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Review

Multidisciplinary Approach and Pivotal Role of Pathologist in Diagnosis of Breast Cancer: Technological Advances: An Updated Review for Breast Health Care experts

PATRA S.B

ABSTRACT

Clinical and pathological diagnosis of breast carcinoma is advancing at the same pace as the global increase in its incidence, morbidity and mortality. Research scientists (bio molecular, pathologists, clinicians and geneticists) are working on war footing for prevention, cure and treatment of breast cancer. In near future, breast cancer diagnosis may advance inexplicably. The pathology report serves not only as a hard copy for clinicians on which various treatment modalities are based , but also as a teaching module for educated cancer patients. The pathologist, who plays a very critical and pivotal role, hardly meets the patient in most institutional set ups. In unlimited resource centers, his/her role is very critical, because patients themselves can challenge clinicians and sue the pathologist.

The scientific document based on observation can be finite, but the pathologist has to go beyond the finite observation, because many technical and clinical variations and limitations have to be taken into consideration. A guarded analytical opinion along with suggestions has to be given for the patient.

Diagnosis of breast carcinoma has leaped rapidly from FNAC to DNA with many intermediaries in between. In some institutes, the best possible cost effective diagnosis is given, whereas in others, molecular studies are done to provide the diagnosis which influences the therapeutic and prognostic outlook.

Key Words- Diagnosis of breast carcinoma, Multidisciplinary approach, global pathologists

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Introduction

In 2003, BHGI (Breast Health Global Initiative) convened a panel of breast cancer experts to develop a consensus recommendation for clinical and pathological diagnosis in limited resource countries [1] and guidelines were updated [2].The International group met again in 2005 at Bethesda, Maryland. The panel, consisting of 12 countries including India, discussed the recent advances in clinical and pathological

diagnosis of breast cancer and charted down the guidelines as per WHO recommendations [3], [4].
It provides a logical, systematic frame work for building Breast Cancer Diagnosis in the best possible way, to be adopted as per the infrastructure and available resources, adhering to the guidelines and implementing it according to the recommendation by BHGI.
There were 4 stratification schemes [Table/Fig 1].
1. Basic-Methods absolutely required for diagnosis.
2. Limited-Large improvement on the basic level.
3. Enhanced-Small improvement on limited level.
4. Maximal-Where unlimited facilities are available for diagnosis and treatment.

Issues related to clinical and pathological diagnosis

Every health care institution (in small / metropolitan city) should follow these guidelines for better heath care and better clinico-pathological coordination and for fewer constraints to authorities, health providers and patients .This would focus & unfold many unknown environmental ,familial & genetic basis of breast breast cancer.

a) Goal of Diagnosis: To determine whether the tumor is benign/malignant, noninvasive/invasive, permitting timely and appropriate care.

b) Definitions:

Clinical diagnosis - Involves clinical examinations supplemented by mammography, CT with or without FNAC and/or core needle biopsy.
Pathological diagnosis – Involves using various investigative tools.ss

C) Simplicity of the process: Tissue retrieval should be adequate, as the patient faces barriers in approaching various clinical experts.

d) Quality of the process: The pathology report should provide all details of pathological findings, including molecular studies if available, to meet the requirements of clinicians. As far as possible, they should discuss with the pathologist, any query not befitting their clinical findings and investigations.

e) Correlation of findings: Pathology report need to be correlated with clinical findings for better results.
The "triple test" is suggested

1-clinical & imaging +ve biopsy –ve.

2-clinical or imaging +ve biopsy negative.

3-A repeat biopsy necessary.

f) Importance of the system: For the implementation of guidelines of BHGI in limited resource countries, in addition to resources needed to perform and interpret the biopsy the following are also essential: provision for tissue labeling, transportation, documentation of the pathology report, communication of the results with health care personnel and patient follow up.

