
Multidisciplinary approach
in the Management of
Locally Advanced Breast
Carcinoma

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CERTIFICATE

This is to certify that this dissertation entitled **"MULTIDISCIPLINARY APPROACH IN THE MANAGEMENT OF LOCALLY ADVANCED BREAST CARCINOMA "** is bonafide work done by **Dr.S.VEDA PADMA PRIYA** under our guidance and supervision in the Department of Surgery, Madurai Medical College, Madurai submitted for the M.S.,(General Surgery) BRANCH 1 EXAMINATION, to be held in March 2008, by the Tamilnadu DR.M.G.R. Medical university, Chennai.

Prof. Dr. K.V.Maheswaran , M.S,
Professor of Surgery
Madurai Medical College
Madurai

Prof. Dr.M. Gobinath, M.S.,
The H.O.D
Department of Surgery
Madurai Medical College
Madurai

Dr.V.Raji.M.D
Dean
Madurai Medical College
Madurai

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"Learn to see,learn to hear,learn to feel,and know that by practice alone you can become expert.Medicine is learned by the bedside and not in the class-room"

- Sir.William Osler

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Contents

INTRODUCTION

In 1943, Haagensen and Stout identified “grave clinical signs” predicting poor outcome in women with primary breast cancer treated with radical mastectomy. These features include the presence of extensive skin edema, satellite nodules, intercostal or parasternal nodules, arm edema, supraclavicular metastasis, inflammatory carcinoma, or distant metastasis, or the presence of two or more of the following: ulceration of the skin, skin edema of limited extent (more than one-third of the breast), fixation to the chest wall, axillary lymph nodes larger than 2.5 cm, or fixation of axillary lymph nodes to the skin or deep structures of the skin. Other clinical signs of locally advanced disease included a single tumor larger than 10 cm in size, multiple tumors in one breast, redness of the skin, and skin involvement. This classical description of the clinical contraindications to the primary surgical management of primary breast cancer is, in general, still valid today. In Haagensen's series of patients with these grave signs, local recurrence rates were 42% despite radical mastectomy, and no patient survived disease-free for 5 years. Patients with these characteristics (and having no distant metastases) are currently included in the category of locally advanced breast cancer (LABC). The poor outcome of these patients

when treated with radical mastectomy led to the investigation of other treatment strategies.

The definition of LABC has evolved from that of Haagensen and Stout, to encompass a

wide spectrum of clinical presentations:

- Large tumors (>5 cm)
- Extensive regional lymph node involvement
- Direct involvement of the underlying chest wall or skin with edema (including peau d'orange) or ulceration or satellite skin nodules confined to the same breast. Other discrete skin changes, such as dimpling or nipple retraction, may occur in T1-3 disease; they do not constitute evidence of a locally advanced tumor.
- Tumors considered inoperable but without distant metastasis (including involvement of the supraclavicular lymph nodes)
- Inflammatory breast cancer (IBC)

Acording to the AJCC staging,LABC comprises of :

T3 Tumor more than 5 cm in greatest dimension

T4 Tumor of any size with direct extension to a. Chest wall or b. Skin

T4a Extension to chest wall, not including pectoralis muscle

T4b Edema (including peau d'orange) or ulceration of the skin of the breast, or satellite skin nodules confined to the same breast

T4c Both T4a and T4b

T4d Inflammatory carcinoma

Regional Lymph Nodes (N)

NX Regional lymph nodes cannot be assessed (e.g., previously removed)

N0 No regional lymph node metastasis

N1 Metastasis in movable ipsilateral axillary lymph node(s)

N2 Metastases in ipsilateral axillary lymph nodes fixed or matted, or in clinically apparent(1) ipsilateral internal mammary nodes in the *absence* of clinically evident axillary lymph node metastasis

N2a Metastasis in ipsilateral axillary lymph nodes fixed to one another (matted) or to other structures

N2b Metastasis only in clinically apparent(1) ipsilateral internal mammary nodes and in the *absence* of clinically evident axillary lymph node metastasis

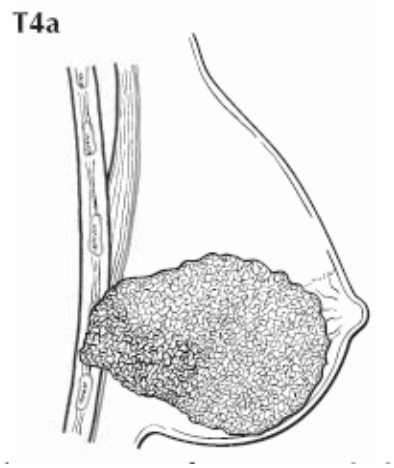
N3 Metastasis in ipsilateral infraclavicular lymph node(s) with or without axillary lymph node involvement, or in clinically apparent(1) ipsilateral internal mammary lymph node(s) and in the *presence* of clinically evident axillary lymph node metastasis; or metastasis in ipsilateral supraclavicular

lymph node(s) with or without axillary or internal mammary lymph node involvement

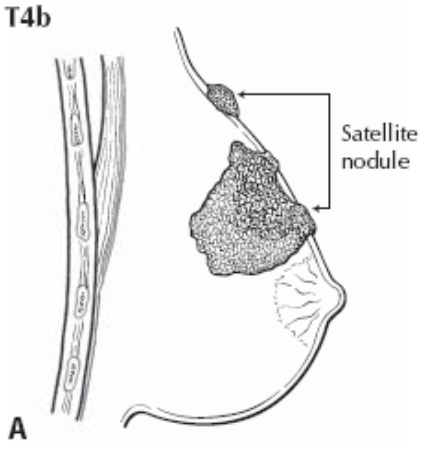
N3a Metastasis in ipsilateral infraclavicular lymph node(s)

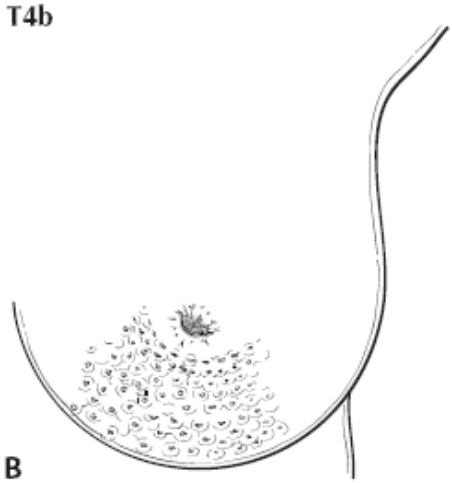
N3b Metastasis in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)

N3c Metastasis in ipsilateral supraclavicular lymph node(s)

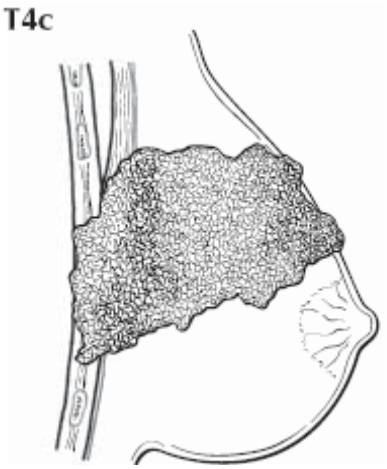


T4 is defined as a tumor of any size with direct extension to chest wall, not including pectoralis muscle.

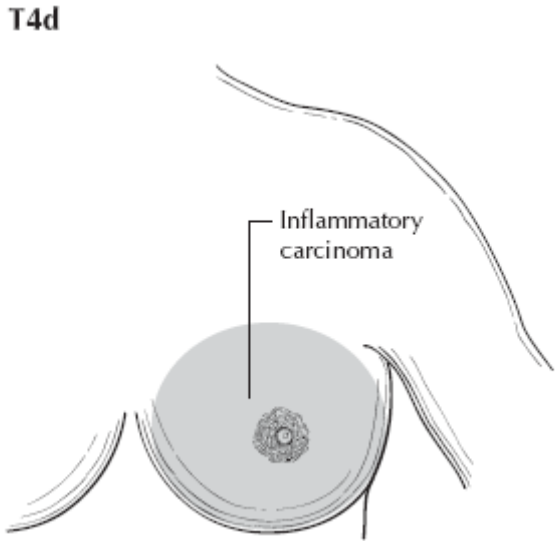




A. T4b, illustrated here as satellite skin nodules, is defined as edema (including peau d'orange) or ulceration of the skin of the breast, or satellite skin nodules confined to the same breast. **B.** T4b illustrated here as edema (including peau d'orange).



T4c is defined as both T4a and T4b.



T4d, inflammatory carcinoma.

Table 1 Stage grouping of LABC

Stage	Tumor size	Node	Metastasis
	T3	N0	M0
IIIA	T0	N1	M0
	T1[(7)]	N2	M2
	T2	N2	M2
	T3	N1	M0
	T3	N2	M0
III B	T4	N0	M0
	T4	N2	M0
	T4	N2	M0

III C	Any T	N3	M0
IV	Any T	Any N	M1

Note: Stage designation may be changed if post-surgical imaging studies reveal the resence of distant metastases, provided that the studies are carried out within 4 months of diagnosis in the absence of disease progression and provided that the patient has not received neoadjuvant therapy.

All T and N permutations included in stage IIB, III or IV comprised many distinct substage possibilities. The presence of T_4 or N_3 or regional M_1 lesions would result in inclusion in the stage IIIB/IV unresectable subcategory. Most of the patients with either T_3 or N_2, but without T_4, N_3 or regional M_1 lesions, are included in the stage II/IIIA or operable subcategory. LABC also includes T_2 tumors that are too large in proportion to the size of the breast.In the most recent TNM staging system, tumours associated with ipsilateral supraclavicular nodal basin have been eliminated from the LABC category because the supraclavicular nodal basin lies outside the primary lymphatic drainage pathways of axilla and internal mammary nodes;tumours associated with supraclavicular nodes have been reclassified as stage IV disease.However as the patients with distant metastases confined to the supraclavicular nodes have a better prognosis than patients with metastases at other sites and can be rendered disease free

with locoregional therapy,metastases limited to the ipsilateral sub-supraclavicular fossa have been included in the category of LABC defined here.

LABC is a heterogeneous group of tumors of varying clinical presentations and biological behavior whose only common bonds are the presence of a large primary tumor, or extensive regional lymph node involvement, and the absence of any evidence of distant metastases. Some patients have a rapid neoplastic evolution, whereas others present with a long history of tumor growth.

The clinical diagnosis of LABC is usually not difficult. Patients uniformly present with a large breast mass. Other symptoms often reported are edema, redness, nipple retraction, pain, skin dimpling, an axillary mass and breast ulceration. Most physical findings are obvious upon inspection or palpation. However, in younger women, some tumors infiltrate the breast diffusely and a discrete mass is difficult to palpate. More than 75% of patients have clinically palpable axillary and/or supraclavicular adenopathy, and 65%-90% of patients have pathologically confirmed lymph node metastasis; >50% have more than four nodes involved. Most of the LABCs are operable; only 25%-30% are diagnosed at an inoperable stage.

A physical examination, bilateral mammogram and ultrasound of the breast and its draining lymphatics determine the extent of involvement within the breast and the nodal chains, the presence of additional tumor foci within the same breast or the contralateral breast, and the extension of the tumor to deeper structures.

A core needle biopsy is quite effective in establishing the diagnosis and also allowing tumor samples to be obtained for hormone receptors, DNA studies and other biomarkers. The sensitivity and specificity of fine-needle aspiration are quite high in LABC. The only disadvantages of cytological diagnosis are the inability to differentiate between in situ and invasive carcinoma, and scant material on which to perform additional studies. Excisional biopsies are not indicated in patients with LABC.

Appropriate staging procedures should be performed in patients with LABC since the probability of distant metastases is high. Approximately 20% of these patients, appropriately staged, have detectable distant metastases at the time of diagnosis.So after a complete history, a physical examination should be performed with great attention to the evaluation of both breasts and all surrounding lymph node-bearing areas. All tumors

Table 2 Diagnosis and pathology

Level of resources	Clinical	Pathology	Imaging and laboratory tests
Basic	History Physical examination Clinical berate examination Surgical blopey Fine – needle aspiration blopey	Interpretation of biopeies Cytology of pethology report decribing tumor size Lymph node status Hietologic type, tumor grade	
Limited	Core needle biopey Image guided sampling (ultraaonographic ± mammographic)	Determination and reporting of ER and PR status	Diagnostic breat ultrasound ± diagnodetic mammography Plain cheet radiography
Enhanced	Preoperative needle localization under memographic of ultra sound guidance	On-site cytopethologist	Liver ultrasound Blood chemiatry profile / CBC Diagnostic mammography bone scan
Maximal	Stereotaatic biopey Sentinel node biopey	HER- 2 neu statue IHC staining if sentinel nodes for sytokertin to detect micrometaataaee	CT scanning . PET acan MIBI scan , breat MRI

should be described by the longest perpendicular diameters in cm, and the presence of palpable axillary, supraclavicular and subclavicular nodes, with exact measurements of their longest perpendicular diameters, should be included. A close-up photograph is useful in the staging of patients with T_4 tumors. Ideally, the initial evaluation should be done simultaneously by the medical oncologist, surgical oncologist and radiotherapist.

Table 3 NCCN – Guide lines for LABC

LOCALLY ADVANCED INVASIVE BREAST CANCER

CLINICAL STAGE	**WORKUP**
Stage III A **T0, N2 , M0** **T1, N2 , M0** **T2, N2 , M0** **T3, N2 , M0** **(Stage III A patients with T3 N 1 M0 disease , see BiNV-1**	**H&P** **CBC Platelets** **Liver function tests** **Chest imaging** **Pathology review** **Prechemotheraphy determination of tumor ER/ PR receptor status and HER2 status**
Stage III B **T4, N0 , M0** **T4, N1 , M0** **T4, N2 , M0**	**Diagnostic bilateral mammogram, ultrasound as necessary** **Bone scan (catergory2B)**
Stage III C **Any T, N3,M0**	**Abdominal CT or US or MRI category 2B)** **Breast MRI (optional)**

After the physical examination and bilateral mammogram, the following additional tests are recommended: a biochemical profile, including tests of liver and renal function, and calcium level; chest x-ray; bone scans;

radiographs of areas that appear to be abnormal on the bone scan; computed tomography of the liver and an ultrasonography of the breast and regional lymph nodes to precisely assess the tumor extent. The importance of an accurate initial assessment of the extent of primary tumor burden cannot be overemphasized since the efficacy of subsequent local treatment will depend mostly on this initial assessment.

Patients with LABC are at great risk for morbid local complications of their disease, including skin breakdown, tissue necrosis, bleeding, pain, and infection. These problems, which may not alter survival, significantly compromise quality of life. Patients with locally advanced breast cancer also have a very high rate of systemic micrometastasis at diagnosis, which if untreated will progress and lead to organ dysfunction and death. There are thus two central goals in the treatment of LABC:

- **Obtaining and maintaining local control with surgery and/or radiotherapy**,
- **Improving overall survival by control of systemic disease with chemotherapy and/or hormonal therapy.**

Arriving at a uniform treatment plan for LABC is limited by the biologic diversity of the disease (there are 13 possible combinations in the current

TNM staging system for stage III breast cancer ranging from minute tumors with bulky axillary disease to large tumors with microscopic axillary disease).

Historical perspective & Review of literature.:

During the last 60 years, the management of LABC has evolved considerably. Initially, patients with LABC were treated with radical mastectomy.Based on the disappointing results of surgery and radiotherapy in patients with LABC, and the early promising results of adjuvant systemic therapy in women with axillary node-positive breast cancer, systemic therapy was subsequently incorporated along with surgery and radiotherapy into the management of patients with LABC, termed "combined modality therapy." Even with such combined modality therapy, the long-term survival rate is approximately 50% among patients with LABC.

Surgery and LABC :

For many years, the Halsted radical mastectomy was the standard treatment for breast cancer.The pioneering work of McWhirter et al in the mid 20th century showed that less mutilating surgery produced results equal to that of radical mastectomy.The failure of halstedian principle of en-bloc

extirpation of the breast and draining lymph nodes to cure many patients of breast cancer,frequent identification of small breast cancer by mammography,and success of moderate doses of radiotherapy in eliminating sub clinical foci of breast cancer led to the development of MRM .MRM is a term used to describe a variety of surgical procedures,but all involve complete removal of the breast and some of the axillar nodes. Table 4 summarizes the results of surgery alone in the treatment of LABC; these studies were retrospective and did not follow uniform staging classifications. Some included stage T1 patients in addition to LABC, and some patients were treated with radiation therapy and chemotherapy. These studies confirmed that surgery alone was inadequate treatment Even with aggressive surgical techniques,patients with advanced local disease had a high incidence of localregional recurrence. Most important, surgery did not change the pattern of distant failure in patients who probably had micrometastatic disease

The advent of radiation therapy in LABC

The use of radiation therapy alone in the treatment of locally advanced noninflammatory breast cancer was no more effective than surgery alone (Table 5). The local recurrence rates of 36% to *72%* were even higher than those reported for surgery alone. This difference in local-regional

failures was no longer evident when patients were treated with a combination of radiation therapy and surgery, which suggested that the two treatment modalities might provide better results if used together. The patients' high rate of distant relapse, however, emphasized the need for systemic therapy as well.

TABLE 4 SURGERY ALONE IN THE TREATMENT OF LABC

Author	Institution	No of patients	5 year local Recurrence Rate (%)	5 year survival (%)	10 year DFS (%)
Haagensan and stout	Columbia-Presbyterian	35	45.7	5.7	-
Schottenfield et al	MSKCC	62	6	53	29
Arnold and Lesnick	Mount sinai hospital	50	50	33	22
Fracchia et al	MSKCC	207	25	43	27.1

Table 5 RADIATION ALONE IN THE TREATMENT OF LOCALLY ADVANCED BREAST CANCER

AUTHOUR	YEAR	INSTITUTION	NO OF PATIENTS	5-YR LOCAL RECURRENCE RATE %	DISEASE FREE SURVIVAL%
Zucali et al	1976	Instituto Nazionale Tumori	321	49	21
Rubens et al	1977	Guy's hospital	184	72	18
Bruckman et al	1979	Joint centre for Radiation therapy	116	36	22
Rao et al	1982	Malinckrodt Institue of Radiology	54	51	16-20
Harris et al	1983	Joint centre for Radiation therapy	137	46	28

Combined Surgery and Radiation Therapy

In early attempts to improve locoregional control in treating patients for LABC, radiation therapy was combined with surgical therapy. Although these studies showed promising results in locoregional control, they failed to address the systemic nature of LABC, and patients still died of metastatic disease. The lessons learned in those years emphasized the need for additional treatment modalities. First, even though combined radiation and surgical therapy delayed the time to first local-regional relapse, there was no

significant survival advantage. Second, preoperative radiation therapy was often able to convert an inoperable breast cancer to an operable one. Third, preoperative radiation therapy did not seem to differ from postoperative radiation in providing additional locoregional control. Last, a combination of surgery and radiation therapy provided the maximum chance for locoregional control over high-dose radiation therapy or surgery alone. Table 6 summarizes selected series in which combination surgery and radiation therapy were used pre or postoperatively to treat LABC patients. The results showed that even combining radiation therapy and surgery did not eliminate locoregional failures.

MULTIMODAL THERAPY

Haagensen and Stout's early paper on the criteria of operability in carcinoma of the breast made clear that the vast majority of patients with locally advanced disease would develop distant metastatic disease. This has been confirmed in multiple trials of surgery and radiation therapy alone or in combination.Multimodality therapy that included surgery, radiation therapy, chemotherapy, and hormonal therapy has had the greatest impact on survival.

TABLE 6 : COMBIMATION SURGERY AND RADIATION THERAPY IN THE TREATMENT OF LOCALLY ADVANCED BREAST CANCER

AUTHOUR	YEAR	INSTITUTION	NO OF PATIENTS	5-YR LOCAL RECURRENCE RATE %	DISEASE FREE SURVIVAL%
(Pre-op)Cade	1949	Westminster Hospital	95	-	10
Zucali et al	1976	Instituto Nazionale Tumori	133	-	45
Whitaker & Battersby	1977	Princess Alexandra Hospital	68	77.9	-
(Post-op)Arnold & Lesnick	1979	Mount Sinai Hospital	54	70	32
Townsend et al	1984	University of Texas	53	11	10-35
Arnold & Lesnick	1979	Mount Sinai Hospital	122	70	30
Bedwinek et al	1982	Malinckrodt Institue of Radiology	93	12-13	-
Montague & Fletcher	1985	M.D Andersn Cancer Centre	132	13	43.3

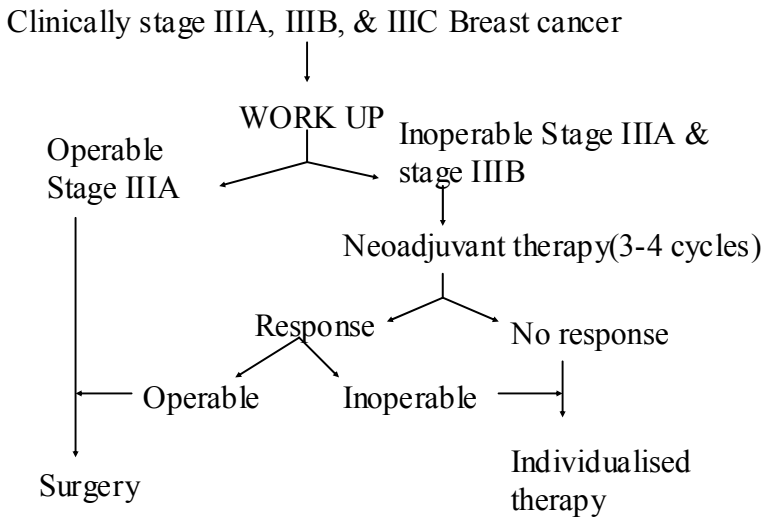
. **TABLE 7 : SUMMARY OF STUDIES WITH SURGERY FOLLOWED BY ADJUVANT CHEMOTHERAPY**

Study	Patients	No of Pts	Treatment Regimens	Duration of Follow-Up	Level Of Evidence	Results/Recommendations
Kletsform et al 1987	Stage III breast cancer patients after MRM	120	1.Radiotherapy 2.VAC 3.Both	5 yr	I	DFS better with combned treatment trhan with either radiotherapy alone or VAC alone
Derman et al	LABC	231	1.Radiotherapy 2.Radiotherapy + low dose CMF 3.Radiotherapy + high dose CMF	56 months	II	No difference in DFS /OS between the three groups
De Placido et al	Stage II / III breast cancer after mastectomy	220	1.CMF chemotherapy alternating with EV 2. CMF chemotherapy	48 mo	II	No difference in DFS /OS between the two groups
Casper et al	LABC treated by MRM / RM	41	6 mo CAF + 6 mo CMFVP	24 mo	II	Median DFS 23 months in CAF + CMFVP group,15 months in CMFVP alone;Median OS 33 Months in CAF + CMFVP , 18 months in CMFVP alone
Olson et al	LABC who underwent Mastectomy & treated with CAFTH	313	1.Radiotherapy 2.Observation + RT if locoregional failure	9.1 year	II	DFS not reported.Median survival 8.3 year in RT group; locoregional recuurance 15% in RT , 24% in observation group

Multidisciplinary approach to LABC :

The clinical management of LABC is complex and should be tailored to the individual patient. Frequently, surgery, radiotherapy and systemic therapy (chemotherapy, hormone therapy) are used. A multidisciplinary approach to LABC is recommended in which treatment is based on the combined opinions of a surgeon, radiation oncologist and medical oncologist. The initial management of LABC requires histological confirmation (e.g., core biopsy, incisional biopsy or skin biopsy) for diagnosis and for determination of hormone receptor and *HER-2 neu* oncogene status. Cytological evaluation by fine-needle aspiration is insufficient.

LABC
Treatment pathways



Systemic therapy: chemotherapy

Operable tumours • ***Patients with operable stage IIIA disease should be offered***

chemotherapy. They should receive adjuvant chemotherapy following surgery, or

primary chemotherapy followed by locoregional management.

Patients with stage IIIA breast cancer have potentially operable tumours. There are 2 approaches for treating these patients. The first is modified radical mastectomy (MRM) followed by adjuvant systemic therapy and radiotherapy, and the second is preoperative chemotherapy followed by surgery and adjuvant chemoradiation.

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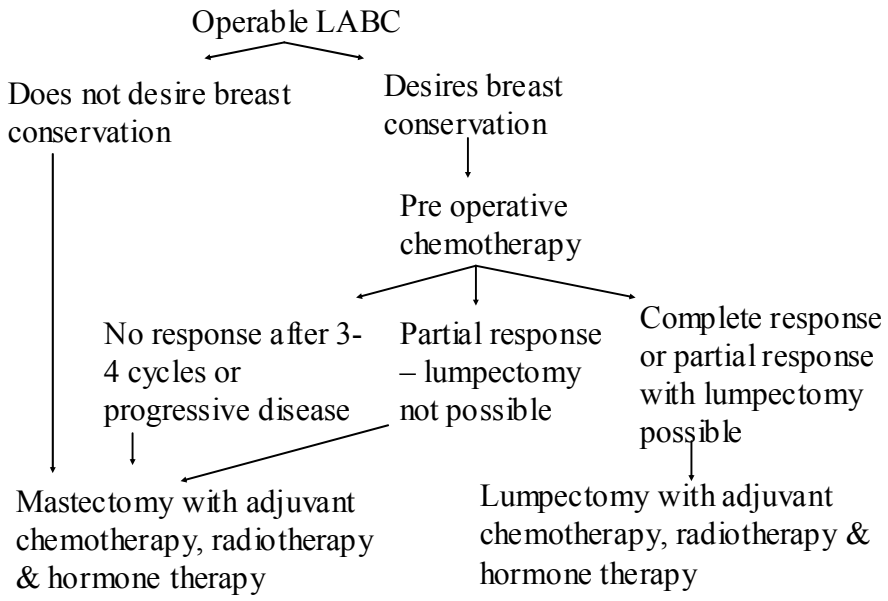
LABC - Management protocol



Choice of chemotherapy

• **Chemotherapy should contain an anthracycline. Acceptable regimens are 6 cycles of FAC, CAF, CEF or FEC. Taxanes are under intense investigation**

Randomized trials have confirmed the superiority of anthracycline-containing regimens such as CEF and CAF over conventional CMF in women with node-negative and node-positive breast cancer. In contrast, in the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-15 trial, 4 cycles of AC chemotherapy was equivalent to 6 months of CMF. Although there are limitations to crossstudy comparisons, it is reasonable to consider that 4 cycles of AC, although equivalent to 6 months of CMF, is

probably inferior to 6 cycles of anthracycline-containing drug regimens such as FAC, CAF, CEF and FEC. In women who cannot receive anthracyclines because of underlying cardiac disease, CMF chemotherapy can be considered.

Six cycles of chemotherapy should be administered. This is based on the trials of adjuvant chemotherapy that showed that 6 cycles of CAF or CEF was superior to 6 cycles of CMF and that 6 cycles of FEC were superior to 3 cycles of FEC.

NON-TRASTUZUMAB CONTAINING REGIMENS (all category 1)

FAC/CAF (fluorouracil/doxorubicin/cyclophosphamide)

FEC/CEF (cyclophosphamide/epirubicin/fluorouracil)

AC (doxorubicin/cyclophosphamide) ± sequential paclitaxel

EC (epirubicin/cyclophosphamide)

TAC (docetaxel/doxorubicin/cyclophosphamide)

A CMF (doxorubicin followed by cyclophosphamide/methotrexate/fluorouracil)

E CMF (epirubicin followed by cyclophosphamide/methotrexate/fluorouracil**)**

CMF (cyclophosphamide/methotrexate/fluorouracil**)**

AC x 4 (doxorubicin/cyclophosphamide) + sequential paclitaxel x 4**,**every 2 weekly regimen with filgrastim support

A T C (doxorubicin followed by paclitaxel followed by cyclophosphamide) every 2 weekly regimen with filgrastim support

FEC T (fluorouracil/epirubicin/cyclophosphamide followed by docetaxel)

Neoadjuvant Therapy

The use of neoadjuvant or induction chemotherapy was first reported in the 1970s . Perez and colleagues reported their results of a pilot study by the Southeastern Cancer Study Group in 1979. This small study included 14 patients (five patients had inflammatory breast cancer and five had recurrences after mastectomy). All patients were treated with 5-flurouracil, Adriamycin (doxorubicin), and cyclophosphamide (FAC) for two courses, followed by local therapy or radiation concurrently with cyclophosphamide and 5-fluorouracil (CF). In the Perez group's study, all patients received an additional eight courses of FAC. All but three of the patients had complete regression of their tumors following radiation therapy. The primary tumor showed partial regression (50% to 75%) in 65% of the patients after the first two courses of FAC.However all the trials concluded that induction

chemotherapy was feasible but did not show any significant survival benefit .

Given the absence of any difference in outcome for patients treated with neoadjuvant versus adjuvant chemotherapy, the decision to use preoperative versus postoperative chemotherapy must be based on other factors. Factors in favor of preoperative chemotherapy include the following:

(1) patients initially presenting with tumors that historically required mastectomy can potentially be down-staged to allow for breast-conservation treatment;

(2) larger tumors that require a cosmetically unsatisfactory lumpectomy at presentation can be down-staged to allow a more cosmetically favorable lumpectomy;

(3) the response of individual patients to systemic chemotherapy can be assessed *in vivo*;

(4) research can be facilitated, for example, by evaluating tissue specimens before and after treatment, to rapidly assess new chemotherapeutic, hormonal, or biologic agents; &

(5) the pathologic response to neoadjuvant chemotherapy is a strong prognostic factor for outcome.

The argument in favor of primary surgery, if possible, with adjuvant systemic therapy is the more accurate pathologic staging, both of the primary tumor as well as the axillary lymph nodes, with the valuable prognostic information acquired for prognosis and guidance of adjuvant therapy.

Numerous studies have demonstrated high rates of down-staging to breast-conservation treatment with the use of neoadjuvant chemotherapy. Although most studies have used doxorubicin- or epirubicin-containing regimens, studies have also begun to evaluate the role of taxane chemotherapy. After neoadjuvant chemotherapy, down-staging of the tumor sufficient to allow breast-conservation treatment has been reported in 22% to 90% of patients. For those patients with sufficient down-staging to permit breast-conservation surgery, definitive breast irradiation is also indicated and is delivered in a manner similar to that for patients not treated with neoadjuvant chemotherapy.

Because physical examination and mammography do not adequately predict the pathologic response to neoadjuvant chemotherapy, alternative imaging methods have been developed to attempt to more accurately predict

a pathologic response and to improve breast-conservation rates. MRI is one promising modality and appears to correlate well with pathologic response.

Hormone therapy likely has a role to play as a neoadjuvant therapy, particularly when the diagnostic biopsy results confirm hormone receptor expression. The addition of endocrine therapy to chemotherapy appears to improve outcome for patients with locally advanced breast cancerThe role of postmastectomy radiation treatment after neoadjuvant chemotherapy is in evolution. The ASCO guidelines recommend that, in general, postmastectomy radiation treatment is indicated after neoadjuvant systemic therapy, although the guidelines recognize that there may be exceptions to this recommendation. The rationale for recommending postmastectomy radiation treatment is the significant down-staging associated with neoadjuvant chemotherapy, for both the primary tumor and axillary lymph nodes, and the fact that most patients who require mastectomy have presented initially with locally advanced tumors (T3 or T4 lesions) or four or more pathologically positive axillary lymph nodes. For postmastectomy radiation treatment after neoadjuvant chemotherapy followed by mastectomy, unresolved issues at this time include which patient and tumor factors (clinical and pathologic) should be used to select those patients who

require treatment and the optimal technical radiation therapy fields, including which regional lymph nodes, if any, should be treated.

Breast Conservation in the Setting of Multimodal Therapy

The concept of breast conservation in patients with LABC was initially practiced to spare patients surgery who already had an extremely poor prognosis. Initial studies with radiation therapy alone accomplished breast conservation, but at the expense of a high rate of local-regional failure and distant relapse. Even studies of multimodal therapy in which only radiation was used as local therapy have had local-regional failure rates as high as 30% to 50%. The ability to reduce local failures by combining surgery and radiation therapy makes breast conservation treatment more appealing. Because induction chemotherapy may result in significant reductions in the size of the primary tumor,

many patients with LABC would be candidates for breast conservation with a combination of surgery and radiation therapy.

In 1990, Bonadonna et al" first reported the use of induction chemotherapy to downstage primary tumors and allow subsequent breast saving surgery. The criterion for breast-saving surgery was a reduction in the tumor size to less than **3** cm. The group was able to avoid mastectomy for 127 (81%) of the 157 patients who had a surgical procedure.The treatment

regimen consisted of three to four cycles of chemotherapy (CMF, FAC, or FEC [5-fluorouracil, epirubicin, cyclophosphamide]),followed by surgery and postoperative radiation therapy. Only116 women received postoperative adjuvant chemotherapy. Complete responses were seen after chemotherapy in 27 women, although histopathologic CR occurred in only nine. Up to 60% of the patients had at least a partial response to the induction chemotherapy. Among the first 83 patients who underwent surgery with at least 12 months of followup,

the disease recurred in 13. Only one of the 75 women treated with breast conservation surgery experienced a local recurrence during this period. One patient treated with mastectomy had a local recurrence, and the remaining 11 patients developed distant metastases.

Targeted therapy – recent advances

Advances in molecular biology are reaching therapeutic application on several fronts. One example is the targeting of the HER-2 tyrosine kinase receptor. Trastuzumab (Herceptin, Genentech, San Francisco) is a humanized monoclonal antibody that binds to HER-2 with great affinity, resulting in growth arrest of HER-2 overexpressing cancer cells. The addition of trastuzumab to AC and paclitaxel improves time to progression, response rates, and overall survival for patients with advanced breast cancer

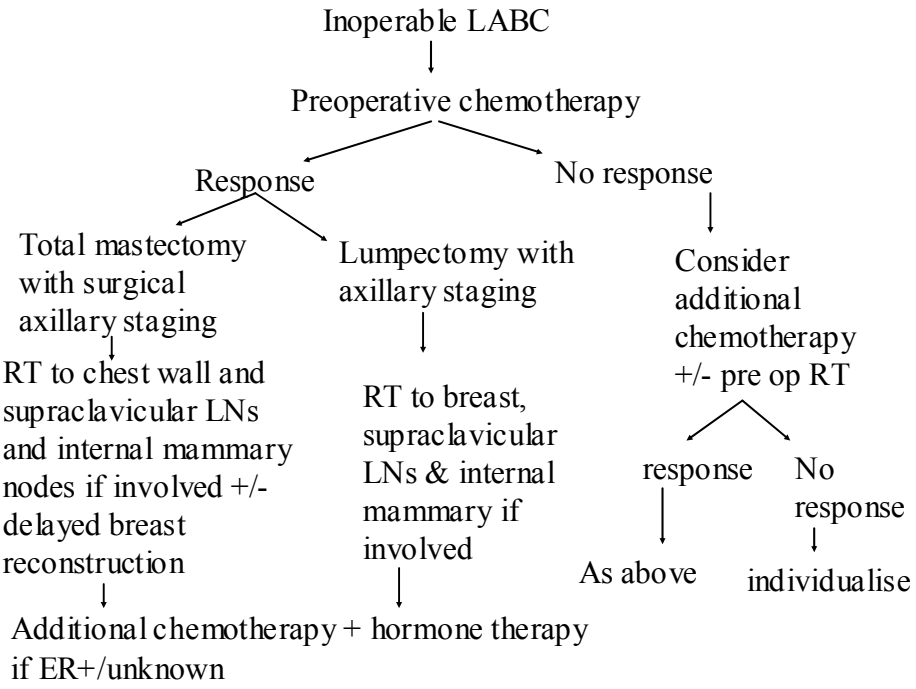
overexpressing HER-2. Monoclonal antibodies are large molecules and are likely to be more effective in the adjuvant setting. Randomized trials that integrate trastuzumab in combination with chemotherapy are under way.

Table 8 BREAST CONSERVATION AFTER MULTIMODALITY TREATMENT IN LABC

Author	Year	Institution	No. of Patients	Breast Conservation Rate (%)	5-Year Survival (%)
Bonadonna et al[11]	1990	Instituto Nazionale Tumori	165*	81	—
Booser et al[12]	1992	M. D. Anderson Cancer Center	146†	27	—
Calais et al[16]	1993	University Hospital, Tours, France	80‡	42.5	73
Scholl et al[47]	1994	Institut Curie, Paris, France	390§	79.7	78–86
Schwartz et al[49]	1994	Thomas Jefferson University	189	36	61¶

Inoperable tumours

• Patients with stage IIIB or IIIC disease, including those with inflammatory breast cancer and those with isolated ipsilateral internal mammary or supraclavicular lymph-node involvement, should be treated with primary anthracycline-based chemotherapy. • Acceptable chemotherapy regimens are FAC, CAF, CEF or FEC. Taxanes are under intense investigation.



NON-TRASTUZUMAB COMBINATIONS

FAC chemotherapy :

5-Fluorouracil 500 mg/m IV days 1 & 8 or days 1 & 4

Doxorubicin 50 mg/m IV day 1 (or by 72 h continuous infusion**)**

Cyclophosphamide 500 mg/m IV day 1 Cycled every 21 days for 6 cycles**.**

CAF chemotherapy

Cyclophosphamide 100 mg/m PO days 1-14

Doxorubicin 30 mg/m IV days 1 & 8

5-Fluorouracil 500 mg/m IV days 1 & 8 Cycled every 28 days for 6 cycles.

AC chemotherapy

Doxorubicin 60 mg/m IV day 1

Cyclophosphamide 600 mg/m IV day 1

Cycled every 21 days for 4 cycles.

