Case Presentation, Discussion and Sharing of Information on Locally Advanced Breast Cancer

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General Data

M.C, 65F

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Chief Complaint

Breast Mass, Left

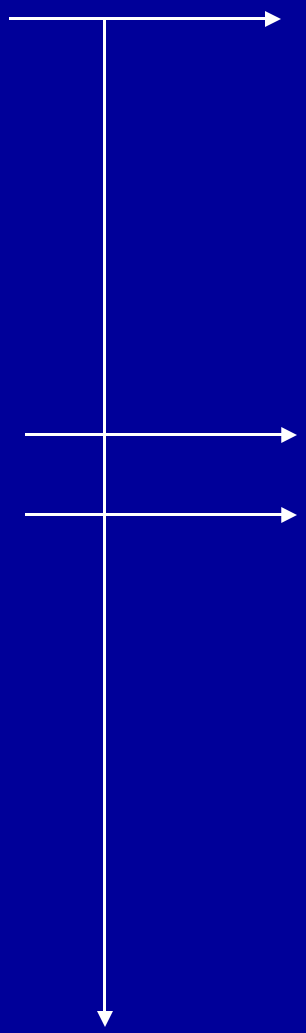
History of Present Illness

2 years PTA → breast mass, Left
gradual increase in size
no other symptoms noted
no consult done

1 year PTA

3months PTA

2 weeks PTA



increased in size

(+) private MD

advised biopsy, refused

self medicated with herbal medicine

(+) Ulceration

persistence of SSx

consult: OMMC Breast Clinic

Past Medical History: unremarkable

Family History: no history of breast cancer in the family

Personal Social History: non-smoker

non-alcoholic beverage drinker

Physical Examination

Conscious, coherent, ambulatory, NICRD

- BP:120/80 CR:85 RR:21
  T:37ºC
- Pink palpebral conjunctiva, anicteric sclerae
- Supple neck, (-) cervical LAD
- Symmetrical chest expansion, clear breath sounds
- Adynamic precordium, normal rate & regular rhythm
- Flat, NABS, soft, nontender
- (-) cyanosis, (-) pallor

Left Breast

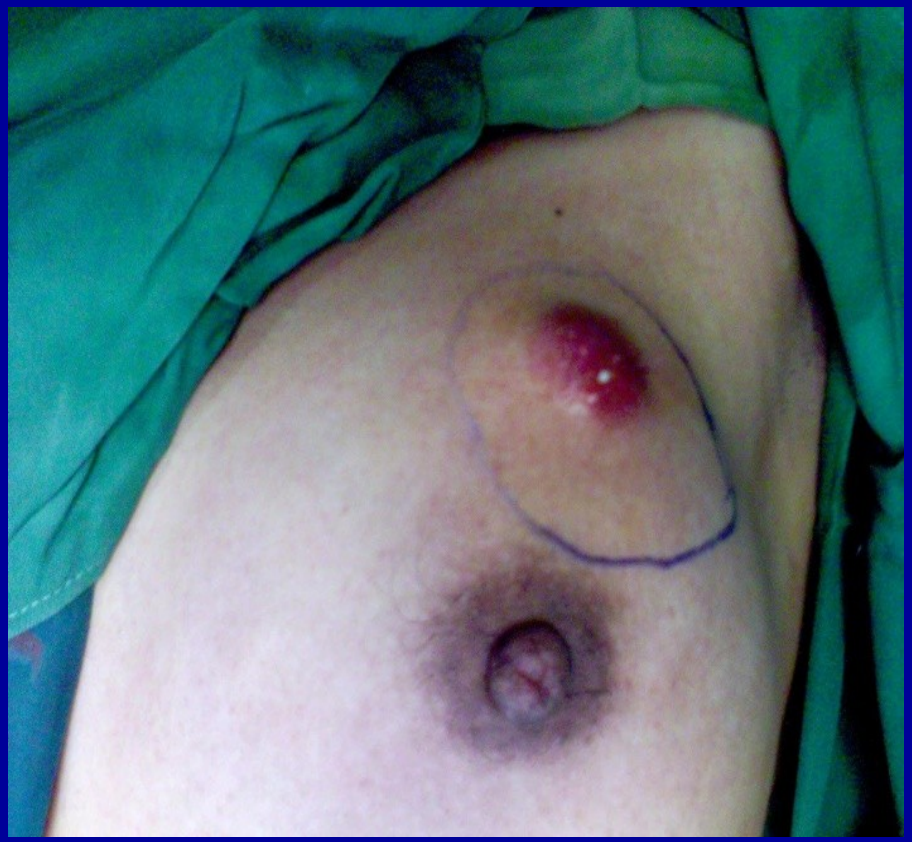
3x4cm, LUOQ area, hard, skin ulceration, movable, irregular border, tender mass