(Table/Fig 1) Resource Allocation For Diagnosis & Pathology

Level of	Clinical	Pathology	Imaging & laboratorytests
Basic	History Physical examination Clinical Breast examination	Interpretation of biopsy Cytology or Pathology report describing tumour size.	* Diagnostic breast Ultra sound +
mamo	Surgical biopsy Fine needle aspiration	lymph node status,histologic type, tumour grade.	graphy
Limited	Core needle biopsy Surgical resection	Determination and reporting of ER/PR status	*Plain chest X-Ray Liver ultrasound Blood chemistry CBC
Enhanced	Preoperative needle localization under mammographic/Ultrasound guidance	* Determination and reporting of margin status Onsite Pathologist	* Diagnostic mammography Bone scan
Maximal	Stereotatic biopsy Sentinel node biopsy	* HER2/neu status * IHC staining for sentinel node for micrometastasis * Molecular Micro array	*CT scan PET scan MIBI scan Bone scan

DIAGNOSTIC PROCEDURES

1. Clinical

*History taking like family history, AIDS, malaria etc.
*Clinical breast examination-(CBE), Nipple discharge, retraction, metastasis [5], [6].
*Serum alkaline phosphatase for skeletal metastasis.

*Diagnostic mammography for synchronous or metachronus tumor in contra lateral breast.
*Diagnostic Ultrasound-------Particularly for an asymptomatic patient and for palpable tumor, for further clinical and pathological investigations.

2. Pathological

From the establishment of initial diagnosis, to determining the stage of malignancy, this carries both prognostic and therapeutic implications.
Basic pathological techniques like FNAC or core needle biopsy are mandatory in limited resource countries .This is done by palpation and/or supplemented by imaging techniques, either in a clinic or operation theatre [7].

Fine Needle Aspiration Cytology (FNAC)

FNAC helps to determine whether the lump is benign or malignant. Problem is encountered with intermediate hyperplastic lesions, where it is difficult to decide, what to do, in such cases if the pathologist's report and clinical findings are complementary, or if the FNAC is very diagnostic., the clinician can go ahead with palliative or other surgical treatment [8]. Provision should be there for a second opinion in regional centers. Multiple samples will enhance the diagnostic accuracy [9].

Core Needle Biopsy

In non-palpable or small tumors, image guided single or multiple core needle (removed by cutting needles) biopsies and automated gun biopsy is recommended after appropriate patient selection [10].
Limitations: Interpretation of certain tumor types like atypical medullary carcinoma and proper tumor grading for intermediate lesions may not be possible [11]

Surgical Biopsy

In patients having large primary tumors, larger tumor samples may be needed for more histopathological information.

Record Keeping

Medical Record

-To know p-TMN (Pathological) and c-TMN (Clinical), for regional and/or global statistical comparative data, ethnic group involved [12]; hence, can keep data for prevailing pattern.
-To communicate the results to other health care providers.
-Diagnostic protocols may enhance the improvement of prevalent techniques. Insufficient samples documented as False +ve. False-ve, true +ve cases recorded.
-It can be useful for planning resource allocation.

Registries

The medical record provides information for individual patients. The registry provides such information for the populations. So, there should be introduction of local, regional and national registries at limited, enhanced and maximal levels.

Follow Up

In addition to its obvious benefits in terms of continuity of care and support of the patient, it is essential for assessing diagnostic performance. The frequency of **insufficient** samples should be documented.

Pathology Report

The accurate pathology report starts with the clinician who provides the necessary data The pathology report gives a predictive knowledge, taking into consideration, clinical and bio molecular parameters [13], which also facilitates the patient's education and respects their autonomy..
-Triple Test is necessary if FNA or Core Biopsy is used [14]
-ER/PR study is recommended if treatment for Tamoxifen, Aromatase inhibitor or surgical/ medical ablation is possible**.**
-HER2/neu based diagnosis and treatment is costly, hence possible only at maximal level set up.