FEC chemotherapy

Cyclophosphamide 75 mg/m PO days 1-14

Epirubicin 60 mg/m IV days 1 & 8

5-Fluorouracil 500 mg/m IV days 1 & 8

With cotrimoxazole support.Cycled every 28 days for 6 cycles**.**

AC followed by paclitaxel chemotherapy

Doxorubicin 60 mg/m IV day 1

Cyclophosphamide 600 mg/m IV day 1 Cycled every 21 days for 4 cycles.Followed by

Paclitaxel 175-225 mg/m by 3 h IV infusion day 1 Cycled every 21 days for 4 cycles. OR

Paclitaxel 80 mg/m by 1 h IV infusion weekly for 12 weeks.

EC chemotherapy

Epirubicin 100 mg/m IV day 1

Cyclophosphamide 830 mg/m IV day 1 Cycled every 21 days for 8 cycles.

TAC chemotherapy

Docetaxel 75 mg/m IV day 1

Doxorubicin 50 mg/m IV day 1

Cyclophosphamide 500 mg/m IV day 1 Cycled every 21 days for 6 cycles.

(All cycles are with filgrastim support).

A followed by CMF chemotherapy

Doxorubicin 75 mg/m IV day 1 Cycled every 21 days for 4 cycles.

Followed by Cyclophosphamide 600 mg/m IV day 1

Methotrexate 40 mg/m IV day 1

5-Fluorouracil 600 mg/m IV day 1 Cycled every 21 days for 8 cycles**.**

E followed by CMF chemotherapy

Epirubicin 100 mg/m IV day 1 Cycled every 21 days for 4 cycles.

Followed by Cyclophosphamide 100 mg/m PO days 1-14

Methotrexate 40 mg/m IV days 1 & 8

5-Fluorouracil 600 mg/m IV days 1 & 8 Cycled every 28 days for 4 cycles.OR

Cyclophosphamide 750 mg/m IV day 1

Methotrexate 50 mg/m IV day 1

5-Fluorouracil 600 mg/m IV day 1 Cycled every 21 days for 4 cycles.

CMF chemotherapy

Cyclophosphamide 100 mg/m PO days 1-14

Methotrexate 40 mg/m IV days 1 & 8

5-Fluorouracil 600 mg/m IV days 1 & 8 Cycled every 28 days for 6 cycles.

Dose-dense AC followed by paclitaxel chemotherapy

Doxorubicin 60 mg/m IV day 1

Cyclophosphamide 600 mg/m IV day 1 Cycled every 14 days for 4 cycles.

Followed by Paclitaxel 175 mg/m by 3 h IV infusion day 1 Cycled every 14 days for 4 cycles.(All cycles are with filgrastim support).

Dose-dense A-T-C chemotherapy

Doxorubicin 60 mg/m IV day 1 Cycled every 14 days for 4 cycles.

Followed by Paclitaxel 175 mg/m by 3 h IV day 1 Cycled every 14 days for 4 cycles.

Followed by Cyclophosphamide 600 mg/m IV day 1 Cycled every 14 days for 4 cycles.

(All cycles are with filgrastim support**).**

FEC followed by docetaxel chemotherapy

5-Fluorouracil 500 mg/m IV day 1

Epirubicin 100 mg/m IV day 1

Cyclophosphamide 500 mg/m day 1 Cycled every 21 days for 3 cycles.

Followed by Docetaxel 100 mg/m day 1 Cycled every 21 days for 3 cycles.

TRASTUZUMAB CONTAINING COMBINATIONS

AC followed by T chemotherapy with Trastuzumab

Doxorubicin 60 mg/m IV day 1

Cyclophosphamide 600 mg/m IV day 1 Cycled every 21 days for 4 cycles.

Followed by Paclitaxel 175 mg/m by 3 h IV day 1 Cycled every 21 days for 4 cycles OR

Paclitaxel 80 mg/m by 1 h IV weekly for 12 wks With Trastuzumab 4 mg/kg IV with first dose of paclitaxel Followed by Trastuzumab 2 mg/kg IV weekly to complete 1 year of treatment. As an alternative, trastuzumab 6 mg/kg IV every 3 wk may be used following the completion of paclitaxel, and given to complete 1year of trastuzumab treatment.

Cardiac monitoring at baseline, 3, 6, and 9 months.

Docetaxel + trastuzumab followed by FEC

Docetaxel 100 mg/m by 1 h IV day 1 Cycled every 21 days for 3 cycles With

Trastuzumab 4 mg/kg IV with first dose of docetaxel day 1 Followed by

Trastuzumab 2 mg/kg IV weekly to complete 9 weeks of trastuzumab.Followed by

5-Fluorouracil 600 mg/m IV day 1

Epirubicin 60 mg/m day 1

Cyclophosphamide 600 mg/m day 1 Cycled every 21 days for 3 cycles

Cardiac monitoring at baseline, after last FEC cycle, at 12 and 36 months after chemotherapy.

TCH (docetaxel, carboplatin, trastuzumab)

Docetaxel 75 mg/m IV day 1 Followed by

Carboplatin AUC 6 IV day 1 Cycled every 21 days for 6 cycles With

Trastuzumab 4 mg/kg week 1 Followed by

Trastuzumab 2 mg/kg for 17 weeks Followed by

Trastuzumab 6 mg/kg IV every 3 weeks to complete 1 year of trastuzumab therapy

Cardiac monitoring at baseline, 3, 6, and 9 months.

AC followed by docetaxel with trastuzumab

Doxorubicin 60 mg/m IV day 1

Cyclophosphamide 600 mg/m day 1 Cycled every 21 days for 4 cycles Followed by

Docetaxel 100 mg/m Cycled every 21 days for 4 cycles With

Trastuzumab 4 mg/kg IV week one Followed by

Trastuzumab 2 mg/kg IV weekly for 11 weeks Followed by

Trastuzumab 6 mg/kg every 21 days to complete 1 y of trastuzumab therapy

Cardiac monitoring at baseline, 3, 6, and 9 months.

Neoadjuvant T followed by FEC chemotherapy with trastuzumab

Trastuzumab 4 mg/kg IV for one dose beginning just prior to first dose of paclitaxel

Followed by

Trastuzumab 2 mg/kg IV weekly for 23 wks

Paclitaxel 225 mg/m by 24 h IV infusion every 21 days for 4 cycles

Followed by

5-Fluorouracil 500 mg/m on days 1 and 4

Epirubicin 75 mg/m IV on day 1

Cyclophosphamide 500 mg/m on day 1 Cycled every 21 days for 4 cycles

Systemic therapy: hormonal therapy

Operable and inoperable tumours

• **Tamoxifen for 5 years should be recommended to pre-and postmenopausal women whose tumours are hormone responsive.**

Schinzinger was the first person to propose that oophorectomy might be of benefit in breast cancer based on the following observations :

- Post menopausal breast atrophies.
- More virulent tumor growth in premenopausal women.

The first reported series of surgical oophorectomy for breast cancer was reported by Thomas Beatson (1896).The report postulated the following effects of oopherectomy

- Significant tumor regression by castration
- Better sense of well being
- Regression of cutaneous metastasis
- Best above age of 40
- No effect on osseous metastatsis

Following Beatson's original report, oophorectomy became widely practiced but then was largely abandoned after only 10 years. The reasons why the procedure was abandoned are (a) the recognition that oophorectomy was not a curative procedure, as was originally thought by Beatson;

(b) the lack of a sound therapeutic rationale; and

(c) the risks of intraabdominal surgery in the early twentieth century.

It was not until the 1940s, when Charles Huggins described the hormonal responsiveness of prostatic cancer, that an interest in the hormonal treatment of breast cancer was resurrected .

The various modalities of endocrine manipulation available in the management of advanced breast cancer include :

Selective Estrogen Receptor Modulators: 1.Tamoxifen

2.Torimefen

Androgens : Fluoxymesterone

Progestins : Megestrol acetate

Medroxyprogesterone acetate

High dose Estrogens

Aromatase inhibitors: 1st generation: Aminoglutethemide

2nd generation: Formestane (Type I) , Fadrazole

3rd generation: Exemestane (Type I) , Anastrazole , Letrozole, Vorozole

Steroidal Antiestrogens: Fulvestrant

LHRH agonists : Leuprolide, Goserelin

Gland ablation : surgical (open/laparoscopic) ; chemical ; radiation

- Ovary ; Pituitary ; Adrenals

SELECTIVE ESTROGEN RECEPTOR MODULATORS :

The SERMs are chemically diverse compounds that lack the steroid structure of estrogens but possess a tertiary structure that allows them to bind to the estrogen receptor.

Examples: Tamoxifen ; Raloxifen ; Tormifen

The **Selective modulation** explained by:

- Differential estrogen-receptor **expression** in a given target tissue
- Differential estrogen-receptor **conformation** on ligand binding
- Differential expression and binding to the estrogen receptor of c**oregulator** proteins

Tamoxifen

Chemically a *triphenylethylene*.the *trans* isomer of which is used as a citrate salt.

Mechanism Of Action: Competitive binding to the estrogen receptor resulting in reduction of transcription of estrogen regulated genes.

Dimethylaminoethoxy side chain and the **trans configuration** are crucial for the antiestrogenic activity of tamoxifen

The net result is a block in the **G1 phase** of the cell cycle and a slowing of cell proliferation.Tamoxifen is thus, a **cytostatic** drug.

Binding and inactivation of estrogen receptor in cancerous cell : Predominant mode of action

Other postulated mechanisms:

Initiation of apoptosis in malignant cells

Reduction of serum IGF-1 and increase in IGF-1 binding proteins are another potential mechanism of action.

Other actions:

Increased sex hormone binding globulin (? Reduced estrogen bioavailability)

Increased TGF β (? Increased pulm fibrosis / breast fibrosis if used concurrently with RT)

Selective activation / inactivation of corepessors and coactivators responsible for selective agonist / antagonist activity

Ancillary benefits of Tamoxifen

Cardiovascular:

Fewer non cancer related deaths due to cardiovascular events.

Fewer hospitalizations for cardiac events

Serum LDL / cholesterol reduced.

Skeletal:

Significant reduction in incidence of fractures of weight bearing bones.

Estrogen agonist action on BMD

Prevention of contralateral breast cancer

Toxicity

Menopausal symptoms:50% - 60% (N.B. 40% - 50% in placebo)

MC in premenopausal

Vaginal dryness and discharge may occur in excess.

Depression:

Maybe seen in as high as 10% of patients.

But no randomized comparisons available.

Ocular toxicity:

Keratopathy

Thromboembolism:Severe thromboembolism seen in ~ 1% patients in the preventive setting.The risk is up to 10 times that experienced by healthy women.This complication is more common in elderly patients with metastatic breast cancer and who are receiving CCT

Carcinogenesis:There is increased risk of endometrial cancers (hazard rate of 1.7 per 1000 – NSABP B 14 data)but mostly low grade & stage I tumors.

Other tumors: Hepatomas & Clear cell sarcomas of ovary

Contraindications to Tamoxifen Treatment :

Absolute: **Retinal macular edema** or degeneration

History of benign or malignant **liver tumor** secondary to oral contraceptives

Pregnancy

Other hormonal therapy (estrogens, oral contraceptives)

Relative: History of thrombophlebitis, particularly hormone related

History of depression, particularly hormone related

Cataract

Drugs: Chlorpromazine, chloroquine, thioridazine, amiodarone, other

Severe vasomotor symptoms

Polycystic ovaries

Radiation oophorectomy

The first series on the effectiveness of radiation oopherectomy was reported by Foveau de Courmelles in 1922.The considerations in advocating Radiation oophorectomy include:1. Non invasive and cheap procedure.

2.Low dose carries little additional morbidity.

3.However takes about 2 – 3 months for effect to appear.

4.For such reason best avoided when prompt relief is needed.

5.Also best reserved for the patient with slow progression of disease.

Technique: Position: Supine

Field selection: Parallel opposing two field technique

Energy : Co60 or 6 MV LINAC

Dose Schedules:

In a younger women 10 – 12 Gy in 5 -6 divided fractions is preferred.

In older women shorter course of radiation can give equivalent ovarian ablation.

Field borders:

The volume of interest is the entire true pelvis

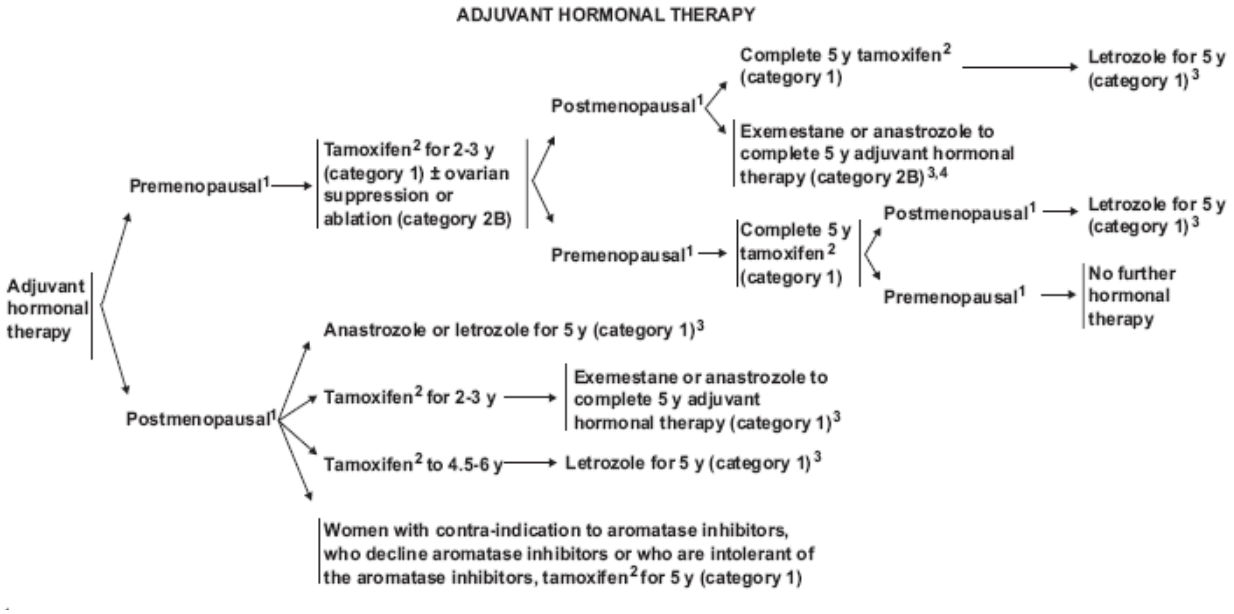
10 x 15 cm field is opened.

Lower border is placed just below the superior border of pubic symphysis.

Recommendations for adjuvant hormonal therapy :

Following completion of chemotherapy, pre- or postmenopausal patients with LABC and hormone-responsive tumours should receive adjuvant tamoxifen therapy, 20 mg/d, for 5 years Tamoxifen should be started after completion of chemotherapy. The aromatase inhibitor, anastrozole, has been compared with tamoxifen in postmenopausal women with early breast cancer following surgery. The early results of that study showed that , compared with tamoxifen, anastrozole was associated with improved DFS and had fewer side effects. The role of aromatase inhibitors as adjuvant therapy in breast cancer is evolving. The role of luteinizing hormone-releasing hormone agonists in premenopausal patients is evolving as new data emerge . Patients who are not candidates for any chemotherapy can be managed with hormonal treatment and then receive locoregional management.

NCCN GUIDELINES FOR HORMONAL THERAPY :



Locoregional management

Operable tumours

• Patients with stage IIIA disease should receive both modified radical mastectomy (MRM) and locoregional radiotherapy if feasible. They may be managed with MRM followed by chemotherapy and

locoregional radiotherapy, or chemotherapy first followed by MRM and locoregional radiotherapy. Breast-conserving surgery is currently not a standard approach.

MRM (mastectomy plus a level 1 and level 2 axillary dissection) remains the standard surgical treatment for operable locally advanced disease. The second half of the 20th century witnessed increasing disillusionment with radical and mutilating forms of surgery for breast cancer. As a result the trend towards breast conservation has increased since the mid-1960s, although a number of centres had adopted this approach since before the Second World War. Again there are a number of different descriptions relating to breast conservation which has caused confusion. Tumourectomy, lumpectomy, tylectomy, segmental mastectomy, and quadrantectomy are all synonymous with a therapeutic procedure in which the primary tumour is removed and the breast is preserved. Unfortunately, these terms are not precisely defined, although they imply the removal of varying amounts of normal breast tissue in association with a primary tumour. The terms ‘lumpectomy&rsquo, ‘tumourectomy&rsquo and lsquo&tylectomy’ imply removal of the tumour with a minimal or no margin of normal breast tissue around it. Segmental mastectomy implies excision of the tumour with a rim of associated normal breast tissue.

However, this term is also somewhat misleading as it implies that the breast is anatomically a segmental organ and that tumours occur in a localized segment. This is clearly not the case. The term lsquo;quadrantectomy’ denotes removal of a breast quadrant, and implies wider excision of normal breast tissue than segmental mastectomy. In practice, however, there is little distinction between these terms and although a number of authorities have recommended the adoption of a uniform nomenclature, none has found universal favour.

Once the questions regarding definition of terms and nomenclature have been addressed the simple, yet fundamentally important question which remains is whether breast conservation provides results as reliable in the treatment of breast cancer as total Mastectomy. Furthermore, is there an additional benefit in terms of cosmetic and emotional adjustment? Finally, if breast conservation is justified, in which patients is this appropriate?

The role of BCS is unclear and the subject of research. Previous studies demonstrating equivalence of BCS to mastectomy were performed in patients with stage I and II disease see guideline In the trials that compared preoperative chemotherapy with chemotherapy administered postoperatively, the proportion of women with tumours greater than 5 cm in diameter ranged from 5% to 27%. Patients with operable stage III disease

who desire to preserve their breast should be made aware that BCS is currently not a standard approach and is generally not recommended.

TABLE 9 THERAPY OVERVIEW : MRM VS BCT

Therapy	Strengths	Weaknesses	Required resources
MRM	Effective local treatment Uses surgical technique widely available Short post treatment convealeacence Limited long term complications RT can be avoided in some cases	Loss of body image (mutilations) Negative psychosocial impact RT is often still necessary	Core surgical resources Trained surgeon General anesthesia Operating room Post operative care facility Pathology Post mastectomy irradiation of the chest wall regional lymphnodes
BCT	Equivalent survival to MRM Preservation of body image Improved quality of life	Slight increase the rate of recurrence compared to MRM Lower acceptance among less educated people Prolonged treatment course Requires access to RT facility	High quality breast imaging Core surgical resources Pathology for margin assessment Surgical services experience in the procedure Breast conserving whole breast irradiation Geographical accessibility Support system that's allows RT over a period of weeks

TABLE 10 Anatomical structures removed in various types of mastectomy

	Skin	Most of gland	All of gland	Areola	P. minor	Pe.major	Level 1 nodes	Level II nodes	Level III nodes	Rotter's nodes	Int mammary N	Supraclavicular N	Mediastinal N
Sub-cutaneous		X											
Total (simple)	X		X	X									
Modified simple)	X		X	X	X								
Total with axillary dissection.	X		X	X	X	X							
Auchincoloss MRM	X		X	X	X	X	X						
Scanlon MRM	X		X	X	X	X	X	X					
Patey MRM	X		X	X	X	X	X	X	X				
Halstead RM	X		X	X	X	X	X	X	X	X			
Urban ERM	X		X	X	X	X	X	X	X	X	X		
Dahl-Iversen ERM	X		X	X	X	X	X	X	X	X	X	X	
Super-radical (Wangensteen)	X		X	X	X	X	X	X	X	X	X	X	X

The contraindications to BCS were determined in 1991 by a panel of representatives from the American College of Surgeons, the American College of Radiology, the College of American Pathologists, and the Society of Surgical Oncology:

Absolute contraindications to breast-conserving surgery:

1.Pregnancy: first and second trimester

2.Multicentricity: two or more gross tumors in separate quadrants

3.Diffuse undetermined or malignant-appearing microcalcifications

4.History of previous irradiation to the breast region *viz* mantle RT

Relative contraindications to breast-conserving surgery

1.Large tumor/breast ratio with respect to acceptable cosmetic results

2.Large breast size

3.Tumor location beneath the nipple

4.History of collagen vascular (connective tissue) disease

A tumor located beneath the nipple might not be considered a contraindicationto breast-conserving surgery if the patient understands the anticipated deficit and desires the procedure. Extremely large breast size is also not a contraindication to breast-conserving surgery if radiation therapy can assure dose homogeneity.

In terms of management of the breast the simplest approach would be to remove the tumour itself, preferably with a margin of normal tissue around it. In theory the more limited procedures of tumourectomy or lumpectomy are likely to be followed by a good cosmetic result but are more likely to be followed by local recurrence because of the likelihood of failure to excise the tumour completely. More extensive forms of conservative surgery such as quadrantectomy are more likely to provide good tumour control but are more liable to be followed by a less satisfactory cosmetic result because of the amount of breast tissue excised.

Nearly all of the series evaluating Skin Sparing Mastectomy comprise Stage 0, I, and II breast carcinomas. Some have also included a few Stage III tumors, which were clinically thought to represent earlier-stage lesions preoperatively .Foster et al evaluated outcomes for SSM with immediate reconstruction in patients with locally advanced disease, specifically Stages IIB and III. With a median follow-up of 49.2 months, the rate of local recurrence was 4%, which is comparable to the reported overall local recurrence rates in the literature. They concluded that this procedure is safe, effective, and has a low

morbidity on women with locally advanced breast carcinoma SSM can be performed for noninvasive or invasive breast cancer. Simmons et al reported that among NSSM patients, 62% had modified radical mastectomies, 37% had total mastectomies, and fewer than 2% had radical mastectomies; and that among SSM patients, 44% had modified

radical mastectomies, 56% had total mastectomies, and none had radical mastectomies .

Postoperative adjuvant chemotherapy or radiation therapy is indicated based upon the size of the primary tumor and the number of positive axillary lymph nodes. A recent study showed that 49% of both NSSM and SSM patients received postoperative adjuvant chemotherapy.Postoperative radiation therapy is typically given because of a tumor size

greater than 5 cm or because of numerous axillary lymph nodes with metastatic disease. In one series, it was performed in 3% of SSM and in 12%of NSSM (P = NS). Although there is some cosmetic disadvantage to postoperative radiation therapy in patients who have tissue-expander reconstruction, patients with autologous reconstruction often maintain an excellent cosmetic outcome. If it is suspected before reconstruction that

postoperative radiation will be indicated, one option is to create the reconstructed breast slightly larger than the contralateral breast, which often results in a more symmetrical long-term outcome after radiation.

Locoregional radiotherapy should be delivered to the chest wall and to the supraclavicular and axillary nodes. The role of internal mammary irradiation is not clear.

When locoregional radiotherapy is delivered following MRM for locally advanced disease, radiation should be delivered to the chest wall,supraclavicular and axillary nodes. Whether treatment to the internal mammary nodes is required is unclear. In many of the studies reviewed for this guideline, the internal mammary nodes were irradiated. However, there are no studies that examined the impact of such radiotherapy. It is not unreasonable to include radiotherapy to the internal mammary nodal region, provided that this can be done without treating an excessive amount of heart or lung tissue. Locoregional radiotherapy has been associated with a modest increase in late non-breast-cancer deaths of cardiac or vascular origin. The recommended dose of radiation is 50 Gy in 25 fractions or equivalent.

Inoperable tumours

• Patients with stage IIIB disease who respond to chemotherapy should receive surgery plus locoregional radiotherapy.

• The locoregional management of patients with stage IIIC disease who respond to chemotherapy is unclear and should be individualized.

• Patients whose disease remains inoperable following chemotherapy should receive locoregional radiotherapy and subsequent surgery if feasible.

The locoregional management of patients with stage IIIC disease who respond to chemotherapy is unclear. In the absence of evidence on this subgroup of patients, it is reasonable that they receive locoregional radiotherapy (including nodal irradiation). The role of completion mastectomy should be individualized and based on such factors as response to chemotherapy and radiotherapy,absence of metastases on re-staging examinations and patient fitness.

Patients who are treated primarily with radiotherapy should be given tumouricidal doses to areas of bulk disease (60–66 Gy in 30 to 33 fractions or equivalent). Higher doses of radiation (70 Gy in 35 fractions by external beam or brachytherapy) to areas of bulk disease may be considered for patients if surgery is felt not to be an option and if tolerance of critical organs permits. Two case series have reported a dose-response relation with higher doses of radiation that resulted in decreased rates of local recurrence

For the patient who has a partial or complete response to chemotherapy and whose lesion is converted to an operable state, the next maneuver is typically mastectomy to debulk gross disease, to facilitate local-regional control, and to allow for the pathologic assessment of response. For patients with a complete or partial response, the optimal chemotherapy to use after local-regional treatment is uncertain. Specifically, it is not clear whether to continue the same chemotherapy as before after local-regional treatment or whether a cross-resistant chemotherapeutic regimen is indicated. The ASCO guidelines recommend postmastectomy radiation treatment, in general, for those patients who require a mastectomy

For the patient whose tumor remains inoperable after first-line systemic chemotherapy, the options are to proceed with second-line chemotherapy or to deliver preoperative radiation treatment. One major goal of treatment is to attempt to convert the lesion from an inoperable to an operable state, because patients without local-regional control have substantially diminished quality of life.

According to the St. Gallen conference,node-negative patients with a low risk for recurrence should not receive adjuvant chemotherapy. These include

- Node-negative infiltrating ductal or lobular carcinoma
- Tumor size less than 1 cm
- Well differentiated (histologic grade 1)
- ER or PR positive
- Age of 35 or more
- Size is less than 3 cm

  Pure mucinous, tubular, papillary, and adenocystic carcinoma if the tumor Contraindications to therapy (toxicity)
- Concurrent incurable, terminal illness
- Severe cardiovascular, hepatic, or renal disease
- Severe bone marrow deficiency
- Severe immunodeficiency
- Mental illness

Locally advanced breast cancer and sentinel node biopsy

Clearly, the status of the axillary lymph nodes still has an important prognostic role in LABC treated with neoadjuvant protocols. The driving question now is when to stage the axilla. Should the axilla be staged prior to and/or following neoadjuvant therapy?

Feasibility of sentinel node biopsy for LABC

Sentinel node biopsy has been extensively studied in early breast cancer and has been found to have an accuracy from 92% to 100% with successful identification of 90–100% However, limited experience in LABC is only now beginning to emerge and very little experience with SLNB after neoadjuvant therapy has been reported. Estimates of the accuracy and false negative rates (FNRs) of SLNB based on published tumor size suggest that for primary lesions greater than 3.0 cm, the accuracy should be as high as 96% . Other groups, have directly evaluated the accuracy of SNB in LABC prior to any treatment. Bedrosian et al. evaluated 104 patients of whom 87 had T2 and 17 had T3 lesions and a clinically negative axillary exam. They were successful in identifying the SN in 99% of the cases with a FNR of only 3%. This would suggest that SLNB before neoadjuvant therapy is highly accurate for patients with large tumors.

Sentinel node biopsy following neoadjuvant treatment of LABC

The experience with neoadjuvant chemotherapy and SLNB is limited but has been successful in several trials and can be considered on a case-by-case basis at institutions that have had abundant experience with SLNB and neoadjuvant chemotherapy. Clearly the role of SLNB in LABC and neoadjuvant therapy has yet to be defined, but certainly this powerful diagnostic tool will play a prominent role.

Table11 Sentinel node following neoadjuvant chemotherapy

Study	Lymphatic mapping technique	Neoadjuvant treatment	Tumor size	Rate of SLN identification	False negative rate	Accuracy
Nason	**Tc sulfur colloid**	**AC+G**	**6-T2 9-T3**	**13/15**	**3/9**	**10/13**
Breslin	**Blue dye only first 23 cases Last 28 + TC SC**	**FAC FAC,TFAC**	**Stage 2a-25 2b-12 3a-14**	**11/17 16/17 16/17**	**3/25**	**40/43**
HAID	**Blue dye + TC- ALB**	**CMF, EC , T/E**	**2-T1 30-T2 1-T3**	**29/33**	**0/29**	**29/29**
Julian	**Isosulfan Blue / TCSC / both**	**AC,AC+T**	**11-T1 20-T2/T3**	**29-31**	**0/29**	**29/29**
Tafra	**Isosulfan Blue / TCSC /**	**N/A**	**1.4 Mean size**	**27/29**	**0/29**	**29/29**
Stearns	**Isosulfan Blue**	**AC, A-T,AC-T**	**25-T3 9-T4**	**23/26**	**1/16**	**22/23**

Reconstructive surgery in LABC:

The goal of reconstructive surgery for patients with locally advanced breast carcinoma can be to repair defects or to repair defects and to recreate the breast mound. In patients with LABC who need or elect to have standard mastectomy and who desire breast reconstruction to improve the cosmetic outcome, reconstruction is often delayed until completion of both adjuvant chemotherapy and irradiation. As most locoregional recurrences are in the

skin or subcutaneous tissue of chest wall a flat post-mastectomy defect often makes irradiation technically easier than does a reconstructed breast mound, especially if the inclusion of the internal mammary nodal basin is necessary. However in selected patients with excellent response to induction chemotherapy or when palliative debulking surgeries are needed, the use of an autogenous flap to create a breast mound or provide skin coverage of the operative defect before radiotherapy is instituted if feasible.

The use of a myocutaneous flap for breast reconstruction, either before or after irradiation, does not interfere with the resumption of chemotherapy or the ability to detect locoregional recurrence. Irradiation of the reconstructed breast mound flap does not impair the flap's blood supply. Provided that the flap has an adequate vascularisation without evidence of significant fat necrosis, the irradiation itself does not alter the cosmetic result except for the anticipated skin tanning and slight fibrosis of the reconstructed breast mound .

The two tissue flaps that have been most frequently used for breast reconstruction are the lattissimus dorsi and rectus abdominis myocutaneous flaps. The advantages of the Latissimus dorsi flap include its reliable blood supply ant the relative rarity of donor site morbidity.The flap is also relatively thin and so matches the thickness of the native chest wall skin

fairly closely and also provides excellent soft tissue coverage. The chief disadvantage of the Latissimus dorsi flap is its limited size;an implant is usually required if the patient desires a reconstructed breast mound.

The Rectus abdominis myocutaneous flaps can be quite large and are most useful for defects too large to repair with a LD flap. The chief disadvantage is that they tend to be bulky and thus do not closely match the thickness of the native chest wall skin. The thickness of the flap can be an advantage, however if the defect is located directly over the central area of the chest wall;in this case the excess flap may be utilized to reconstruct a breast mound.

The two main types of Rectus abdominis myocutaneous flaps are the transverse rectus abdominis myocutaneous flap(TRAM) and the vertical rectus abdominis myocutaneous flap(VRAM).The TRAM flap has a greater arc of rotation and a more symmetrical and easiliy concealed donor site than does the VRAM flap.The VRAM flap leaves a more noticeable donor scar but is easier to construct and has a more reliable blood supply.

For major chest wall resections,the rectus abdominis flap is capable of covering a wide area from the clavicle to the costal margin and from the sternum to the midaxillary line.Because the flap is bulky,it provides sufficient chest wall stability even when upto five ribs or the entire sternum

is resected, without the need for prosthetic mesh. Marlex,a nonabsorbable durable mesh can be used for flat surfaces of the chest wall. If the defect is large,a sandwich of Marlex and methyl methacrylate can be formed to restore a more normal contour. If the mesh is covered by well vascularised tissue, the risk of infection and extrusion is usually low.

Immediate breast reconstruction (IBR) is now recognized as an esthetically acceptable and oncologically safe treatment option for many early-stage breast cancer patients

who undergo mastectomy. However, patients with locally advanced breast cancer (LABC) historically have been considered poor candidates for IBR for several

reasons: (1) concerns regarding increased risk of local recurrence (LR) and possible delays in detecting LR; (2) concerns that prolonged recovery from extensive surgery would result in delays in postoperative chemotherapy ; (3) concern about a possibly higher risk of wound infections in patients who have received preoperative chemotherapy; and (4) concerns regarding the technical difficulties of irradiating the reconstructed breast. Despite these issues, IBR has been performed in many women with LABC, because of (1) strong patient preference, unclear preoperative assessment of extent of

disease, or (3) need to provide soft tissue coverage for an extensive mastectomy defect.

INFLAMMATORY BREAST CARCINOMA

In 1814**,** Sir Charles Bell first recognized the clinical evolution of IBC when he wrote: "a purple color on the skin over the tumor accompanied by shooting pains, is a very unpropitious beginning.”Later in the nineteenth century, Klotz described ”mastitis carcinomatosa” as a variant of carcinoma of the breast characterized by its fulminant course.” In 1889, Bryant reported the association of dermal lymphatic invasion with the clinical characteristics of 1BC.’ The term *inflammatory* was coined by Lee and Tannenbaum in 1924.T heir paper was the first to describe in great detail the clinical characteristics of IBC in a series of 24 patients.Several other names have been used to describe this entity including *carcinoma mastitoides*,

carcinoma e ysipeloides, lactation cancer, and *malignant lymph~ngitis*B.~e~tw een 1908 and 1911, the term *acute carcinoma* was used by several investigators, and Leitch, in 1909, introduced the french term “peau d’orange” in an English literature paper. Taylor and Meltzer subsequently described two clinical varieties of inflammatory breast cancer:

(1) Primary inflammatory breast cancer, characterized by a sudden onset of the above symptoms in a breast which previously appears normal;

(2) Secondary inflammatory breast cancer, defined by inflammatory symptoms and signs which appear in a breast with a previous mass, in the chest wall postmastectomy

or in the contralateral breast .

Inflammatory breast cancer is a distinct clinical subtype of locally advanced breast cancer, with a particularly aggressive behavior and poor prognosis. Clinically, inflammatory breast cancer typically presents with the rapid onset of breast erythema, warmth, and edema, often without a discrete underlying mass. The swelling of the breast can be quite pronounced, producing significant tenderness.Although histologic proof of malignancy is critical prior to treatment of IBC, documenting dermal lymphatic permeation is not critical in establishing the diagnosis of IBC.

IBC is defined under the current American Joint Committee on Cancer (AJCC) manual for staging of cancer as T4d NO-2 stage III b, carcinoma of the breast. This corresponds to Haagensen's stage D of the Columbia Clinical Classification. Bonnier et al. classified patients into three groups according to clinical and histopathological features

Group A included patients with typical inflammatory breast cancer (diffuse enlargement of the breast, often no palpable tumour, redness and oedema of the skin).Ipsilateral enlargement of the axillary nodes was often detected and emboli of carcinoma cells in the subdermal lymphatics were often found.

Group B included patients with occult inflammatory breast cancer, in which the presence of tumour emboli in dermal lymphatics was not associated with inflammatory symptoms and signs.

Group C included patients with pseudo-inflammatory breast cancer. Symptoms were similar to those of groupA. However a tumour mass was more readily palpable and the sub-dermal lymphatics were never involved.Furthermore, the axillary nodes were rarely involved.

Evaluation of IBC

Evaluation of patients presenting with IBC must be multidisciplinary.This includes a thorough documentation of physical findings and extent of disease, including axillary and supraclavicular lymph

node enlargement. Bilateral mammograms are performed to ensure that this is a unilateral process and as a baseline for future reference. Although core-needle biopsy affords the most efficient proof of malignancy, we prefer an incisional biopsy including skin to determine dermal lymphatic involvement . Hormone receptor analysis, DNA content, and Sphase fraction are routinely perfornted. Metastatic work-up includes CT scans of the chest and upper abdomen, including liver and adrenalglands; bone scintigraphy; liver enzymes; and carcinoembryonic antigen determination.Bryant" attributed the inflammatory signs in this type of cancer to diffuse lymphatic blockage by cancer cells, but this finding is not specific for IBC. Inflammatory breast cancer exhibits all the usual microscopic features of infiltrating ductal carcinoma. IBCs are poorly differentiated and without evidence of glandular formation.

Neglected locally advanced breast cancer can develop secondary inflammatory characteristics, but should be distinguished from primary inflammatory carcinoma as these secondary inflammatory breast cancers may follow a more indolent course and can be treated as other locally advanced breast tumors. Three biological features make inflammatory breast cancer a unique clinical entity :

(1) Rapidity of progression

(2) High angiogenic and angioinvasive capability

(3) Aggressive behaviour from inception.

van Golen et al. found that overexpression of RhoC GTPase and the lost in inflammatory breast cancer (LIBC) protein were highly correlated with an inflammatory breast cancer phenotype. These tumors are more likely to be high grade, aneuploid, and hormone-receptor negative and have a high S-phase fraction and p53 mutations. Despite these differences in biologic characteristics, prognostic factors for inflammatory breast cancer are similar to those for locally advanced disease, with axillary lymph node involvement predicting poorer survival. Other negative prognostic factors for inflammatory carcinoma include negative ER status, extensive erythema of the breast, and p53 mutations.

Management of IBC

The optimal treatment of inflammatory breast cancer requires careful coordination of multimodal therapy among medical, radiation, and surgical oncologists.Current treatment for inflammatory breast cancer centres upon neoadjuvant chemotherapy. The advent of neoadjuvant chemotherapy has greatly improved disease-free and overall survival for inflammatory breast cancer Ueno et al., in their series of 178patients, report overall survival of

40% at 5 years and 33% at 10 years. Given that inflammatory breast cancer metastasises early, sub-clinical systemic disease is likely to exist, which may be controlled by neoadjuvant chemotherapy. The initial component of treatment hence should be induction chemotherapy with an anthracycline-based regimen or an anthracycline and taxane combination. Definitive local therapy can then be achieved with radiation therapy, mastectomy, or both. . After local therapy, patients should receive further adjuvant chemotherapy, as the risk of relapse remains high, followed by adjuvant radiotherapy, if not previously given.

