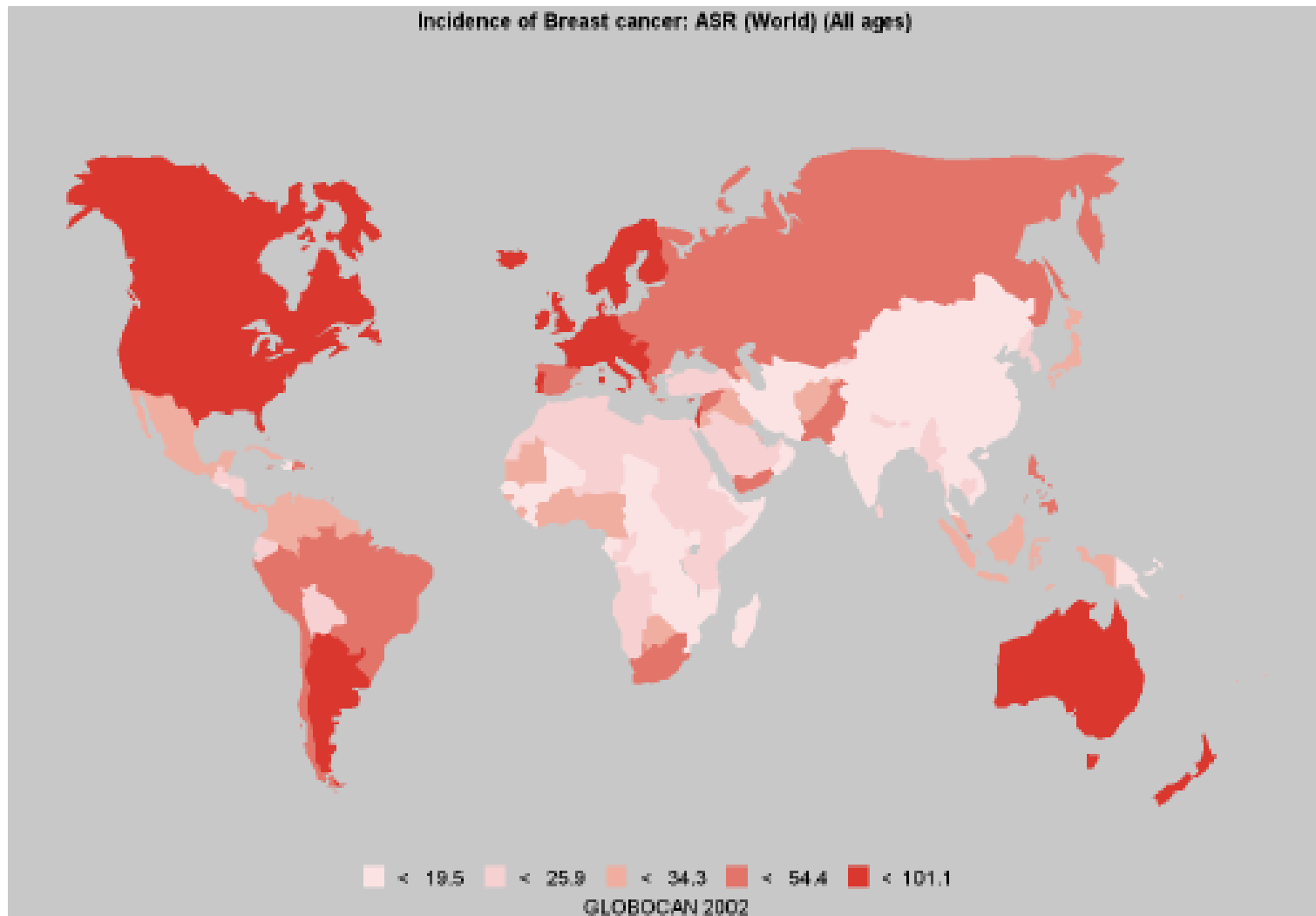


THE ROLE OF PATHOLOGY IN THE EVALUATION OF BREAST CANCER

Pr Jean-Marie DANGOU