(+) palpable axillary mass, 1x1.5cm hard, movable

(-) SCN

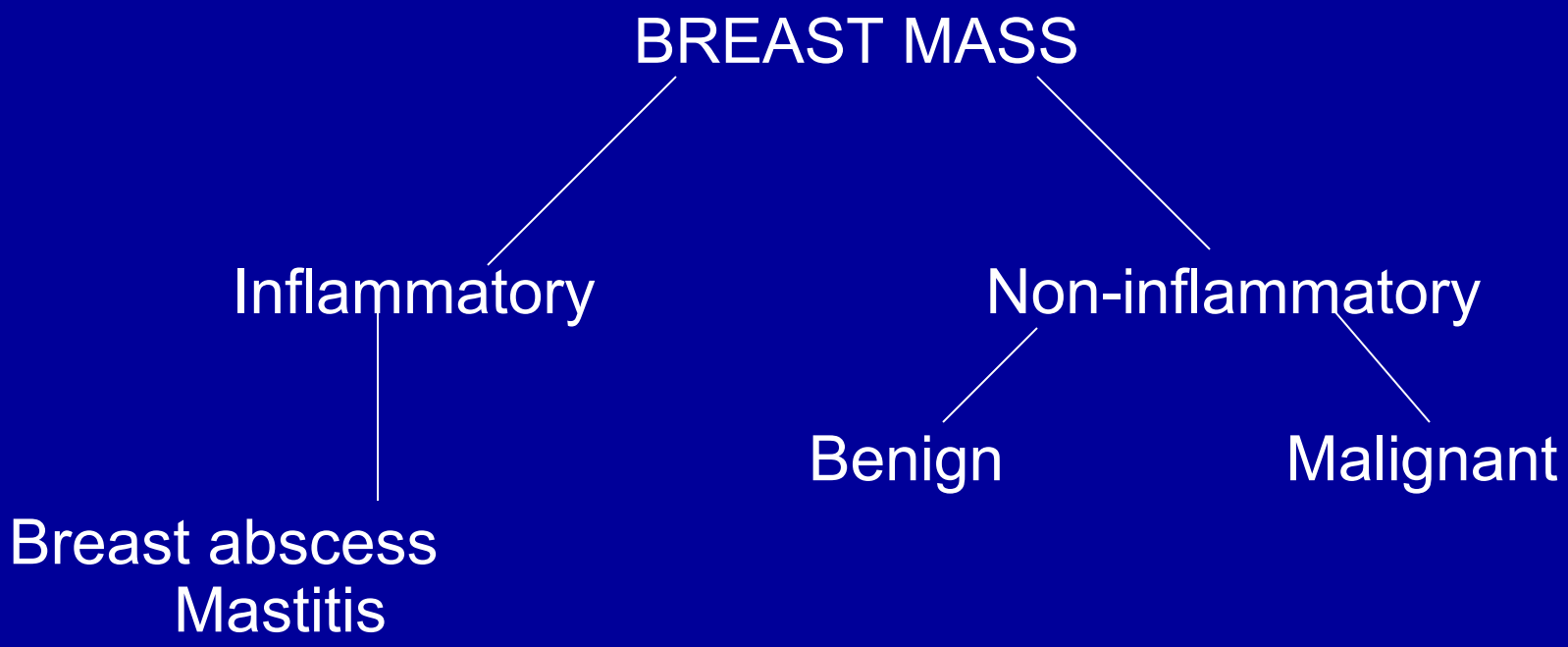
Right Breast

Normal



Salient Features

- 65F
- 3x4cm, hard, with irregular border, movable, tender, with skin ulceration, LUOQ, Breast, Left
- (+) palpable axillary mass, 1x1.5cm hard, movable
- (-) SCN
- Normal Right Breast Exam


BREAST MASS
Inflammatory
Non-inflammatory
Benign
Malignant
Breast abscess
Mastitis

Clinical Diagnosis

Diagnosis	Certainty	Treatment
NonInflammatory Breast Cancer	85%	Surgical
Inflammatory Breast Cancer	15%	Surgical

Do I need a para-clinical diagnostic procedure?

