial scars and papillomas, which may be associated with malignancy
- The reporting of breast cytologic results is more demanding than histologic analysis and requires greater expertise.

Needle Core Biopsy (NCB)

This automated biopsy system obtains core needle samples. The device is pressed against the tissue at the appropriate location and angle and then the needle is fired into the tissue. After confirming that the core needle has sampled the appropriate tissue, the needle is withdrawn and the tissue sample ejected from the needle into a sample container. Some units use a co-axial needle, a canula is advanced into the tissue until it reaches the area to be sampled, the sampling needle is then fired through the canula into the lesion (Figures 1 and 2).

- 8-18 gauge needles are used large enough to withdraw "chunks" of tissue, with cellular layers undisturbed
- Pathologist can give more information about the tumor - can see if it is invading surrounding tissue or still within ducts
- Can be used for palpable and non-palpable lumps
- Most often used with image-guidance, and for non-palpable lumps
- Two types:
  a. Stereotactic
  b. Ultrasound

Classification system for the categorization of breast NCB: (UK scoring system)

- B1 unsatisfactory or normal tissue
- B2 benign representative lesion

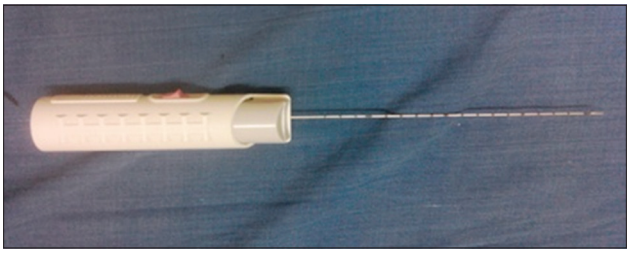

Figure 1: Bard's Core biopsy needle (18 guage)

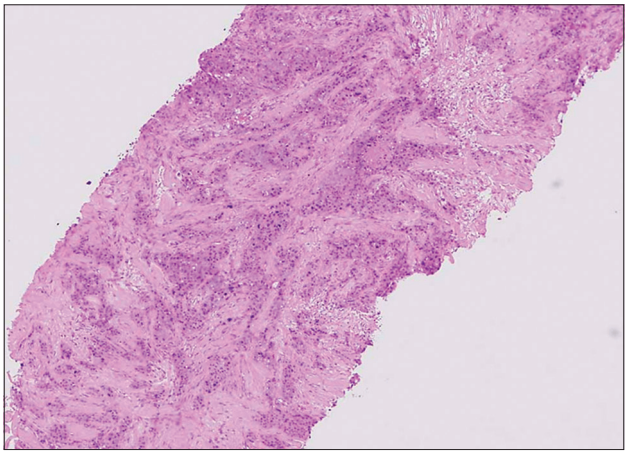

Figure 2: Core biopsy showing an invasive ductal carcinoma

- B3 equivocal
- B4 malignant, but diagnosis cannot be categorically made owing to a technical artifact or the small size of the biopsy
- B5 malignant, either *in-situ* or invasive

Advantages of core biopsy

- Rapidly replacing FNAC as a procedure of choice for the triple assessment of the breast problems
- Core biopsy is a more reliable predictor of the pathology and can distinguish between benign and malignant tumors and between *in-situ* and invasive cancers
- In majority (83%) of core biopsies, the findings reflect histology at excision
- Gives a good guide to the grade and histological type of the cancer
- Also used to assess the receptor (ER and PR) status
- Good tool to assess effect of neo-adjuvant chemotherapy on the grade of breast cancer

Limitations of core biopsy

- Should be representative of the lesion (inadequate sampling)

- In papillary lesions, capsule rupture may cause leakage of cells into the stroma - false +ve for invasion
- 10% of cases require additional biopsy and a propensity to underestimate certain pathology exists: "borderline" pathology[6]: i.e.,
  - Atypical ductal hyperplasia (ADH) - atypical ductal hyperplasia (over 50% of all cases of ADH diagnosed with core biopsy prove malignant at surgery, and invasive carcinoma is found in up to 33% of core biopsy-confirmed ductal carcinoma *in-situ* (DCIS)
  - Papilloma/invasive papillary lesion
  - Adenosis, radial scar
- Non-concordant result
- A few false-positive results have been reported
- The reported false-negative rate for malignancy is in the range of 2-6.7%, with a mean rate of 4.4%. These false-negative results are more likely to occur with micro calcifications.