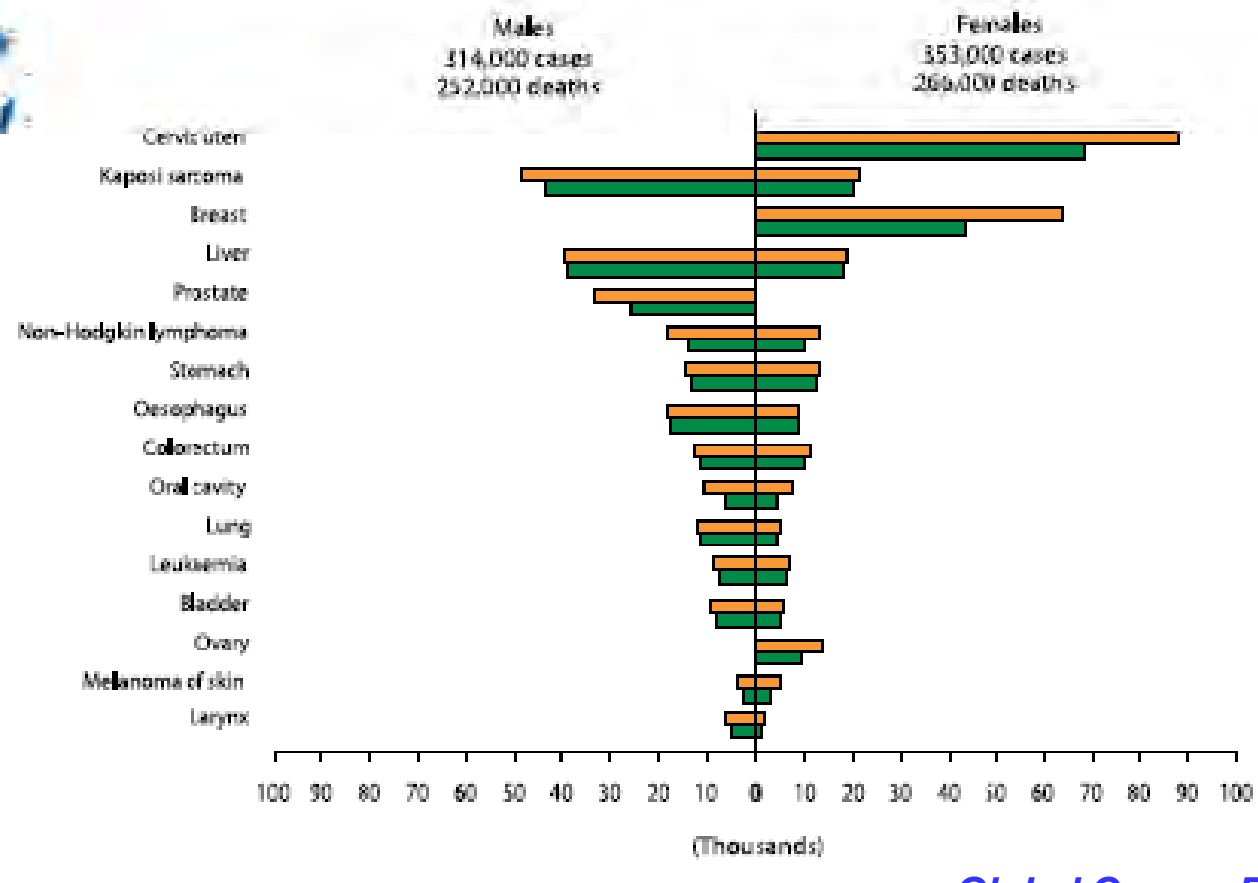
Introduction



Globocan, 2002

Introduction

WHO African Region (AFRO)