YES

Paraclinical Diagnostic Procedure

	Benefit	Risk	Cost	Availability
FNAB	Accuracy - 92.8% Sensitivity – 83% Specificity – 95%	Bleeding + pain	50	+
Core needle biopsy	Accuracy – 99% Sensitivity – 94% Specificity – 95%	Bleeding ++ pain	400	+
Incision biopsy	Accuracy – >99% Sensitivity – 94% Specificity – 95%	Bleeding ++ pain Infection Tumor spread	600	+

FNAB Result

Smears show some groups of ductal cells exhibiting atypia with other individual cells showing the same features in the background. The individual cells exhibiting irregular nuclear contour and hyperchromatic nuclei.

Diagnosis: Cell findings suggestive of malignant ductal cells

Pre-Treatment Diagnosis

Diagnosis	Certainty
Breast CA, Left Stage IIIB (T4N1M0)	98%
Inflammatory Breast Cancer, Left	2%

- Clinical Stage: Breast Ca, Left, Stage IIIB (T4N1M0)

Goals of Treatment

- Resolution of the mass
- Axillary clearance
- Increase survival
- Low locoregional recurrence
- No complications

Pre-op Preparation

- *Discussion of Treatment Options*

Treatment Options: Neodjuvant vs Adjuvant

	Benefit		Risk	Cost	Availability
	Overall survival	Local recurrence			
Neoadjuvant Chemotherapy + Surgery + RT	Same (P=0.42) (DFS: 0.18)	Same	Cytotoxicity Delay of surgery	35k	✔
Surgery + Adjuvant Chemotherapy + RT	Same (P=0.42) (DFS: 0.18)	Same	Cytotoxicity	35k	✔

Deo ST et al. RCT neoadjuvant vs adjuvant Chemotherapy in LABC. 2002
CR: 14%, PR: 52% (66%)

Treatment Options: Extent of Surgery

	Benefit		Risk	Cost	Availability
	Overall survival	Disease Free Survival	Operative complications		
Radical Mastectomy	**Same**	**Same**	**++**	**5k**	✔
Modified Radical Mastectomy	**Same**	**Same**	**+**	**5k**	✔

^ *Maddox, W et al. 1987*

Pre-op Preparation

- Informed consent secured
- Psychosocial support provided
- Optimized patient's physical health
- Patient screened for any health condition
- Operative materials secured