Predictive Value of Pathology Report

Histopathology type, tumor size, lymph node status and tumor grade are absolute requirements for the predictive value at least at the basic level, as it determines the type of therapy.

Role of Pathologist In Multidisciplinary Institutions And Unlimited Resource Centers

There are many challenges for pathologists in multidisciplinary breast cancer diagnosis in institutions with unlimited resources, because of molecular and genetic advances

Steps are suggested where the breast cancer clinical team and the patients can ensure optimal outcome from the pathology report, where the pathologist's role is very different from limited resource countries [15].The multidisciplinary team consists of :

1-The pathologist.

2-Radiologists, oncosurgeon, oncophysician, oncotherapist, nurse, social worker and physical therapist .

Initial Diagnosis of Breast Cancer

CORE NEEDLE BIOPSY-A good biopsy gives treatment options like conservative Surgery or nonadjuvent therapy.

Tumor grading is possible. If the sample is adequate and if supplemented with ER/PR, HER2/Neu can outline treatment modalities.

DCIS can be treated by lumpectomy.

FNAC

Either single or multiple only, can give a diagnosis of malignancy under IMAGE GUIDE by quick dip method, and can be later confirmed by PAP. No treatment decisions can be taken at this point.

But flow cytometric studies can be done and other molecular studies can be done, Including cancer genomics and proteomics.

Pathology Report, Patient's Perceptive.

The pathology report is the patient's teaching module, as patients in countries with unlimited resources are always concerned, whether there is an ERROR.

The patient may ask for a second opinion in such cases.

Pathology Report as Patient Teaching Module In Unlimited Resource Centers

A Second Opinion

Opinion variation may be very trivial. It may vary from grade-1 to grade-2 due to the observer's interpretation of nuclear contour, size and tubule formation, which may not affect the treatment much. Hence, the patient has to be informed of such variations by the treating doctor or pathologist.

Hormone Receptor Status

The ER/PR status can not be relied upon due to:

1. Variability in setting norms.11% to 10% staining is considered to be low positive. Some laboratories report it as positive or negative, which is tough to interpret.
2. Technical errors may occur.
3. Two different tissue samples in two labs may give variable results.
4. Sensitivity of the technique used, may give variable results.

Both the pathologist and the clinician should take this into consideration and proceed accordingly. Generally, ER/PR negative cancer and HER2/neu positive cases have a poor survival rate and an early metastasis. The pathologist should put in the report as prognostication for the patient's perceptive.

Special Cancer Types and Subtleties of Interpretation

As stated earlier, core needle biopsy will not give required information like grade, special

cancer types, or even a sampling variation of molecular features. Hence, a pathologist should be very watchful and give only guarded and minimum information in such maximal facility institutions, after thorough discussion with the clinical team.

HER2/Neu status and Breast Cancer

HER2/Neu directed therapy can change cancer prognosis[16]. Women with estrogen and progesterone-receptor (ER/PR) negative and HER2-positive disease have a poor prognosis, and should be treated aggressively after the initial diagnosis. This confirms the need for novel treatment strategies for HER2-positive and ER/PR-negative patients, and emphasizes the survival difference in HER2-positive patients depending on their ER and PR status. The pathologist's role is only to report the molecular findings and give a foot note of the probable prognosis.

Issues on the ER/PR and Her2/Neu Status

Even for a triple negative patient (ER –ve, PR –ve and HER2/neu– ve), there is no molecular based therapy. Pathologists, while reporting, should keep in mind the real negative results, as the test results may vary right from fixation, tissue handling and sampling errors. Only chemotherapy and other adjuvant therapy can be given. But metastatic spread, even with adequate therapy, is affected by a new molecular factor found recently i.e. Fascin, an actin based expression as mentioned below.

