

WHAT DO BREAST SURGEONS NEED FROM PATHOLOGISTS ?

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ROLE OF THE PATHOLOGIST

- I. **Pre-operatively:**
 1. Diagnosis of malignancy.
 2. Axillary LN evaluation.
 3. Evaluation of biological markers.
- II. **Intra-operatively:**
 1. Confirmation of malignancy.
 2. Assessment of safety margins.
 3. Sentinel LN analysis.
- III. **Post-operatively:**
 1. Tumor: size, number, grade...
 2. Evaluation of safety margins.
 3. Evaluation of biological markers.
 4. Axillary LN evaluation.
 5. Evaluation of effect of NAC.



Pre-operatively:

1. Diagnosis of malignancy.



22-gauge



8/ 11-gauge

❖ Satisfactory specimen should contain ≥ 6 cell clusters (each cluster has ≥ 5 cells) or should have ≥ 10 intact bipolar cells per 10 medium-power fields.

❖ Number of cores required is ideally **5**.

[Lester et al, *Cancer Cytopath*,1997;81(1), 16-21.]

[Brenner et al, *Am J Roentgenol*. 1996;166: 341-6.]

FNAC vs CNB

	CNB (n = 2013)	FNAC (n = 3095)	P value
Inadequate sample	6.9%	17.7%	<0.001
Conclusive diagnosis	85.4%	72.6%	<0.001
Absolute sensitivity	93.1%	74.4%	<0.001
Absolute diagnostic accuracy	84.5%	71.9%	<0.001

• Although FNAC is **cheaper and easier** to perform, interpretation requires **vast experience** and even then, it is **more often inconclusive** requiring additional CNB.

[Willems SM, *J Clin Pathol*2012;65:287-92]

• FNAC is **in decline** and many screening units in the UK have abandoned it completely.

[Pusiol et al, *Irj Path*2014;9 (3):234-5]

Categories for reporting Breast Needle Core Biopsies.

- B1 = Benign
- B2 = Normal
- B3 = Uncertain malignant potential (equivocal)
- B4 = Suspicious for malignancy
- B5 = malignant

[The UK National Health Service Breast Screening Programme]

2. AXILLARY LN EVALUATION.

▪ Method:

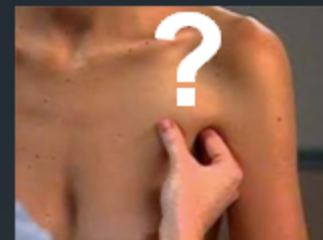
Axillary US + FNAC or CNB.

▪ Indications:

Clinically Suspicious LNs,
before embarking onto ALND.

▪ Rationale:

Clinical examination of the axilla is falsely positive:
in **53%** of patients with moderately suspicious nodes and
in **23%** of patients with highly suspicious nodes.



(Specht et al: J Am Coll Surg 2005; 200:10–14.)

If needle Bx is -ve, do SLN (ALND is avoided)

If needle Bx is +ve, do ALND (SLN is avoided)

3. EVALUATION OF BIOLOGICAL MARKERS

□ Indications:

- If NAC is planned.
- In advanced, inoperable / irresectable tumors.

□ Which:

- ER and PR.
- HER-2/neu.
- KI-67.

II. Intra-operatively (FS):

1. Diagnosis/Confirmation of malignancy.

- Results of needle Bx may be equivocal.

- With needle Bx, FPR is 1.1 %.

FNR is 6.7 %.

[Cocilovo C: Surg. of the breast principles and art, ed. Spear S, publ. Lippincott W&W; p. 13]

- Between 1985 – 1995, Frozen section examination of the primary breast tumor has decreased from (20-35%) to (4-8%) of FS specimens at Ben-Taub Hosp. (Houston, Texas)

- Frozen section examination is generally inappropriate in clinically non-palpable lesions.

[European guidelines for quality assurance in breast cancer screening and diagnosis
Annals of Oncology (2008), 19, 614-622.]

Problems with Frozen Section:

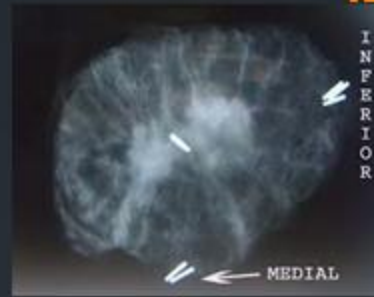
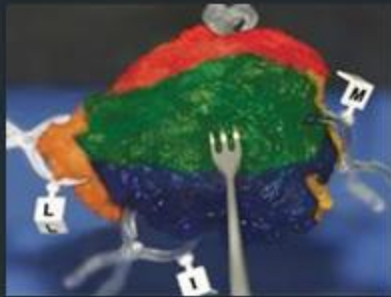
- Artifacts may be caused by Diathermy, tissue-crushing...
- With Frozen section, FPR varies from 0.03% to 0.1%,
FNR varies from 0.5% to 1.0%.
- Diagnostic errors can result from:
 1. Interpretation (57%).
 2. Microscopic sampling (24%).
 3. Gross sampling (9.5%).
 4. Lack of communication between the pathologist and the surgeon (9.5%).
- Frozen section diagnosis may be deferred in 0.5% to 3% of all breast biopsies.