Operative Technique

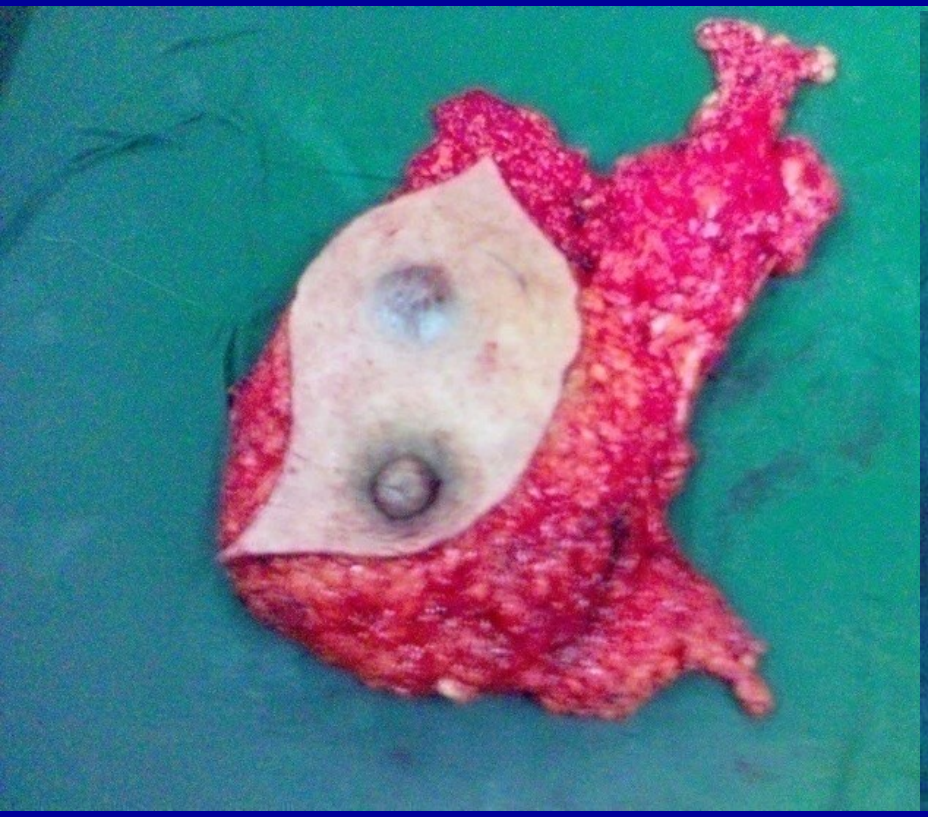
- Patient placed under GA with left arm extended
- Transverse elliptical incision
- Superior & inferior flaps created
- Breast tissue dissected from the pectoralis major fascia
- Clavipectoral fascia opened
- Axillary vein identified
- Palpable axillary LNs dissected
- Lymphatics ligated
- Right breast and axillary LNs removed enbloc

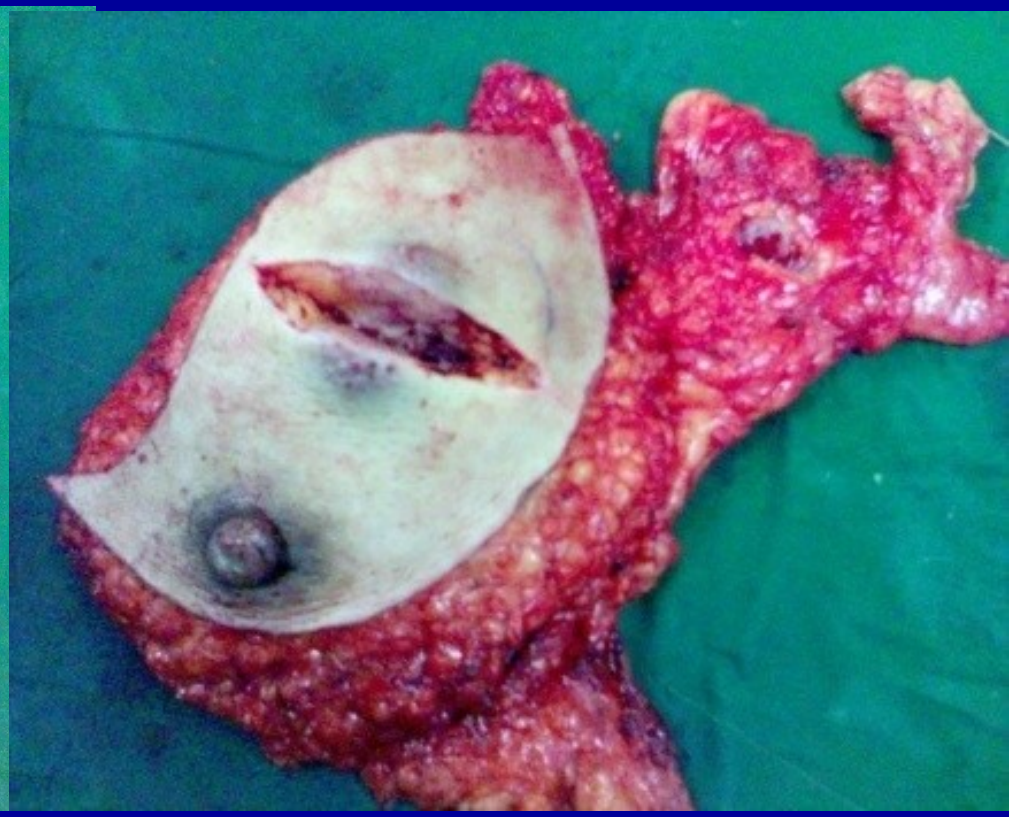
Intra-operative findings

- Left breast measured 14 x10cm with a 3x3 cm hard gritty mass, movable at the upper outer quadrant.