Role of surgery in IBC

Early experience with surgery for inflammatory breast cancer was uniformly disappointing, with high rates of recurrence and poor overall survival. The role of surgery is now being re-evaluated due to the effectiveness of neoadjuvant chemotherapy, whichhas resulted in downstaging of disease with decreased tumour burden . This provides a greater opportunity for adequate surgical resection.Curcio et al.found that a successful outcome for surgery for inflammatory breast cancer following neoadjuvant chemotherapy depended upon achieving negative excision margins. Lopez and Porter noted that consistently achieving tumour-free

resection margins can be technically difficult in inflammatory breast cancer patients, and may require complex reconstructions with myocutaneous flaps and extensive cutaneous dissection. Breast conservation is rarely possible.

TABLE 12 RETROSPECTIVE STUDIES OF CHEMOTHERAPY FOR INFLAMMATORY BREAST CANCER

Authors	Year	No of patients	Treatment regimen	Response rate (%)	Median survival (Months)	5 years survival (%)	5 years survival (%)
DeLena	1978	36	CT+RT±CT	67	25	24	NA
Pawlicki	1983	72	CT+S±RT	70	NA	28	NA
Keiling	1985	41	CT+S+CT	NA	NA	63	NA
Roueesse	1989	170	CT+RT+CT+H	74	Na	47	NA
Koh	1990	106	CT±S±RT+CT	69	45	38	NA
Mailosel	1990	43	CT+S+CT+RT+H	88	46	75	NA
Moores	1991	38	CT+S±RT	79	56	45	NA
Picrce	1992	46	CT+H±S+RT	98	NA	36	NA
Chevallier	1993	178	CT+RT±CT±S	71	37	32	NA
Palangie	1994	223	CT+RT	NA	41	41	NA

Perez	**1994**	**86**	**CT+S+RT**	**NA**	**36**	**40**	**35**
Ueno	**1997**	**178**	**CT+RT±S+CT**	**NA**	**NA**	**NA**	**28**
Harris	**2007**	**54**	**CT+RT+S**	**NA**	**62**	**56**	**35**

Sentinel lymph node biopsy may also be unsuitable in the setting of inflammatory breast cancer due to the high level of nodal involvement found in this disease. Also since cancer infiltrates the dermis and lymphatics in inflammatory breast cancer, the underlying architecture may be disrupted to the extent that sentinel lymph node biopsy is not of value Relatively few women with inflammatory breast cancer have been offered reconstructive surgery following surgery . Concerns about reconstruction include delays to adjuvant treatment, difficulty in the detection of recurrence and increase in morbidity. Given the improved multimodality treatment of inflammatory breast cancer, reconstructive

procedures should be offered as part of comprehensive therapy, as long as a positive margin at resection is not expected(Chin et al). The exact indications for surgery and the optimal operation, however, remain unclear.

Radiotherapy was the mainstay of care for inflammatory breast cancer for many years, but the results were unimpressive. Radiotherapy alone has been shown to improve local control rates in treatment of inflammatory

breast cancer, but to have no effect on survival Since the introduction of neoadjuvant chemotherapy, and the return of surgery,

radiotherapy is now seen as an important part of a multimodality treatment approach, rather than treatment on its own. The importance of radiotherapy relates primarily to its function in loco-regional control.

No substantial improvement in survival from hormone therapy for inflammatory breast cancer has been shown , which is not surprising given that patients with inflammatory breast cancers are more frequently oestrogen and progesterone receptor negative compared with other breast cancers. Nevertheless, if the tumour is oestrogen receptor positive it is currently advised that patients receive 5 years of treatment with either tamoxifen or aromatase inhibitors.

Recent discoveries of the distinct biologic features that characterize inflammatory carcinoma can lead the way toward the development of new therapies. For instance, farnesyl transferase inhibitors have been shown to reverse the invasive phenotype of RhoC GTPase-overexpressing cell lines. Other possible therapeutic targets include mediators of angiogenesis such as vascular endothelial growth factor, basic fibroblast growth factor, and Flt-1, which are overexpressed in inflammatory breast cancers.

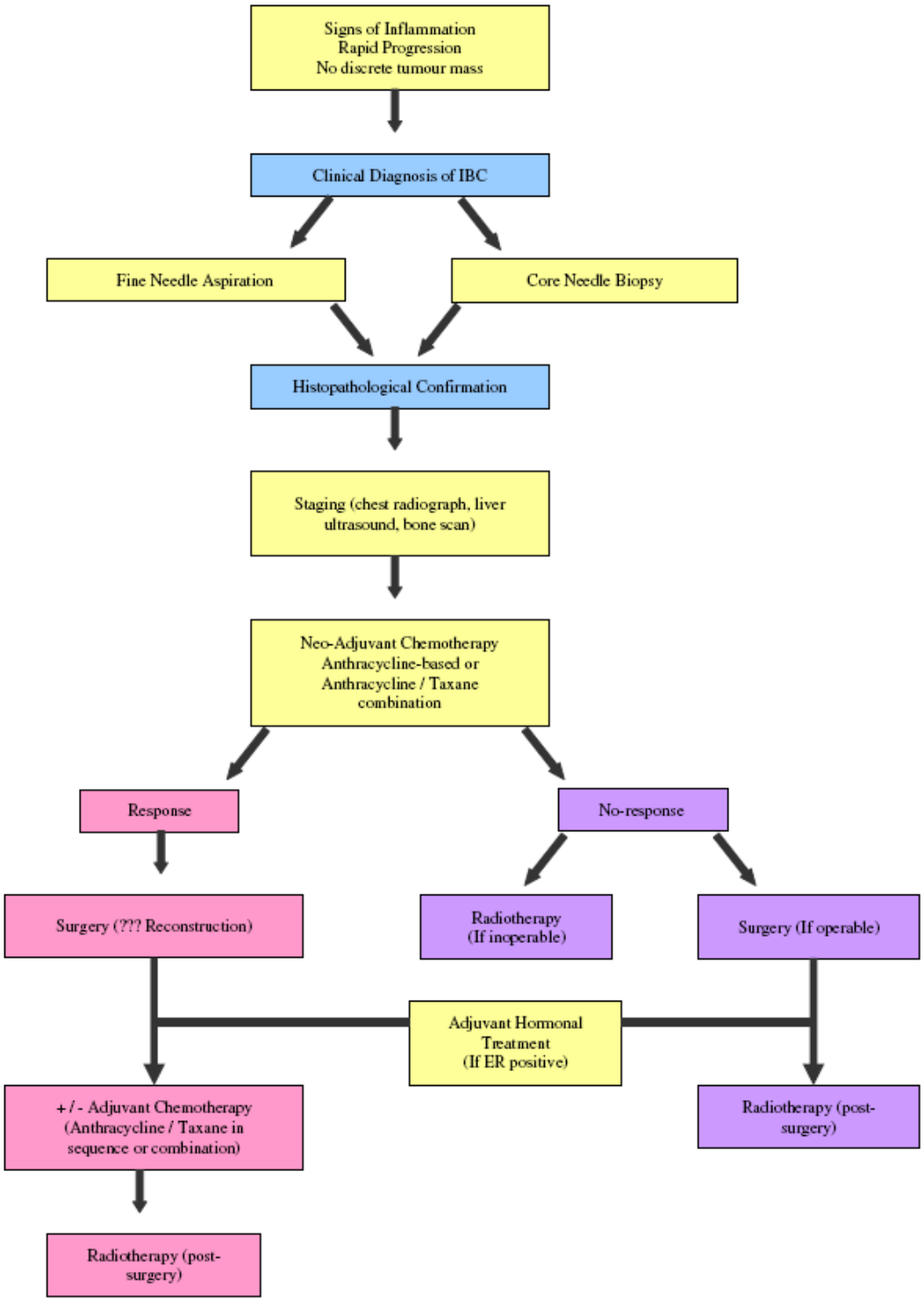


Fig. 2. Algorithm for the diagnosis and treatment of "inflammatory" breast cancer.

Allocation of resources :

The treatment of breast cancer requires an integrated, multidisciplinary approach using multiple resources in a focused, disease-oriented manner. Existing evidence-based

guidelines outlining optimal approaches to the treatment of breast cancer have been defined and disseminated, but do consider the multiple deficits in infrastructure and the availability of therapies in limited-resource countries. Marked heterogeneity exists among countries and also between regions of the same country with regard to social, economic, and health system development. Therefore a uniform approach for all limited-resource countries is neither practical nor realistic. The BHGI has proposed a stepwise, systematic approach for building national or regional breast health treatment systems by stratifying health care resources into four levels—basic, limited, enhanced, and maximal—based on the contribution of incremental resources in improving clinical outcomes.

Table13 Treatment and Allocation of Resources: Locally Advanced Breast Cancer

Level of Resources	Local-regional Treatment		Systemic Treatment (Adjuvant)	
	Surgery	**Radiation Therapy**	**Chemotherapy**	**Endocrine Therapy**
Basic	Modified radical mastectomy		Neoadjuvant AC, FAC, or classical CMF[a]	Ovarian ablation Tamoxifen
Limited		Postmastectomy irradiation of the chest wall and regional nodes		
Enhanced	Breast-conserving therapy[b]	Breast-conserving whole-breast irradiation	Taxanes	Aromatase inhibitors LH-RH agonists
Maximal	Reconstructive surgery		Growth factors Dose-dense chemotherapy	

[a]Requires blood chemistry profile and complete blood count (CBC) testing.

[b]Breast-conserving therapy requires mammography and reporting of margin status.

AC, doxorubicin and cyclophosphamide; CMF, cyclophosphamide, methotrexate, and 5-fluorouracil; EC, epirubicin and cyclophosphamide; FAC, 5-fluorouracil, doxorubicin, and cyclophosphamide; LH-RH, luteinizing hormone releasing hormone.

SURVEILLANCE/FOLLOW-UP

Despite advances in the multidisciplinary approach in the management of locally advanced breast cancer that has improved the

prognosis as well as the quality of life considerably ,the overall survival remains almost constant.That the prognosis is stage dependant has been well established.

Interval history and physical exam every 4-6 months for 5 years, then every 12 months Mammogram every 12 months (and 6-12 months post-RT if breast conserved)

Women on tamoxifen: annual gynecologic assessment every 12 months if uterus present Women on an aromatase inhibitor or who experience ovarian failure secondary to treatment should have monitoring of bone health Assess and encourage adherence to adjuvant hormonal therapy**.**

Patient education on recurrence, morbidity of treatment ,psycho social aspects,prosthesis before ,during & at completion of treatment

Breast self examination – monthly

Haematology,Bioprofile,Imaging

Assay for tumour markers } not recommended routinely

AIMS & OBJECTIVES

1. To ascertain the incidence of LABC among the women presenting with breast cancer.
2. To define the optimal treatment for women with stage III or locally advanced breast cancer (LABC).
3. To ascertain the feasibility of the defined optimal treatment and to advocate it among patients with LABC.

Period of study : May 2005 – October 2007

Methods

We conducted a review of the literature in the English-language retrieved from internet and medical journals regarding the management of locally advanced breast cancer.Search terms used were “breast neoplasms,” “locally advanced breast cancer,” “stage III breast cancer,” “drug therapy,” “neo-adjuvant,” “primary systemic therapy,” “radiotherapy or irradiation,” “surgery,” “randomized trials” and “high-dose therapy.” Additional data were identified by reviewing references in retrieved reports and by monitoring major conferences on breast cancer. The main outcomes considered are locoregional control (defined as freedom from recurrence in the breast, chest wall or regional lymph nodes), disease-free survival (DFS; defined as survival free of breast cancer recurrence) and overall survival (OS).

Numerous setbacks encountered in the process of synthesizing the results of the studies from the review of the literature included :

1. Majority of the studies were from the western population that differed vastly from the Indian scenario.
2. The studies included different populations of patients with differing prognoses; for example, some studies included patients with inflammatory breast cancer whereas other studies did not.
3. In studies evaluating systemic therapies, local therapy (surgery/radiotherapy) was often not standardized.
4. The TNM tumour-staging system changed, in that tumours associated with ipsilateral supraclavicular nodal involvement that were initially considered LABC were considered metastatic breast cancer between 1987 and 2002 and are now considered LABC again.
5. The randomized trials that were available were old, had small patient numbers and used systemic therapy combinations that are often not used today.
6. The various recent advances available as of today could not be utilized in the study owing to patient's socioeconomic ceiling.For example hormone receptor assay /her-2 neu assay /bone scan could not be advocated.

7. Breast reconstruction / breast conservation could not be tried for the lack of infrastructure and patient compliance.

Patients and methods

Between May 2005 and October 2007, a total of 43 cases of carcinoma breast were admitted in our surgical unit in the Government Rajaji Hospital,Madurai.All of those admitted were staged according to the AJCC TNM classification. Staging work-up

consisted of a complete bloodcount (CBC), blood chemistry, chest X-ray,and ultrasonography of the liver.Either FNAC/ Trucut / incisional biopsy were used to confirm the diagnosis of carcinoma breast.of the 43 patients,

one of them was of male sex ; 42 were of female sex.For all practical purposes only the 42 female breast carcinoma were considered for the study.

18 were right – sided & 24 left-sided, one of stage I ; four of stage II ; 29 of stage III ; 8 of stage IV.

Of the 30 cases of LABC, (29 of III & 1 of II)

one of them was inflammatory carcinoma

18 were post – menopausal & 12 were pre- menopausal.

The HPE in all the cases were of infiltrating ductal carcinoma.Since ER status could not be ascertained,all of the cases were considered ER + for all practical purposes.

All of the cases of LABC except for the inflammatory carcinoma underwent modified radical mastectomy,followed by adjuvant chemoradiation & Hormonal therapy .Adjuvant chemotherapy consisted of 6 cycles of CAF regimen.Adjuvant radiation included EBRT of 5000 Gy to the tumour bed & nodal basins.Receptor status could not be ascertained. So, the receptor status was considered positive for all practical purposes and adjuvant hormonal therapy in the form of tamoxifen 10 mg bd was instituted for a period of 5 years.

CONCLUSIONS

The incidence of LABC among the study population was approximately **69%.**LABC forms the majority of the cases of breast cancer at the time of initial presentation itself.The significance of this conclusion is that what cases are classified at a specific instance as LABC once belonged

to the category of early breast cancer and subsequently evolved into LABC due to either patient's negligence or inappropriate intervention or aggressive tumour biology.Thus as prevention is always better than cure it is recommended that the following measures can be adopted to address this problem :

1. Health education regarding self breast examination
2. Screening mammography
3. Identifiation of high risk population and specific management
4. Surveillance when family history is positive for breast cancer.Metastatic work-up is mandatory.

Hormone receptor assay may be useful in planning treatment

For better management of patients with LABC, the following is recommended:

• Early diagnosis of breast cancer is vital for better results of treatment. General education about early symptoms of the disease and access to medical facilities are important in diminishing breast cancer mortality in our country.

• Cellular biological markers such as Her-2, P53, etc. should be evaluated as prognostic factors in prospective randomized studies.

• Randomized trials are recommended for comparing new adjuvant regimens

Lack of treatment compliance and/or failure to provide standard-of-care treatment in high-risk breast cancer can lead to a higher incidence of metastatic cancer and mortality.

Introduction

In 1943, Haagensen and Stout identified “grave clinical signs” predicting poor outcome in women with primary breast cancer treated with radical mastectomy. These features include the presence of extensive skin edema, satellite nodules, intercostal or parasternal nodules, arm edema, supraclavicular metastasis, inflammatory carcinoma, or distant metastasis, or the presence of two or more of the following: ulceration of the skin, skin edema of limited extent (more than one-third of the breast), fixation to the chest wall, axillary lymph nodes larger than 2.5 cm, or fixation of axillary lymph nodes to the skin or deep structures of the skin. Other clinical signs of locally advanced disease included a single tumor larger than 10 cm in size, multiple tumors in one breast, redness of the skin, and skin involvement. This classical description of the clinical contraindications to the primary surgical management of primary breast cancer is, in general, still valid today. In Haagensen's series of patients with these grave signs, local recurrence rates were 42% despite radical mastectomy, and no patient survived disease-free for 5 years. Patients with these characteristics (and having no distant metastases) are currently included in the category of locally advanced breast cancer (LABC). The poor outcome of these patients when treated with radical mastectomy led to the investigation of other treatment strategies.

The definition of LABC has evolved from that of Haagensen and Stout, to encompass a wide spectrum of clinical presentations:

- Large tumors (>5 cm)
- Extensive regional lymph node involvement
- Direct involvement of the underlying chest wall or skin with edema (including peau d'orange) or ulceration or satellite skin nodules confined to the same breast.

Other discrete skin changes, such as dimpling or nipple retraction, may occur in T1-3 disease; they do not constitute evidence of a locally advanced tumor.

- Tumors considered inoperable but without distant metastasis (including involvement of the supraclavicular lymph nodes)

- Inflammatory breast cancer (IBC)

Acording to the AJCC staging,LABC comprises of :

T3 Tumor more than 5 cm in greatest dimension

T4 Tumor of any size with direct extension to a. Chest wall or b. Skin

T4a Extension to chest wall, not including pectoralis muscle

T4b Edema (including peau d'orange) or ulceration of the skin of the breast, or satellite skin nodules confined to the same breast

T4c Both T4a and T4b

T4d Inflammatory carcinoma

Regional Lymph Nodes (N)

NX Regional lymph nodes cannot be assessed (e.g., previously removed)

N0 No regional lymph node metastasis

N1 Metastasis in movable ipsilateral axillary lymph node(s)

N2 Metastases in ipsilateral axillary lymph nodes fixed or matted, or in clinically apparent(1) ipsilateral internal mammary nodes in the *absence* of clinically evident axillary lymph node metastasis

N2a Metastasis in ipsilateral axillary lymph nodes fixed to one another (matted) or to other structures

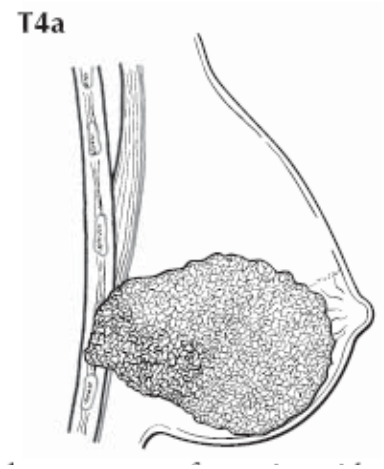
N2b Metastasis only in clinically apparent(1) ipsilateral internal mammary nodes and in the *absence* of clinically evident axillary lymph node metastasis

N3 Metastasis in ipsilateral infraclavicular lymph node(s) with or without axillary lymph node involvement, or in clinically apparent(1) ipsilateral internal mammary lymph node(s) and in the *presence* of clinically evident axillary lymph node metastasis; or metastasis in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement

N3a Metastasis in ipsilateral infraclavicular lymph node(s)

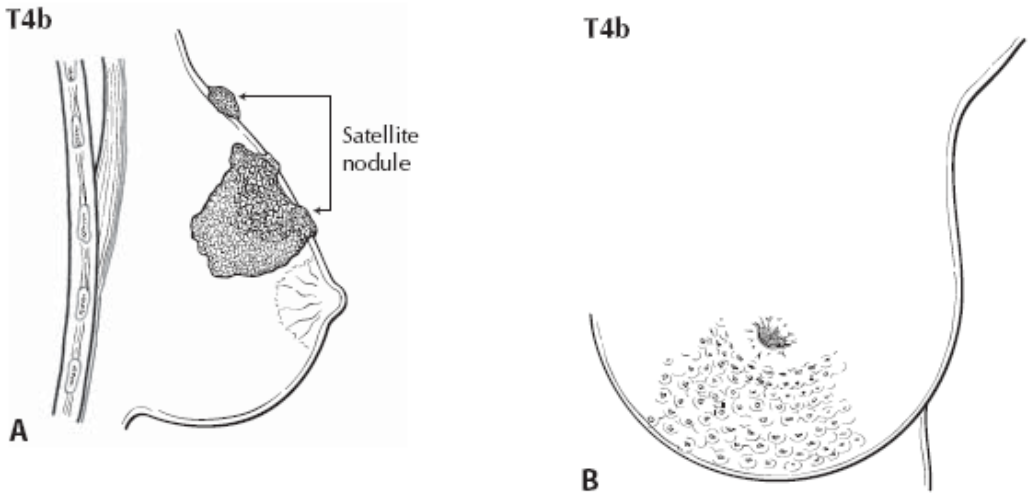
N3b Metastasis in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)

N3c Metastasis in ipsilateral supraclavicular lymph node(s)

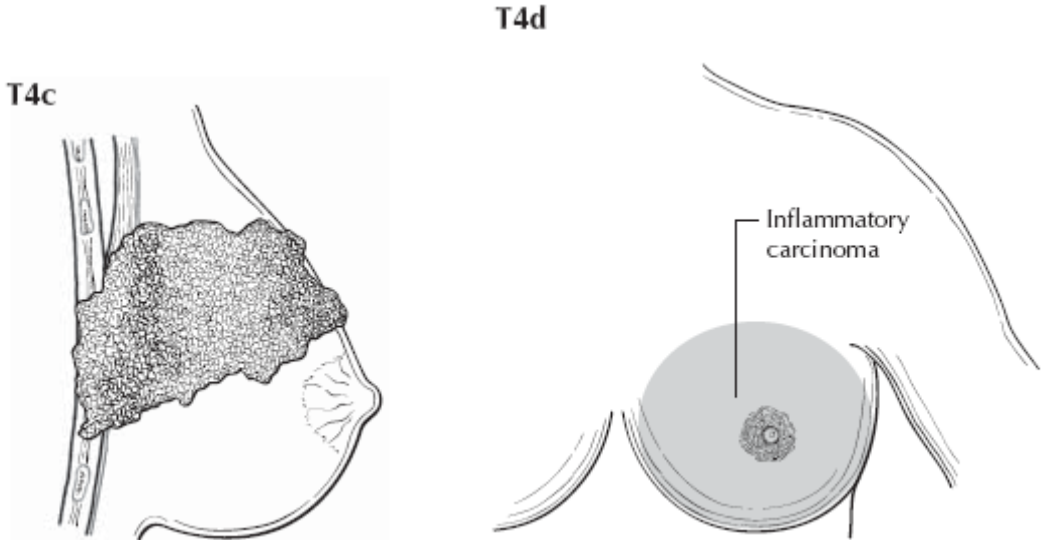


T4 is defined as a tumor of any size with direct extension to chest wall, not including pectoralis muscle.

T4b



A. T4b, illustrated here as satellite skin nodules, is defined as edema (including peau d'orange) or ulceration of the skin of the breast, or satellite skin nodules confined to the same breast. **B.** T4b illustrated here as edema (including peau d'orange).



T4c is defined as both T4a and T4b.

T4d, inflammatory carcinoma.

Table 1 : Stage Grouping of Carcinoma Breast.

	T3	N0	M0
IIIA	T0	N2	M0
	T1[(7)]	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
IIIB	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
IIIC	Any T	N3	M0
IV	Any T	Any N	M1

Note: Stage designation may be changed if post-surgical imaging studies reveal the presence of distant metastases, provided that the studies are carried out within 4 months of diagnosis in the absence of disease progression and provided that the patient has not received neoadjuvant therapy.

All T and N permutations included in stage IIB, III or IV comprised many distinct substage possibilities. The presence of T_4 or N_3 or regional M_1 lesions would result in inclusion in the stage IIIB/IV unresectable subcategory. Most of the patients with either T_3 or N_2, but without T_4, N_3 or regional M_1 lesions, are included in the stage II/IIIA or operable subcategory. LABC also includes T_2 tumors that are too large in proportion to the size of the breast.In the most recent TNM staging system, tumours associated with ipsilateral supraclavicular nodal basin have been eliminated from the LABC category because the supraclavicular nodal basin lies outside the primary lymphatic drainage pathways of axilla and internal mammary nodes;tumours associated with supraclavicular nodes have been reclassified as stage IV disease.However as the patients with distant

metastases confined to the supraclavicular nodes have a better prognosis than patients with metastases at other sites and can be rendered disease free with locoregional therapy,metastases limited to the ipsilateral sub-supraclavicular fossa have been included in the category of LABC defined here.

LABC is a heterogeneous group of tumors of varying clinical presentations and biological behavior whose only common bonds are the presence of a large primary tumor, or extensive regional lymph node involvement, and the absence of any evidence of distant metastases. Some patients have a rapid neoplastic evolution, whereas others present with a long history of tumor growth.

The clinical diagnosis of LABC is usually not difficult. Patients uniformly present with a large breast mass. Other symptoms often reported are edema, redness, nipple retraction, pain, skin dimpling, an axillary mass and breast ulceration. Most physical findings are obvious upon inspection or palpation. However, in younger women, some tumors infiltrate the breast diffusely and a discrete mass is difficult to palpate. More than 75% of patients have clinically palpable axillary and/or supraclavicular adenopathy, and 65%-90% of patients have pathologically confirmed lymph node metastasis; >50% have more than four nodes involved. Most of the LABCs are operable; only 25%-30% are diagnosed at an inoperable stage.

A physical examination, bilateral mammogram and ultrasound of the breast and its draining lymphatics determine the extent of involvement within the breast and the nodal chains, the presence of additional tumor foci within the same breast or the contralateral breast, and the extension of the tumor to deeper structures.

A core needle biopsy is quite effective in establishing the diagnosis and also allowing tumor samples to be obtained for hormone receptors, DNA studies and other biomarkers. The sensitivity and specificity of fine-needle aspiration are quite high in LABC. The only disadvantages of cytological diagnosis are the inability to differentiate between in situ and invasive carcinoma, and scant material on which to perform additional studies. Excisional biopsies are not indicated in patients with LABC.

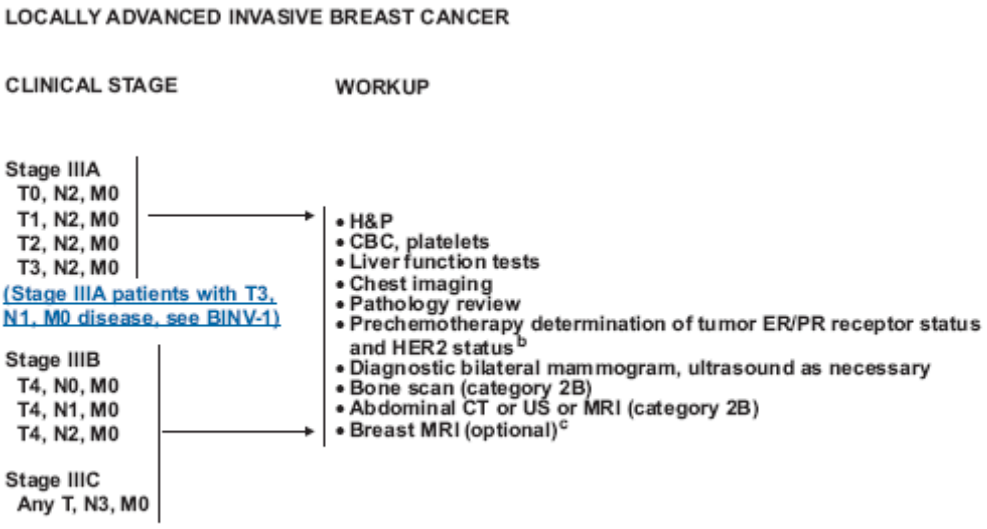
Table 2. Diagnosis and Pathology

Level of resources	Clinical	Pathology	Imaging and laboratory tests
Basic	History Physical examination Clinical breast examination Surgical biopsy Fine-needle aspiration biopsy	Interpretation of biopsies Cytology or pathology report describing tumor size, lymph node status, histologic type, tumor grade	
Limited	Core needle biopsy Image-guided sampling (ultrasonographic ± mammographic)	Determination and reporting of ER and PR status Determination and reporting of margin status	Diagnostic breast ultrasound ± diagnostic mammography Plain chest radiography Liver ultrasound Blood chemistry profile/CBC
Enhanced	Preoperative needle localization under mammographic or ultrasound guidance	On-site cytopathologist	Diagnostic mammography Bone scan
Maximal	Stereotactic biopsy Sentinel node biopsy	HER-2/*neu* status IHC staining of sentinel nodes for cytokeratin to detect micrometastases	CT scanning, PET scan, MIBI scan, breast MRI

CBC, complete blood count; CT, computed tomography; ER, estrogen receptor; IHC, immunohistochemistry; MIBI, 99mTc-sestamibi; MRI, magnetic resonance imaging; PET, positron emission tomography; PR, progesterone receptor.

Appropriate staging procedures should be performed in patients with LABC since the probability of distant metastases is high. Approximately 20% of these patients, appropriately staged, have detectable distant metastases at the time of diagnosis.So after a complete history, a physical examination should be performed with great attention to the evaluation of both breasts and all surrounding lymph node-bearing areas. All tumors should be described by the longest perpendicular diameters in cm, and the presence of palpable axillary, supraclavicular and subclavicular nodes, with exact measurements of their longest perpendicular diameters, should be included. A close-up photograph is

useful in the staging of patients with T_4 tumors. Ideally, the initial evaluation should be done simultaneously by the medical oncologist, surgical oncologist and radiotherapist.



After the physical examination and bilateral mammogram, the following additional tests are recommended: a biochemical profile, including tests of liver and renal function, and calcium level; chest x-ray; bone scans; radiographs of areas that appear to be abnormal on the bone scan; computed tomography of the liver and an ultrasonography of the breast and regional lymph nodes to precisely assess the tumor extent. The importance of an accurate initial assessment of the extent of primary tumor burden cannot be overemphasized since the efficacy of subsequent local treatment will depend mostly on this initial assessment.

Patients with LABC are at great risk for morbid local complications of their disease, including skin breakdown, tissue necrosis, bleeding, pain, and infection. These problems, which may not alter survival, significantly compromise quality of life. Patients with

locally advanced breast cancer also have a very high rate of systemic micrometastasis at diagnosis, which if untreated will progress and lead to organ dysfunction and death. There are thus two central goals in the treatment of LABC:

obtaining and maintaining local control with surgery and/or radiotherapy,

improving overall survival by control of systemic disease with chemotherapy and/or hormonal therapy.

Arriving at a uniform treatment plan for LABC is limited by the biologic diversity of the disease (there are 13 possible combinations in the current TNM staging system for stage III breast cancer ranging from minute tumors with bulky axillary disease to large tumors with microscopic axillary disease).

Historical perspective & Review of literature.:

During the last 60 years, the management of LABC has evolved considerably. Initially, patients with LABC were treated with radical mastectomy.Based on the disappointing results of surgery and radiotherapy in patients with LABC, and the early promising results of adjuvant systemic therapy in women with axillary node-positive breast cancer, systemic therapy was subsequently incorporated along with surgery and radiotherapy into the management of patients with LABC, termed “combined modality therapy.” Even with such combined modality therapy, the long-term survival rate is approximately 50% among patients with LABC.

Surgery and LABC :

For many years, the Halsted radical mastectomy was the standard treatment for breast cancer.The pioneering work of McWhirter et al in the mid 20th century showed that less mutilating surgery produced results equal to that of radical mastectomy.The failure of halstedian principle of en-bloc extirpation of the breast and draining lymph nodes to cure many patients of breast cancer,frequent identification of small breast cancer by mammography,and success of moderate doses of radiotherapy in eliminating sub clinical foci of breast cancer led to the development of MRM .MRM is a term used to describe a variety of surgical procedures,but all involve complete removal of the breast and some of the axillar nodes. Table 3 summarizes the results of surgery alone in the treatment of LABC; these studies were retrospective and did not follow uniform staging classifications. Some included stage I1 patients in addition to LABC, and some patients were treated with radiation therapy and chemotherapy. These studies confirmed that surgery alone was inadequate treatment Even with aggressive surgical techniques,patients with advanced local disease had a high incidence of localregional recurrence. Most important, surgery did not change the pattern of distant failure in patients who probably had micrometastatic disease

The advent of radiation therapy in LABC

The use of radiation therapy alone in the treatment of locally advanced noninflammatory breast cancer was no more effective than surgery alone (Table 4). The local recurrence rates of 36% to *72%* were even higher than those reported for surgery alone. This difference in local-regional failures was no longer evident when patients were treated with a combination of radiation therapy and surgery, which suggested that the two

treatment modalities might provide better results if used together. The patients' high rate of distant relapse, however, emphasized the need for systemic therapy as well.

Table 3. SURGERY ALONE IN TREATMENT OF LOCALLY ADVANCED BREAST CANCER

Author	Institution	No. of Patients	5-Year Local Recurrence Rate (%)	5-Year Survival (%)	10-Year Disease-Free Survival (%)
Haagensen and Stout[25]	Columbia-Presbyterian	35	45.7	5.7	—
Schottenfeld et al[48]	Memorial Sloan-Kettering Cancer Center	62	6*	53	29†
Arnold and Lesnick[5]	Mount Sinai Hospital	50	50	33	22
Fracchia et al[24]	Memorial Sloan-Kettering Cancer Center	207	25‡	43	27.1

*Includes stage II and III patients
†10-year survival. Thirty patients were treated with postoperative radiation
‡Node-positive only

Table 4. RADIATION ALONE IN THE TREATMENT OF LOCALLY ADVANCED BREAST CANCER

Author	Year	Institution	No. of Patients	5-Year Local Recurrence Rate (%)	5-Year Disease-Free Survival (%)
Zucali et al[56]	1976	Instituto Nazionale Tumori	321	49*	21
Rubens et al[44]	1977	Guy's Hospital	184	72	18
Bruckman et al[13]	1979	Joint Center for Radiation Therapy	116‡	36†	22
Rao et al[43]	1982	Mallinckrodt Institute of Radiology	54	51	16–20
Harris et al[26]	1983	Joint Center for Radiation Therapy	137	46	28

*Local recurrence at 2 years.
†Some patients treated with excisional biopsy and/or interstitial implant.
‡41 patients received some adjuvant therapy.

Combined Surgery and Radiation Therapy

In early attempts to improve locoregional control in treating patients for LABC, radiation therapy was combined with surgical therapy. Although these studies showed promising results in locoregional control, they failed to address the systemic nature of LABC, and patients still died of metastatic disease. The lessons learned in those years emphasized the need for additional treatment modalities. First, even though combined radiation and surgical therapy delayed the time to first local-regional relapse, there was no significant survival advantage. Second, preoperative radiation therapy was often able to convert an inoperable breast cancer to an operable one. Third, preoperative radiation therapy did not seem to differ from postoperative radiation in providing additional locoregional control. Last, a combination of surgery and radiation therapy provided the maximum chance for locoregional control over high-dose radiation therapy or surgery alone. Table 5 summarizes selected series in which combination surgery and radiation therapy were used pre or postoperatively to treat LABC patients. The results showed that even combining radiation therapy and surgery did not eliminate locoregional failures.

MULTIMODAL THERAPY

Haagensen and Stout's early paper on the criteria of operability in carcinoma of the breast made clear that the vast majority of patients with locally advanced disease would develop distant metastatic disease. This has been confirmed in multiple trials of surgery and radiation therapy alone or in combination.Multimodality therapy that included surgery, radiation therapy, chemotherapy, and hormonal therapy has had the greatest impact on survival.

Table 5. COMBINATION SURGERY AND RADIATION THERAPY IN TREATMENT OF LOCALLY ADVANCED BREAST CANCER

Author	Year	Institution	No. of Patients	Local Recurrence Rate (%)	5-Year Survival (%)
Preoperative Radiation					
Cade[15]	1949	Westminster Hospital	95	—	10
Zucali et al[56]	1976	Instituto Nazionale	133	—	45
Whitaker and Battersby[54]	1977	Princess Alexandra Hospital	68	77.9	—
Arnold and Lesnick[5]	1979	Mount Sinai Hospital	54	70*	32
Townsend et al[52]	1984	University of Texas	53	11	10–35
Postoperative Radiation					
Arnold and Lesnick[5]	1979	Mount Sinai Hospital	122	70*	30
Bedwinek et al[8]	1982	Mallinckrodt Institute of Radiology	93†	12–13	—
Montague and Fletcher[35]	1985	M. D. Anderson Cancer Center	132	13	43.3‡

*Includes distant relapses.
†17 patients had preoperative radiation.
‡10-year disease-free survival.