Core biopsy over FNAC

- Conversion to core biopsy from FNAC for the preoperative diagnosis of breast lesion.

Increases sensitivity and specificity and reduces inadequate and suspicious rates:

- Stereotactic core-needle biopsy using a 14-gauge needle is widely accepted to be sensitive (90.5%) and specific (98.3%) in diagnosing breast masses, compared with 62.4% and 86.9%, respectively, for FNA.[7]
- The absolute and complete sensitivities were 80 and 93% for NCB in the diagnosis of cancer as compared to 65 and 82% for FNAC in 31 cases that were studied - authors favored core biopsy over FNA.[8]

Vacuum assisted biopsy

- Limitations outlined above for the core biopsy in particular with regard to DCIS and ADH have been overcome to some extent by the application of vacuum during the core biopsy procedure
- 6% of vacuum-biopsy DCIS were found to be invasive carcinoma at surgery compared with 21% with 14-gauge core biopsy
- Repeat biopsy rates for inadequate sampling of microcalcifications is also significantly lower when using vacuum biopsy (11.6%) compared with core biopsy (23.7%).

FNAC over core biopsy

Hardcore cytologists would argue that

- Samples a larger area with varied morphology at imaging
- Some studies favor FNAC over NCB as a less expensive, faster, and more sensitive test. For accessible, palpable lesions FNAC can be performed relatively straightforwardly and takes approximately 5 min in experienced hands. Therefore and for these cases, FNAC is easier to plan than CNB in an outpatient clinic. This advantage is often used as a strong argument in favor of FNAC over CNB
- FNAC allows immediate definitive diagnosis in a proportion of patients, within the outpatient department
- FNA smears containing micro-biopsies are of ample help in establishing a firm diagnosis, tumor typing, and predicting possible primary sites in metastatic tumors, which were not possible by cytology alone. Hence, this technique can be utilized to enhance the diagnostic accuracy of FNAC, if put into practice in evaluation of routine cytology smears, without increasing any financial burden on patients.

Combined FNAC and core biopsy[9,10]

There is controversy in the literature about the role of combining FNAC and NCB in the assessment of breast lesions. Some authors recommend combining the two techniques. FNAC may sample a larger or slightly different area of breast tissue than NCB, resulting in a smaller number of false negative cases when the two techniques are combined, as was evident in studies high lighting the importance of a multidisciplinary approach in the preoperative assessment of impalpable breast lesions-"quadruple approach!"

Changing terminologies

Atypical hyperplasia and DCIS

The lack of consensus for differentiating between hyperplasia, atypical hyperplasia and carcinoma *in-situ* is confounded by several factors-inter observer reproducibility, definitions and criteria employed by various investigators and variability of the risk reported towards the development of cancer. One definition characterizes atypical duct hyperplasia as having "the cytologic and architectural features of the non-necrotic forms of intraductal carcinoma (IDC) and the changes may involve two or more ductules (but) the involved ducts/ductules measure <2 mm in aggregated

diameter."[11] Others require "at least 2 spaces completely involved" by cells with appropriate cytologic features but do not include a measured dimension in their definition.[12] Differences also exist in regard to definitions of structural growth patterns designated micropapillary and cribriform, which are frequently seen in "non-necrotic" variants of intrductal carcinoma and in hyperplasias.

DCIS is characterized by proliferation of malignant epithelial cells, contained within the basement membrane of the mammary ductal tree. This definition only helps to define DCIS in relation to invasive carcinoma and applies to a morphologically well-defined lesion. The criteria for identifying low-grade DCIS and atypical ductal hyperplasias are still a grey zone and to differentiate these various lesions one from the other at morphology is unclear.

On a routine hematoxylin and eosin stained slide, the minimum requirement for the diagnosis of DCIS is complete involvement of one or more duct cross-sections by uniform population of cells, the aggregate cross diameter of which exceeds 2 mm. Lesions displaying partial involvement of duct cross-sections of 2 mm or less in aggregate cross-sectional diameter qualify as ADH. It is worth noting that the size criterion only applies for non-necrotic, low-grade variants of DCIS.