Introduction



- Establishes the diagnosis (primary responsibility)
- Functions as a consultant
 - Clinical and pathologic staging: TNM; SBR; ...
 - Information for standard treatments
 - Evaluate new treatments
 - Prognosis estimates
 - Evaluate end results of treatment

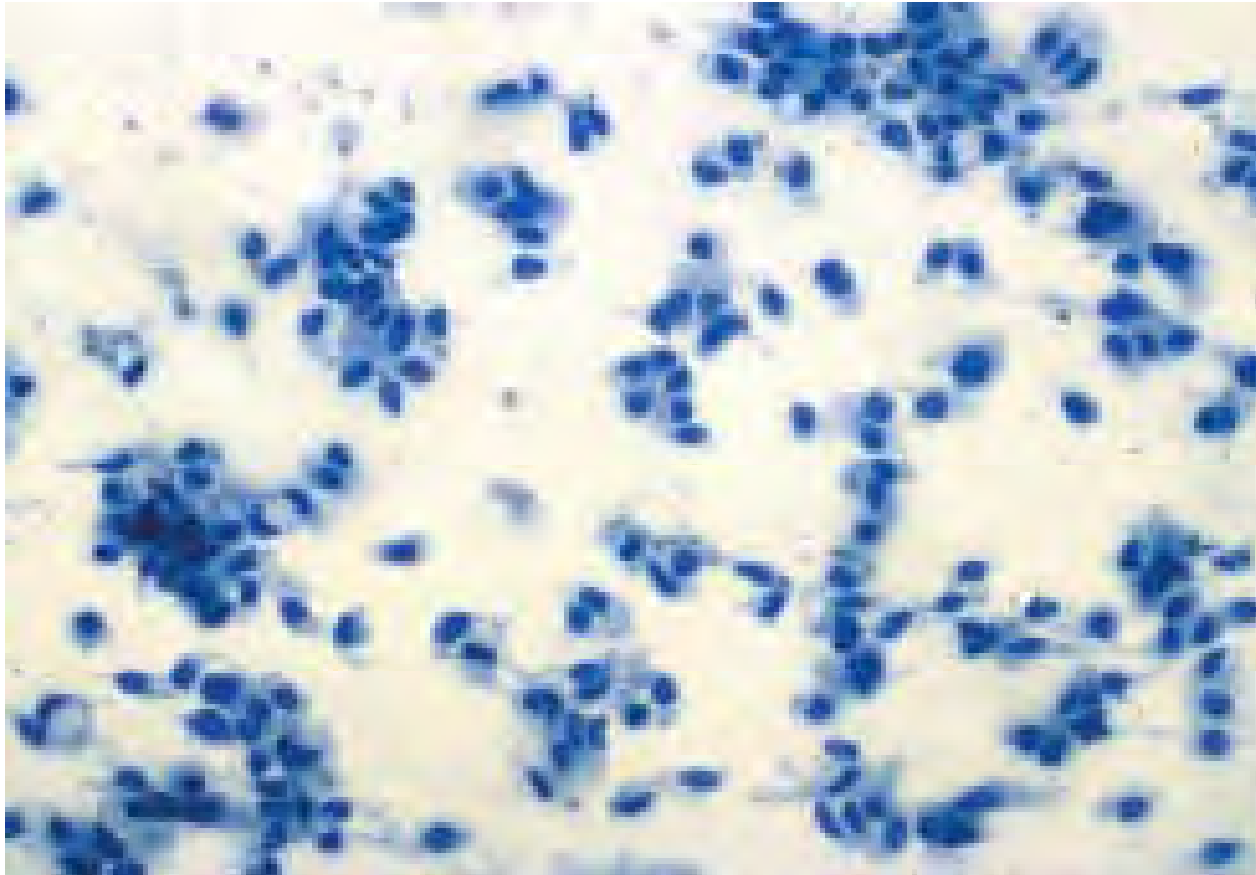
Diagnostic methodology



- FNA Biopsy

- Initially used in patient with palpable clinical breast cancers. Expanded mammographically detected non palpable breast lesions
- Cell dissociation, arrangement in small clusters, nuclei larger than 16 μ m, anisonucleosis, irregular nuclear borders, nucleoli, necrosis
- High sensitivity and specificity of the procedure
- Its use to prove benignancy is hazardous