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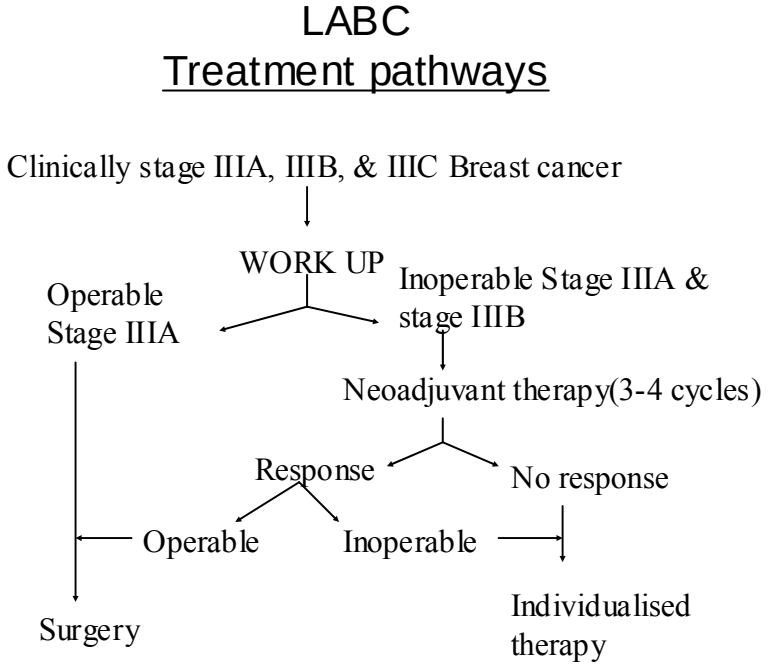
Table 2: Summary of studies with surgery followed by adjuvant chemotherapy

Study	Patients	No. of patients	Treatment regimens	Duration of follow-up	Level of evidence	Results/comments
Klefstrom et al, 1987[11]	Stage III breast cancer patients after modified radical mastectomy	120	1. Radiotherapy 2. VAC chemotherapy 3. Both	Minimum 5 yr	I	DFS better with combined treatment than with either radiotherapy alone or VAC alone ($p < 0.001$) (percentages not reported). OS better with combined treatment than with radiotherapy alone ($p < 0.001$) or VAC alone ($p < 0.01$) (percentages not reported)
Derman et al, 1989[12]	Patients with LABC (55% had mastectomy)	231	1. Radiotherapy 2. Radiotherapy + low-dose CMF chemotherapy 3. Radiotherapy + high-dose CMF chemotherapy	Median 56 mo	II	No difference in DFS or OS between the 3 groups (percentages and p values not reported)
De Placido et al, 1995[26]	Patients with stage II or III breast cancer after mastectomy (78 patients had stage III disease)	220	1. CMF chemotherapy alternating with EV chemotherapy 2. CMF chemotherapy alone	Median 48 mo	II	No difference in DFS or OS between the 2 groups (percentages and p values not reported)
Casper et al, 1987[27]	Patients with LABC treated by modified radical or radical mastectomy	41	1. 6 mo CAF chemotherapy + 6 mo CMFVP chemotherapy 2. 12 mo CMFVP chemotherapy	Median 24 mo	II	Median DFS 23 mo in CAF + CMFVP group, 15 mo in CMFVP group ($p = 0.05$). Median OS 33 mo in CAF + CMFVP group, 18 mo in CMFVP group ($p = 0.26$)
Olson et al (ECOG trial), 1997[53]	Patients with LABC who underwent mastectomy and were then treated with CAFTH chemotherapy	313	1. Radiotherapy 2. Observation + radiotherapy if locoregional failure	Median 9.1 yr	II	DFS not reported. Median survival 8.3 yr in radiotherapy group, 8.1 yr in observation group ($p = 0.94$). Locoregional recurrence 15% in radiotherapy group, 24% in observation group (p value not reported). Median time to relapse 4.7 yr in radiotherapy group, 5.2 yr in observation group ($p = 0.68$)

Note: ECOG = Eastern Clinical Oncology Group, LABC = locally advanced breast cancer, DFS = disease-free survival, OS = overall survival, V = vincristine, A = adriamycin, C = cyclophosphamide, M = methotrexate, F = 5-fluorouracil, E = epirubicin, P = prednisone, T = tamoxifen, H = fluoxymesterone.

Multidisciplinary approach to LABC :

The clinical management of LABC is complex and should be tailored to the individual patient. Frequently, surgery, radiotherapy and systemic therapy (chemotherapy, hormone therapy) are used. A multidisciplinary approach to LABC is recommended in which treatment is based on the combined opinions of a surgeon, radiation oncologist and medical oncologist. The initial management of LABC requires histological confirmation (e.g., core biopsy, incisional biopsy or skin biopsy) for diagnosis and for determination of hormone receptor and *HER-2 neu* oncogene status. Cytological evaluation by fine-needle aspiration is insufficient.



Systemic therapy: chemotherapy

Operable tumours • ***Patients with operable stage IIIA disease should be offered chemotherapy. They should receive adjuvant chemotherapy following surgery, or***

primary chemotherapy followed by locoregional management.

Patients with stage IIIA breast cancer have potentially operable tumours. There are 2 approaches for treating these patients. The first is modified radical mastectomy (MRM) followed by adjuvant systemic therapy and radiotherapy, and the second is preoperative chemotherapy followed by surgery and adjuvant chemoradiation.

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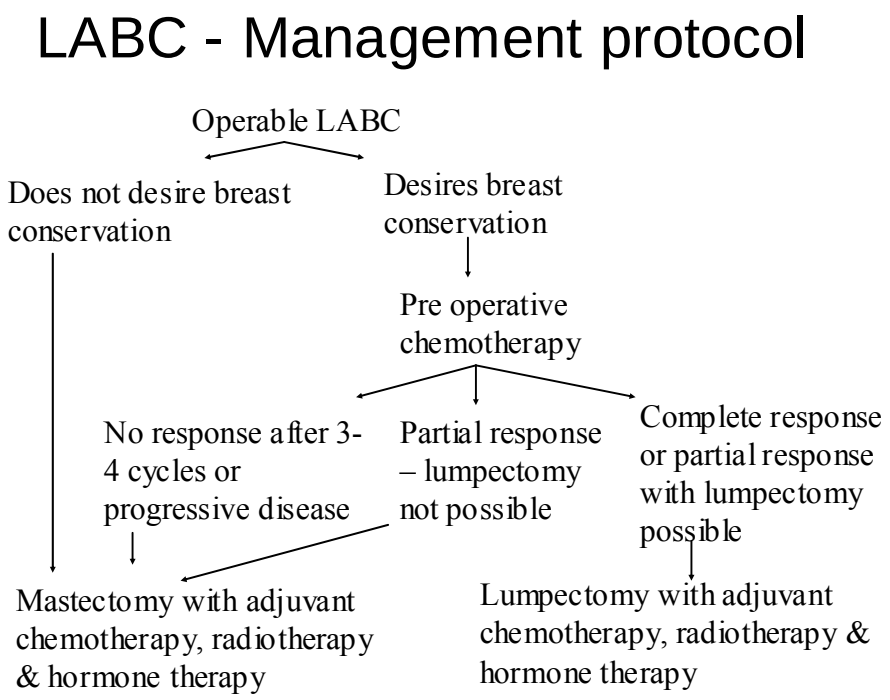


Choice of chemotherapy

• Chemotherapy should contain an anthracycline. Acceptable regimens are 6 cycles of FAC, CAF, CEF or FEC. Taxanes are under intense investigation

Randomized trials have confirmed the superiority of anthracycline-containing regimens such as CEF and CAF over conventional CMF in women with node-negative and node-positive breast cancer. In contrast, in the National Surgical Adjuvant Breast and Bowel

Project (NSABP) B-15 trial, 4 cycles of AC chemotherapy was equivalent to 6 months of CMF. Although there are limitations to crossstudy comparisons, it is reasonable to consider that 4 cycles of AC, although equivalent to 6 months of CMF, is probably inferior to 6 cycles of anthracycline-containing drug regimens such as FAC, CAF, CEF and FEC. In women who cannot receive anthracyclines because of underlying cardiac disease, CMF chemotherapy can be considered.

Six cycles of chemotherapy should be administered. This is based on the trials of adjuvant chemotherapy that showed that 6 cycles of CAF or CEF was superior to 6 cycles of CMF and that 6 cycles of FEC were superior to 3 cycles of FEC.

NON-TRASTUZUMAB CONTAINING REGIMENS (all category 1)

FAC/CAF (fluorouracil/doxorubicin/cyclophosphamide)

FEC/CEF (cyclophosphamide/epirubicin/fluorouracil)

AC (doxorubicin/cyclophosphamide) ± sequential paclitaxel

EC (epirubicin/cyclophosphamide)

TAC (docetaxel/doxorubicin/cyclophosphamide)

A CMF (doxorubicin followed by cyclophosphamide/methotrexate/fluorouracil)

E CMF (epirubicin followed by cyclophosphamide/methotrexate/fluorouracil**)**

CMF (cyclophosphamide/methotrexate/fluorouracil**)**

AC x 4 (doxorubicin/cyclophosphamide) + sequential paclitaxel x 4**,**every 2 weekly regimen with filgrastim support

A T C (doxorubicin followed by paclitaxel followed by cyclophosphamide) every 2 weekly regimen with filgrastim support

FEC T (fluorouracil/epirubicin/cyclophosphamide followed by docetaxel)

Neoadjuvant Therapy

The use of neoadjuvant or induction chemotherapy was first reported in the 1970s . Perez and colleagues reported their results of a pilot study by the Southeastern Cancer Study Group in 1979. This small study included 14 patients (five patients had inflammatory breast cancer and five had recurrences after mastectomy). All patients were treated with 5-flurouracil, Adriamycin (doxorubicin), and cyclophosphamide (FAC) for two courses, followed by local therapy or radiation concurrently with cyclophosphamide and 5-fluorouracil (CF). In the Perez group's study, all patients received an additional eight courses of FAC. All but three of the patients had complete regression of their tumors following radiation therapy. The primary tumor showed partial regression (50% to 75%) in 65% of the patients after the first two courses of FAC.However all the trials concluded that induction chemotherapy was feasible but did not show any significant survival benefit **.**

Given the absence of any difference in outcome for patients treated with neoadjuvant versus adjuvant chemotherapy, the decision to use preoperative versus postoperative chemotherapy must be based on other factors. Factors in favor of preoperative chemotherapy include the following:

(1) patients initially presenting with tumors that historically required mastectomy can potentially be down-staged to allow for breast-conservation treatment;

(2) larger tumors that require a cosmetically unsatisfactory lumpectomy at presentation can be down-staged to allow a more cosmetically favorable lumpectomy;

(3) the response of individual patients to systemic chemotherapy can be assessed *in vivo*;

(4) research can be facilitated, for example, by evaluating tissue specimens before and after treatment, to rapidly assess new chemotherapeutic, hormonal, or biologic agents; & (5) the pathologic response to neoadjuvant chemotherapy is a strong prognostic factor for outcome.

The argument in favor of primary surgery, if possible, with adjuvant systemic therapy is the more accurate pathologic staging, both of the primary tumor as well as the axillary lymph nodes, with the valuable prognostic information acquired for prognosis and guidance of adjuvant therapy.

Numerous studies have demonstrated high rates of down-staging to breast-conservation treatment with the use of neoadjuvant chemotherapy. Although most studies have used doxorubicin- or epirubicin-containing regimens, studies have also begun to evaluate the role of taxane chemotherapy. After neoadjuvant chemotherapy, down-staging of the tumor sufficient to allow breast-conservation treatment has been reported in 22% to 90% of patients. For those patients with sufficient down-staging to permit breast-conservation surgery, definitive breast irradiation is also indicated and is delivered in a manner similar to that for patients not treated with neoadjuvant chemotherapy.

Because physical examination and mammography do not adequately predict the pathologic response to neoadjuvant chemotherapy, alternative imaging methods have been developed to attempt to more accurately predict a pathologic response and to improve breast-conservation rates. MRI is one promising modality and appears to correlate well with pathologic response.

Hormone therapy likely has a role to play as a neoadjuvant therapy, particularly when the diagnostic biopsy results confirm hormone receptor expression. The addition of endocrine therapy to chemotherapy appears to improve outcome for patients with locally advanced breast cancerThe role of postmastectomy radiation treatment after neoadjuvant chemotherapy is in evolution. The ASCO guidelines recommend that, in general, postmastectomy radiation treatment is indicated after neoadjuvant systemic therapy, although the guidelines recognize that there may be exceptions to this recommendation. The rationale for recommending postmastectomy radiation treatment is the significant down-staging associated with neoadjuvant chemotherapy, for both the primary tumor and axillary lymph nodes, and the fact that most patients who require mastectomy have presented initially with locally advanced tumors (T3 or T4 lesions) or four or more pathologically positive axillary lymph nodes. For postmastectomy radiation treatment after neoadjuvant chemotherapy followed by mastectomy, unresolved issues at this time include which patient and tumor factors (clinical and pathologic) should be used to select those patients who require treatment and the optimal technical radiation therapy fields, including which regional lymph nodes, if any, should be treated.

Breast Conservation in the Setting of Multimodal Therapy

The concept of breast conservation in patients with LABC was initially practiced to spare patients surgery who already had an extremely poor prognosis. Initial studies with radiation therapy alone accomplished breast conservation, but at the expense of a high rate of local-regional failure and distant relapse. Even studies of multimodal therapy in which only radiation was used as local therapy have had local-regional failure rates as high as 30% to 50%. The ability to reduce local failures by combining surgery and

radiation therapy makes breast conservation treatment more appealing. Because induction chemotherapy may result in significant reductions in the size of the primary tumor, many patients with LABC would be candidates for breast conservation with a combination of surgery and radiation therapy.

In 1990, Bonadonna et al" first reported the use of induction chemotherapy to downstage primary tumors and allow subsequent breast saving surgery. The criterion for breast-saving surgery was a reduction in the tumor size to less than **3** cm. The group was able to avoid mastectomy for 127 (81%) of the 157 patients who had a surgical procedure.The treatment regimen consisted of three to four cycles of chemotherapy (CMF, FAC, or FEC [5-fluorouracil, epirubicin, cyclophosphamide]),followed by surgery and postoperative radiation therapy. Only116 women received postoperative adjuvant chemotherapy. Complete responses were seen after chemotherapy in 27 women, although histopathologic CR occurred in only nine. Up to 60% of the patients had at least a partial response to the induction chemotherapy. Among the first 83 patients who underwent surgery with at least 12 months of followup,

the disease recurred in 13. Only one of the 75 women treated with breast conservation surgery experienced a local recurrence during this period. One patient treated with mastectomy had a local recurrence, and the remaining 11 patients developed distant metastases.

Targeted therapy – recent advances

Advances in molecular biology are reaching therapeutic application on several fronts. One example is the targeting of the HER-2 tyrosine kinase receptor. Trastuzumab (Herceptin, Genentech, San Francisco) is a humanized monoclonal antibody that binds to

HER-2 with great affinity, resulting in growth arrest of HER-2 overexpressing cancer cells. The addition of trastuzumab to AC and paclitaxel improves time to progression, response rates, and overall survival for patients with advanced breast cancer overexpressing HER-2. Monoclonal antibodies are large molecules and are likely to be more effective in the adjuvant setting. Randomized trials that integrate trastuzumab in combination with chemotherapy are under way.

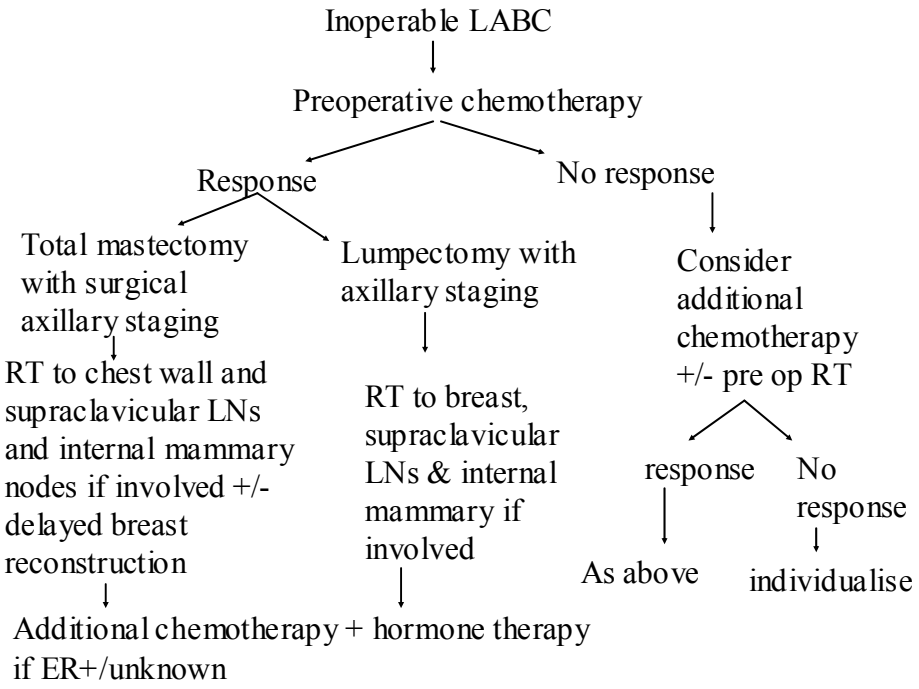
Table 7. BREAST CONSERVATION AFTER MULTIMODALITY TREATMENT IN LOCALLY ADVANCED BREAST CANCER

Author	Year	Institution	No. of Patients	Breast Conservation Rate (%)	5-Year Survival (%)
Bonadonna et al[11]	1990	Instituto Nazionale Tumori	165*	81	—
Booser et al[12]	1992	M. D. Anderson Cancer Center	146†	27	—
Calais et al[16]	1993	University Hospital, Tours, France	80‡	42.5	73
Scholl et al[47]	1994	Institut Curie, Paris, France	390§	79.7	78–86
Schwartz et al[49]	1994	Thomas Jefferson University	189	36	61¶

*Includes patients with stage II disease.
†Some patients refused breast conservation treatment.
‡Includes some patients with stage II disease.
§Patients had surgery if they had persistent tumor after radiation therapy.
¶Five-year survival rate for patients having a response to chemotherapy.

Inoperable tumours

• Patients with stage IIIB or IIIC disease, including those with inflammatory breast cancer and those with isolated ipsilateral internal mammary or supraclavicular lymph-node involvement, should be treated with primary anthracycline-based chemotherapy. • Acceptable chemotherapy regimens are FAC, CAF, CEF or FEC. Taxanes are under intense investigation.



NON-TRASTUZUMAB COMBINATIONS

FAC chemotherapy :

5-Fluorouracil 500 mg/m IV days 1 & 8 or days 1 & 4

Doxorubicin 50 mg/m IV day 1 (or by 72 h continuous infusion**)**

Cyclophosphamide 500 mg/m IV day 1 Cycled every 21 days for 6 cycles**.**

CAF chemotherapy

Cyclophosphamide 100 mg/m PO days 1-14

Doxorubicin 30 mg/m IV days 1 & 8

5-Fluorouracil 500 mg/m IV days 1 & 8 Cycled every 28 days for 6 cycles.

AC chemotherapy

Doxorubicin 60 mg/m IV day 1

Cyclophosphamide 600 mg/m IV day 1

Cycled every 21 days for 4 cycles.

FEC chemotherapy

Cyclophosphamide 75 mg/m PO days 1-14

Epirubicin 60 mg/m IV days 1 & 8

5-Fluorouracil 500 mg/m IV days 1 & 8

With cotrimoxazole support.Cycled every 28 days for 6 cycles**.**

AC followed by paclitaxel chemotherapy

Doxorubicin 60 mg/m IV day 1

Cyclophosphamide 600 mg/m IV day 1 Cycled every 21 days for 4 cycles.Followed by

Paclitaxel 175-225 mg/m by 3 h IV infusion day 1 Cycled every 21 days for 4 cycles. OR

Paclitaxel 80 mg/m by 1 h IV infusion weekly for 12 weeks.

EC chemotherapy

Epirubicin 100 mg/m IV day 1

Cyclophosphamide 830 mg/m IV day 1 Cycled every 21 days for 8 cycles.

TAC chemotherapy

Docetaxel 75 mg/m IV day 1

Doxorubicin 50 mg/m IV day 1

Cyclophosphamide 500 mg/m IV day 1 Cycled every 21 days for 6 cycles.

(All cycles are with filgrastim support).

A followed by CMF chemotherapy

Doxorubicin 75 mg/m IV day 1 Cycled every 21 days for 4 cycles.

Followed by Cyclophosphamide 600 mg/m IV day 1

Methotrexate 40 mg/m IV day 1

5-Fluorouracil 600 mg/m IV day 1 Cycled every 21 days for 8 cycles**.**

E followed by CMF chemotherapy

Epirubicin 100 mg/m IV day 1 Cycled every 21 days for 4 cycles.

Followed by Cyclophosphamide 100 mg/m PO days 1-14

Methotrexate 40 mg/m IV days 1 & 8

5-Fluorouracil 600 mg/m IV days 1 & 8 Cycled every 28 days for 4 cycles.OR

Cyclophosphamide 750 mg/m IV day 1

Methotrexate 50 mg/m IV day 1

5-Fluorouracil 600 mg/m IV day 1 Cycled every 21 days for 4 cycles.

CMF chemotherapy

Cyclophosphamide 100 mg/m PO days 1-14

Methotrexate 40 mg/m IV days 1 & 8

5-Fluorouracil 600 mg/m IV days 1 & 8 Cycled every 28 days for 6 cycles.

Dose-dense AC followed by paclitaxel chemotherapy

Doxorubicin 60 mg/m IV day 1

Cyclophosphamide 600 mg/m IV day 1 Cycled every 14 days for 4 cycles.

Followed by Paclitaxel 175 mg/m by 3 h IV infusion day 1 Cycled every 14 days for 4 cycles.(All cycles are with filgrastim support).

Dose-dense A-T-C chemotherapy

Doxorubicin 60 mg/m IV day 1 Cycled every 14 days for 4 cycles.

Followed by Paclitaxel 175 mg/m by 3 h IV day 1 Cycled every 14 days for 4 cycles.

Followed by Cyclophosphamide 600 mg/m IV day 1 Cycled every 14 days for 4 cycles.

(All cycles are with filgrastim support**).**

FEC followed by docetaxel chemotherapy

5-Fluorouracil 500 mg/m IV day 1

Epirubicin 100 mg/m IV day 1

Cyclophosphamide 500 mg/m day 1 Cycled every 21 days for 3 cycles.

Followed by Docetaxel 100 mg/m day 1 Cycled every 21 days for 3 cycles.

TRASTUZUMAB CONTAINING COMBINATIONS

AC followed by T chemotherapy with Trastuzumab

Doxorubicin 60 mg/m IV day 1

Cyclophosphamide 600 mg/m IV day 1 Cycled every 21 days for 4 cycles.

Followed by Paclitaxel 175 mg/m by 3 h IV day 1 Cycled every 21 days for 4 cycles OR

Paclitaxel 80 mg/m by 1 h IV weekly for 12 wks With Trastuzumab 4 mg/kg IV with first dose of paclitaxel Followed by Trastuzumab 2 mg/kg IV weekly to complete 1 year of

treatment. As an alternative, trastuzumab 6 mg/kg IV every 3 wk may be used following the completion of paclitaxel, and given to complete 1year of trastuzumab treatment.
Cardiac monitoring at baseline, 3, 6, and 9 months.

Docetaxel + trastuzumab followed by FEC

Docetaxel 100 mg/m by 1 h IV day 1 Cycled every 21 days for 3 cycles With
Trastuzumab 4 mg/kg IV with first dose of docetaxel day 1 Followed by
Trastuzumab 2 mg/kg IV weekly to complete 9 weeks of trastuzumab.Followed by
5-Fluorouracil 600 mg/m IV day 1
Epirubicin 60 mg/m day 1
Cyclophosphamide 600 mg/m day 1 Cycled every 21 days for 3 cycles
Cardiac monitoring at baseline, after last FEC cycle, at 12 and 36 months after chemotherapy.

TCH (docetaxel, carboplatin, trastuzumab)

Docetaxel 75 mg/m IV day 1 Followed by
Carboplatin AUC 6 IV day 1 Cycled every 21 days for 6 cycles With
Trastuzumab 4 mg/kg week 1 Followed by
Trastuzumab 2 mg/kg for 17 weeks Followed by
Trastuzumab 6 mg/kg IV every 3 weeks to complete 1 year of trastuzumab therapy
Cardiac monitoring at baseline, 3, 6, and 9 months.

AC followed by docetaxel with trastuzumab

Doxorubicin 60 mg/m IV day 1

Cyclophosphamide 600 mg/m day 1 Cycled every 21 days for 4 cycles Followed by

Docetaxel 100 mg/m Cycled every 21 days for 4 cycles With

Trastuzumab 4 mg/kg IV week one Followed by

Trastuzumab 2 mg/kg IV weekly for 11 weeks Followed by

Trastuzumab 6 mg/kg every 21 days to complete 1 y of trastuzumab therapy

Cardiac monitoring at baseline, 3, 6, and 9 months.

Neoadjuvant T followed by FEC chemotherapy with trastuzumab

Trastuzumab 4 mg/kg IV for one dose beginning just prior to first dose of paclitaxel

Followed by

Trastuzumab 2 mg/kg IV weekly for 23 wks

Paclitaxel 225 mg/m by 24 h IV infusion every 21 days for 4 cycles Followed by

5-Fluorouracil 500 mg/m on days 1 and 4

Epirubicin 75 mg/m IV on day 1

Cyclophosphamide 500 mg/m on day 1 Cycled every 21 days for 4 cycles

Systemic therapy: hormonal therapy

Operable and inoperable tumours

• Tamoxifen for 5 years should be recommended to pre-and postmenopausal women whose tumours are hormone responsive.

Schinzinger was the first person to propose that oophorectomy might be of benefit in breast cancer based on the following observations :

- Post menopausal breast atrophies.

- More virulent tumor growth in premenopausal women.

The first reported series of surgical oophorectomy for breast cancer was reported by Thomas Beatson (1896).The report postulated the following effects of oopherectomy

- Significant tumor regression by castration
- Better sense of well being
- Regression of cutaneous metastasis
- Best above age of 40
- No effect on osseous metastatsis

Following Beatson's original report, oophorectomy became widely practiced but then was largely abandoned after only 10 years. The reasons why the procedure was abandoned are (a) the recognition that oophorectomy was not a curative procedure, as was originally thought by Beatson;

(b) the lack of a sound therapeutic rationale; and

(c) the risks of intraabdominal surgery in the early twentieth century.

It was not until the 1940s, when Charles Huggins described the hormonal responsiveness of prostatic cancer, that an interest in the hormonal treatment of breast cancer was resurrected .

The various modalities of endocrine manipulation available in the management of advanced breast cancer include :

Selective Estrogen Receptor Modulators: 1.Tamoxifen

2.Torimefen

Androgens : Fluoxymesterone

Progestins : Megestrol acetate

Medroxyprogesterone acetate

High dose Estrogens

Aromatase inhibitors: 1st generation: Aminoglutethemide

2nd generation: Formestane (Type I) , Fadrazole

3rd generation: Exemestane (Type I) , Anastrazole ,

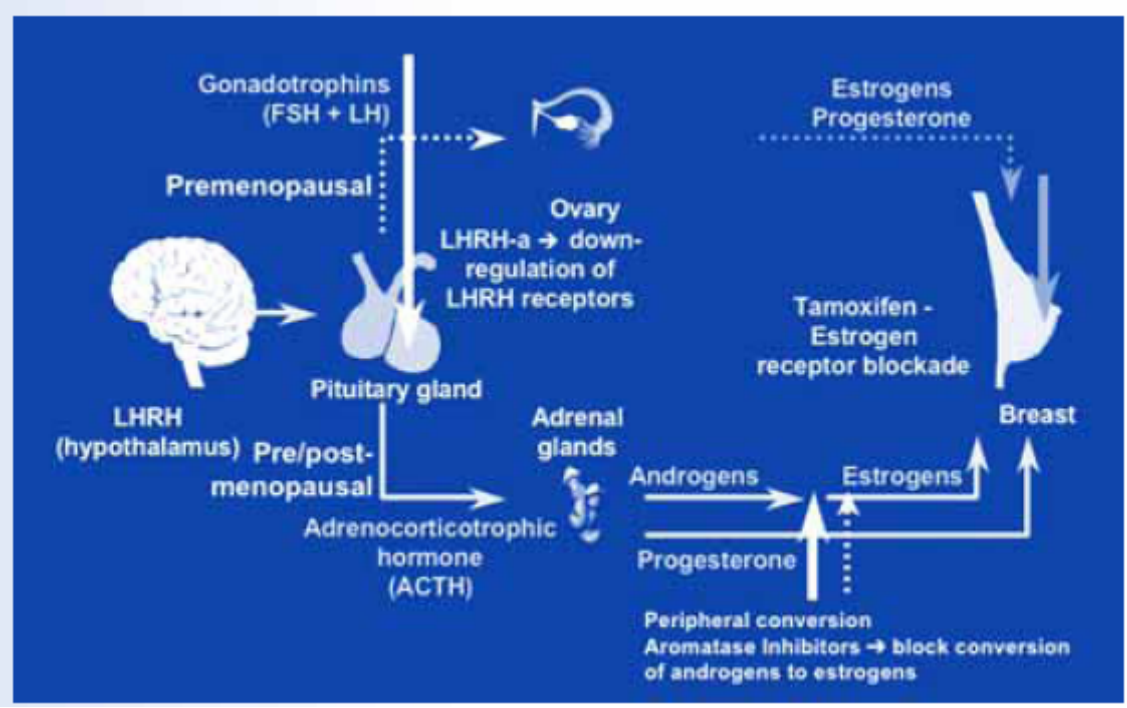
Letrozole, Vorozole

Steroidal Antiestrogens: Fulvestrant

LHRH agonists : Leuprolide, Goserelin

Gland ablation : surgical (open/laparoscopic) ; chemical ; radiation

- Ovary ; Pituitary ; Adrenals



<u>SELECTIVE ESTROGEN RECEPTOR MODULATORS</u> :

The SERMs are chemically diverse compounds that lack the steroid structure of estrogens but possess a tertiary structure that allows them to bind to the estrogen receptor.

Examples: Tamoxifen ; Raloxifen ; Tormifen

The **Selective modulation** explained by:

- Differential estrogen-receptor **expression** in a given target tissue
- Differential estrogen-receptor **conformation** on ligand binding
- Differential expression and binding to the estrogen receptor of c**oregulator** proteins

Tamoxifen

Chemically a *triphenylethylene*.the *trans* isomer of which is used as a citrate salt.

Mechanism Of Action: Competitive binding to the estrogen receptor resulting in reduction of transcription of estrogen regulated genes.

Dimethylaminoethoxy side chain and the **trans configuration** are crucial for the antiestrogenic activity of tamoxifen

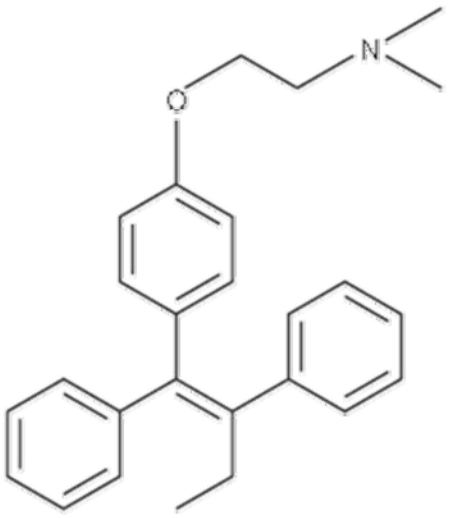
The net result is a block in the **G1 phase** of the cell cycle and a slowing of cell proliferation.Tamoxifen is thus, a **cytostatic** drug.

Binding and inactivation of estrogen receptor in cancerous cell : Predominant mode of action

Other postulated mechanisms:

Initiation of apoptosis in malignant cells

Reduction of serum IGF-1 and increase in IGF-1 binding proteins are another potential mechanism of action.



Tamoxifen

Other actions:

Increased sex hormone binding globulin (? Reduced estrogen bioavailability)

Increased TGF β (? Increased pulm fibrosis / breast fibrosis if used concurrently with RT)

Selective activation / inactivation of corepessors and coactivators responsible for selective agonist / antagonist activity

Ancillary benefits of Tamoxifen

Cardiovascular:

Fewer non cancer related deaths due to cardiovascular events.

Fewer hospitalizations for cardiac events

Serum LDL / cholesterol reduced.

Skeletal:

Significant reduction in incidence of fractures of weight bearing bones.

Estrogen agonist action on BMD

Prevention of contralateral breast cancer

Toxicity

Menopausal symptoms:50% - 60% (N.B. 40% - 50% in placebo)

MC in premenopausal

Vaginal dryness and discharge may occur in excess.

Depression:

Maybe seen in as high as 10% of patients.

But no randomized comparisons available.

Ocular toxicity:

Keratopathy

Thromboembolism:Severe thromboembolism seen in ~ 1% patients in the preventive setting.The risk is up to 10 times that experienced by healthy women.This complication is more common in elderly patients with metastatic breast cancer and who are receiving CCT

Carcinogenesis:There is increased risk of endometrial cancers (hazard rate of 1.7 per 1000 – NSABP B 14 data)but mostly low grade & stage I tumors.

Other tumors: Hepatomas & Clear cell sarcomas of ovary

Contraindications to Tamoxifen Treatment :

Absolute: **Retinal macular edema** or degeneration

History of benign or malignant **liver tumor** secondary to oral contraceptives

Pregnancy

Other hormonal therapy (estrogens, oral contraceptives)

Relative: History of thrombophlebitis, particularly hormone related

History of depression, particularly hormone related

Cataract

Drugs: Chlorpromazine, chloroquine, thioridazine, amiodarone, other

Severe vasomotor symptoms

Polycystic ovaries

Radiation oophorectomy

The first series on the effectiveness of radiation oopherectomy was reported by Foveau de Courmelles in 1922.The considerations in advocating Radiation oophorectomy include:1. Non invasive and cheap procedure.

2.Low dose carries little additional morbidity.

3.However takes about 2 – 3 months for effect to appear.

4.For such reason best avoided when prompt relief is needed.

5.Also best reserved for the patient with slow progression of disease.

Technique: Position: Supine

Field selection: Parallel opposing two field technique

Energy : Co60 or 6 MV LINAC

Dose Schedules:

In a younger women 10 – 12 Gy in 5 -6 divided fractions is preferred.

In older women shorter course of radiation can give equivalent ovarian ablation.

Field borders:

The volume of interest is the entire true pelvis

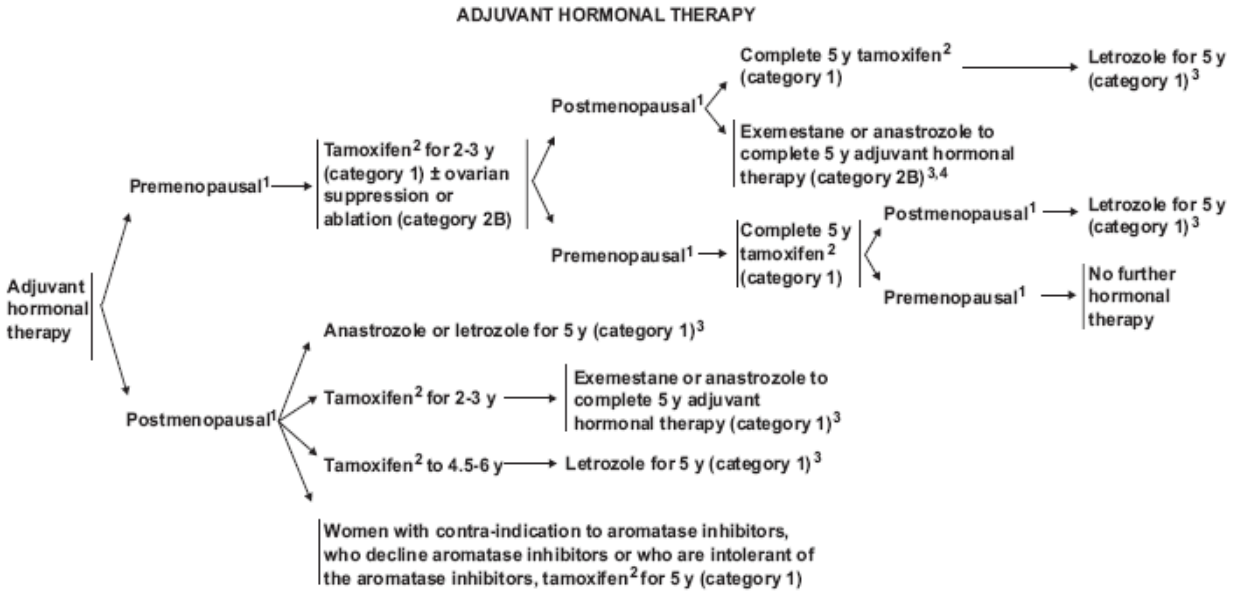
10 x 15 cm field is opened.

Lower border is placed just below the superior border of pubic symphysis.

Recommendations for adjuvant hormonal therapy :

Following completion of chemotherapy, pre- or postmenopausal patients with LABC and hormone-responsive tumours should receive adjuvant tamoxifen therapy, 20 mg/d, for 5 years Tamoxifen should be started after completion of chemotherapy. The aromatase inhibitor, anastrozole, has been compared with tamoxifen in postmenopausal women with early breast cancer following surgery. The early results of that study showed that , compared with tamoxifen, anastrozole was associated with improved DFS and had fewer side effects. The role of aromatase inhibitors as adjuvant therapy in breast cancer is evolving. The role of luteinizing hormone-releasing hormone agonists in premenopausal patients is evolving as new data emerge . Patients who are not candidates for any chemotherapy can be managed with hormonal treatment and then receive locoregional management.

NCCN Guidelines for hormonal therapy :



Locoregional management

Operable tumours

• Patients with stage IIIA disease should receive both modified radical mastectomy (MRM) and locoregional radiotherapy if feasible. They may be managed with MRM followed by chemotherapy and locoregional radiotherapy, or chemotherapy first followed by MRM and locoregional radiotherapy. Breast-conserving surgery is currently not a standard approach.

MRM (mastectomy plus a level 1 and level 2 axillary dissection) remains the standard surgical treatment for operable locally advanced disease. The second half of the 20th century witnessed increasing disillusionment with radical and mutilating forms of surgery for breast cancer. As a result the trend towards breast conservation has increased since the mid-1960s, although a number of centres had adopted this approach since before the Second World War. Again there are a number of different descriptions relating to breast conservation which has caused confusion. Tumourectomy, lumpectomy, tylectomy, segmental mastectomy, and quadrantectomy are all synonymous with a therapeutic procedure in which the primary tumour is removed and the breast is preserved. Unfortunately, these terms are not precisely defined, although they imply the removal of varying amounts of normal breast tissue in association with a primary tumour. The terms ‘lumpectomy&rsquo, ‘tumourectomy&rsquo and lsquo&tylectomy’ imply removal of the tumour with a minimal or no margin of normal breast tissue around it. Segmental mastectomy implies excision of the tumour with a rim of associated normal breast tissue. However, this term is also somewhat misleading as it implies that the breast

is anatomically a segmental organ and that tumours occur in a localized segment. This is clearly not the case. The term lsquo;quadrantectomy’ denotes removal of a breast quadrant, and implies wider excision of normal breast tissue than segmental mastectomy. In practice, however, there is little distinction between these terms and although a number of authorities have recommended the adoption of a uniform nomenclature, none has found universal favour.