[Rogers et al. *Arch Pathol Lab Med* 1987, 111; 514–517.]

COMMUNICATION.. COMMUNICATION.. COMMUNICATION..

- Same Language: e.g. Type of specimen (lumpectomy, quadrantectomy, skin / nipple sparing mastectomy...)
- Operative details: (Laterality, site of tumor, orientation of specimen..)
- Previous ttt: NAC, previous RT...

Breast specimen orientation:



Breast specimen orientation:

- In a prospective study containing 122 lumpectomy specimens that were routinely oriented with stitches, the overall disorientation rate was 31.1%.
- Presence of skin/muscle on the specimen did not contribute to better orientation.
- Specimen volumes: "The larger the better". (Disorientation rate was 78% with specimens <20 cm³ and only 20% with larger specimens (> 20 cm³) ($p < 0.001$).
- ✓ *Better techniques are necessary to minimize the specimen disorientation.*

[Molina et al. *Ann. Surg Oncol*, 2009, 16 (2), 285-8.]

Methods of intra-operative specimen examination:

- Smears can be prepared in 1 of 3 ways:
 - Cytologic imprints:** in which the tumor is directly pressed against a slide.
 - Squash preparations:** in which a 1-mm fragment of tumor is gently pressed between 2 slides.
 - Scrape preparation:** in which a clean scalpel is scraped along the tumor surface and the material is then transferred and smeared onto a slide. The latter technique is quite useful when the tumor is highly fibrotic.
- The material is immediately fixed in ethanol for maximum preservation of the cellular details.

Techniques of margin assessment:

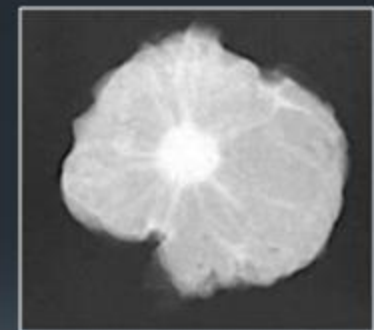
- Frozen section**
 - Imprint cytology**
- adds 20–30 min to operation time.
- Ultrasound:** accurate, rapid, yet it has a limited role with DCIS and multifocal tumors.



2. Assessment of safety margins.

- Retrospective analyses of surgical series show a 2–3 fold increase in local recurrence of the breast tumor if the margin is positive.
[Wood CW: St Gallen 2013 Proceedings Book]
- Approximately 25% (to 66% !) of patients undergoing BCS for breast cancer will require a second operation to achieve adequate margins.
[Jacobson et al: *Am J Surg*, 2008 , 196 (4), 556-8]
- Careful gross examination of the breast specimen is usually all that is required to assess margin status. Only if the tumor closely approximates a specific margin, a frozen section of that margin should be done.
[Lauricira R: *Arch of Path & Lab Med*:2005, 129, (12), 1565-74.]

4. Specimen mammography.



Do additional shaved margins at the time of lumpectomy eliminate the need for re-excision?

4. Shaving additional margins: at the closest aspects grossly, or on all 6 surfaces.
6. Radiofrequency spectroscopy.
7. Optical coherence tomography.

□ Conclusion:

- Excising additional shaved margins at the original surgery reduced re-operations by 48%.
- There is a balance between removing additional margins and desirable cosmesis after BCS; so the decision to take extra margins should be based on the surgeon's judgment.

[Jacobson et al. *Am J Surg*, 2008, 196 (4), 556-8]

3. Sentinel LN examination.

□ Methods:

- ❖ Frozen Section: (sensitivity 52-100%) - (FNR: 11%, FPR: 5%).
- ❖ H & E.
- ❖ IHC.
- ❖ OSNA (One-Step Nucleic acid Amplification assay).

□ Highest accuracy:

- ❖ 1 FS + 2 adjacent 5µm thick sections (one H&E and one IHC) from each of 2 levels 50µm apart.
- ❖ Found 23% occult met. in 368 historical LN-ve patients at MSKCC.

(Viale et al, *Ann Surg*, 2008, 247: 136-42)

Low-Volume Metastatic Involvement – Implication for ALND & Systemic Treatment

□ Non-SLN involvement :

- ❖ SLN with isolated tumor cells ($\leq 0.2\text{mm}$) , pN0 (i+):.....12%.
- ❖ SLN with micro-metastatic disease (0.2 - 2 mm) , pN1 (mi):.....20% .
- ❖ SLN with macro-metastatic disease (>2 mm) , pN1:.....40% - 58%.