FNA suspect of cancer



Diagnostic methodology



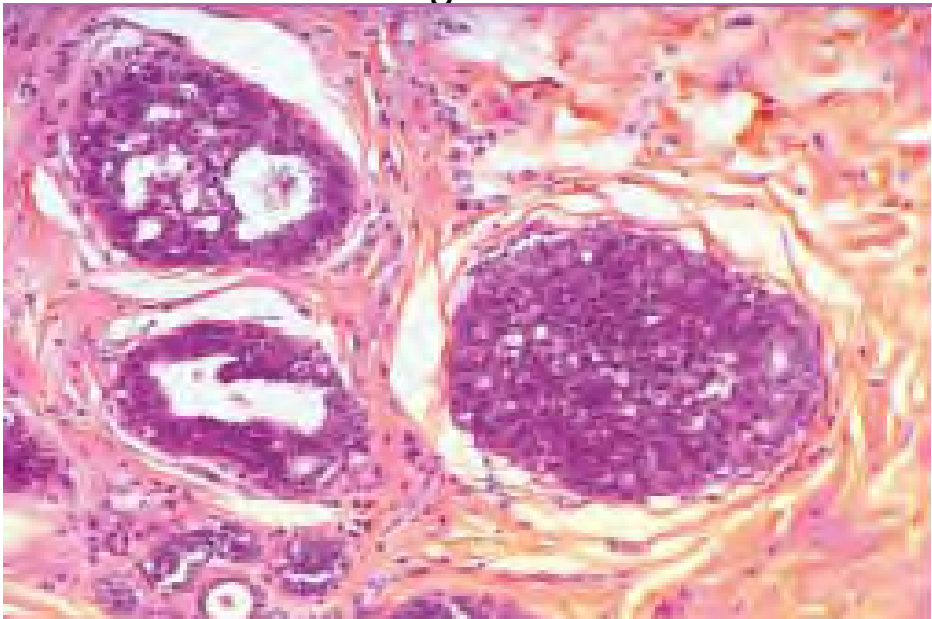
- Rapid Frozen section: well accepted means of establishing a diagnosis during intra operative consultation
- Frozen section are technically comparable to paraffin sections (except extensive sampling)
- Accurate diagnosis more important than a rapid one
- Mammographically detected non palpable lesions:
 - Work with surgeon and the radiologist
 - Confirm presence of the lesion in the excised specimen
 - Radiogram from the uncut excised mass for comparison with the clinical mammogram
 - Fillets of the entire specimen at intervals of 3-5 mm and a radiogram
 - Samples with the lesion used for Frozen section
- Intra operative assessment of sentinel nodes

Factors relating to selection of therapy and prognosis

- Primary carcinomas

- In situ

- Many intraductal carcinomas detected by mammography or an incidental microscopic findings
- Factors influencing management: size, extent, histologic type and differentiation, nuclear grade
- Poorly differentiated nuclear morphology, comedo type of coagulation necrosis



Lobular carcinoma in situ (well differentiated)