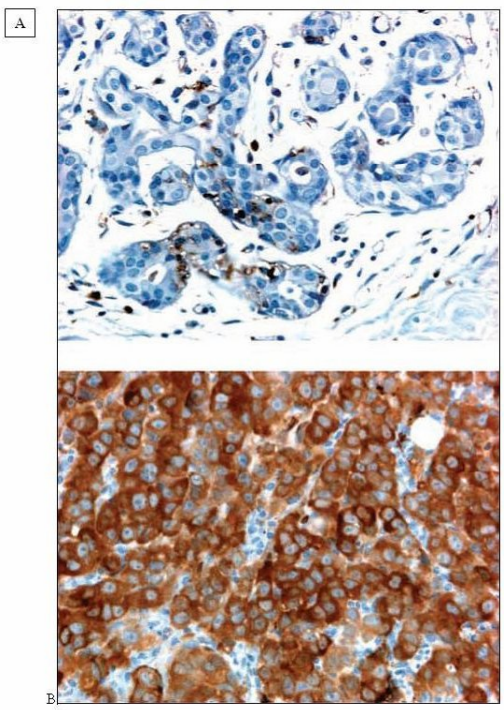
Molecular Research.

A pathologist who is a morphologist, basically looking under simple H&E slides as Dr Juan Rosai has rightly said, "There is a marriage between a morphologist and molecular biologist"[(17]. In his article, he has mentioned the following. "Provided any new technique provides information of prognostic or therapeutic significance beyond that current gold standard, these technologies can be simply viewed as different ways to explore the various levels of complexity within the tree of life: DNA–RNA–protein–cell–tissue–organism, starting with the genotype and ending with the phenotype.

BUT NEW MOLECULAR RESEARCH HAS ITS OWN SINGNIFICANCE MAY UNFOLD CERTAIN INTRICACIES IN CANCER DIAGNOSIS, BIOLOGICAL BEHAVIOR & TREATMENT MODALITIES.

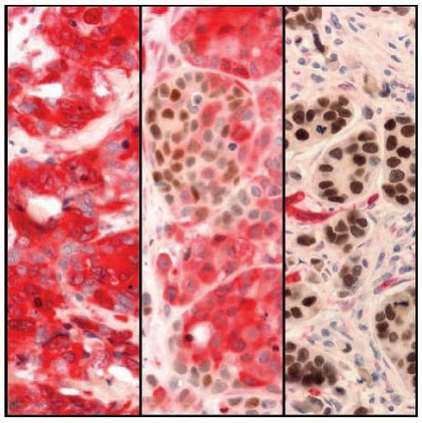
NEW MOLECULAR RESEARCH

Recently the expression of "fascin", an actin-bundling motility-associated protein, has been found to be responsible for less disease free interval and overall survival in ER and PR negative cases. There was no correlation between fascin expression and HER2 status, or between fascin expression and the pattern of metastases. [Table/Fig 2], [Table/Fig 3]. Given fascin's role in altering cell motility, over expression may contribute to a more aggressive clinical course in ER/PR-negative breast cancers [18].



(Table/Fig 2) Normal breast ductal epithelium is negative for fascin, whereasmyoepithelial cells show moderate staining (A, _400).

Typical 3+immunohistochemistry fascin-positive breast cancer case observedwith neighboring endothelial cells serving as an positive control (B,_400).



(Table/Fig 3) Double labeling of fascin in red and ER in brown from three separate TMA tissue cores, fascin-positive/ER-negative (A,_400),fascin-positive/ER-positive (B, _400), and fascin-negative/ER-positive(C, _400). The dual-positive case (B) has no individual cell that co express fascin and ER. The ER-positive case shows no fascin-positive tumor cells although it displays fascin-positive internal control endothelial cells ©.

Oncotype DX™ for predicting risk of breast cancer recurrence

Oncotype DX™ is a novel genetic test designed to accurately predict relapse in women with node-negative and ER-positive breast cancers, who are receiving tamoxifen. This test kit is now commercially available from 'Genomic Health'. This is the first genetic test marketed for predicting outcomes of patients with cancer. Patients with breast cancer may request information about the relevance of Oncotype DX™ for treatment of their disease [19].