Once the questions regarding definition of terms and nomenclature have been addressed the simple, yet fundamentally important question which remains is whether breast conservation provides results as reliable in the treatment of breast cancer as total Mastectomy.

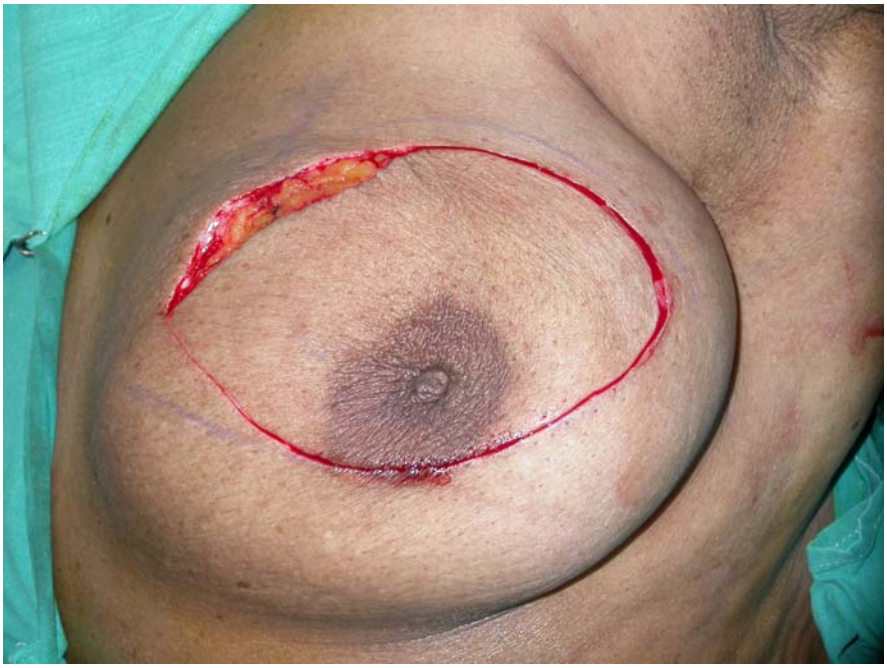
Table 1. Therapy Overview: Modified Radical Mastectomy and Breast-Conserving Therapy

Therapy	Strengths	Weaknesses	Required resources
Modified radical mastectomy	Effective local treatment Uses surgical techniques widely available Rapid treatment Short posttreatment convalescence Limited long-term complications Radiation therapy can be avoided in some cases	Loss of body image (mutilation) Negative psychosocial impact Radiation therapy is often still necessary	Core surgical resources Trained surgeon General anesthesia Operating room Postoperative care facility Pathology[a] Postmastectomy irradiation of the chest wall and regional lymph nodes[b]
Breast-conserving therapy[c]	Equivalent survival to modified radical mastectomy Preservation of body image for the woman Improved quality of life	Slight increase in the rate of recurrence (in breast) compared with modified radical mastectomy Lower acceptance among less educated people Prolonged treatment course Requires access to a radiation therapy facility	High-quality breast imaging (mammography and, if available, ultrasound) Core surgical resources (same as for modified radical mastectomy) Pathology for margin assessment[a] Surgical services experienced in the procedure Breast-conserving whole-breast irradiation[d] Geographic accessibility Support systems that allow receipt of radiation therapy over a period of weeks

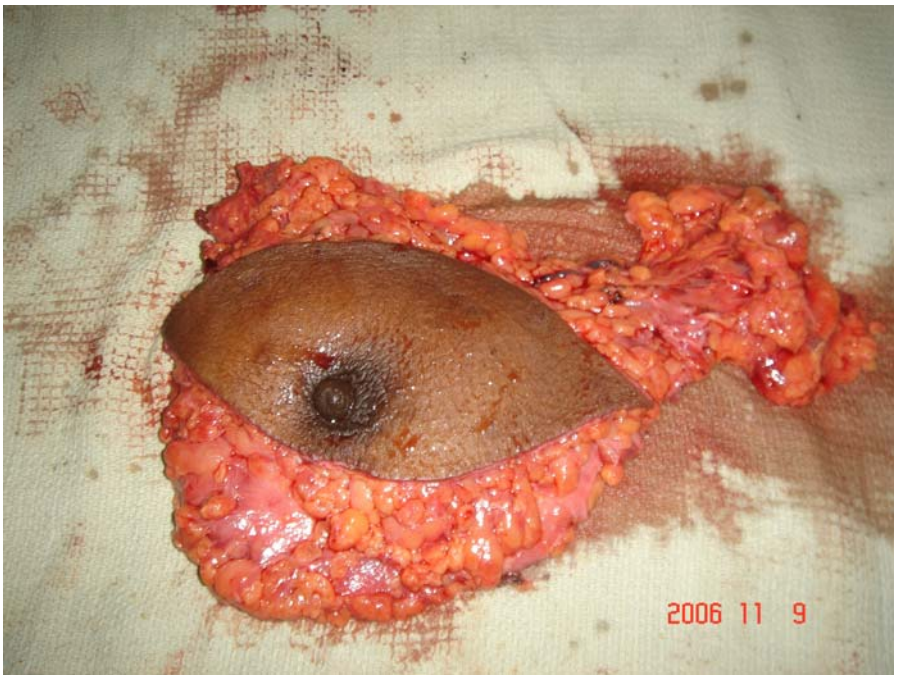
[a]See the accompanying Diagnosis and Pathology guideline in this supplement (9).
[b]See Table 2 for required resources.
[c]Breast-conserving surgery followed by radiation therapy.
[d]Required resources are the same as those for postmastectomy radiation therapy (see Table 2).

The role of BCS is unclear and the subject of research. Previous studies demonstrating equivalence of BCS to mastectomy were performed in patients with stage I and II disease see guideline In the trials that compared preoperative chemotherapy with chemotherapy administered postoperatively, the proportion of women with tumours greater than 5 cm in diameter ranged from 5% to 27%. Patients with operable stage III disease who desire to

preserve their breast should be made aware that BCS is currently not a standard approach and is generally not recommended.



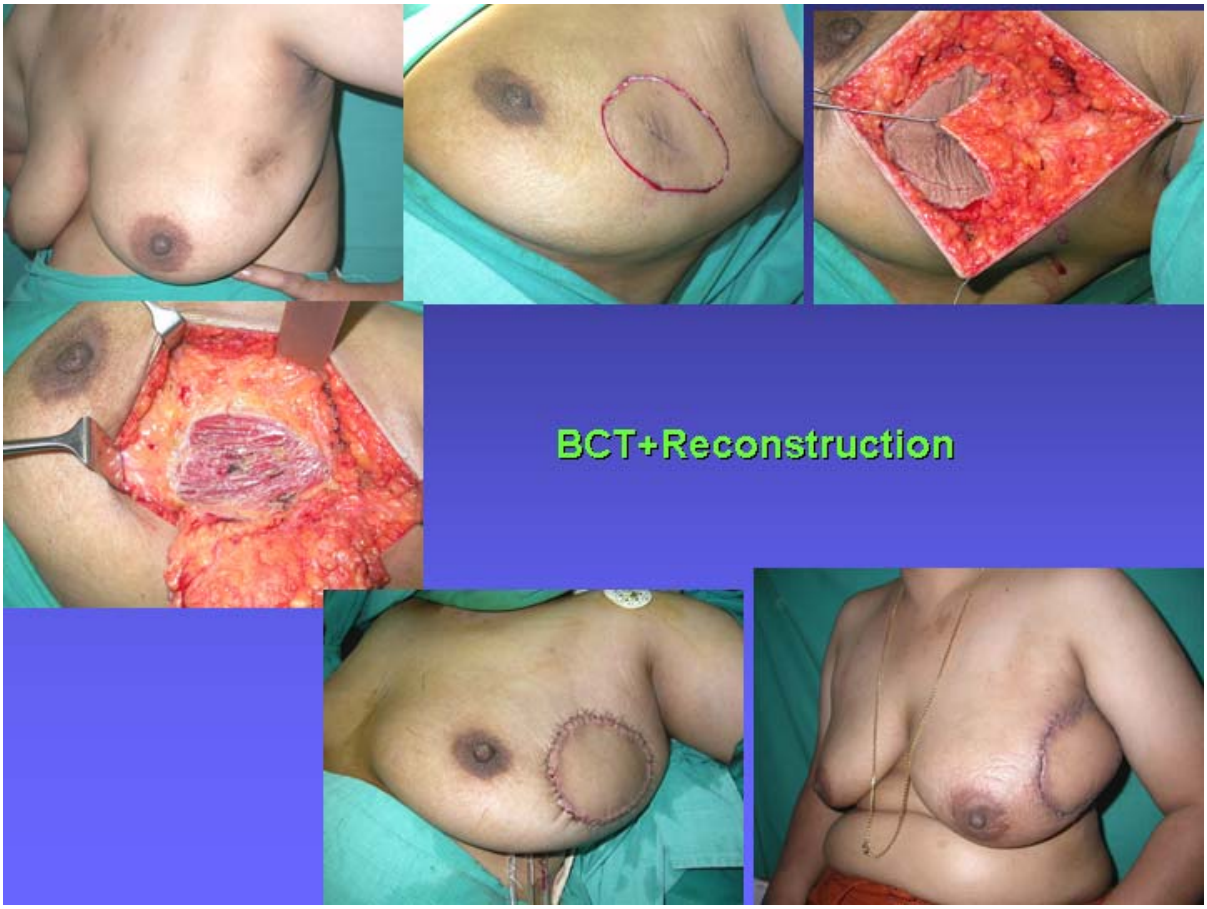
Colour plate 1 : standard incision for MRM



Colour plate 2 : Specimen of MRM

Anatomical structures removed in various types of mastectomy

	Skin	Most of gland	All of gland	Areola	P. minor	Pe.major	Level 1 nodes	Level II nodes	Level III nodes	Rotter's nodes	Int mammary N	Supraclavicular N	Mediastinal N
Sub-cutaneous		X											
Total (simple)	X		X	X									
Modified simple)	X		X	X	X								
Total with axillary dissection.	X		X	X	X	X							
Auchincoloss MRM	X		X	X	X	X	X						
Scanlon MRM	X		X	X	X	X	X	X					
Patey MRM	X		X	X	X	X	X	X	X				
Halstead RM	X		X	X	X	X	X	X	X	X			
Urban ERM	X		X	X	X	X	X	X	X	X	X		
Dahl-Iversen ERM	X		X	X	X	X	X	X	X	X	X	X	
Super-radical (Wangensteen)	X		X	X	X	X	X	X	X	X	X	X	X



Colour plate 3 : Breast reconstruction therapy

T he contraindications to BCS were determined in 1991 by a panel of representatives from the American College of Surgeons, the American College of Radiology, the College of American Pathologists, and the Society of Surgical Oncology:

Absolute contraindications to breast-conserving surgery:

1.Pregnancy: first and second trimester

2.Multicentricity: two or more gross tumors in separate quadrants

3.Diffuse undetermined or malignant-appearing microcalcifications

4.History of previous irradiation to the breast region *viz* mantle RT

Relative contraindications to breast-conserving surgery

1.Large tumor/breast ratio with respect to acceptable cosmetic results

2.Large breast size

3.Tumor location beneath the nipple

4.History of collagen vascular (connective tissue) disease

A tumor located beneath the nipple might not be considered a contraindicationto breast-conserving surgery if the patient understands the anticipated deficit and desires the procedure. Extremely large breast size is also not a contraindication to breast-conserving surgery if radiation therapy can assure dose homogeneity.

In terms of management of the breast the simplest approach would be to remove the tumour itself, preferably with a margin of normal tissue around it. In theory the more limited procedures of tumourectomy or lumpectomy are likely to be followed by a good cosmetic result but are more likely to be followed by local recurrence because of the likelihood of failure to excise the tumour completely. More extensive forms of conservative surgery such as quadrantectomy are more likely to provide good tumour control but are more liable to be followed by a less satisfactory cosmetic result because of the amount of breast tissue excised.

Nearly all of the series evaluating Skin Sparing Mastectomy comprise Stage 0, I, and II breast carcinomas. Some have also included a few Stage III tumors, which were clinically thought to represent earlier-stage lesions preoperatively .Foster et al evaluated outcomes for SSM with immediate reconstruction in patients with locally advanced disease, specifically Stages IIB and III. With a median follow-up of 49.2 months, the rate of local recurrence was 4%, which is comparable to the reported overall local recurrence rates in the literature. They concluded that this procedure is safe, effective, and has a low

morbidity on women with locally advanced breast carcinoma SSM can be performed for noninvasive or invasive breast cancer. Simmons et al reported that among NSSM patients, 62% had modified radical mastectomies, 37% had total mastectomies, and fewer than 2% had radical mastectomies; and that among SSM patients, 44% had modified radical mastectomies, 56% had total mastectomies, and none had radical mastectomies . Postoperative adjuvant chemotherapy or radiation therapy is indicated based upon the size of the primary tumor and the number of positive axillary lymph nodes. A recent study showed that 49% of both NSSM and SSM patients received postoperative adjuvant chemotherapy.Postoperative radiation therapy is typically given because of a tumor size greater than 5 cm or because of numerous axillary lymph nodes with metastatic disease. In one series, it was performed in 3% of SSM and in 12%of NSSM (P = NS). Although there is some cosmetic disadvantage to postoperative radiation therapy in patients who have tissue-expander reconstruction, patients with autologous reconstruction often maintain an excellent cosmetic outcome. If it is suspected before reconstruction that postoperative radiation will be indicated, one option is to create the reconstructed breast slightly larger than the contralateral breast, which often results in a more symmetrical long-term outcome after radiation.

Locoregional radiotherapy should be delivered to the chest wall and to the supraclavicular and axillary nodes. The role of internal mammary irradiation is not clear.

When locoregional radiotherapy is delivered following MRM for locally advanced disease, radiation should be delivered to the chest wall,supraclavicular and axillary nodes.

Whether treatment to the internal mammary nodes is required is unclear. In many of the studies reviewed for this guideline, the internal mammary nodes were irradiated. However, there are no studies that examined the impact of such radiotherapy. It is not unreasonable to include radiotherapy to the internal mammary nodal region, provided that this can be done without treating an excessive amount of heart or lung tissue. Locoregional radiotherapy has been associated with a modest increase in late non-breast-cancer deaths of cardiac or vascular origin. The recommended dose of radiation is 50 Gy in 25 fractions or equivalent.

Inoperable tumours

• Patients with stage IIIB disease who respond to chemotherapy should receive surgery plus locoregional radiotherapy.

• The locoregional management of patients with stage IIIC disease who respond to chemotherapy is unclear and should be individualized.

• Patients whose disease remains inoperable following chemotherapy should receive locoregional radiotherapy and subsequent surgery if feasible.

The locoregional management of patients with stage IIIC disease who respond to chemotherapy is unclear. In the absence of evidence on this subgroup of patients, it is reasonable that they receive locoregional radiotherapy (including nodal irradiation). The role of completion mastectomy should be individualized and based on such factors as response to chemotherapy and radiotherapy,absence of metastases on re-staging examinations and patient fitness.

Patients who are treated primarily with radiotherapy should be given tumouricidal doses to areas of bulk disease (60–66 Gy in 30 to 33 fractions or equivalent). Higher doses of radiation (70 Gy in 35 fractions by external beam or brachytherapy) to areas of bulk disease may be considered for patients if surgery is felt not to be an option and if tolerance of critical organs permits. Two case series have reported a dose-response relation with higher doses of radiation that resulted in decreased rates of local recurrence

For the patient who has a partial or complete response to chemotherapy and whose lesion is converted to an operable state, the next maneuver is typically mastectomy to debulk gross disease, to facilitate local-regional control, and to allow for the pathologic assessment of response. For patients with a complete or partial response, the optimal chemotherapy to use after local-regional treatment is uncertain. Specifically, it is not clear whether to continue the same chemotherapy as before after local-regional treatment or whether a cross-resistant chemotherapeutic regimen is indicated. The ASCO guidelines recommend postmastectomy radiation treatment, in general, for those patients who require a mastectomy

For the patient whose tumor remains inoperable after first-line systemic chemotherapy, the options are to proceed with second-line chemotherapy or to deliver preoperative radiation treatment. One major goal of treatment is to attempt to convert the lesion from an inoperable to an operable state, because patients without local-regional control have substantially diminished quality of life.

According to the St. Gallen conference,node-negative patients with a low risk for recurrence should not receive adjuvant chemotherapy. These include

Node-negative infiltrating ductal or lobular carcinoma

Tumor size less than 1 cm

Well differentiated (histologic grade 1)

ER or PR positive

Age of 35 or more

size is less than 3 cm

Pure mucinous, tubular, papillary, and adenocystic carcinoma if the tumor

Contraindications to therapy (toxicity)

Concurrent incurable, terminal illness

Severe cardiovascular, hepatic, or renal disease

Severe bone marrow deficiency

Severe immunodeficiency

Mental illness

Locally advanced breast cancer and sentinel node biopsy

Clearly, the status of the axillary lymph nodes still has an important prognostic role in LABC treated with neoadjuvant protocols. The driving question now is when to stage the axilla. Should the axilla be staged prior to and/or following neoadjuvant therapy?

Feasibility of sentinel node biopsy for LABC

Sentinel node biopsy has been extensively studied in early breast cancer and has been found to have an accuracy from 92% to 100% with successful identification of 90–100% However, limited experience in LABC is only now beginning to emerge and very little experience with SLNB after neoadjuvant therapy has been reported. Estimates of the accuracy and false negative rates (FNRs) of SLNB based on published tumor size suggest

that for primary lesions greater than 3.0 cm, the accuracy should be as high as 96% . Other groups, have directly evaluated the accuracy of SNB in LABC prior to any treatment. Bedrosian et al. evaluated 104 patients of whom 87 had T2 and 17 had T3 lesions and a clinically negative axillary exam. They were successful in identifying the SN in 99% of the cases with a FNR of only 3%. This would suggest that SLNB before neoadjuvant therapy is highly accurate for patients with large tumors.

Sentinel node biopsy following neoadjuvant treatment of LABC

The experience with neoadjuvant chemotherapy and SLNB is limited but has been successful in several trials and can be considered on a case-by-case basis at institutions that have had abundant experience with SLNB and neoadjuvant chemotherapy. Clearly the role of SLNB in LABC and neoadjuvant therapy has yet to be defined, but certainly this powerful diagnostic tool will play a prominent role.

Table 3
Sentinel node following neoadjuvant chemotherapy

Study	Lymphatic mapping technique	Neoadjuvant treatment	Tumor size (clinically staged)	Rate of SLN identification	False-negative rate (FNR)	Accuracy
Nason [47]	Tc-Sulfur Colloid	AC+G	6-T2 9-T3	13/15 (87%)	3/9 (33%)	10/13 (77%)
Breslin [48]	Blue Dye only First 23 cases	FAC, High dose FAC, T-FAC, Tam only	25-stage IIa 12-stage IIb	11/17 (65%) 16/17 (94%)	3/25 (12%)	40/43 (93%)
	Last 28 added Tc-SC		14-stage IIIa	16/17 (94%) 43/51 (84%)		
Haid [49]	Patent Blue dye and Tc-Albumin	CMF, EC, T/E	2-T1 30-T2 1-T3	29/33 (88%)	0/29 (0%)	29/29 (100%)
Julian [53]	Isosulfan Blue or unfiltered Tc-SC or Both	AC, AC+T	11-T1 20-T2 or T3	29/31 (94%)	0/29 (0%)	29/29 (100%)
Tafra [50]	Isosulfan Blue and Tc-SC	N/A	Mean size of 1.4 (T1c)	27/29 (93%)	0/29 (0%)	29/29 (100%)
Stearns [51]	Isosulfan Blue	AC, A-T, AC-T	25-T3 9-T4	23/26 (88%)	1/16 (6%)	22/23 (96%)

AC, doxorubicin, cyclophosphamide; G, filgrastrim; FAC, 5-fluorouracil, doxorubicin, cyclophosphamide; T, tamoxifen; CMF, cyclophosphamide, methotrexate, fluorouracil; EC, epirubicin, cyclophosphamide; E, exemestane.

Reconstructive surgery in LABC:

The goal of reconstructive surgery for patients with locally advanced breast carcinoma can be to repair defects or to repair defects and to recreate the breast mound.In patients with LABC who need or elect to have standard mastectomy and who desire breast reconstruction to improve the cosmetic outcome,reconstruction is often delayed until completion of both adjuvant chemotherapy and irradiation.As most locoregional recurrences are in the skin or subcutaneous tissue of chest wall,a flat post-mastectomy defect often makes irradiation technically easier than does a reconstructed breast mound,especially if the inclusion of the internal mammary nodal basin is necessary.However in selected patients with excellent response to induction chemotherapy or when palliative debulking surgeries are needed,the use of an autogenous flap to create a breast mound or provide skin coverage of the operative defect before radiotherapy is instituted if feasible.

The use of a myocutaneous flap for breast reconstruction,either before or after irradiation,does not interfere with the resumption of chemotherapy or the ability to detect locoregional recurrence.Irradiation of the reconstructed breast mound flap does not impair the flap's blood supply.Provided that the flap has an adequate vascularisation without evidence of significant fat necrosis,the irradiation itself does not alter the cosmetic result except for the anticipated skin tanning and slight fibrosis of the reconstructed breast mound .

The two tissue flaps that have been most frequently used for breast reconstruction are the lattissimus dorsi and rectus abdominis myocutaneous flaps.The advantages of the Latissimus dorsi flap include its reliable blood supply ant the relative rarity of donor site

morbidity.The flap is also relatively thin and so matches the thickness of the native chest wall skin fairly closely and also provides excellent soft tissue coverage.The chief disadvantage of the Latissimus dorsi flap is its limited size;an implant is usually required if the patient desires a reconstructed reast mound.

The Rectus abdominis myocutaneous flaps can be quite large and are most useful for defects too large to repair with a LD flap.The chief disadvantage is that they tend to be bulky and thus do not closely match the thickness of the native chest wall skin.The thickness of the flap can be an advantage,however if the defect is located directly over the central area of the chest wall;in this case the excess flap may be utilized to reconstruct a breast mound.

The two main types of Rectus abdominis myocutaneous flaps are the transverse rectus abdominis myocutaneous flap(TRAM) and the vertical rectus abdominis myocutaneous flap(VRAM).The TRAM flap has a greater arc of rotation and a more symmetrical and easiliy concealed donor site than does the VRAM flap.The VRAM flap leaves a more noticeable donor scar but is easier to construct and has a more reliable blood supply.

For major chest wall resections,the rectus abdominis flap is capable of covering a wide area from the clavicle to the costal margin and from the sternum to the midaxillary line.Because the flap is bulky,it provides sufficient chest wall stability even when upto five ribs or the entire sternum is resected,without the need for prosthetic mesh.Marlex,a nonabsorbable durable mesh can be used for flat surfaces of the chest wall.If the defect is large,a sandwich of Marlex and methyl methacrylate can be formed to restore a more normal contour.If the mesh is covered by well vascularised tissue,the risk of infection and extrusion is usually low.

Immediate breast reconstruction (IBR) is now recognized as an esthetically acceptable and oncologically safe treatment option for many early-stage breast cancer patients who undergo mastectomy. However, patients with locally advanced breast cancer (LABC) historically have been considered poor candidates for IBR for several reasons: (1) concerns regarding increased risk of local recurrence (LR) and possible delays in detecting LR; (2) concerns that prolonged recovery from extensive surgery would result in delays in postoperative chemotherapy ; (3) concern about a possibly higher risk of wound infections in patients who have received preoperative chemotherapy; and (4) concerns regarding the technical difficulties of irradiating the reconstructed breast. Despite these issues, IBR has been performed in many women with LABC, because of (1) strong patient preference, unclear preoperative assessment of extent of disease, or (3) need to provide soft tissue coverage for an extensive mastectomy defect.

INFLAMMATORY BREAST CARCINOMA

In 1814**,** Sir Charles Bell first recognized the clinical evolution of IBC when he wrote: "a purple color on the skin over the tumor accompanied by shooting pains, is a very unpropitious beginning.”Later in the nineteenth century, Klotz described ”mastitis carcinomatosa” as a variant of carcinoma of the breast characterized by its fulminant course.” In 1889, Bryant reported the association of dermal lymphatic invasion with the clinical characteristics of 1BC.’ The term *inflammatory* was coined by Lee and Tannenbaum in 1924.T heir paper was the first to describe in great detail the clinical

characteristics of IBC in a series of 24 patients.Several other names have been used to describe this entity including *carcinoma mastitoides, carcinoma e ysipeloides, lactation cancer,* and *malignant lymph~ngitis*B.~e~tw een 1908 and 1911, the term *acute carcinoma* was used by several investigators, and Leitch, in 1909, introduced the french term "peau d'orange" in an English literature paper. Taylor and Meltzer subsequently described two clinical varieties of inflammatory breast cancer:

(1) Primary inflammatory breast cancer, characterized by a sudden onset of the above symptoms in a breast which previously appears normal;

(2) Secondary inflammatory breast cancer, defined by inflammatory symptoms and signs which appear in a breast with a previous mass, in the chest wall postmastectomy or in the contralateral breast .

Inflammatory breast cancer is a distinct clinical subtype of locally advanced breast cancer, with a particularly aggressive behavior and poor prognosis. Clinically, inflammatory breast cancer typically presents with the rapid onset of breast erythema, warmth, and edema, often without a discrete underlying mass. The swelling of the breast can be quite pronounced, producing significant tenderness.Although histologic proof of malignancy is critical prior to treatment of IBC, documenting dermal lymphatic permeation is not critical in establishing the diagnosis of IBC.

IBC is defined under the current American Joint Committee on Cancer (AJCC) manual for staging of cancer as T4d NO-2 stage III b, carcinoma of the breast. This corresponds

to Haagensen's stage D of the Columbia Clinical Classification. Bonnier et al. classified patients into three groups according to clinical and histopathological features

Group A included patients with typical inflammatory breast cancer (diffuse enlargement of the breast, often no palpable tumour, redness and oedema of the skin).Ipsilateral enlargement of the axillary nodes was often detected and emboli of carcinoma cells in the subdermal lymphatics were often found.

Group B included patients with occult inflammatory breast cancer, in which the presence of tumour emboli in dermal lymphatics was not associated with inflammatory symptoms and signs.

Group C included patients with pseudo-inflammatory breast cancer. Symptoms were similar to those of groupA. However a tumour mass was more readily palpable and the sub-dermal lymphatics were never involved.Furthermore, the axillary nodes were rarely involved.

Evaluation of IBC

Evaluation of patients presenting with IBC must be multidisciplinary.This includes a thorough documentation of physical findings and extent of disease, including axillary and supraclavicular lymph node enlargement. Bilateral mammograms are performed to ensure that this is a unilateral process and as a baseline for future reference. Although core-needle biopsy affords the most efficient proof of malignancy, we prefer an incisional biopsy including skin to determine dermal lymphatic involvement . Hormone receptor analysis, DNA content, and Sphase fraction are routinely perfornted. Metastatic work-up includes CT scans of the chest and upper abdomen, including liver and adrenalglands; bone scintigraphy; liver enzymes; and carcinoembryonic antigen determination.Bryant"

attributed the inflammatory signs in this type of cancer to diffuse lymphatic blockage by cancer cells, but this finding is not specific for IBC. Inflammatory breast cancer exhibits all the usual microscopic features of infiltrating ductal carcinoma. IBCs are poorly differentiated and without evidence of glandular formation.

Neglected locally advanced breast cancer can develop secondary inflammatory characteristics, but should be distinguished from primary inflammatory carcinoma as these secondary inflammatory breast cancers may follow a more indolent course and can be treated as other locally advanced breast tumors.

Three biological features make inflammatory breast cancer a unique clinical entity :

(1) Rapidity of progression

(2) High angiogenic and angioinvasive capability

(3) Aggressive behaviour from inception.

van Golen et al. found that overexpression of RhoC GTPase and the lost in inflammatory breast cancer (LIBC) protein were highly correlated with an inflammatory breast cancer phenotype. These tumors are more likely to be high grade, aneuploid, and hormone-receptor negative and have a high S-phase fraction and p53 mutations. Despite these differences in biologic characteristics, prognostic factors for inflammatory breast cancer are similar to those for locally advanced disease, with axillary lymph node involvement predicting poorer survival. Other negative prognostic factors for inflammatory carcinoma include negative ER status, extensive erythema of the breast, and p53 mutations.

Management of IBC

The optimal treatment of inflammatory breast cancer requires careful coordination of multimodal therapy among medical, radiation, and surgical oncologists.Current treatment for inflammatory breast cancer centres upon neoadjuvant chemotherapy. The advent of neoadjuvant chemotherapy has greatly improved disease-free and overall survival for inflammatory breast cancer Ueno et al., in their series of 178patients, report overall survival of 40% at 5 years and 33% at 10 years. Given that inflammatory breast cancer metastasises early, sub-clinical systemic disease is likely to exist, which may be controlled by neoadjuvant chemotherapy. The initial component of treatment hence should be induction chemotherapy with an anthracycline-based regimen or an anthracycline and taxane combination. Definitive local therapy can then be achieved with radiation therapy, mastectomy, or both. . After local therapy, patients should receive further adjuvant chemotherapy, as the risk of relapse remains high, followed by adjuvant radiotherapy, if not previously given.

Role of surgery in IBC

Early experience with surgery for inflammatory breast cancer was uniformly disappointing, with high rates of recurrence and poor overall survival. The role of surgery is now being re-evaluated due to the effectiveness of neoadjuvant chemotherapy, whichhas resulted in downstaging of disease with decreased tumour burden . This provides a greater opportunity for adequate surgical resection.Curcio et al.found that a successful outcome for surgery for inflammatory breast cancer following neoadjuvant chemotherapy depended upon achieving negative excision margins. Lopez and Porter noted that consistently achieving tumour-free resection margins can be technically

difficult in inflammatory breast cancer patients, and may require complex reconstructions with myocutaneous flaps and extensive cutaneous dissection. Breast conservation is rarely possible.

Table 1
Retrospective studies of neoadjuvant chemotherapy for "inflammatory" breast cancer (only studies with patient numbers with IBC of greater than $n = 35$ are included)

Authors	Year	No. of patients	Treatment regimen	Response rate (%)	Median survival (months)	5-yr survival (%)	10-yr survival (%)
DeLena et al. [53]	1978	36	CT + RT ± CT	67	25	24 (3 yr)	NA
Pawlicki et al. [73]	1983	72	CT + S ± RT	70	NA	28 (3 yr)	NA
Keiling et al. [74]	1985	41	CT + S + CT	NA	NA	63	NA
Rouesse et al. [75]	1989	170	CT + RT + CT + H	74	NA	47	NA
Koh et al. [76]	1990	106	CT ± S + RT + CT	69	45	38	NA
Mailosel et al. [77]	1990	43	CT + S + CT + RT + H	88	46	75	NA
Moore et al. [78]	1991	38	CT + S ± RT	79	56	45	NA
Pierce et al. [79]	1992	46	CT + H ± S + RT	98	NA	36	NA
Chevallier et al. [80]	1993	178	CT + RT ± CT ± S	71	37	32	NA
Palangie et al. [22]	1994	223	CT + RT	NA	41	41	NA
Perez et al. [81]	1994	86	CT + S + RT	NA	36	40	35
Ueno et al. [43]	1997	178	CT + RT ± S + CT	NA	NA	NA	28 (15 yr)
Harris et al. [25]	2003	54	CT + RT + S	NA	62	56	35

CT, chemotherapy; RT, radiotherapy; S, surgery; H, hormonal therapy; NA, figures not available.

Sentinel lymph node biopsy may also be unsuitable in the setting of inflammatory breast cancer due to the high level of nodal involvement found in this disease. Also since cancer infiltrates the dermis and lymphatics in inflammatory breast cancer, the underlying architecture may be disrupted to the extent that sentinel lymph node biopsy is not of value

Relatively few women with inflammatory breast cancer have been offered reconstructive surgery following surgery . Concerns about reconstruction include delays to adjuvant treatment, difficulty in the detection of recurrence and increase in morbidity. Given the improved multimodality treatment of inflammatory breast cancer, reconstructive

procedures should be offered as part of comprehensive therapy, as long as a positive margin at resection is not expected(Chin et al). The exact indications for surgery and the optimal operation, however, remain unclear.

Radiotherapy was the mainstay of care for inflammatory breast cancer for many years, but the results were unimpressive. Radiotherapy alone has been shown to improve local control rates in treatment of inflammatory breast cancer, but to have no effect on survival Since the introduction of neoadjuvant chemotherapy, and the return of surgery, radiotherapy is now seen as an important part of a multimodality treatment approach, rather than treatment on its own. The importance of radiotherapy relates primarily to its function in loco-regional control.

No substantial improvement in survival from hormone therapy for inflammatory breast cancer has been shown , which is not surprising given that patients with inflammatory breast cancers are more frequently oestrogen and progesterone receptor negative compared with other breast cancers. Nevertheless, if the tumour is oestrogen receptor positive it is currently advised that patients receive 5 years of treatment with either tamoxifen or aromatase inhibitors.

Recent discoveries of the distinct biologic features that characterize inflammatory carcinoma can lead the way toward the development of new therapies. For instance, farnesyl transferase inhibitors have been shown to reverse the invasive phenotype of RhoC GTPase-overexpressing cell lines. Other possible therapeutic targets include mediators of angiogenesis such as vascular endothelial growth factor, basic fibroblast growth factor, and Flt-1, which are overexpressed in inflammatory breast cancers.

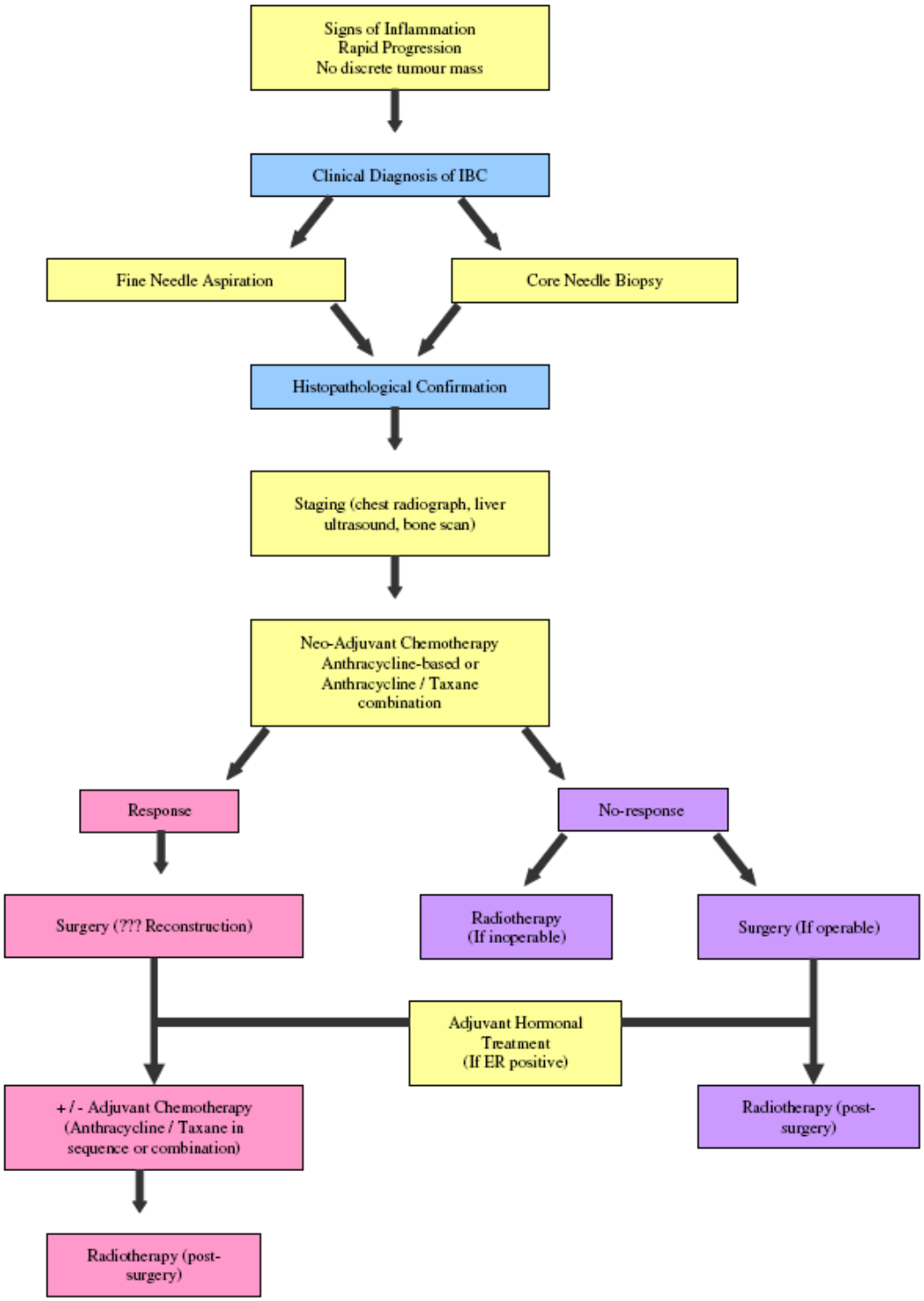


Fig. 2. Algorithm for the diagnosis and treatment of "inflammatory" breast cancer.