DCIS is not a single entity. It is now considered as a heterogeneous group of lesions that differ in their growth pattern, histological, cytological features and biological potential. Therefore, the need arises for a classification system that takes into consideration clinical implications.

The frequency of subsequent invasive carcinoma is considerably higher after IDC than after lesions usually diagnosed as hyperplasias or even atypical hyperplasias. A view was held that due to the problems in defining proliferative lesions and their diagnostic reproducibility, it was suggested by Tavassoli and workers that in a futile effort to distinguish between atypical hyperplasia and *in-situ* carcinoma; the lesions should be amalgamated into a term called mammary intraepithelial neoplsia or ductal intraepithelial neoplasia just as other organs like the cervix and vagina have a terminology such as CIN and VIN.[13] However, since its acceptance by WHO in 2003, this terminology has never become popular with either the reporting pathologists or the clinicians. The latter in particular seem to understand more clearly the concept of atypical ductal hyperplasia and carcinoma *in-situ*.

Columnar cell lesions (CCLs)[14-17]

CCLs of the breast are a group of lesions that have posed difficulties in interpretation to pathologists for years. They are characterized by the presence of columnar epithelial cells lining variably dilated terminal duct lobular units. The lining cells may be bland with no atypia or show changes, which may be mistaken for atypical ductal hyperplasia or DCIS. Luminal cells of these TDLUs in their simplest forms (columnar cell change) show apical snouts and luminal secretions with or without calcification. Columnar cell hyperplasia (CCH) refers to acini lined by more than two layers of columnar epithelial cells showing the above-described changes along with the formation of micro papillae. CCL and CCH may display cytologic atypia termed as CCL with atypia and CCH with atypia respectively; together known as "flat epithelial atypia" formerly called as "clinging carcinoma." These lesions generally show low-grade atypia. High-grade cytologic atypia is not a feature of CCLs and is always diagnosed as high-grade DCIS. Recently, there has arisen a pronounced interest in these lesions because they are being encountered with increasing frequency in breast biopsies performed for the presence of mammographic microcalcifications.

The clinical significance of these lesions unfortunately is not fully understood, and the lack of uniformity in diagnostic criteria has further complicated issues. CCLs are found to be associated with tubular carcinomas and lobular carcinoma *in-situ* and their presence in core biopsies should be viewed with caution as the full spectrum of surrounding changes cannot be viewed.

CCLs are ER and PgR positive, basal cytokeratin (CK5/6 and CK14 negative), exhibit low numbers of genetic alterations, features that are similar to those of low grade *in-situ* and invasive carcinoma. In addition, common chromosomal alterations between CCL and more advanced atypical lesions within individual terminal duct lobular units suggest a common molecular evolution. These data further support the hypothesis that CCLs are an intermediary step in the development of some forms

of low grade *in-situ* as well as invasive lobular and ductal carcinomas.

Radial and complex sclerosing scars[18]

These are complex sclerosing lesions, which are being increasingly picked up on mammographic guided biopsies because of their resemblance to microcarcinomas on imaging. They are associated with a sclerotic center with radially arranged spokes of epithelial proliferation. Smaller lesions are called radial scars and those above 1 cm as complex sclerosing lesions. About 10-20% of these are known to be associated with carcinomas.

Molecular markers in breast carcinoma

Molecular markers in breast carcinoma are used to identify subsets of tumors with significant prognostic and therapeutic implications. Ancillary IHC studies for hormone receptors (HRs) such as ER, PR, and HER2, act as prognostic or predictor indicators in breast cancer and are the most commonly used and are mandatory to be performed in every breast cancer report. Breast carcinoma is highly heterogeneous at both the clinical and molecular level. Therefore, separating breast cancer into various subsets based on its biological behavior for therapeutic options is helpful. Progesterone receptors serve as an indicator of an intact ER pathway, which reflects the dependence of the ER/PR axis and predicts which patients will respond to hormone therapy because adequate estrogen levels are required to transcribe PR. Accurate and quantitative assessment of HRs is critical when using IHC studies. Several factors influence results and have to be kept in mind while standardizing procedures. ER and PR receptor status is reported either by the Macarthy's histoscore[19] or by the American Society of Clinical Oncology and College of American Pathologists (CAP). Criteria:[20] Both methods take into consideration the intensity of the nuclear stain as well as percentage of cells stained. Her2 neu is generally performed by IHC,[19] FISH or presently even by the reverse transcription-polymerase chain reaction (RT-PCR). IHC scores with 2+ result should always be ratified by the FISH technique.