(Bilimoria et al, 2009)

- Omission of any axillary treatment (ALND or axill. RT) resulted in a significantly higher 5-year recurrence rate in pN1(mi) but not in pN0 (i+) patients (5% vs. 1%)

(The Dutch MIRROR study: ASCO,2009)

- Micrometastatic involvement is associated with a worse DFS and OS if systemic treatment is withheld.
- Patients who receive systemic medication have an identical prognosis to N0 patients.

Macroscopic Metastatic Involvement – Implications for Further Axillary Treatment:

Rationale of ACOSOG Z0011

1. Non-SLN Involvement:

> SLN with macro-metastatic disease (>2 mm): 40% to 58%.

(Bilimoria et al, 2009)

2. No significant difference in loco regional recurrence or OAS was found when ALND was omitted after +ve SLN (*in suitable tumors*)

(Giuliano et al, 2011)

Biopsy Results	Guidelines
Negative sentinel lymph node(s)	No further axillary surgery required. ALND may be omitted.
Positive lymph node at presentation (proven by FNA or core needle biopsy)	ALND should be performed.
Positive sentinel lymph node(s) 1 or 2 positive sentinel lymph nodes	ALND may be omitted if: <ul style="list-style-type: none"> - Primary tumor ≤ 5 cm - Clinically negative axilla - Successful breast conservation - Will receive whole-breast radiation therapy and likely systemic therapy ACOSOG Z0011 data do not apply to the following patients: <ul style="list-style-type: none"> - Those undergoing mastectomy - Those receiving neoadjuvant chemotherapy - Those receiving partial-breast radiation therapy or radiation therapy in the prone position For these patients, the standard of care is completion ALND.
3 or more positive sentinel lymph nodes	Completion ALND should be performed.

ALND = axillary lymph node dissection, FNA = fine-needle aspiration.

III. Post-operatively:

1. Tumor: state, number, size...

▪ State of specimen: Sectioned, fragmented...

▪ Number: Pts. with multiple invasive tumors carry a higher risk for +ve LNs, but if LNs are -ve the risk for distant metastases does not increase.

▪ Size: When multiple tumors, only the size of the largest one is used for T classification. The sizes of multiple tumors should not be added together. The suffix "m" is just added.

▪ Histologic type: Tubular, Mucinous, Cribriform and Adenoid cystic carcinoma have very good prognosis.

▪ Grade: correlates with DFS & OS.

▪ Associated DCIS:

▪ Skin invasion: Invasion of dermis (or even epidermis) is not classified as T4-b; but only skin ulceration is.

▪ Muscle invasion: Invasion of pectoralis major is not classified as T4-a; but only invasion through the whole thickness of the muscle into chest wall.

▪ L / V emboli: Dermal L / V invasion is a dire prognostic factor; but cannot be classified as "inflammatory carcinoma (T4-d)" unless other features (like erythema / edema of >1/3 of the breast) are present.

2. Safety margin assessment:

Margin:	Definition	% of residual tumor at re-excision
Negative:	Tumor >1 mm from the inked margins.	21%
Close:	Tumor ≤1 mm of the inked margin, but not transecting it.	30%
Indeterminate:	Biopsy specimen not inked or fragmented.	56%
Positive:	Tumor at the inked margins.	63%

[Chrisoula et al. *The Breast J*, 2006; (12), 150-3.]

- It is postulated that positive specimen scrape cytology could be a better indicator of inadequate margins than involved tumor bed biopsies or +ve SM judged by conventional histology.

[England et al. *Eur J Surg Oncol*, 1994, 20 (4): 425-9.]

Is additional resection mandatory with Close / +ve margins after BCS ?

- Sufficient data are available to suggest that in the era of effective systemic therapy, excellent radiation therapy techniques, and boost doses when indicated, **NO MARGIN** of normal breast tissue beyond the tumor has been shown to be clearly **SUPERIOR** to **ONE LAYER** of cells between the ink and the tumor.
- Nevertheless, wise judgment must integrate all of the known factors to reach the best recommendation.
- A microscopic focus of tumor at the margin **VS.** the margin inking on the whole tumor surface.

[Wood CW, St Gallen, 2013 Proceedings Book]

3. Biological markers.

□ **ER and PR:**

- Exposure to heat (diathermy).
- Prolonged ischaemia time.
- Acidic fixatives.
- Fixation time in NBF: Optimally 8h - 3 weeks.
- Decalcification.
- Incorrect / Non-optimised antigen retrieval method.
- Type of antibody.