Allocation of resources :

The treatment of breast cancer requires an integrated,multidisciplinary approach using multiple resources in a focused, disease-oriented manner. Existing evidence-based guidelines outlining optimal approaches to the treatment of breast cancer have been defined and disseminated,but do consider the multiple deficits in infrastructure and the availability of therapies in limited-resource countries. Marked heterogeneity exists among countries and also between regions of the same country with regard to social, economic, and health system development.Therefore a uniform approach for all limited-resource countries is neither practical nor realistic. The BHGI has proposed a stepwise, systematic approach for building national or regional breast health treatment systems by stratifying health care resources into four levels—basic, limited,enhanced, and maximal—based on the contribution of incremental resources in improving clinical outcomes.

Table. Treatment and Allocation of Resources: Locally Advanced Breast Cancer

Level of Resources	Local-regional Treatment		Systemic Treatment (Adjuvant)	
	Surgery	**Radiation Therapy**	**Chemotherapy**	**Endocrine Therapy**
Basic	Modified radical mastectomy		Neoadjuvant AC, FAC, or classical CMF[a]	Ovarian ablation Tamoxifen
Limited		Postmastectomy irradiation of the chest wall and regional nodes		
Enhanced	Breast-conserving therapy[b]	Breast-conserving whole-breast irradiation	Taxanes	Aromatase inhibitors LH-RH agonists
Maximal	Reconstructive surgery		Growth factors Dose-dense chemotherapy	

[a]Requires blood chemistry profile and complete blood count (CBC) testing.

[b]Breast-conserving therapy requires mammography and reporting of margin status.

AC, doxorubicin and cyclophosphamide; CMF, cyclophosphamide, methotrexate, and 5-fluorouracil; EC, epirubicin and cyclophosphamide; FAC, 5-fluorouracil, doxorubicin, and cyclophosphamide; LH-RH, luteinizing hormone releasing hormone.

SURVEILLANCE/FOLLOW-UP

Despite advances in the multidisciplinary approach in the management of locally advanced breast cancer that has improved the prognosis as well as the quality of life considerably ,the overall survival remains almost constant.That the prognosis is stage dependant has been well established.

Interval history and physical exam every 4-6 months for 5 years, then every 12 months

Mammogram every 12 months (and 6-12 months post-RT if breast conserved)

Women on tamoxifen: annual gynecologic assessment every 12 months if uterus present

Women on an aromatase inhibitor or who experience ovarian failure secondary to treatment should have monitoring of bone health

Assess and encourage adherence to adjuvant hormonal therapy**.**

Patient education on recurrence, morbidity of treatment ,psycho social aspects,prosthesis before ,during & at completion of treatment

Breast self examination – monthly

Haematology,Bioprofile,Imaging

Assay for tumour markers } not recommended routinely

LABC
-Database of my surgical unit

Aims & objectives :

1. To ascertain the incidence of LABC among the women presenting with breast cancer.

2.To define the optimal treatment for women with stage III or locally advanced breast cancer (LABC).

3.To ascertain the feasibility of the defined optimal treatment and to advocate it among patients with LABC.

Period of study : May 2005 – October 2007

Methods

We conducted a review of the literature in the English-language retrieved from internet and medical journals regarding the management of locally advanced breast cancer.Search terms used were “breast neoplasms,” “locally advanced breast cancer,” “stage III breast cancer,” “drug therapy,” “neo-adjuvant,” “primary systemic therapy,” “radiotherapy or irradiation,” “surgery,” “randomized trials” and “high-dose therapy.” Additional data were identified by reviewing references in retrieved reports and by monitoring major conferences on breast cancer. The main outcomes considered are locoregional control (defined as freedom from recurrence in the breast, chest wall or regional lymph nodes), disease-free survival (DFS; defined as survival free of breast cancer recurrence) and overall survival (OS).

Numerous setbacks encountered in the process of synthesizing the results of the studies from the review of the literature included :

1.Majority of the studies were from the western population that differed vastly from the Indian scenario.

2.The studies included different populations of patients with differing prognoses; for

example, some studies included patients with inflammatory breast cancer whereas other studies did not.

3.In studies evaluating systemic therapies, local therapy (surgery/radiotherapy) was often not standardized.

4.The TNM tumour-staging system changed, in that tumours associated with ipsilateral supraclavicular nodal involvement that were initially considered LABC were considered metastatic breast cancer between 1987 and 2002 and are now considered LABC again.

5.The randomized trials that were available were old, had small patient numbers and used systemic therapy combinations that are often not used today.

6.The various recent advances available as of today could not be utilized in the study owing to patient's socioeconomic ceiling.For example hormone receptor assay /her-2 neu assay /bone scan could not be advocated.

7.Breast reconstruction / breast conservation could not be tried for the lack of infrastructure and patient compliance.

Patients and methods

Between May 2005 and October 2007, a total of 43 cases of carcinoma breast were admitted in our surgical unit in the Government Rajaji Hospital,Madurai.All of those admitted were staged according to the AJCC TNM classification. Staging work-up

consisted of a complete bloodcount (CBC), blood chemistry, chest X-ray,and ultrasonography of the liver.Either FNAC/ Trucut / incisional biopsy were used to confirm the diagnosis of carcinoma breast.

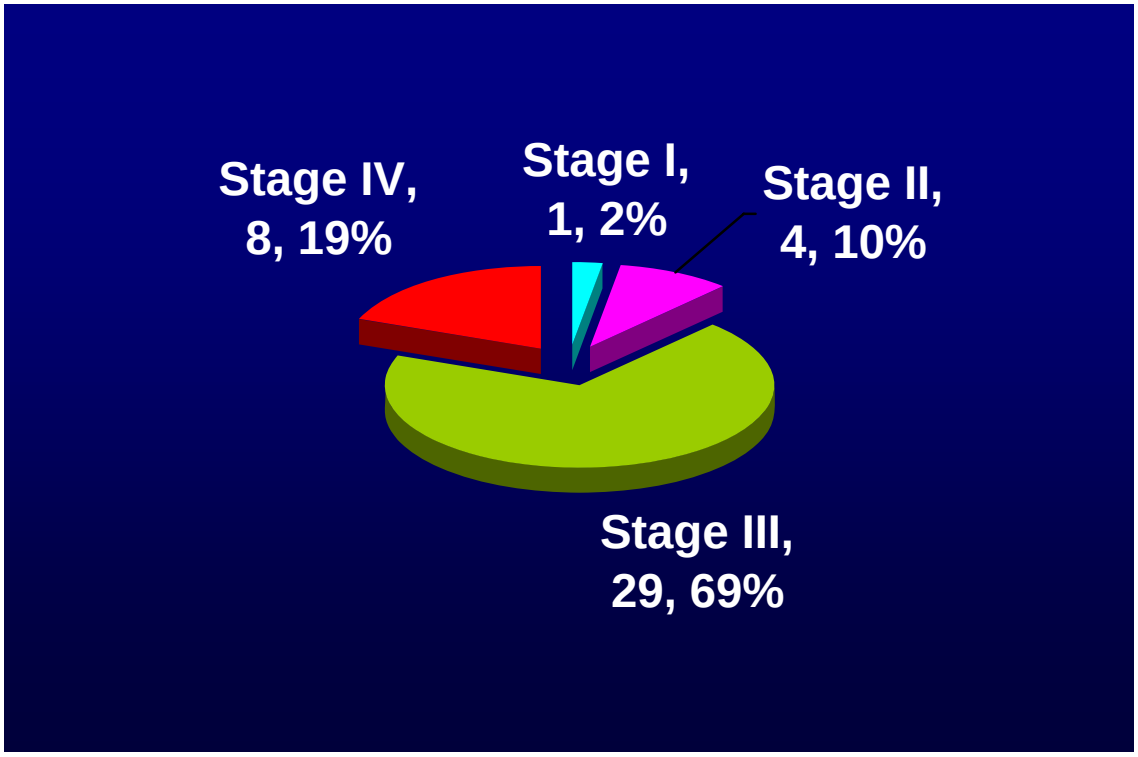


Figure : Carcinoma breast stage distribution in our study population.

Of the 43 patients,

one of them was of male sex ; 42 were of female sex.For all practical purposes only the 42 female breast carcinoma were considered for the study.

18 were right – sided & 24 left-sided,

one of stage I ; four of stage II ; 29 of stage III ; 8 of stage IV.

Of the 30 cases of LABC, (29 of III & 1 of II)

one of them was inflammatory carcinoma

18 were post – menopausal & 12 were pre- menopausal.

The HPE in all the cases were of infiltrating ductal carcinoma.Since ER status could not be ascertained,all of the cases were considered ER + for all practical purposes.

All of the cases of LABC except for the inflammatory carcinoma underwent modified radical mastectomy,followed by adjuvant chemoradiation & Hormonal therapy .Adjuvant chemotherapy consisted of 6 cycles of CAF regimen.Adjuvant radiation included EBRT of 5000 Gy to the tumour bed & nodal basins.Receptor status could not be ascertained. So, the receptor status was considered positive for all practical purposes and adjuvant hormonal therapy in the form of tamoxifen 10 mg bd was instituted for a period of 5 years.

Conclusions :

The incidence of LABC among the study population was approximately **69%.**LABC forms the majority of the cases of breast cancer at the time of initial presentation itself.The significance of this conclusion is that what cases are classified at a specific instance as LABC once belonged to the category of early breast cancer and subsequently evolved into LABC due to either patient's negligence or inappropriate intervention or aggressive tumour biology.Thus as prevention is always better than cure it is recommended that the following measures can be adopted to address this problem :

1.Health education regarding self breast examination

2.screening mammography

3.Identifiation of high risk population and specific management

4.Surveillance when family history is positive for breast cancer.

Metastatic work-up is mandatory.

Hormone receptor assay may be useful in planning treatment

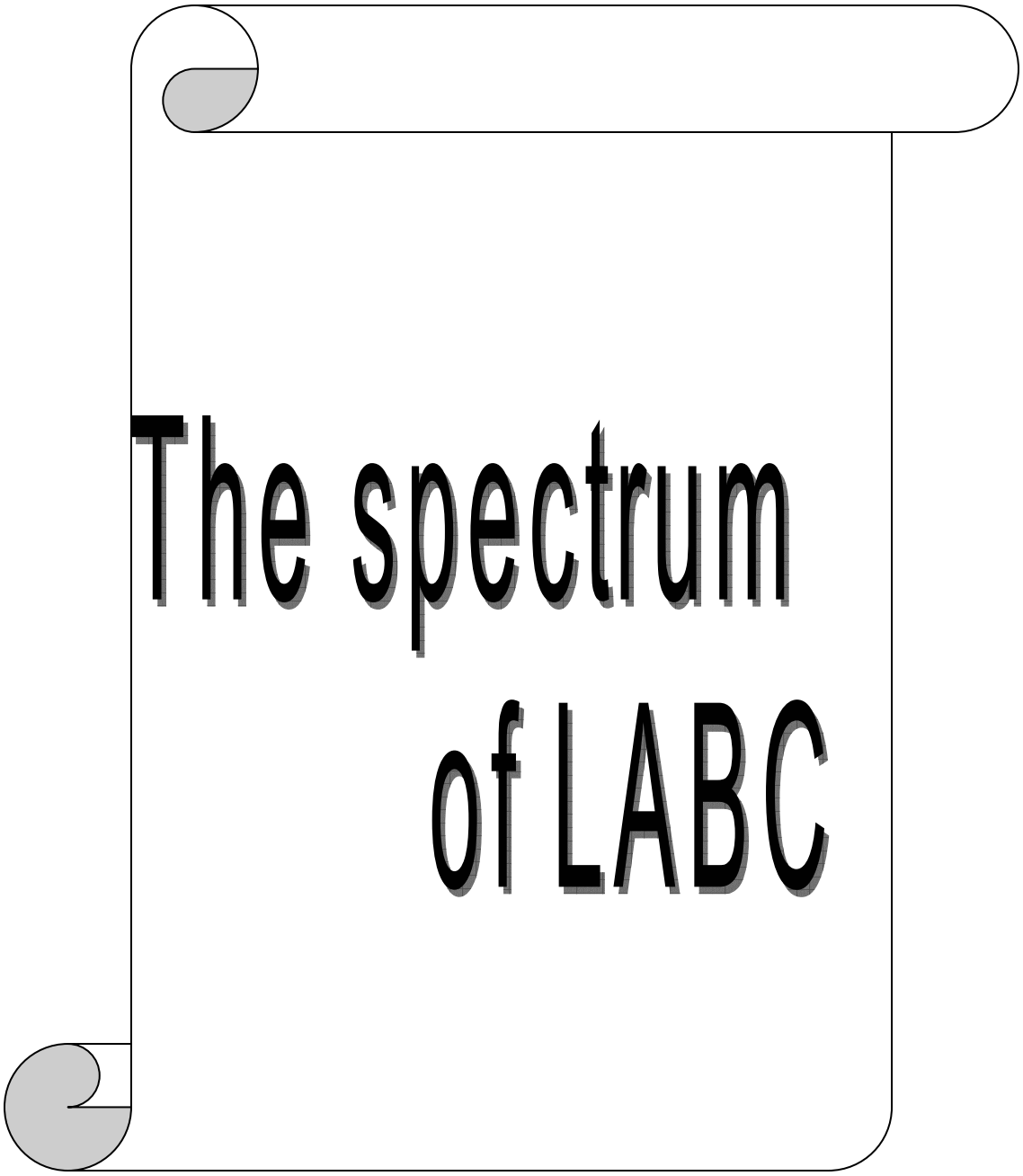
For better management of patients with LABC, the following is recommended:

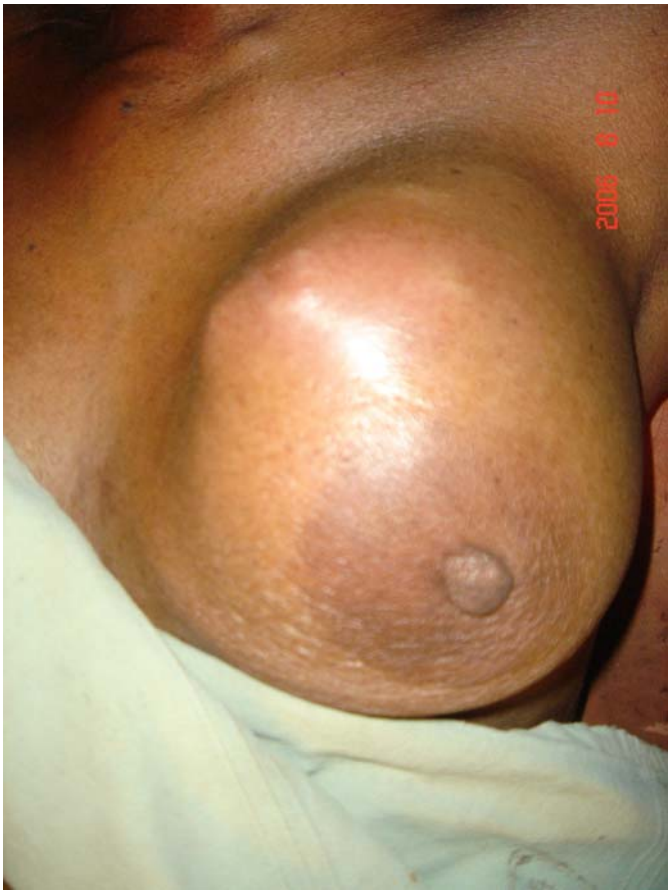
• Early diagnosis of breast cancer is vital for better results of treatment. General education about early symptoms of the disease and access to medical facilities are important in diminishing breast cancer mortality in our country.

• Cellular biological markers such as Her-2, P53, etc. should be evaluated as prognostic factors in prospective randomized studies.

• Randomized trials are recommended for comparing new adjuvant regimens

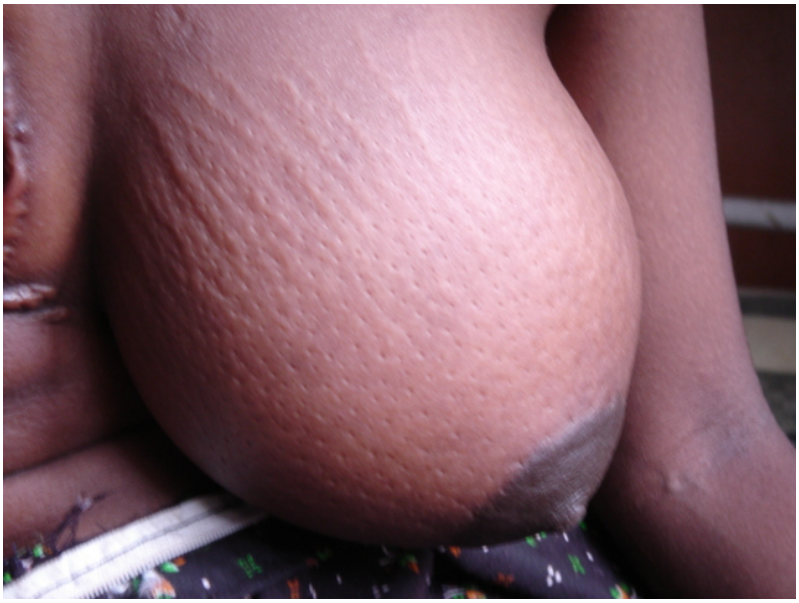
Lack of treatment compliance and/or failure to provide standard-of-care treatment in high-risk breast cancer can lead to a higher incidence of metastatic cancer and mortality.


The spectrum
of LABC

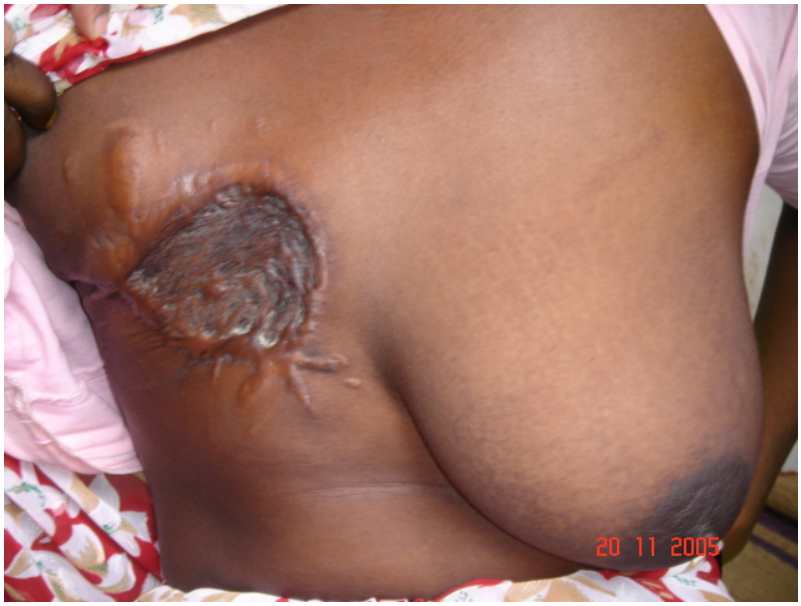


Colour plate : 4 : T 4 tumour – shiny skin +

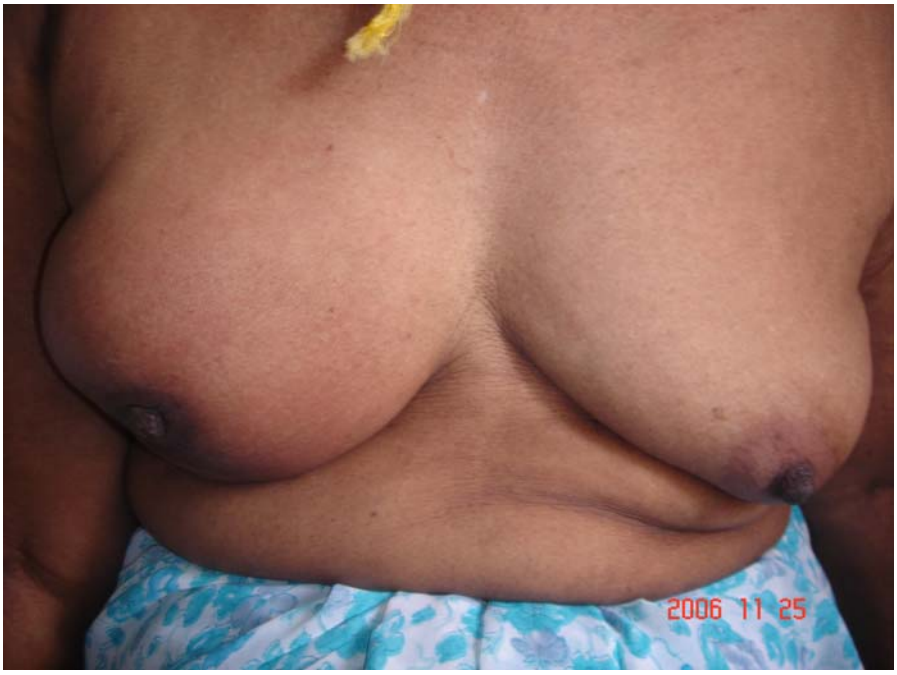
Colour plate : 5 : Fungating carcinoma (T4c)



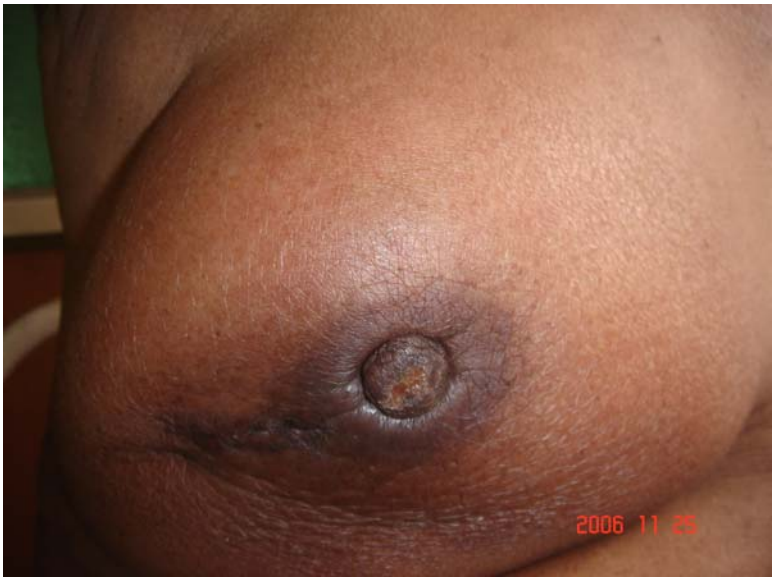
Colour plate : 6 : Inflammatory breast carcinoma



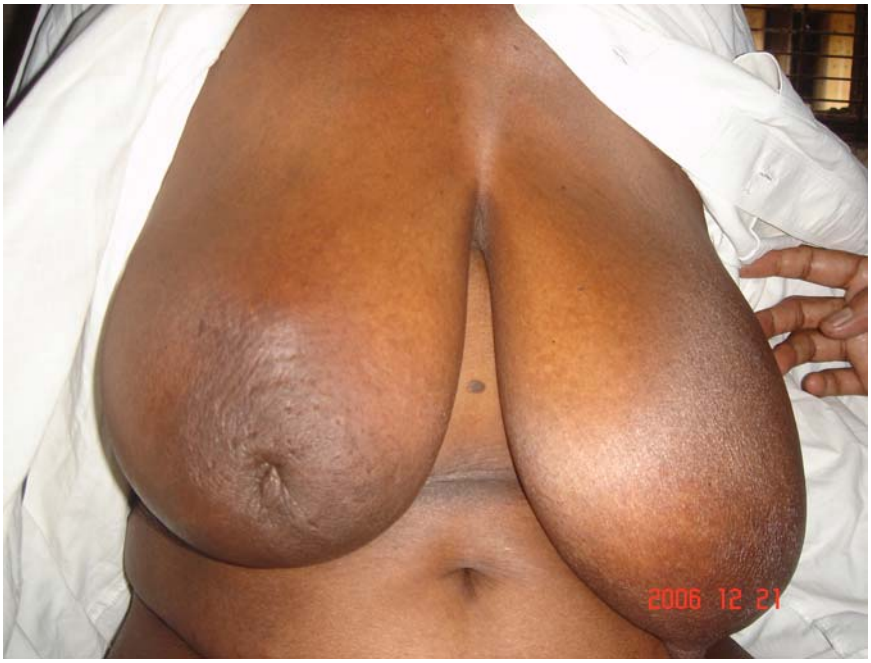
Colour plate :7: After chemotherapy



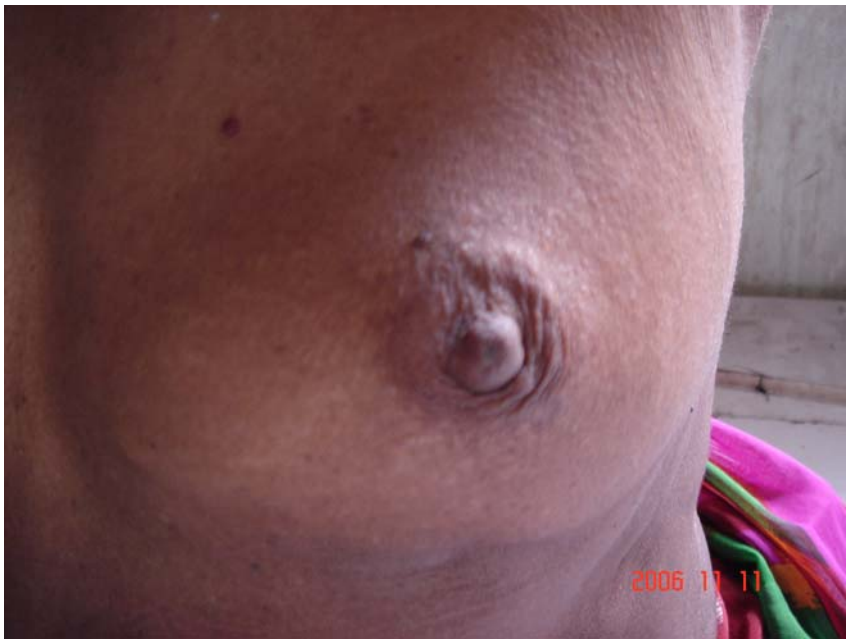
Colour plate 8: T4b tumour



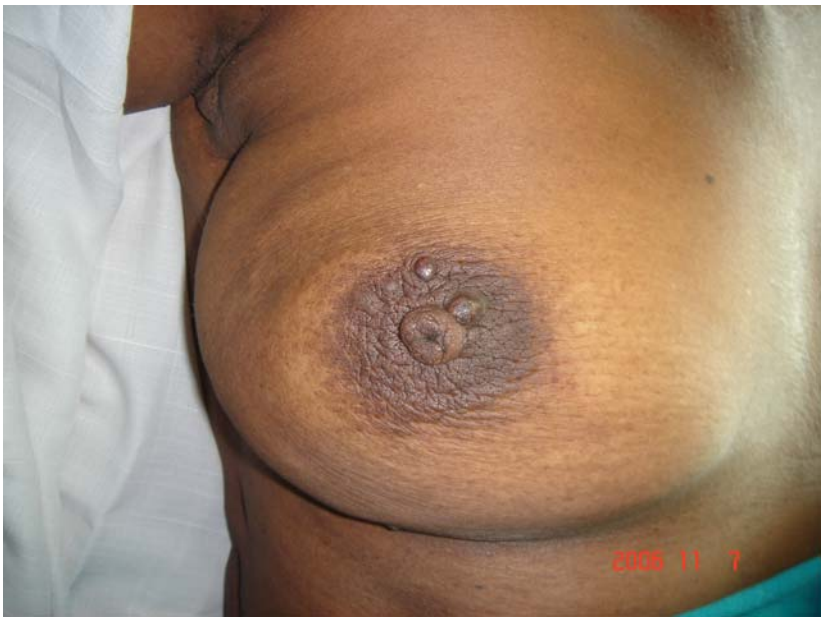
Colour plate 9: Nipple retraction



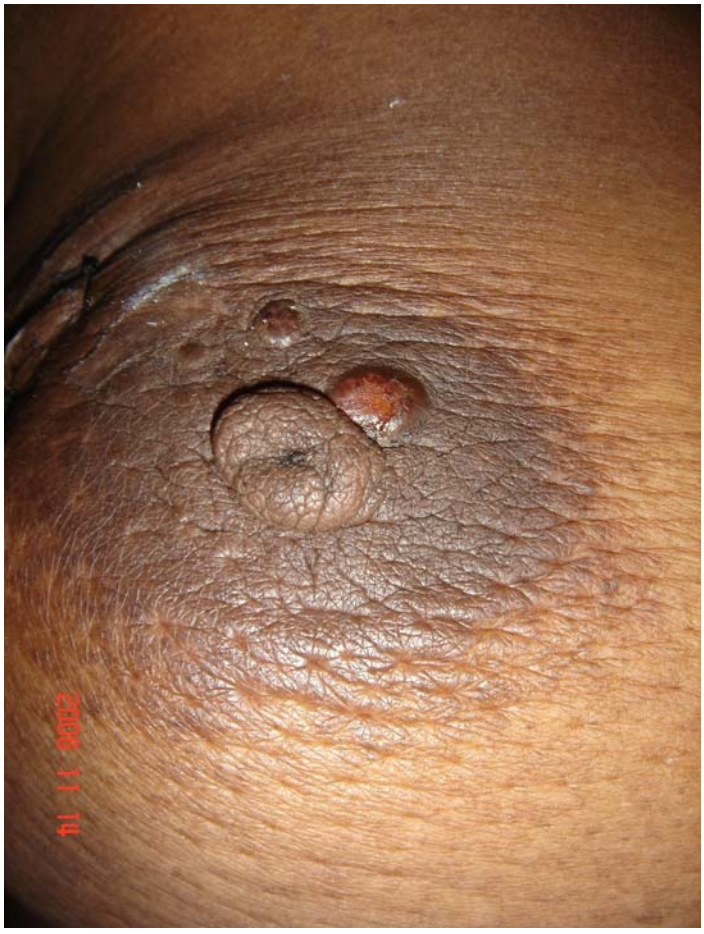
Colour plate 10 : Nipple inversion

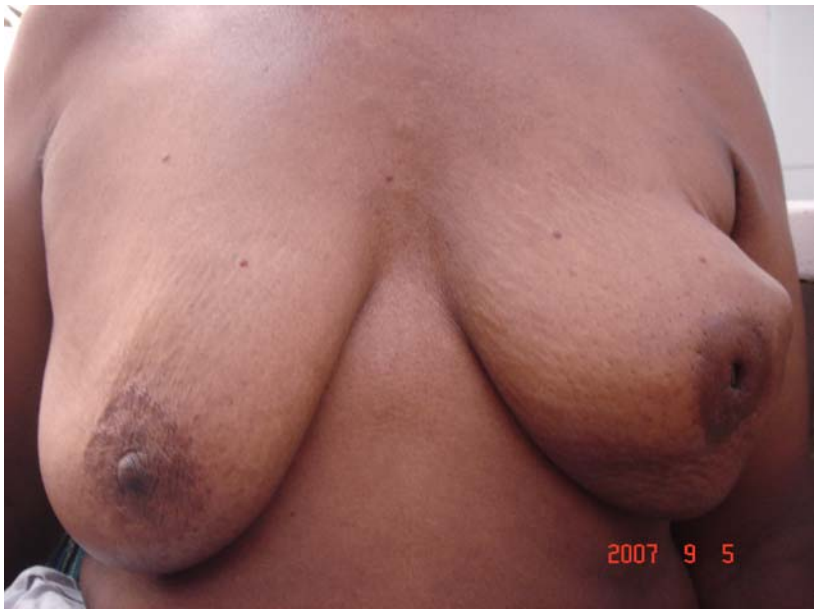


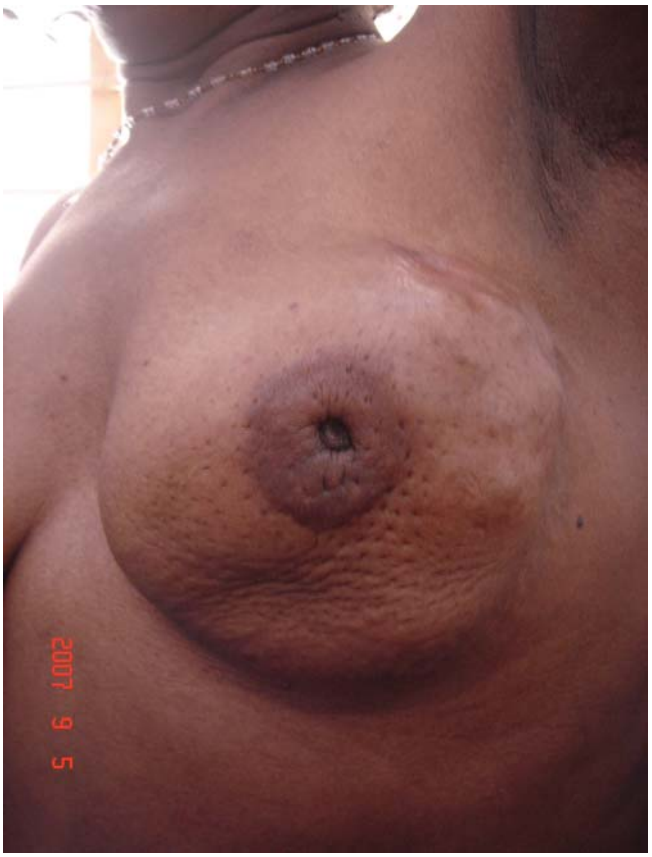
Colour plate 11 : T3 tumour



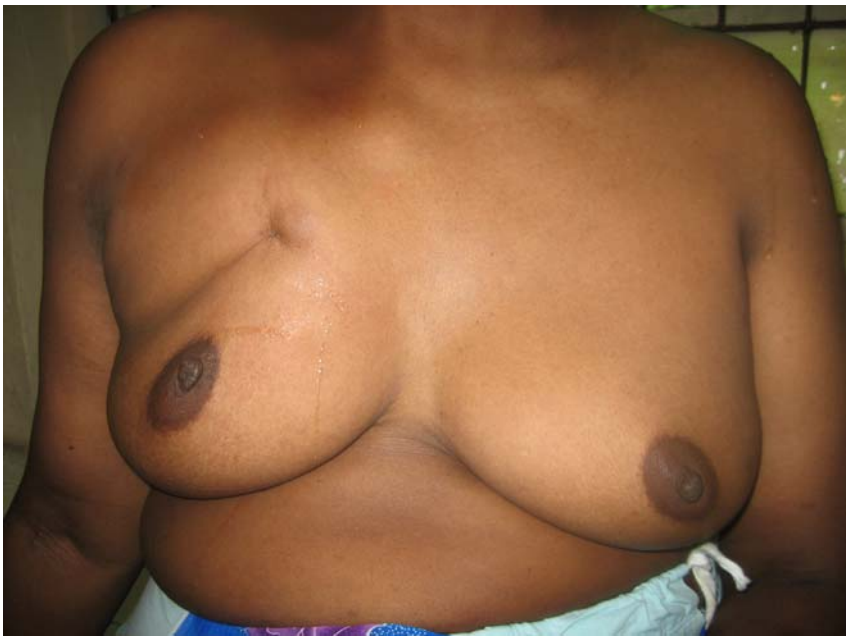
Colour plate 12 & 13 : satellite nodules +