Based on the expression of various gene sets, the researchers have categorized breast cancers into 5 subsets with prognostic significance, such as the luminal A, luminal B, HER2 overexpressing, basal –like, and normal breast-like subtypes.

Molecular subtypes of breast carcinoma[20]

Luminal subtypes

The high expression of the genes normally expressed by luminal epithelium resulted in the names of luminal subtypes. The luminal tumors express CK8/18, GATA3, and ER related genes, which is why they are designated as the ER^+ group. The estrogen receptor is highly expressed in luminal Type A tumors with low levels of proliferation-related genes resulting in a usually low histologic grade and excellent prognosis. The estrogen receptor is expressed in lower levels in luminal Type B tumors, with higher proliferation-related genes, often resulting in a higher histologic grade and a significantly worse prognosis. A significant number of HER2 overexpressed, ER^+ cancers fall into the luminal B category, rather than the HER2 subtype.

HER2 subtypes

Tumors in this group are characterized by amplification of ERBB2 (formerly HER2) genes on band 17q12. These tumors often demonstrate 3^+ HER2 IHC staining and are completely negative for ER and PR. Therefore, as mentioned previously, the HER2 overexpressed but ER^+ tumors would best fit into the luminal B category. The HER2 subtype tends to have an aggressive clinical course.

Basal - like subtypes

These tumors express basal/myoepithelial cell genes, such as CK4, CK14, CK17, caveolins 1 and 2, nestin, P- cadherin, CD44, and EGFR. In addition, they are usually triple-negative tumors for ER, PR and HER2. A few cases harbor EGFR gene amplification or aneusomy as well as KIT gene expression. This subtype has also been noted to have an aggressive clinical behavior with high histologic grade, high proliferative index, metaplastic areas, central necrosis, pushing borders, and a prominent lymphocytic infiltrate. Basal-like tumors are more commonly found in women of Hispanic or African descent and show a high response rate to chemotherapy. The immunohistochemical and morphologic features of basal-like tumors are similar to those arising in women with BRCA1 germline mutations because of abnormalities in the BRCA1 pathway. However, most women with basal-like carcinomas do not have germline BRCA1 mutations.

Breast like subtypes

These tumors often express adipose tissue and other nonepithelial cell genes, including basal cell

genes, and typically cluster with healthy breast and fibroadenomas. The clinical significance of this group has yet to be determined. However, some researchers have proposed that this subtype was misrepresented because of poor tissue sampling, creating a false category.

Gene expression profiling

Gene expression profiling is a method of providing vast amount of information about carcinoma, their behavior and prognostic factors. Patterns of gene expression and their interpretation predict the metastatic potential of these malignancies. Perou *et al*. proposed the first molecular classification of breast cancer using gene expression analysis on DNA microarrays. The intrinsic gene set, or the genes in which the expression patterns were analyzed, were characteristic of a specific tumor. Thus emerged by these studies the molecular subtypes of carcinomas outlined above with studies characterizing a group of genes which were related to the ER pathway, PR pathway or even metastatic potential. Predictive gene sets which are currently available are MammaPrint (Amsterdam) and Oncotype Dx (Genomic Health Insurance, California).

The mammaprint was the first prognostic gene set available in clinical practice and was developed in Amsterdam. It is based on a 70 gene set profile using an oligonucleotide array. This gene set helps in deciding whether the patient should receive adjuvant chemotherapy.

The oncotype D_X is another commercially available RT-PCR based assay which provides a recurrence score (RS) based on a 21 gene panel associated with cancer prognosis. The test has been shown to provide predictive and prognostic information in ER^+, lymph node-negative tumors by providing a RS value, which varies from 0 to 100 and predicts the risk of a 100 years recurrence. Patients who have a low score, <18; intermediate score 18-31; and high score 31 or greater. Patients with a high score will benefit from chemotherapy.

Conclusion

The approach to diagnosis of breast carcinoma, the unmasking of grey zones due to screening by mammography and the end result of such new lesions discovered have prompted variations and newer insight into the pathology and management of this cancer. A new molecular classification has resulted in targeted therapy and the gene signatures obtained by these molecular techniques prognosticate their behavior and response to treatment.

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