Factors relating to selection of therapy and prognosis

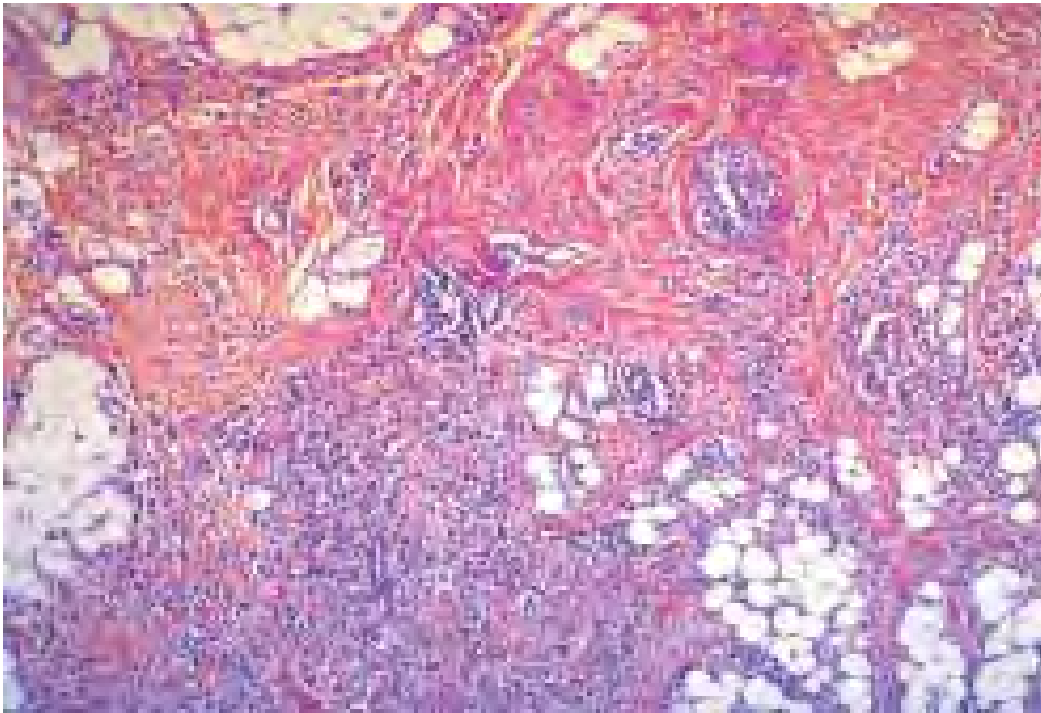
- Primary carcinomas

- Micro invasive

- Minimal breast cancer = breast carcinoma in situ or invasive carcinoma not greater than 0.5cm (*Gallager & Martin, Cancer, 23:855-873, 1969*)
- Others modified the extent of the invasive component to not greater than 1.0cm
- More precise TNM classification
 - Tis: intraductal carcinoma
 - T1a: invasive cancer of 0.5cm or less in greater dimension
 - T1b: invasive cancer greater than 0.5cm but no more than 1.0cm
- Need for the Pathologist to report carcinoma in situ as well as the measured size of small infiltrating carcinoma using the pathologic TNM

Factors relating to selection of therapy and prognosis

- Primary carcinomas
 - Invasive
 - Invasive cancer greater than 1.0cm
 - Cancer cells found in the connective and adipose tissues
 - Histologic type to be determined



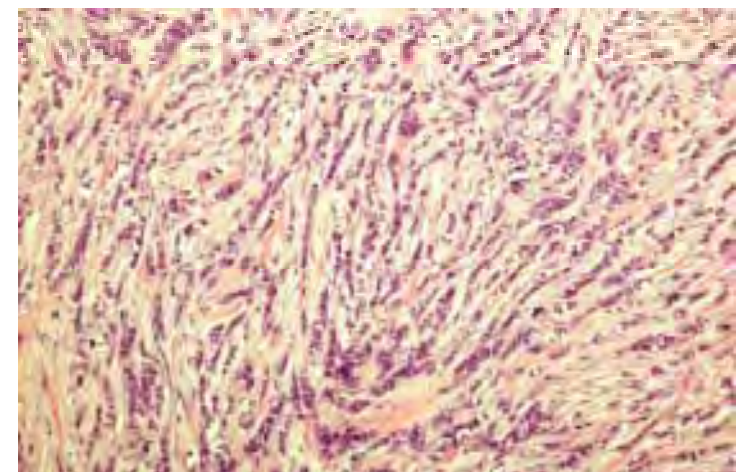
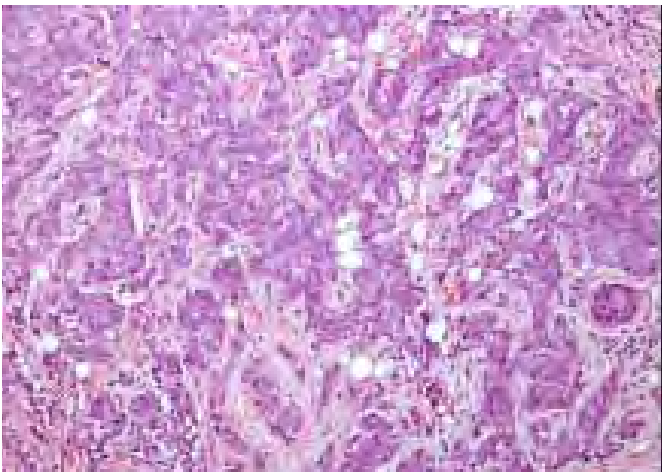
***Infiltrating ductal carcinoma
(poorly differentiated)***