One of the first steps in the development of ncotype DX™ was perfecting the reverse transcriptase-polymerase chain reaction (RT-PCR) to detect m-RNA levels in paraffin-embedded (EPE) tumor tissues. This study compared a 48-gene assay from frozen or EPE tissues from the same tumor. This study also showed that RT-PCR on archival material was concordant with immunohistochemistry assays for estrogen receptor, progesterone receptor and HER2 receptor.

It would appear from these data, that the test could be clinically useful in reassuring 50% of patients with ER-positive, node-negative and low-risk disease, that they are unlikely to benefit from adjuvant chemotherapy in addition to tamoxifen. Whether or not patients with intermediate and high-risk breast cancer will benefit from adjuvant chemotherapy in addition to tamoxifen remains to be determined; however, a more accurate determination of the risk of relapse can undoubtedly help patients in their decision making.

The Human Genome Team is taking pathologists and Breast cancer health care experts from the unknown to the known in scientific domain. In future, many things will be revealed .So in countries with unlimited resources, breast cancer diagnosis to a certain extent, is dependent on pathologists who are engaged in routine diagnostic work, but its prognosis, biological behavior and the patient's future, but is dependent on

molecular biologists and geneticists to a larger extent in modern era Such facilities is beyond the reach of patients in many counties.
But wherever such facilities are available for a debatable case, should be utilized. In certain developing countries, it is available in some institutions.

A New Digital Image Histopathology

Pathologists in enhanced & maximal resource centers use 'A new Digital Image' microscopy to speed up cancer diagnosis [20]. The ultra-rapid virtual scanner gives pathologists a quicker way to break down a biopsy. No pathologist or special lab is needed for the test, just the machine. Situated on top of the microscopes, a 24-megapixel camera captures multiple images. Then the photographs are digitally transmitted immediately over the Internet. "If a patient comes in here at 11 o'clock in the morning, by 3 o'clock in the afternoon, they'll have gotten a diagnosis," A new cancer scanner can be used for any type of cancer, the results can be seen worldwide in an instant over the Internet and an opinion can be taken by dynamic telepathology. More than half of the breast cancer patients, who sought a second opinion from a multidisciplinary tumor board, received a change in their recommended treatment plan, which is a boon to heath providers in developing countries.

Nanotechnology and breast cancer diagnosis [21]

Nanotechnology is a function-based technology to measure the softness of the so-called morphologically benign cells. As cancer cells are softer than benign or atypical cells, they can be detected by AFM microscopy, which, by putting a cantilever on the cell membrane, can detect the cell softness in the cells of lesions which appear to be benign. In contrast to structure-based approach in other molecular tests it has a function-based approach. Besides giving out a diagnosis on the functional basis of individual tumor cells, it can even solve many genome-oriented diagnoses, which cannot be solved by existing Genomic technologies. But it is not easily accessible even in technically advanced resource centers in developing countries Its use in Breast cancer till today is mostly missing malignant cells in effusions by conventional microscopy.

Summary & Concluding remarks

Keep your knowledge abreast, work according to the perview of the institution where you are working, encourage the junior pathologists for modern technological applications, be satisfied with simple H and E stain light microscopy if it is the only available resource and do the best for the patients at large. As far as possible, pathologists in a different set up, from small cities to metropolitan cities, from limited resource centers to expanded resource centers, should try to follow a set of norms in the best possible way, balancing objective technological findings and their analytical power and inner intuition, keeping in mind all variables at all levels, from clinics to laboratory, to dispatch of reports.

Looking into all types of objective tests from FNAC to DNA, many individual breast cancers are similar where clinicians and pathologists may say that they have done their best and that the rest was "beyond science", until other technical advances like Nanotechnology are available, whose applications promise a brighter future for breast cancer patients.

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