Prognostic & predictive Multi-gene Indicators:

□ HER-2/ neu:

- Prolonged Ischaemia time >1h. (ASCO/ CAP guidelines)
- Prolonged fixation in Formalin (> 1week)
- Use of a non-formalin fixative.
- Decalcification (fixation involving acid) : DNA denaturation.

[Yildiz-Aktas : *Modern Pathology*; 2012 ; 25, 1098–1105]

□ Oncotype DX[®]:

- ❖ The *Oncotype DX[®]* test (Genomic Health) is used in (ER+), (LN-) and (HER2-) early breast cancer patients, who are assessed as being at intermediate risk for cancer spread, where the decision to prescribe chemotherapy remains unclear.
- ❖ The assay is performed on RNA extracted from FFPE tissue.
- ❖ 16 cancer-related genes and 5 reference genes are assessed and a recurrence score (RS) is generated :
 - Low risk ≤ 17
 - Intermediate risk = 18 – 30
 - High risk > 30

□ The cost of the *Oncotype DX[®]* test is £ 2580 .

□ Mammaprint[®]:

- The 70 genes included in this test focus on proliferation, invasion, metastasis, stromal integrity and angiogenesis.
- It is done only on fresh tissue or frozen samples but not on paraffin embedded samples.
- Patients are categorized as High risk (will need CTh)
Or Low risk (will need only Hormonal ttt)



3.1 Impact of Adding Chemotherapy to Tamoxifen According to Oncotype DX Recurrence Score in Women with ER-Positive, Node-Negative Disease

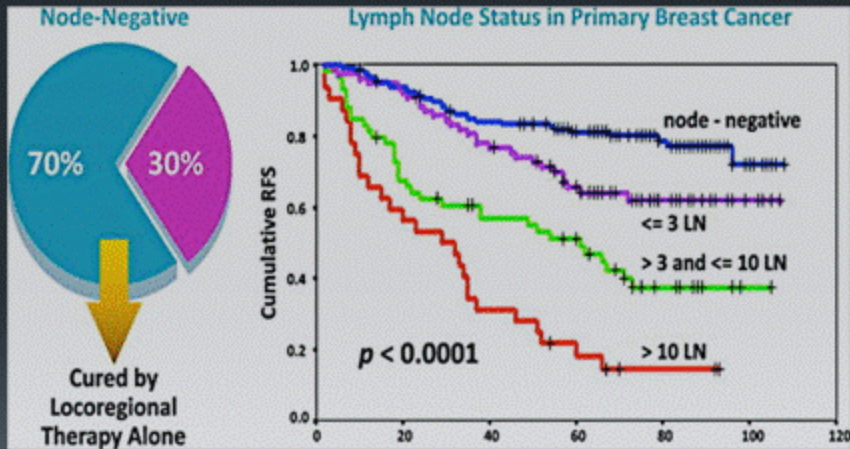
Risk group	10-year distant recurrence-free survival		p-value
	Tamoxifen (n = 227)	Tamoxifen with chemotherapy (n = 424)	
Low (RS < 18)	97%	96%	0.61
Intermediate (RS = 18-30)	91%	89%	0.39
High (RS ≥ 31)	61%	88%	<0.001

Chemotherapy = MF or CMF; RS = recurrence score

SOURCE: Paik S et al. *J Clin Oncol* 2006;24(23):3726-34. [Abstract](#)

4. Axillary LN evaluation.

- The most powerful prognostic indicator:



- At least 10 LNs should be removed.

DCIS:

University of Southern California /
Van-Nuys prognostic index:

Factor	1	2	3
Size (mm)	≤ 15	16-40	≥ 41
Margin (mm)	≥ 10	1-9	< 1
Pathologic classification	Non-high grade No Necrosis	Non-high grade with Necrosis	High grade With / without Necrosis
Age (y)	≥ 61	40 - 60	≤ 39

From 1 to 3 points are awarded to each factor and a total score (USC/VNPI) is calculated.

DCIS:

Diagnosis:

- The presence of stromal fragments and tubular structures of tumor cells in breast FNA specimens may help in the distinction of IDC from DCIS.
- When findings on FNA specimens fail to distinguish IDC from DCIS, core needle biopsy or FNA of suspected sites for metastasis is needed for confirmation of stromal invasion.

The application of USC/VNPI

USC/VNPI	Recommended treatment
4-6	Excision only
7-9	Excision + RT
10-12	Mastectomy

Evaluation after NAC:

□ Prognostic Indicator:

❖ Patients with good response have a good, long term DFS and OAS.

□ Therapeutic modification:

❖ In patients with poor or no response, treatment may be changed or modified.

CONCLUSION:

- The surgeon & the pathologist represent both sides of the same coin.
- Their close collaboration is essential to reach the ideal care required by women suspected of harboring breast cancer.

THANK YOU