- (+) levels 1 and 2 axillary LNs, multiple, not matted, largest of which measured 1x1cm.

Specimen





- Washed with NSS
- Hemostasis
- Drains placed, anchored with silk 3-0
- Flaps apposed
- DSD
- Drain in negative pressure

Final Diagnosis:

Breast CA, Left

Stage IIIB (T4N1M0)

Operation Done

Modified Radical Mastectomy, Left

Post-operative

- Use of analgesics resulting in a pain-free post-operative period
- Arm rehabilitation exercises
- Discharge within 48 hours post-operation, with tube drain, and with instructions on:
  - care of tube drain
  - intake of analgesics
  - arm rehabilitation exercises

- First follow-up visit 5-7 days of discharge
- Second follow-up is 30 days after the operation
- Adjuvant treatment is started within 6 weeks of the operation

Final Histopathologic Report

- SP MRM, Left, Invasive Ductal Carcinoma, Histologic Grade I (Bloom Richardson), 4 cm in widest diameter
- Positive for Tumor:
  - 5/10 axillary nodes
  - Superficial skin
- Negative for Tumor
  - Basal line of resection
  - Superior and inferior margins

Pathologic Stage

- Breast Cancer Stage IIIB (T4b pN2 M0)
- SP MRM, L

Adjuvant Treatment

Patient's Prognostic and Predictive factors

- Age: 65F
- Nodal Status: N2
- Tumor: T4
- Histologic type: Invasive Ductal Carcinoma
- Grade: BR Grade I
- Hormone-receptor status: *ER/PR unknown*

Hormonal vs Cellular Markers

	Benefit		Risk	Cost	Availability
	Determine Treatment plan	Sensitivity			
ER/PR Assay	+++	///	none	2K	✔
Her2/Neu oncogene	+++	/	none	3k	✔

Immunohistochemical Report

- ER Assay: Positive
  - Nuclear Staining: +2
  - ER Receptor: 90%
  - Allred Score: 7
- PR Assay
  - Nuclear Staining: +3
  - ER Receptor: 90%
  - Allred Score: 8

Patient's Prognostic and Predictive factors

1. Age: 65F
2. Nodal Status: N2
3. Tumor: T4
4. Histologic type: Invasive Ductal Carcinoma
5. Grade: BR Grade I
6. Hormone-receptor status: Positive

High Risk Postmenopausal Breast Ca IIIB

Goals of Treatment

- Increase survival
- Locoregional control
- Disease free survival

Multimodality Treatment

- Hormonal Therapy
- Hormonal Therapy + Chemotherapy
- Hormonal Therapy + RT
- Aromatase Inhibitor

Treatment Options	Benefit		Risk	Cost	Availability
	Overall survival	Local recurrence			
Chemotherapy (CAF)	*30%*	*35%*	cytotoxicity	35K	/
Chemotherapy + Tamoxifen	*30%+++*	*35%*	Cytoxicity + Tamoxifen related adverse effects	60K	/
Tamoxifen**	30%	35%	Tamoxifen related adverse effects	20K	/
Tamoxifen + RT**	45%	8%	Tamoxifen related adverse effects + RT effects	30K+	/
Anastrazole^^	3% difference (86.9% vs 84.5%)	Longer time to recur Decrease Recurrence 26%	Decrease tamoxifen related effects	70K	/
Anastrazole + RT	*No data*	*No data*	*radiotoxicity*	*80K*	*/*

***Danish Breast Cancer Cooperative Group. 1999*

^^ ATAC

Outcome

- Resolution of the breast mass
- Live patient
- No complications
- Satisfied patient
- No medico-legal suit

Surveillance

FOLLOW-UP

- Frequency of follow-up:

  First 2 years – every 6 months

  After 2 years – yearly

  Patients are given instructions to consult earlier if with symptoms
- Symptom-directed metastatic work-up
- Annual gynecologic evaluation is not advised for patients on Tamoxifen

Discussion

TREATMENT PROTOCOL FOR BREAST CARCINOMA

- Determining the optimal individual adjuvant therapy for breast cancer patients is a challenging undertaking because it requires translating data from large clinical trials.