WHO Histologic Classification of Breast Tumors

- Epithelial Tumors
 - Benign
 - Malignant
 - Non invasive
 - Intraductal carcinoma 8500/2
 - Lobular carcinom in situ 8520/2
 - Invasive
 - Invasive ductal carcinoma 8500/3
 - Invasive ductal carcinoma with a predominant IDC component 8500/3
 - Invasive ductal carcinoma with a predominant lobular in situ component 8520/3
 - Mucinous carcinoma 8480/3
 - Medullary carcinoma 8510/3
 - Papillary carcinoma 8503/3
 - Tubular carcinoma 8211/3
 - Adenoid cystic carcinoma 8200/3
 - Secretory (juvenile) carcinoma 8502/3
 - Apocrine carcinoma 8401/3
 - Carcinoma with metaplasia: Squamous type (8570/3); Spindle cell type (8572/3); Cartlagenous and osseous type (8571/3)
 - Mixed type
 - Others
 - Paget disease of the nipple 8540/3

Pathology of the primary cancer: prognostic indicators

- Histologic type
 - Survival generally related to specific histologic types
 - Infiltrating ductal carcinoma n.o.s: 65-70% of all breast cancers associated with a 10-years survival rate of 50 to 60%.
 - More favorable types: adenoid cystic, medullary with lymphocytic infiltrate, mucinous, papillary and tubular
 - Less favorable types: Scirrhus, inflammatory type



Pathology of the primary cancer: prognostic indicators

- Histologic type
 - Infiltrating ductal carcinoma n.o.s: large proportion → innate biologic aggressiveness
 - Degree of differentiation
 - Histologic grading (HG) based on tubule formation, anaplasia and mitotic rate (*Bloom, Richardson*)
 - HG I: 81% survival at 5 years and 41% at 20 years
 - HG II: 54% survival at 5 years and 29% at 20 years
 - HG III: 34% survival at 5 years and 21% at 20 years
 - Nuclear differentiation (Nuclear grade) (*Black & Speer, 1957*)
 - NG 1: anaplasia NG 2: intermediate
 - NG 3: well differentiated
 - NG independent predictor of prognosis
 - Major objection to the grading: subjectivity - intraobserver and interobserver variation
 - Grading most significant when 3 rather than 4 grades are used; Favorable prognosis, intermediate group and very unfavorable prognosis (*Henson, Arch Path Lab Med, 112:1091-1096, 1988*)