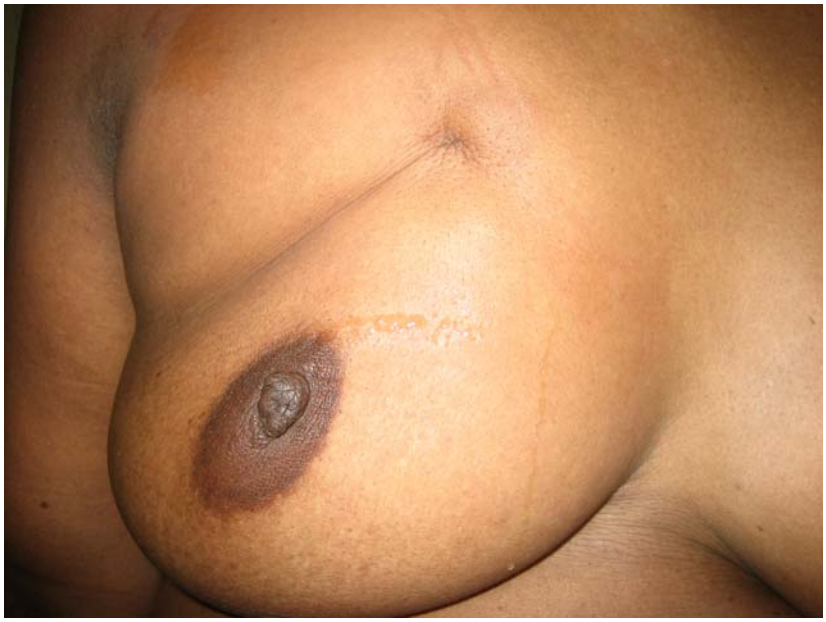




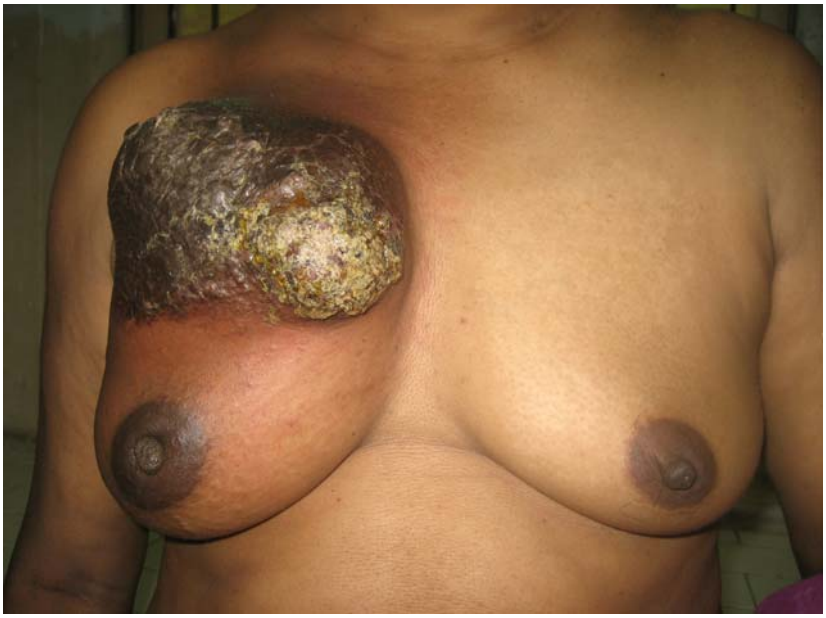


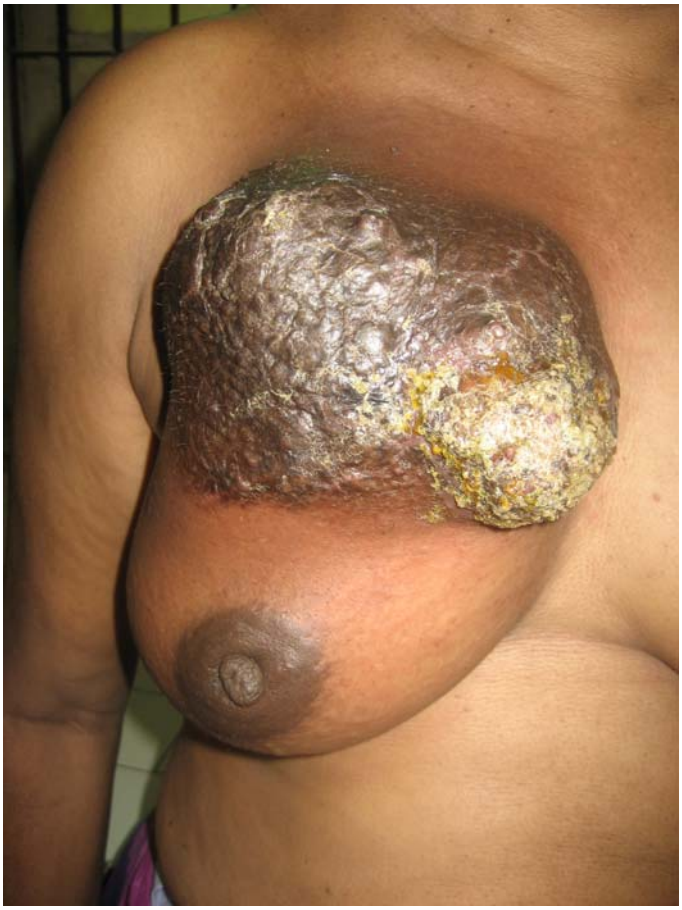
colour plate 14 & 15 : peau d’ orange



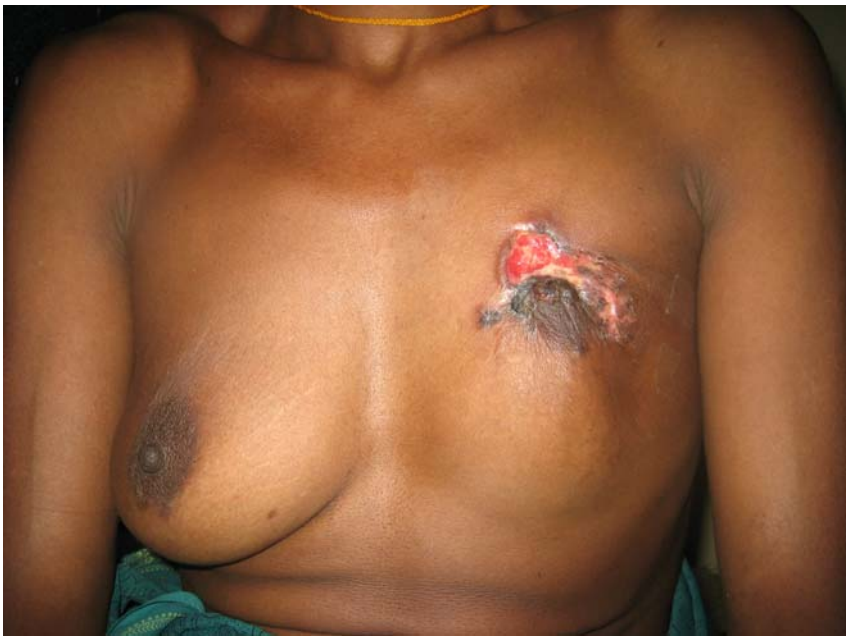


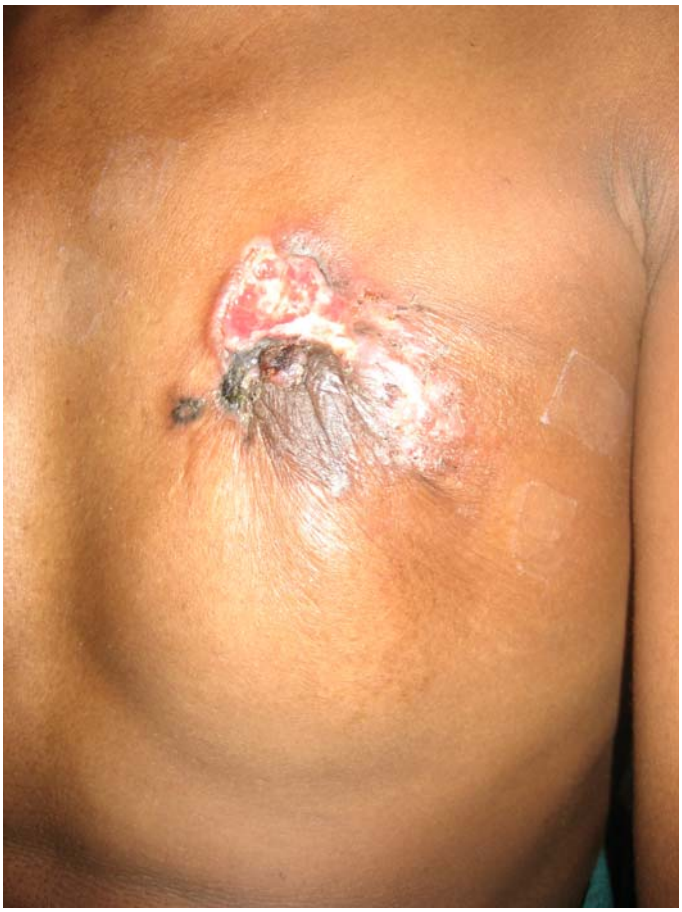
Colour plate 16 & 17 : T4a(chest wall fixity)



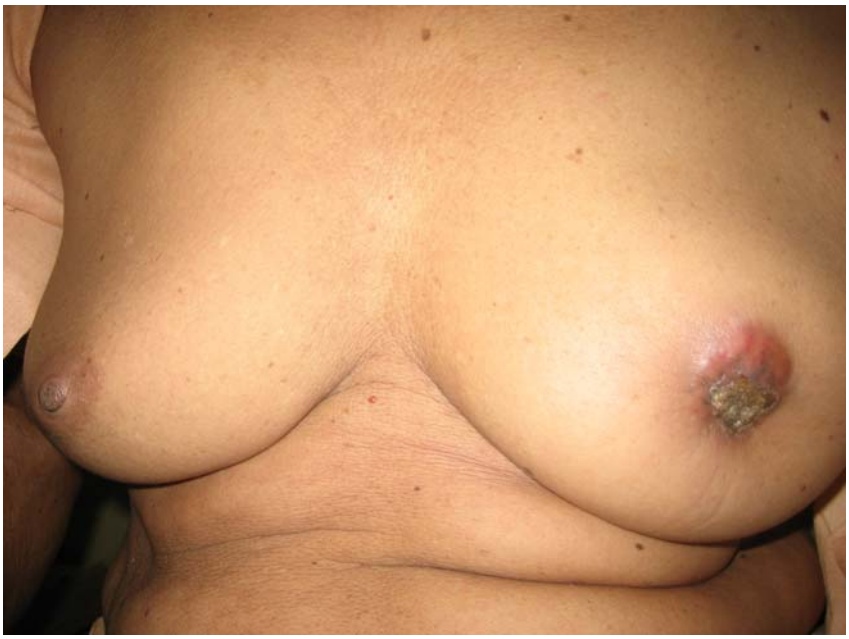


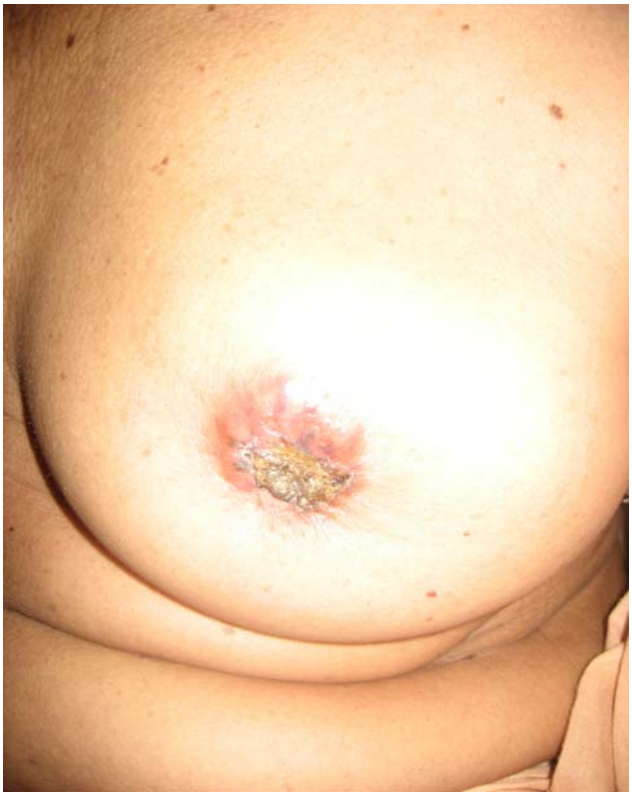
Colour plate 18 & 19 : LABC at its worst !



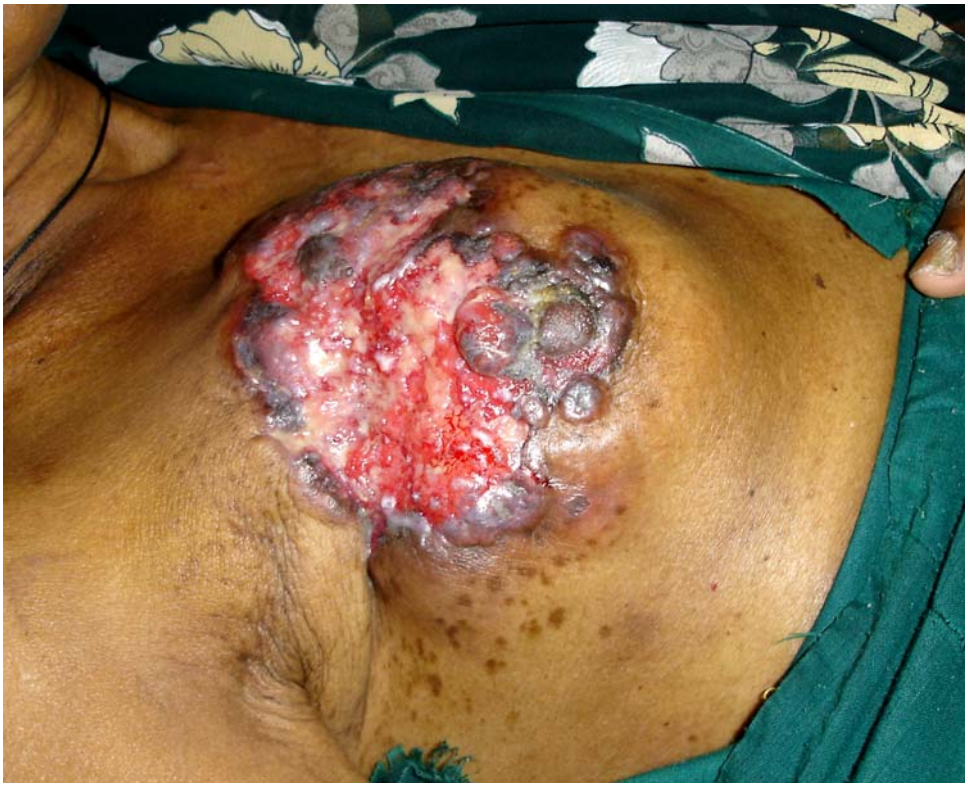


Colour plate 20 & 21 : ulcerative malignancy





Colour plate 22 & 23 : Nipple destruction



Colour plate 24 : Fungating carcinoma of breast

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Abbreviations used

LABC – Locally advanced breast carcinoma

IBC – Inflammatory breast carcinoma

MRM – Modified Radical Mastectomy

SSM – Skin sparing mastectomy

BCT – Breast conservation surgery

NSSM – Non skin sparing mastectomy

AJCC – American joint committee on cancer

ASCO –American society of clinical oncology

NCCN – National cancer comprehensive network

BHGI – Breast health global initiative

VRAM – Vertical rectus abdominis myocutaneous flap

TRAM – Transverse rectus abdominis myocutaneous flap

CBC – Complete blood count

LR – Local recurrence

CR – Complete response

PR – Partial response

IBR – Immediate breast reconstruction

OS – Overall survival

DFS – Disease free survival

SLNB – Sentinel lymph node biopsy

SERM – Selective estrogen receptor modulator

RT – Radiotherapy

NACT – Neoadjuvant chemotherapy

DNA – Deoxy-ribonucleic acid

EBRT – External Beam Radiotherapy

HPE – Histopathological evaluation

LHRH – Leutinising hormone releasing hormone

FNAC – Fine needle aspiration cytology

LD – Latissimus dorsi myocutaneous flap

Master Chart

S.No	Pt	Age	Menopausal	Side	TNM	Stage	Treatment
1	L	54	Post	Rt	$T_3N_1M_0$	III A	MRM +RT+ CT+ Tmx
2	K	50	Pre	Lt	$T_3N_1M_0$	III A	MRM + B/L Oopherectomy + RT + CT + Tmx
3.	S	24	Pre	Lt	$T_{4d}N_1M_0$	III B	CT + B/L Oopherectomy + Tmx
4	S	60	Post	Lt	$T_{4b}N_2M_0$	III B	MRM + CT + RT + Tmx
5	M	52	Post	Lt	TxN_1Mx	IV	Local excision + CT + Tmx
6	V	50	Post	Lt	$T_3N_2M_0$	III B	MRM + CT + RT + Tmx
7	G	41	Post oopherectomy	Rt	TxNxMx	IV	Local excision + CT + Tmx
8	K	55	Pre	Lt	T_3NoM_0	II B	MRM + B/L Oopherectomy + RT + CT + Tmx
9	V	57	Post	Rt	$T_3N_1M_0$	III A	MRM + CT + RT + Tmx
10.	S	40	Post oopherectomy	Rt	$TxNxM_1$	IV	CT + Tmx
11	M	56	Post	Rt	$T_{4b}N_0M_0$	III B	MRM + CT + RT + Tmx

12	P	45	Post	Lt	TxN_0Mx	IV	CT + Tmx
S.no	Pt	Age	Menopausal	Side	TNM	Stage	Treatment
13	N	35	Pre	Lt	$T_4cN_2M_1$	IV	CT + Tmx
14	G	40	Pre	Rt	$T_3N_1M_1$	IV	CT + Tmx
15	D	50	Pre	Lt	$T_2N_1M_0$	II A	MRM + B/L Oopherectomy + RT + CT + Tmx
16	M	50	Post	Lt	$T_3N_1M_0$	III A	MRM + CT + RT + Tmx
17	R	45	Pre	Lt	$T_2N_1M_0$	II B	MRM + B/L Oopherectomy + RT + CT + Tmx
18	V	42	Pre	Rt	T_2NoMo	II A	MRM + B/L Oopherectomy + RT + CT + Tmx
19	M	55	Pre	Rt	$T_2N_2M_0$	III A	MRM + B/L Oopherectomy + RT + CT + Tmx
20	M	60	Post	Lt	$T_{4b}N_3M_1$	IV	CT + Tmx
21	S	45	Pre	Rt	$T_3N_1M_0$	III B	MRM + B/L Oopherectomy + RT + CT + Tmx
22	M	60	Post	Lt	$T_{4b}N_1M_0$	III A	MRM + CT + RT + Tmx
23	K	60	Post	Rt	$T_{4b}N_1M_0$	III A	SM + CT + RT + Tmx

24	D	50	Post	Rt	$T_{4b}N_1M_0$	III A	MRM + CT + RT + Tmx
S.No	Pt	Age	Menopausal	Side	TNM	Stage	Treatment
25	R	40	Pre	Lt	$T_3N_1M_0$	III A	MRM + B/L Oopherectomy + RT + CT + Tmx
26	J	50	Pre	Rt	$T_3N_1M_0$	III A	MRM + B/L Oopherectomy + RT + CT + Tmx
27	G	70	Post	Rt	$T_{4b}N_1M_0$	III B	MRM + CT + RT + Tmx
28	K	55	Post	Lt	$T_3N_1M_0$	III A	MRM + CT + RT + Tmx
29	J	55	Pre	Rt	TisN0Mo	I	MRM
30	N	55	Pre	Lt	$T_{4b}N_1M_0$	III B	MRM + B/L Oopherectomy + RT + CT + Tmx
31	G	68	Post	Rt	$T_{4b}N_1M_0$	III B	MRM + CT + RT + Tmx
32	J	65	Post	Lt	$T_3N_1M_0$	III A	MRM + CT + RT + Tmx
33	L	40	Pre	Lt	$T_3N_1M_0$	III A	MRM + B/L Oopherectomy + RT + CT + Tmx
34	M	63	Post	Rt	$T_{4b}N_1M_0$	III B	MRM + CT + RT + Tmx
35	P	70	Post	Lt	$T_{4b}N_2M_0$	III B	MRM + CT + RT + Tmx
36	R	50	Pre	Rt	$T_{4b}N_1M_0$	III B	MRM + B/L Oopherectomy+ CT + RT

							+ Tmx
37	S	45	Post	Rt	$T_{4b}N_1M_0$	III B	MRM + CT + RT + Tmx
38	C	35	Pre	Lt	$T_{4c}N_1M_0$	III B	MRM + SSG +B/L Oopherectomy+ CT + RT + Tmx
39	K	61	Post	Lt	$T_{4b}N_3M_1$	IV	CT + Tmx
40	M	51	Post	Lt	$T_{4b}N_1M_0$	III B	MRM + CT + RT + Tmx
41	M	55	Post	Rt	$T_{4b}N_1M_0$	III B	MRM + CT + RT + Tmx
42	G	50	Post	Lt	$T_{4c}N_1M_0$	III B	SM + CT + RT + Tmx

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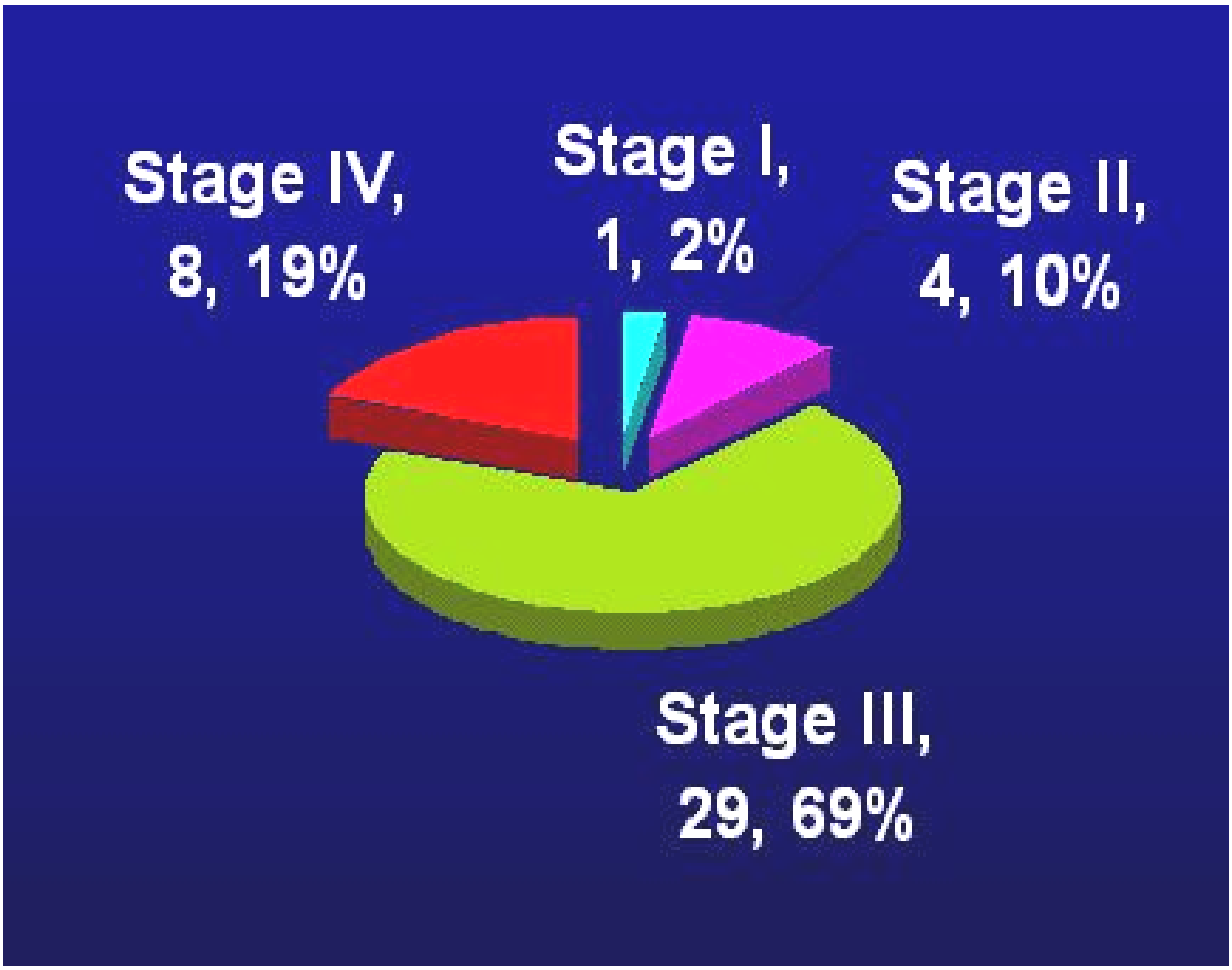
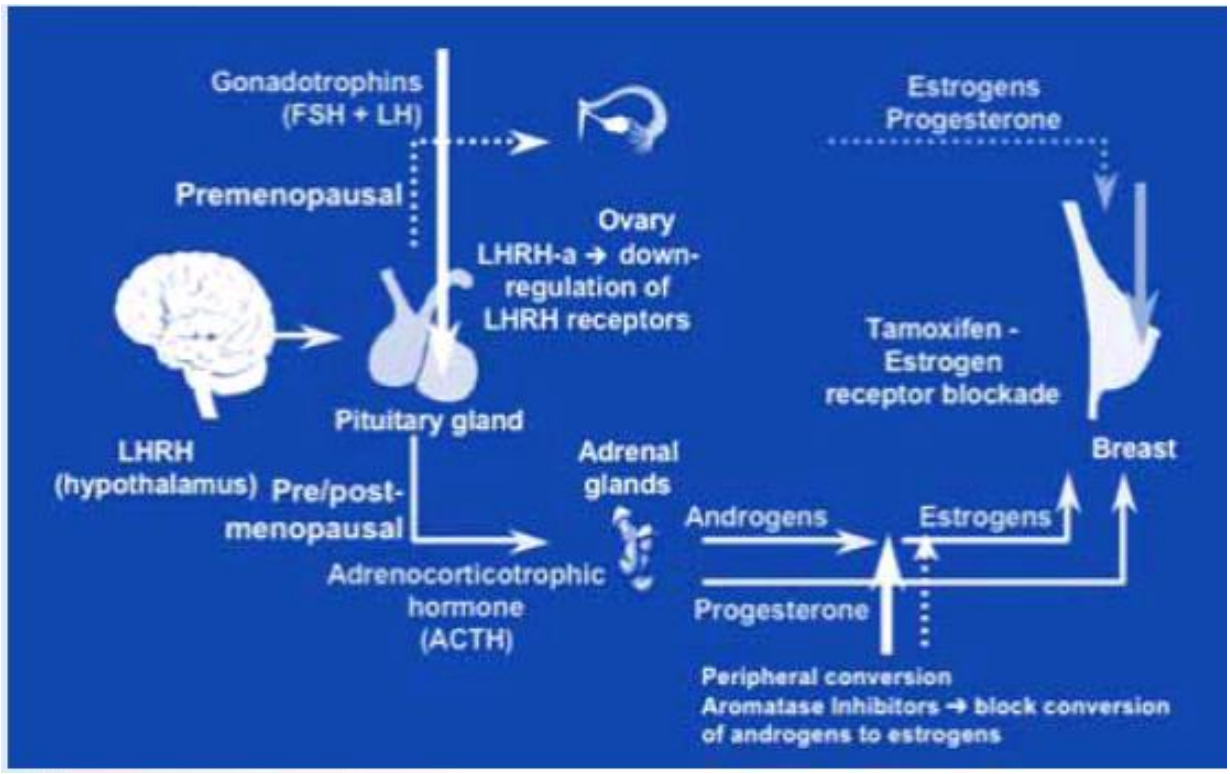
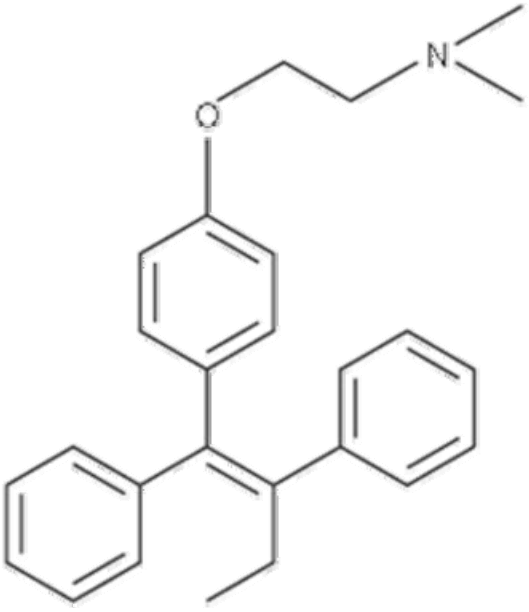


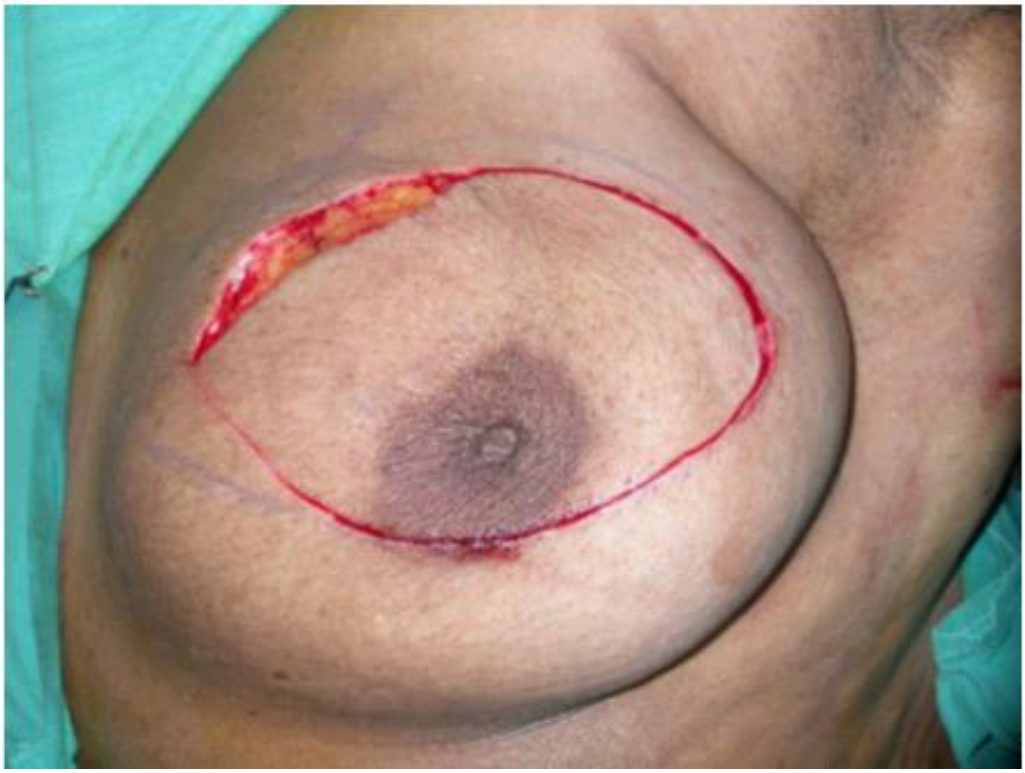
Figure : Carcinoma breast stage distribution in our study population.



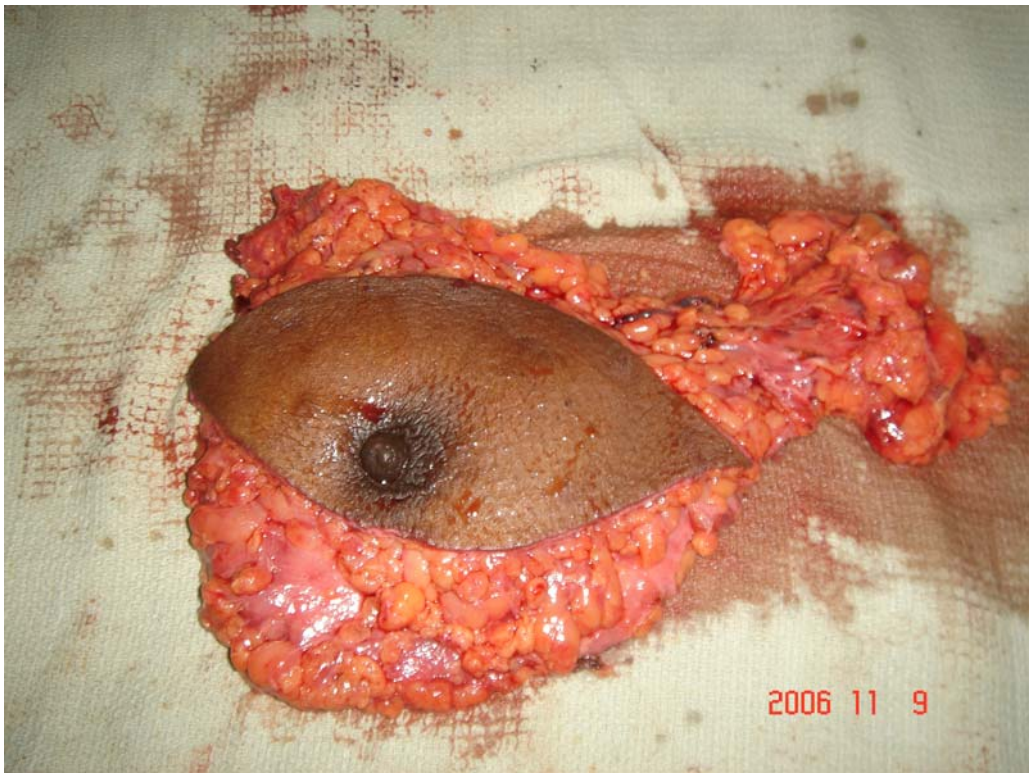
HORMONAL MANIPULATION IN CA BREAST



TAMOXIFEN

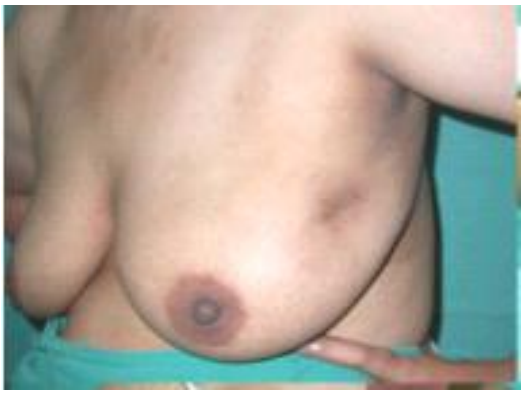
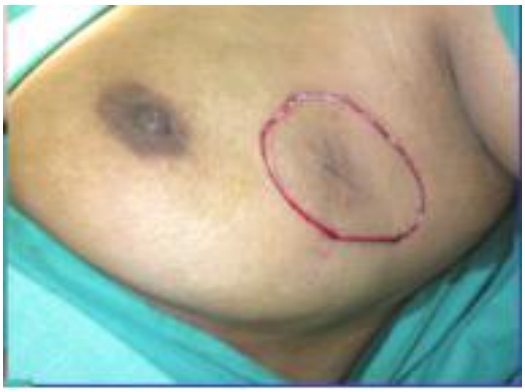
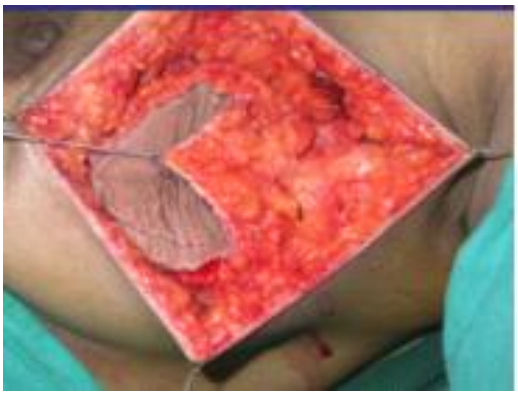
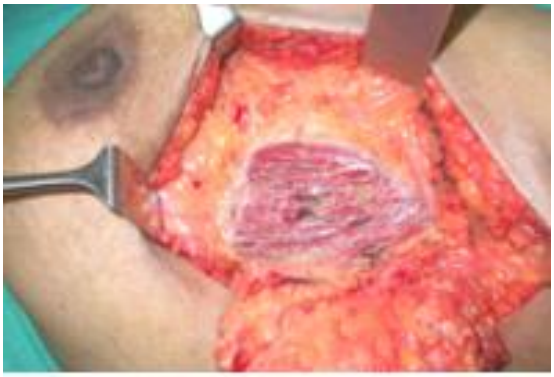
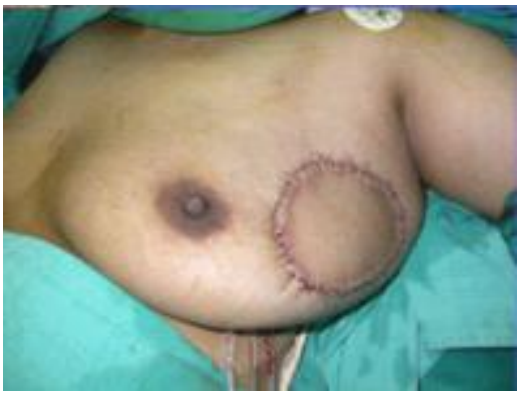
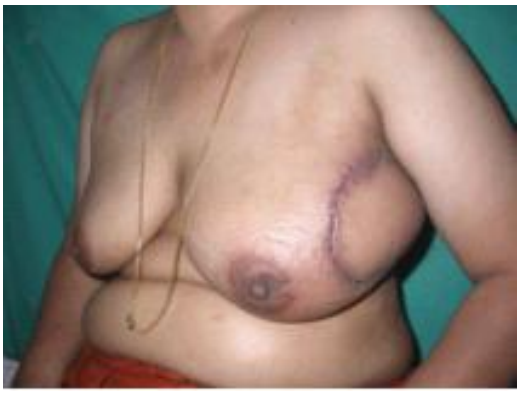