- Choosing adjuvant therapy for women with breast cancer includes consideration of four issues:
- A) evaluation of risk of relapse
- B) extrapolation of results from clinical trials
- C) therapeutic ratio
- D) the patient's preferences

- Data from recently completed phase III adjuvant trials and worldwide consensus conferences document the benefits of adjuvant therapy in improving disease-free survival and overall survival for patients diagnosed with invasive breast cancer >1.0 cm in size.

- The benefits of hormonal therapy are clear, but limited to patients with estrogen receptor-positive breast cancer.

- Anthracyclines lead to improved outcomes compared with nonanthracycline regimens.
- Taxanes appear to improve disease-free survival in patients with node-positive disease, although longer follow-up is required to assess their impact on overall survival.

- Some countries have reported a reduction in the mortality rate from breast cancer over the past several years. The improved survival rate is due, at least in part, to the use of adjuvant systemic therapy.

- Appropriate local therapy (SURGERY) remains the cornerstone of treatment for patients with nonmetastatic breast cancer.

- Systemic chemotherapy, with or without hormonal therapy based on the biological characteristics of the tumor, is the current standard of treatment for patients with node-positive breast cancer, and for a large portion of those with node-negative disease and invasive tumors measuring >1.0 cm.

- Ultimately, the success of adjuvant therapy will depend not only on optimizing current regimens, but also on
  - exploring new therapeutic targets
  - understanding of individual tumor and patient characteristics
  - critical analysis and integration of data

- A large amount of data has been accumulated over the last few years, helping us to better understand the utilization of ovarian ablation, hormonal therapy, and chemotherapy, as well as local treatments for patients with early breast cancer.

- Some of these data were discussed as part of the:

  1. Early Breast Cancer Trialists' Group (EBCTG) conferences in 1998 and 2000

  2. 2000 National Institutes of Health (NIH) Consensus Conference

  3. 2005 9th St. Gallen meeting

- The overall results from the studies discussed are consistent with significant improvements in disease-free and overall survival for all groups of patients: pre- or postmenopausal, node positive or negative.

PROGNOSTIC AND PREDICTIVE FACTORS IN THE ADJUVANT SETTING

- Selection of adjuvant systemic therapy is based on patient characteristics and prognostic and predictive factors.

2. Nodal status
3. tumor size
4. histologic type
5. grade
6. hormone-receptor status
7. age

ADJUVANT TREATMENT

N0		No adjuvant treatment
N(+)	Pre-menopausal	
	ER (+)	Chemotherapy OR Surgical oophorectomy + Tamoxifen
	ER (-)	Chemotherapy
	ER Unknown	Chemotherapy
	Post-menopausal	
	ER (+)	Tamoxifen
	ER (-)	Chemotherapy
	ER Unknown	Tamoxifen

- Tamoxifen is given 20 mg daily for a period of 5 years

PROGNOSTIC AND PREDICTIVE FACTORS IN THE ADJUVANT SETTING

- Hormonal receptor status is recommended as predictive of response to tamoxifen and aromatase inhibitors.
- The role of HER2 as both prognostic and predictive is still debated, but increasing amounts of data support its value as both

PROGNOSTIC AND PREDICTIVE FACTORS IN THE ADJUVANT SETTING

- The St. Gallen's conference meeting panel recommended that patients be divided into risk categories to help make decisions regarding adjuvant treatment.

✂ Low risk of recurrence: *Node negative AND all of the ff:*

a. pT<2cm AND
b. Grade 1 AND
c. Absence of peritumoral vascular invasion AND
d. Her2/neu gene neither overexpressed nor amplified AND
e. > 35 years

- Tamoxifen or no therapy was recommended for those patients.

PROGNOSTIC AND PREDICTIVE FACTORS IN THE ADJUVANT SETTING

2. Intermediate risk: *Node negative AND at least one of the ff:*
   a. pT> 2cm OR
   b. Grade 2-3m OR
   c. Presence of peritumoral vascular invasion OR
   d. Her2/neu gene overexpressed or amplified OR
   e. <35 years

   Node positive (1-3) AND

   a. Her2/neu gene neither overexpressed nor amplified

- Recommendations for these patients included various combination of tamoxifen and/or chemotherapy.