Pathology of the primary cancer: prognostic indicators

- Lymphatic and Blood Vessel Invasion
 - Indicator of probable dissemination of the cancer
 - Problem with morphologic identification of tumor emboli in blood and lymphatic vessels: Elastic stains very helpful; IHC to identify endothelium (*Ulex europaeus* agglutinin I lectin)
- Breast conservation
 - Increase number of patients with invasive breast carcinoma who elect treatment by excision of the cancer and radiation therapy
 - Pathologic studies of the primary tumor identified indicators of risk for local recurrence (*Fischer, Cancer, 1986*)
 - Lumpectomy alone: factors for recurrence – tumor size ≥ 2 cm, HG & NG poorly differentiated, lymphatic permeation
 - Lumpectomy + irradiation: only intralymphatic extension
 - (*Harris et al, Ann Surg, 1985*) 3 significant pathologic features associated with local recurrence: prominent carcinoma in situ in the tumor; CIS in adjacent grossly normal tissue; NG 3

Pathology of the primary cancer: prognostic indicators

- Breast conservation

- Guidelines reported for the evaluation of patients with mammographically non palpable carcinomas with micro calcifications (*Schnitt, N Engl J Med, 1988*)

- Specimen radiograph
- Careful gross description of the excised specimen
- Inking of specimen margins before sectioning
- Microscopic examination with description of the relationship of the calcification to the lesion and the lesion to the margin
- Repeat excision of the primary site if residual micro calcifications are seen on postbiopsy mammography or the tumor involves margins of resection microscopically

Pathology of the primary cancer: prognostic indicators

- Axillary Lymph Nodes

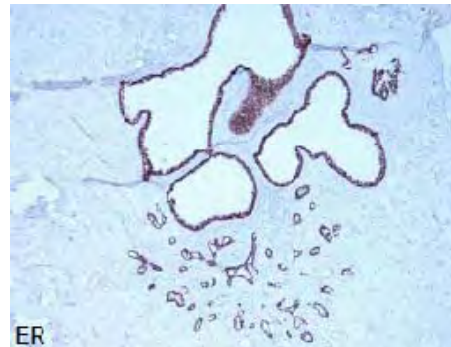
- Presence of axillary lymph node metastasis is an indicator of distant metastasis, and as the number of axillary lymph node metastases increase, the survival rate decreases.

- Axillary dissection: remove at least 10 and preferably 13 or more lymph node

- Steroid Receptors

- Presence or absence of receptors factors influencing the type of adjuvant therapy selected

- IHC methods to detect the ER/PR in paraffin-embedded tissues and frozen section



Pathology of the primary cancer: prognostic indicators

- DNA Flow Cytometry

- DNA histograms combining DNA index and S-phase fraction (Type I: diploid DNA & low SPF; Type III: aneuploid DNA & high SPF)

- Detection of Occult Metastases by Monoclonal Antibodies

- Clinical significance of occult metastases detected by IHC & ICC not elucidated yet.

- Multivariate Analysis

- Mitotic activity: mitotic index (MI), mitotic activity index (MAI), mitotic grade (MG) = nb of mitosis per 10 high power field (HPF)
 - MG 1 = 0 -10/10HPF
 - MG 2 = 11 to 20/10HPF
 - MG 3 = > 21/10HPF
- Multivariate Prognostic Index (MPI) – tumor size, presence/absence lymph node metastasis and MI → stronger prognostic significance



Oncogenes in Breast Cancer

- Genes involved in normal cell growth and differentiation as well as abnormal expression of genes are important in determining the growth and invasion of breast cancers
 - The greater amplification of oncogene *HER-2/neu*, the worse the prognosis.
 - Trastuzumab is effective only for patients whose HER2 test is positive
 - Amplification of *c-myc* oncogene did not correlate with outcome and may rather, be related to the development of breast carcinoma.
- Potential for identifying oncogene markers derived from the primary carcinoma that can alone determine the need for adjuvant therapy and serve as independent predictors of recurrence and survival is very exciting