PROGNOSTIC AND PREDICTIVE FACTORS IN THE ADJUVANT SETTING

3. **High risk**: a. *Node positive (1-3) AND* Her2/neu gene overexpressed or amplified

   b. *Node positive (> 4)*

- Recommendations for these patients included various combinations of tamoxifen and/or chemotherapy.

LOCAL THERAPY

- Radiation therapy : recommended to reduce local recurrence for
  a. lumpectomy or quadrantectomy
  b. mastectomy but have four or more involved axillary lymph nodes
  c. mastectomy for tumors measuring >5.0 cm

Bellon J. Harris J. Which extent of adjuvant radiotherapy is standard? Breast 2005; 14 (suppl): S8-S9.

Ragaz J. OlivottoIA, Spinelli JJ et al. Locoregional radiation therapy in patients with high risk breast cancer receiving adjuvant chemotherapy: 20 year resut of the British Columbia randomized trial. J Natl Cancer Inst 2005; 97: 116-126.

HORMONAL THERAPY

- Ovarian ablation and Tamoxifen was found to be as effective as cyclophosphamide methotrexate and fluorouracil (CMF), for endocrine responsive premenopausal women.

Pritchard k. Adjuvant endocrine therapies for pre/perimenopausal women. Breast 2005; 14 (Suppl):S9

Dellapasqua S. Colleoni M, Gelber RD et al. Adjuvant endocrine therapy for premenopausal women with early breast cancer. J Clinical Oncol 2005; 23: 1736-1750

HORMONAL THERAPY

- The different consensus conferences recommended tamoxifen for 5 years for patients with estrogen receptor-positive breast cancer whose tumors measured >1.0 cm, independent of menopausal state or lymph-node status.
- This was based on large amounts of data, including the findings from the EBCTG demonstrating a highly statistically significant 47% reduction in annual odds of recurrence and a 26% reduction in annual odds of death.

HORMONAL THERAPY

- There was a clear consensus that tamoxifen should not be recommended for patients with estrogen receptor-negative breast cancer. Studies failed to demonstrate benefit for tamoxifen in patients with estrogen receptor-negative breast cancer, but also did not demonstrate that tamoxifen decreased contralateral breast cancer in patients with primary estrogen receptor-negative disease.

- The presence or absence of HER2 expression should not be a determinant of whether to use hormonal therapy, based on currently available data.

Fisher B, Anderson S, Tan-Chiu E et al. Tamoxifen and chemotherapy for axillary node-negative, estrogen receptor-negative breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-23. J Clin Oncol 2001;19:931–942.

Hutchins L, Green S, Ravdin P et al. CMF versus CAF with or without tamoxifen in high-risk node-negative breast cancer patients and a natural history follow up study in low-risk node-negative patients: update of tamoxifen results. Proc Am Soc Clin Oncol 1998;17:1a.

HORMONAL THERAPY

- Regarding patient follow-up while on tamoxifen, neither routine transvaginal ultrasound nor endometrial biopsies are recommended as screening procedures.

HORMONAL THERAPY

- The role of aromatase inhibitors

  The ATAC trial provides conclusive evidence that adjuvant treatment with Arimidex for 5 years provides superior disease-free survival compared with tamoxifen in hormone-receptor-positive patients

Howell A on behalf of the ATAC Trialists' Group. Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. The Lancet 2005; 365 (9453): 60-62.

HORMONAL THERAPY

- The Kaplan-Meier plot shows the statistically significant reduction in the proportion of patients experiencing a first event with Arimidex treatment compared with tamoxifen in the hormone-receptor-positive population, with a hazard ratio of 0.83.
- This represents a 17% reduction in relative risk.
- The difference becomes apparent from the 1st year of treatment and continues beyond the full 5-year treatment period.

- Reduced risk of breast cancer recurrence The ATAC trial demonstrated that 5 years of adjuvant treatment with Arimidex significantly reduced the risk of disease recurrence compared with tamoxifen 26% further reduction in the risk of recurrence (HR =0.74; p= <0.002)

- 53% further reduction in the risk of contralateral breast cancer (HR = 0.47; p = 0.001)

- 16% further reduction in the risk of distant recurrence (HR = 0.84; p= 0.06)

- This means that for every 4 patients who recur while on tamoxifen, one patient could have remained disease free if they had been treated with Arimidex instead

CHEMOTHERAPY

- The EBCTG meta-analysis published in 1998, after review of adjuvant therapy trials that started before 1990, reported that chemotherapy reduced the annual odds of recurrence by in patients younger than 50 years of age by 40% with estrogen receptor-negative tumors and by 33% in those with estrogen receptor-positive disease.

CHEMOTHERAPY

- In patients older than 50 there was a 30% reduction in the annual odds of recurrence in estrogen receptor-negative tumors and an 18% reduction in those with estrogen receptor-positive tumors.

- Irrespective of hormonal receptor status, there was a statistically significant **reduction** in annual odds of death for both women under 50 (27%) and for those aged 50-69 (11%).

- For the overall group of women (irrespective of age), polychemotherapy significantly reduced the annual odds of recurrence and death by 24% and 15%, respectively.

CHEMOTHERAPY

- The 2000 NIH Consensus Conference addressed several issues regarding chemotherapy worthy of mention.

2. It was recommended that the majority of women should receive systemic chemotherapy for four to six courses.
3. One of the challenges of this strategy is that most of the studies comparing an equal number of cycles of anthracycline with nonanthracycline regimens demonstrate a benefit for anthracyclines, and one study demonstrated that four cycles of adriamycin and cyclophosphamine (AC) were equivalent to six cycles of oral CMF.

CHEMOTHERAPY

- The use of anthracyclines resulted in a survival benefit when compared with CMF-like regimens, with improvement in the annual odds of recurrence and death of 11% and 12%, respectively.

TARGETED THERAPIES

- An exciting area of research is the incorporation of targeted treatments in the adjuvant setting.

- The only targeted therapy approved for use in the metastatic setting, other than anti-estrogens, is trastuzumab, an agent that is now being evaluated in four well-planned worldwide adjuvant trials conducted by cooperative groups.

- Completion of recruitment and analysis of the data that may demonstrate a benefit of this anti-HER2 monoclonal antibody when added to chemotherapy could be a major advance in the treatment of patients at high risk of relapse following resection of invasive breast cancer.

References

1. Cady, B et al. Surgical Oncology Clinics of North America. PRCT in Oncology. Saunders. 2002.
2. Cameron, J et al. Current Surgical Therapy. Mosby. 8th ed. 2004.
3. Deo, ST et al. RCT on Neoadjuvant vs Adjuvant Chemotherapy in Stage III breast Cancer. 2000.
4. Feig, BW et al. The MD Anderson Surgical Oncology Handbook. 4th ed. Lippincot. 2006.

Thank you

Multiple Choice Questions
MCQ’s

MCQ

1. The following TNM Classification falls into locally advanced breast cancer

- T3N1M0
- T2N1M0
- T4N1M0
- a and c only

MCQ

2. What is the single most reliable indicator of prognosis in patients with breast cancer ?

- Stage
- Age
- Histologic type
- ER/PR assay

Multiple Correct Response
MCR

Multiple Correct Response MCR

- Write A if 1, 2, 3 are correct
- Write B if 1 and 3 are correct
- Write C if 2 and 4 are correct
- Write D if only 4 is correct
- Write E if all are correct

MCR

3. Selection of adjuvant systemic therapy is based on patient characteristics, prognostic and predictive factors which is/are

2. Nodal status
3. Tumor size
4. Histologic type
5. Hormone-receptor status

Answer: E

MCR

4. According to St. Gallen's conference meeting panel, the following prognosticators is/are low risk for tumor recurrence.

Node negative AND

1. pT<2cm AND
2. Grade 1 AND
3. Absence of peritumoral vascular invasion AND
4. <35 years

Answer: A

MCR

5. RT is recommended to reduce local recurrence in which of the following?
    1. lumpectomy or quadrantectomy
    2. mastectomy but have four or more involved axillary lymph nodes
    3. mastectomy for tumors measuring >5.0 cm
    4. tumors involving the skin

Answer: E

END