Diagnostic Resource Allocation table for LMIC

Level of resources	Clinical	Imaging and Lab Tests	Pathology
Basic	<p>History</p> <p>Physical examination</p> <p>Clinical breast examination (CBE)</p> <p>Tissue sampling for cancer diagnosis (cytologic or histologic) prior to initiation of treatment</p>		<p>Pathology diagnosis obtained for every breast lesion by any available sampling procedure</p> <p>Pathology report containing appropriate diagnostic and prognostic/predictive information to include tumor size, lymph node status, histologic type and tumor grade</p> <p>Process to establish hormone receptor status possibly including empiric assessment of response to therapy[†]</p> <p>Determination and reporting of TNM stage</p>
Limited	<p>US-guided FNAB of sonographically suspicious axillary nodes</p> <p>Sentinel lymph node (SLN) biopsy with blue dye[‡]</p>	<p>Diagnostic breast ultrasound (US)</p> <p>Plain chest and skeletal radiography</p> <p>Liver US</p> <p>Blood chemistry profile[*]</p> <p>Complete blood count (CBC)[*]</p>	<p>Determination of ER status by IHC[†]</p> <p>Determination of margin status, DCIS content, presence of LVI</p> <p>Frozen section or touch prep SLN analysis</p>
Enhanced	<p>Image guided breast sampling</p> <p>Preoperative needle localization under mammo and/or US guidance</p> <p>SLN biopsy using radiotracer[†]</p>	<p>Diagnostic mammography</p> <p>Specimen radiography</p> <p>Bone scan, CT scan</p> <p>Cardiac function monitoring</p>	<p>Measurement of HER-2/neu overexpression or gene amplification[†]</p> <p>Determination of PR status by IHC</p>
Maximal		<p>PET scan, MIBI scan, breast MRI, BRCA1/2 testing</p> <p>Mammographic double reading</p>	<p>IHC staining of sentinel nodes for cytokeratin to detect micrometastases</p> <p>Pathology double reading</p> <p>Gene profiling tests</p>

CHECKLIST FOR SPECIMEN EVALUATION

- **Type of specimen received**
 - FNA
 - Trochar biopsy
 - Incisional biopsy
 - Excisional biopsy
 - Mastectomy (specify type)
- **Gross description**
 - Laterality & type of specimen
 - Skin
 - Nipple
 - Pectoralis major
 - Pectoralis minor
 - Axillary contents
 - Other
 - Tumor (s)
 - Size
 - Location
 - Quadran(s)
 - Depth
 - Pattern of invasion
 - Operating room consultation report
 - Tissue taken for ER/PR or other markers
 - Gross tumor on margin of resection
- **Axillary Lymph Nodes**
 - Location
 - Total number
 - Number with metastasis
 - Highest lymph node present in dissection and status
 - Statement in reference to capsular violation
- **Histologic classification**
 - Use the revised WHO classification of breast tumors
 - Classify by dominant pattern
- **Additional Histologic Factors**
 - Histologic grade with degree of differentiation
 - Grade 1
 - Grade 2
 - Grade 3
 - Grade 4
 - Presence/absence of microscopic tumor in margin of resection
 - Involvement of adjacent structures
 - Character of breast tissue remote from primary cancer
- **ER/PR**
- **Additional prognosis factors**



Conclusion

- The correct approach to specimens requires integration of clinical and imaging findings. A careful history and explanation is of great help to the pathologist in the diagnosis of many specimen.
- Safeguards are required, checks and quality-control schemes. The evaluation of the post treatment tumour residue helps in determining tumour response to treatment, establishing prognosis and adjusting adjuvant regimens.
- By providing diagnostic information and by characterizing the biologic behaviour of a breast lesion, a pathologist plays a critical role in a patient's life.



Conclusion

- Pathologists must be part of the clinical team. New analytical techniques and therapeutic targets make it essential that we learn from past mistakes and integrate pathologists into the research teams pursuing clinical trials and the assessment of new bio-markers.
- We must place emphasis on effectively using the talent and expertise of pathologists.



Prognosis

Treatment

Imaging

Gene Expression
Pharmacogenomics

Biomarkers

Traditional
Pathology

**The value of traditional pathology
has not diminished.
It simply will no longer be sufficient.**