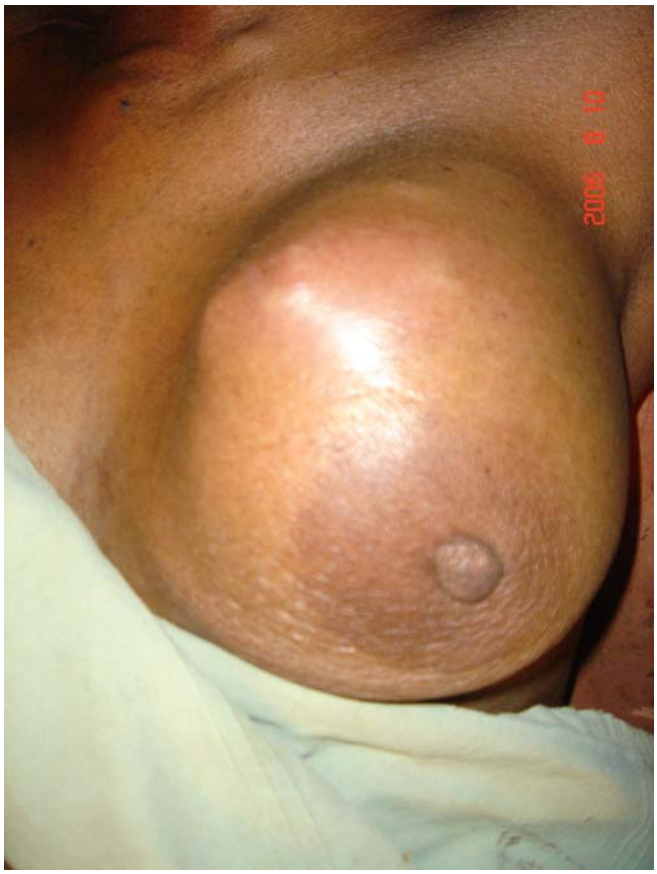
STANDARD INCISION FOR MRM



SPECIMEN OF MRM

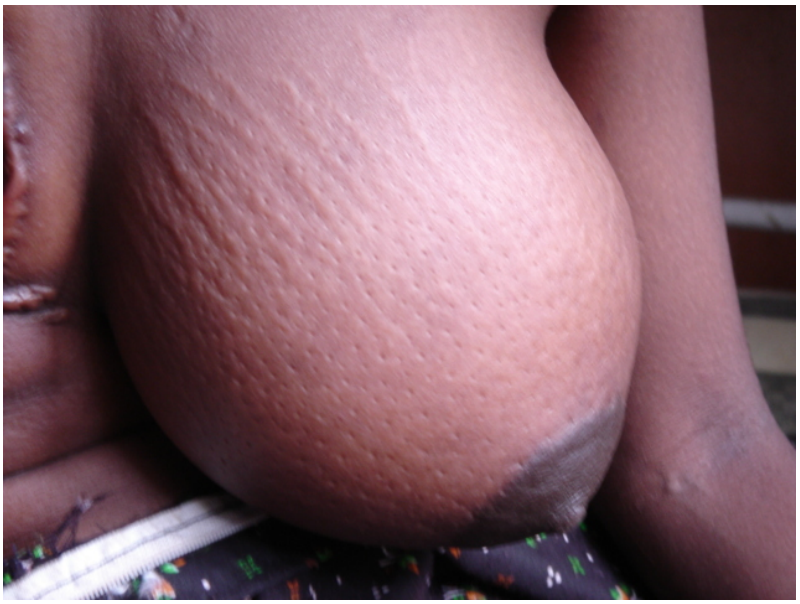
BCT + RECONSTRUCTION

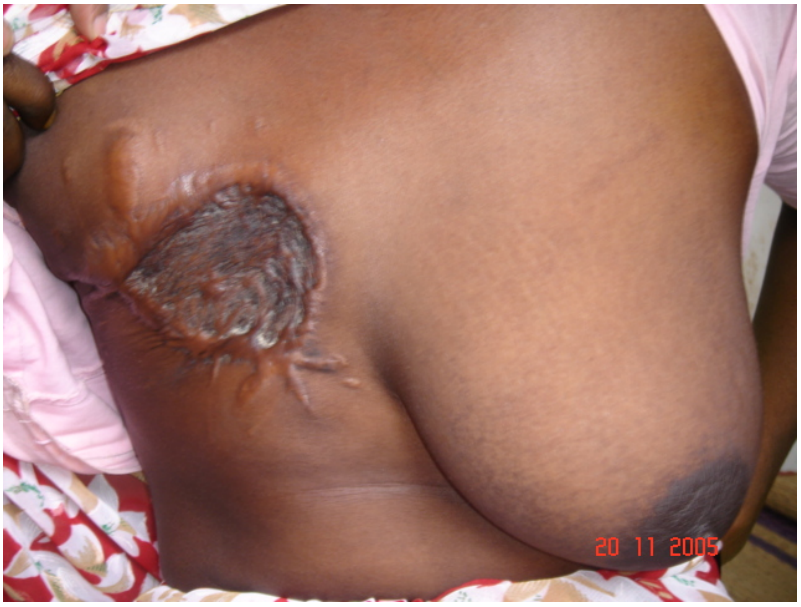


T 4 tumour – shiny skin +

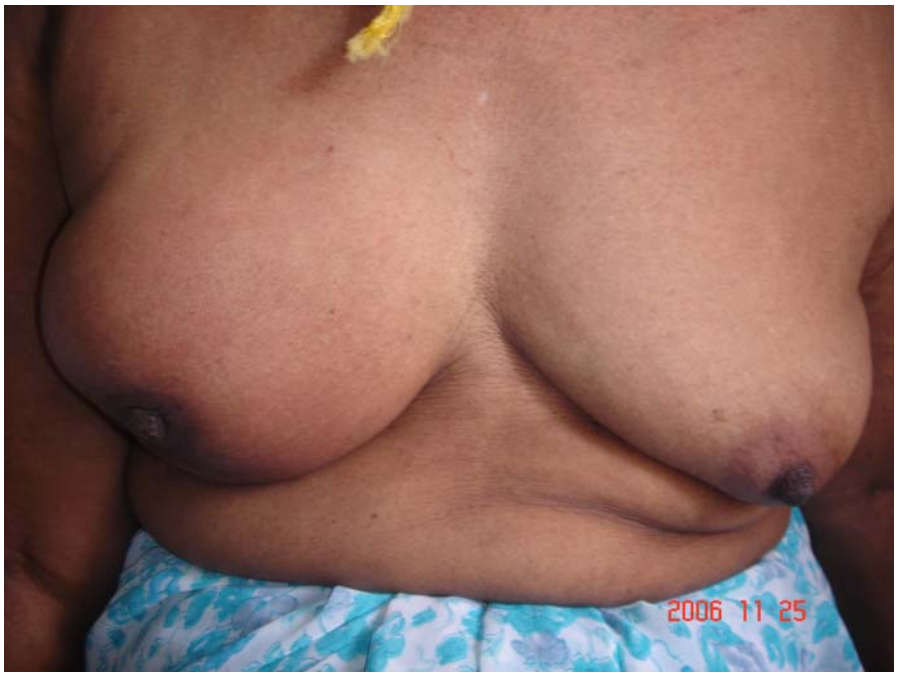
Fungating carcinoma (T4c)



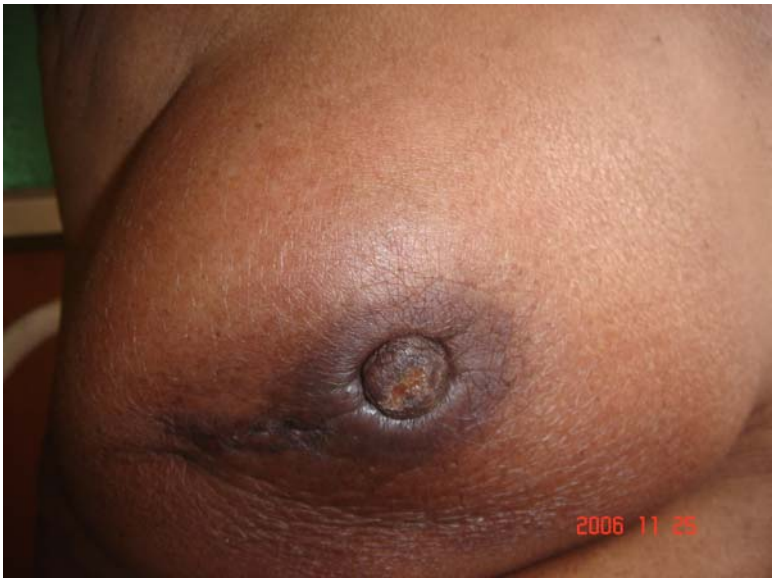
Inflammatory breast carcinoma



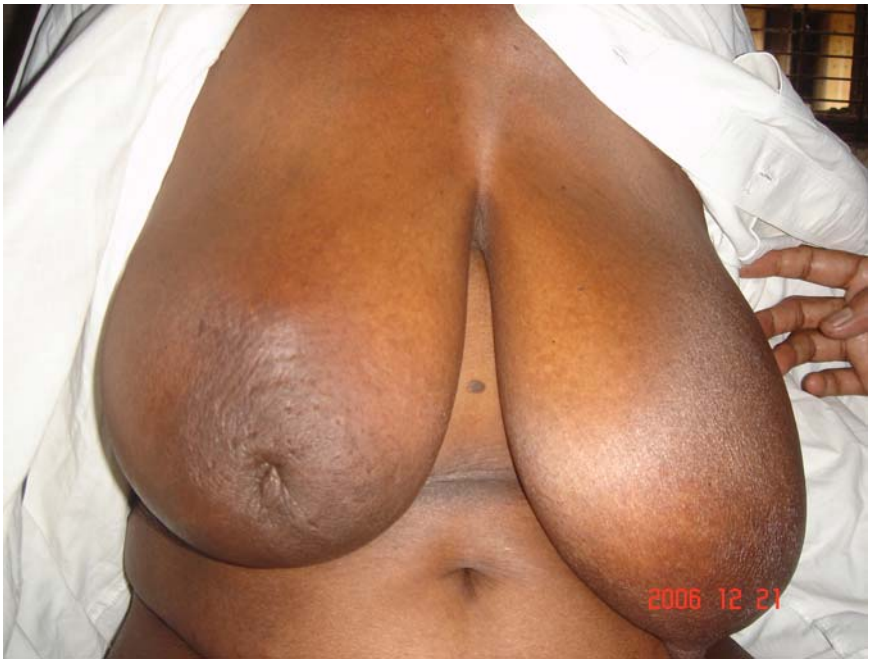
After chemotherapy



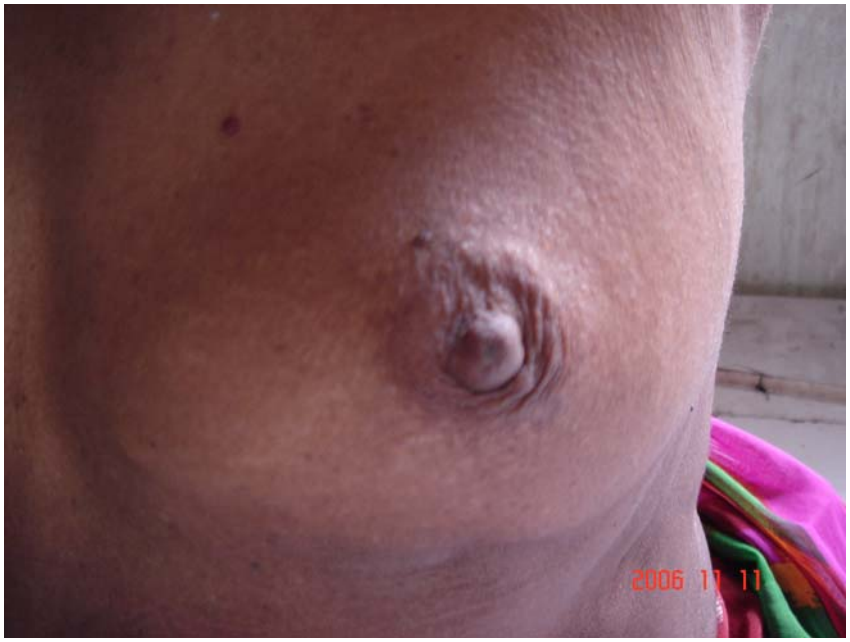
T4b tumour



Nipple retraction

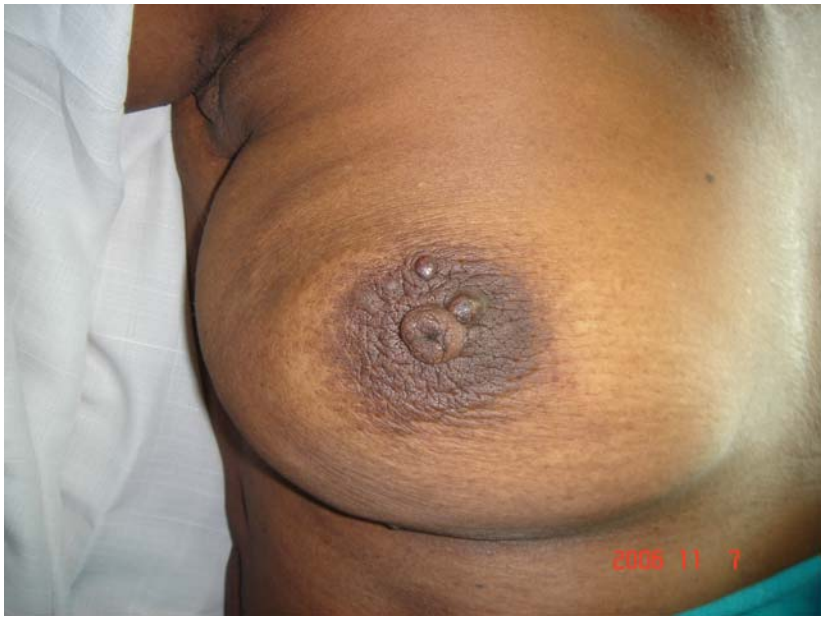


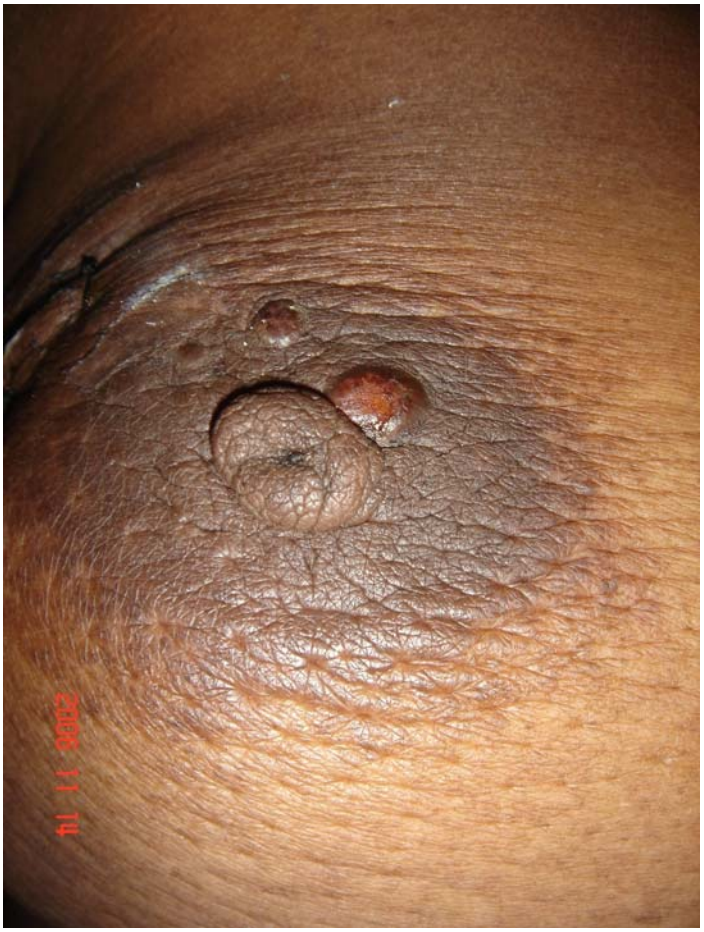
Nipple inversion



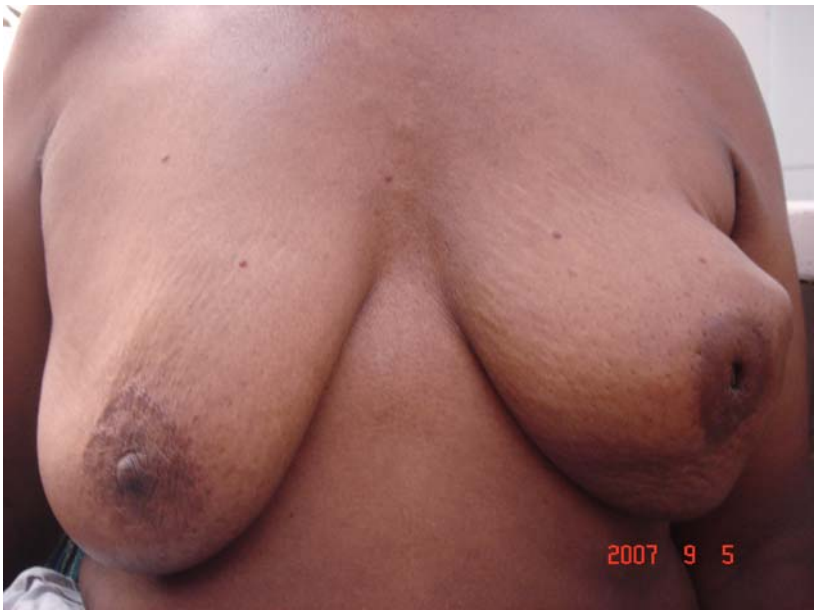
T3 tumour

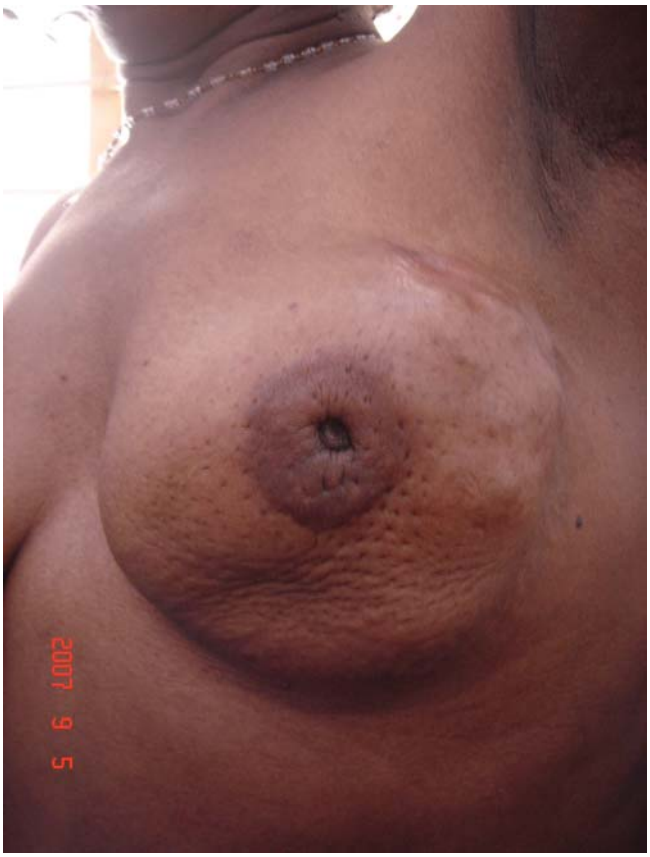
SATELLITE NODULES +



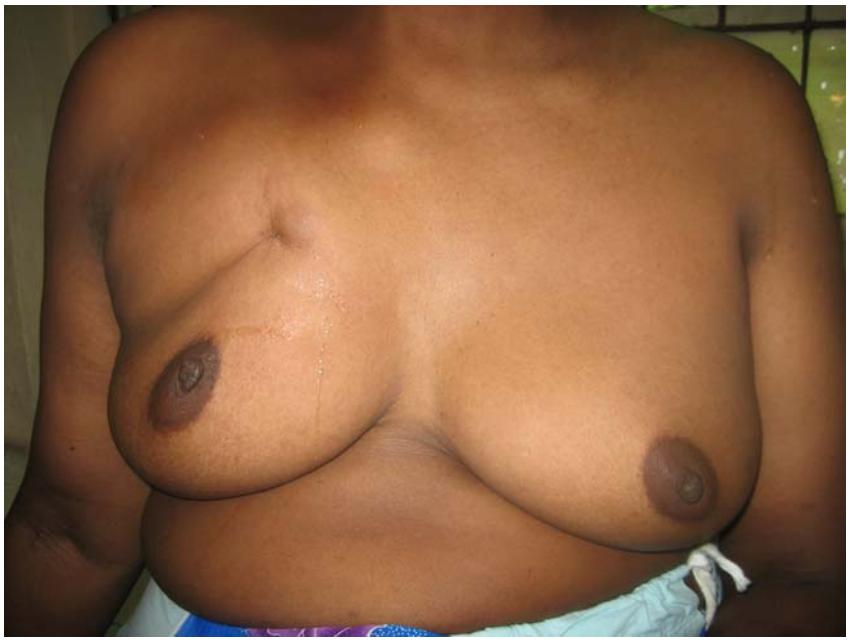


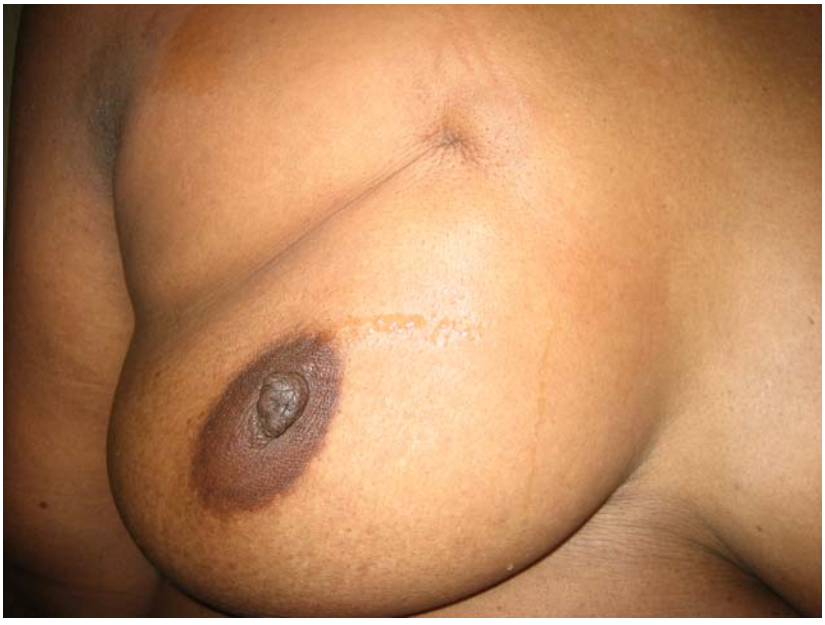
PEAU D’ ORANGE



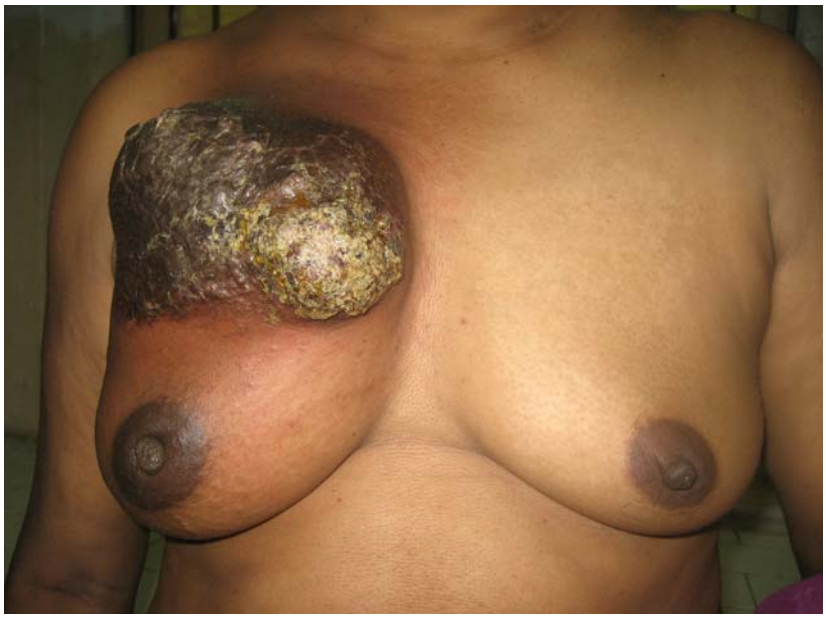


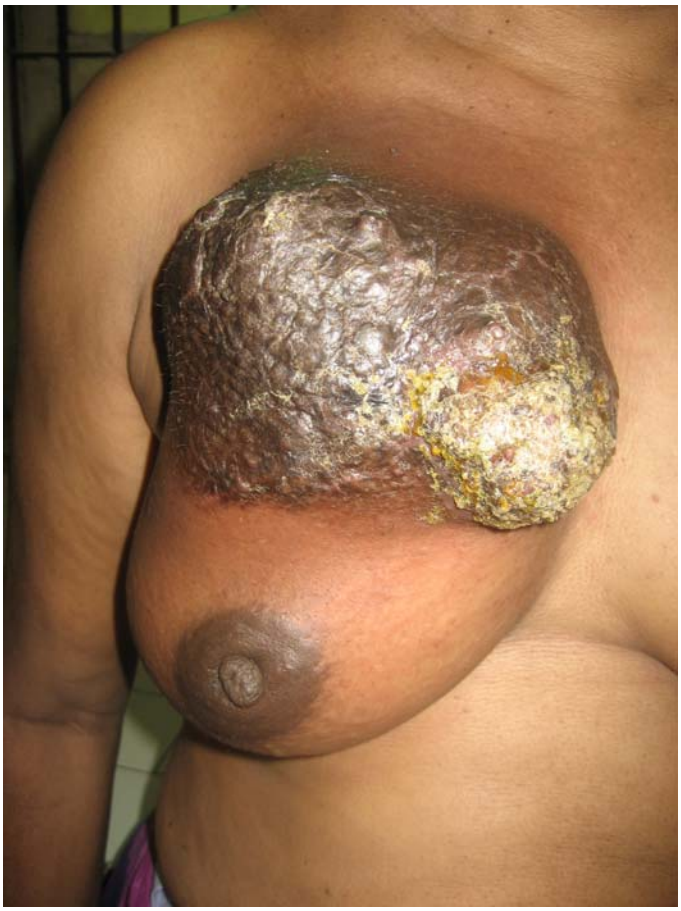
T4A(CHEST WALL FIXITY)



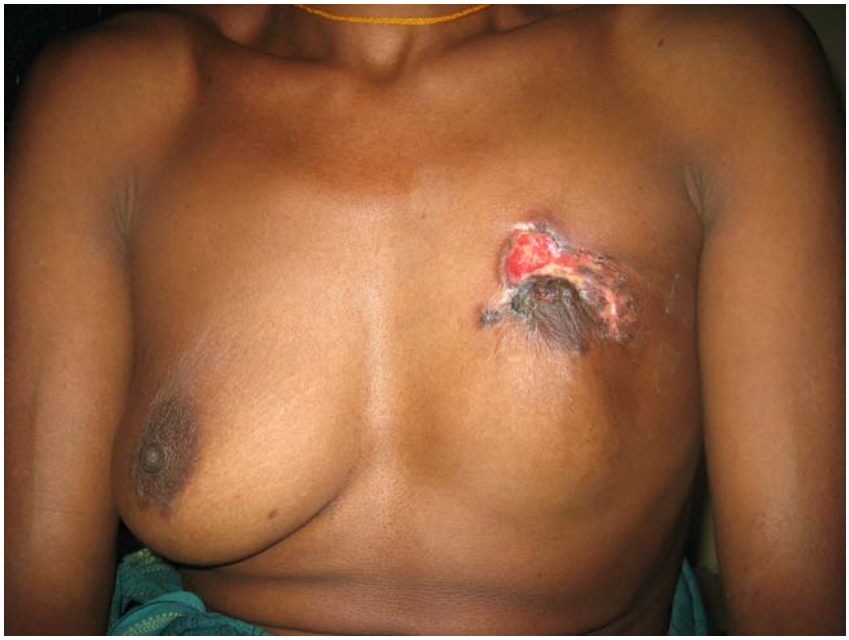


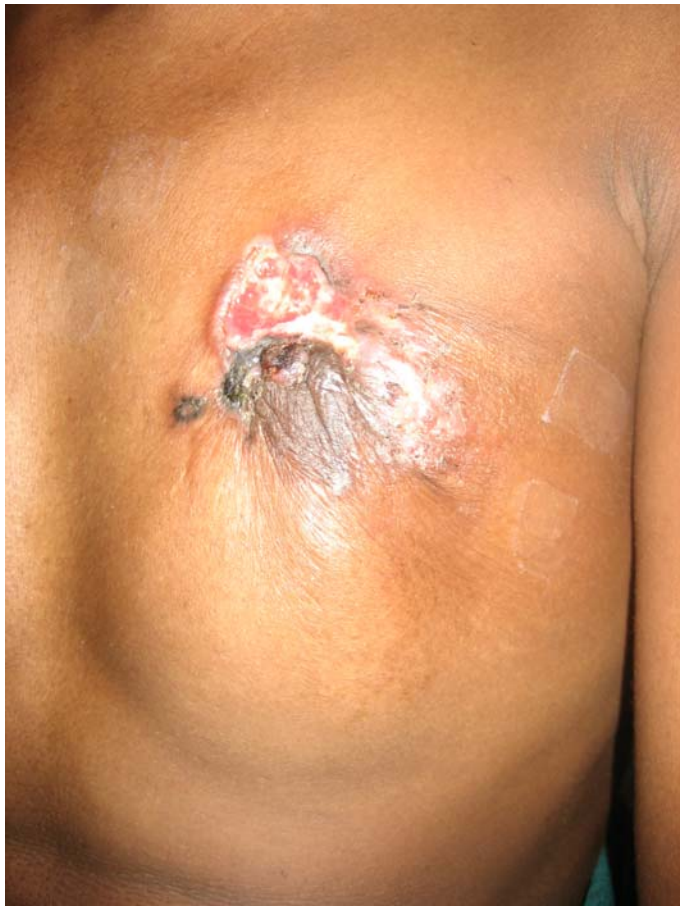
LABC AT ITS WORST !



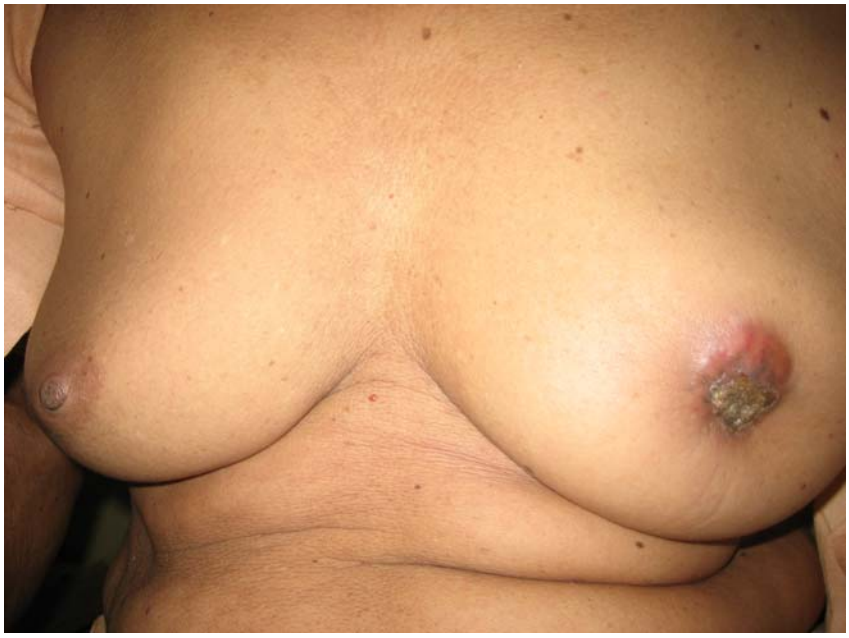


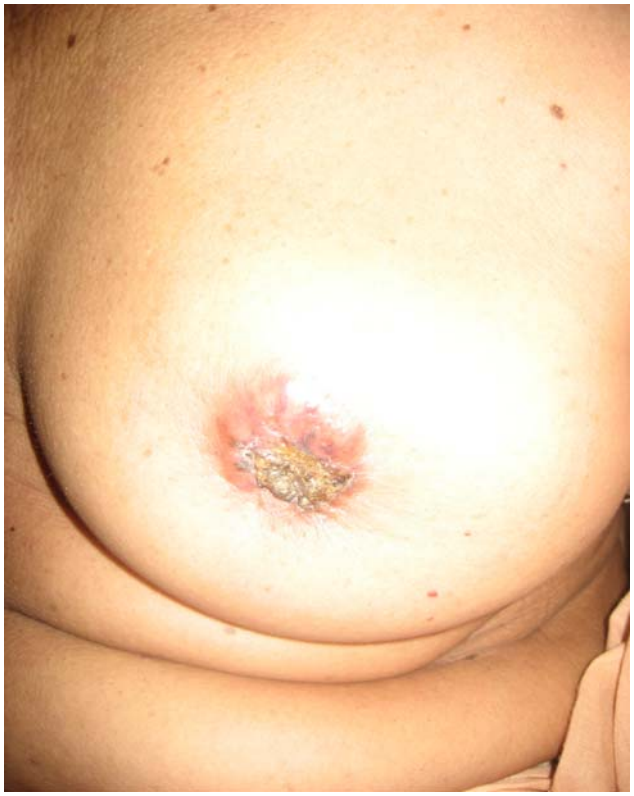
ULCERATIVE MALIGNANCY





NIPPLE DESTRUCTION





ABBREVIATIONS USED

LABC – Locally advanced breast carcinoma

IBC – Inflammatory breast carcinoma

MRM – Modified Radical Mastectomy

SSM – Skin sparing mastectomy

BCT – Breast conservation surgery

NSSM – Non skin sparing mastectomy

AJCC – American joint committee on cancer

ASCO –American society of clinical oncology

NCCN – National cancer comprehensive network

BHGI – Breast health global initiative

VRAM – Vertical rectus abdominis myocutaneous flap

TRAM – Transverse rectus abdominis myocutaneous flap

CBC – Complete blood count

LR – Local recurrence

CR – Complete response

PR – Partial response

IBR – Immediate breast reconstruction

OS – Overall survival

DFS – Disease free survival

SLNB – Sentinel lymph node biopsy

SERM – Selective estrogen receptor modulator

RT – Radiotherapy

NACT – Neoadjuvant chemotherapy

DNA – Deoxy-ribonucleic acid

EBRT – External Beam Radiotherapy

HPE – Histopathological evaluation

LHRH – Leutinising hormone releasing hormone

FNAC – Fine needle aspiration cytology

LD – Latissimus dorsi myocutaneous flap

MASTER CHART

S.No	Pt	Age	Menopausal	Side	TNM	Stage	Treatment
1	L	54	Post	Rt	$T_3N_1M_0$	III A	MRM +RT+ CT+ Tmx
2	K	50	Pre	Lt	$T_3N_1M_0$	III A	MRM + B/L Oopherectomy + RT + CT + Tmx
3.	S	24	Pre	Lt	$T_{4d}N_1M_0$	III B	CT + B/L Oopherectomy + Tmx
4	S	60	Post	Lt	$T_{4b}N_2M_0$	III B	MRM + CT + RT + Tmx
5	M	52	Post	Lt	TxN_1Mx	IV	Local excision + CT + Tmx
6	V	50	Post	Lt	$T_3N_2M_0$	III B	MRM + CT + RT + Tmx
7	G	41	Post oopherectomy	Rt	TxNxMx	IV	Local excision + CT + Tmx
8	K	55	Pre	Lt	T_3NoM_0	II B	MRM + B/L Oopherectomy + RT + CT + Tmx
9	V	57	Post	Rt	$T_3N_1M_0$	III A	MRM + CT + RT + Tmx
10.	S	40	Post oopherectomy	Rt	$TxNxM_1$	IV	CT + Tmx
11	M	56	Post	Rt	$T_{4b}N_0M_0$	III B	MRM + CT + RT + Tmx
12	P	45	Post	Lt	TxN_0Mx	IV	CT + Tmx

S.no	Pt	Age	Menopausal	Side	TNM	Stage	Treatment
13	N	35	Pre	Lt	$T_4cN_2M_1$	IV	CT + Tmx
14	G	40	Pre	Rt	$T_3N_1M_1$	IV	CT + Tmx
15	D	50	Pre	Lt	$T_2N_1M_0$	II A	MRM + B/L Oopherectomy + RT + CT + Tmx
16	M	50	Post	Lt	$T_3N_1M_0$	III A	MRM + CT + RT + Tmx
17	R	45	Pre	Lt	$T_2N_1M_0$	II B	MRM + B/L Oopherectomy + RT + CT + Tmx
18	V	42	Pre	Rt	T_2NoMo	II A	MRM + B/L Oopherectomy + RT + CT + Tmx
19	M	55	Pre	Rt	$T_2N_2M_0$	III A	MRM + B/L Oopherectomy + RT + CT + Tmx
20	M	60	Post	Lt	$T_{4b}N_3M_1$	IV	CT + Tmx
21	S	45	Pre	Rt	$T_3N_1M_0$	III B	MRM + B/L Oopherectomy + RT + CT + Tmx
22	M	60	Post	Lt	$T_{4b}N_1M_0$	III A	MRM + CT + RT + Tmx
23	K	60	Post	Rt	$T_{4b}N_1M_0$	III A	SM + CT + RT + Tmx
24	D	50	Post	Rt	$T_{4b}N_1M_0$	III A	MRM + CT + RT + Tmx

S.No	Pt	Age	Menopausal	Side	TNM	Stage	Treatment
25	R	40	Pre	Lt	$T_3N_1M_0$	III A	MRM + B/L Oopherectomy + RT + CT + Tmx
26	J	50	Pre	Rt	$T_3N_1M_0$	III A	MRM + B/L Oopherectomy + RT + CT + Tmx
27	G	70	Post	Rt	$T_{4b}N_1M_0$	III B	MRM + CT + RT + Tmx
28	K	55	Post	Lt	$T_3N_1M_0$	III A	MRM + CT + RT + Tmx
29	J	55	Pre	Rt	TisN0Mo	I	MRM
30	N	55	Pre	Lt	$T_{4b}N_1M_0$	III B	MRM + B/L Oopherectomy + RT + CT + Tmx
31	G	68	Post	Rt	$T_{4b}N_1M_0$	III B	MRM + CT + RT + Tmx
32	J	65	Post	Lt	$T_3N_1M_0$	III A	MRM + CT + RT + Tmx
33	L	40	Pre	Lt	$T_3N_1M_0$	III A	MRM + B/L Oopherectomy + RT + CT + Tmx
34	M	63	Post	Rt	$T_{4b}N_1M_0$	III B	MRM + CT + RT + Tmx
35	P	70	Post	Lt	$T_{4b}N_2M_0$	III B	MRM + CT + RT + Tmx
36	R	50	Pre	Rt	$T_{4b}N_1M_0$	III B	MRM + B/L Oopherectomy+ CT + RT + Tmx

37	S	45	Post	Rt	$T_{4b}N_1M_0$	III B	MRM + CT + RT + Tmx
38	C	35	Pre	Lt	$T_{4c}N_1M_0$	III B	MRM + SSG +B/L Oopherectomy+ CT + RT + Tmx
39	K	61	Post	Lt	$T_{4b}N_3M_1$	IV	CT + Tmx
40	M	51	Post	Lt	$T_{4b}N_1M_0$	III B	MRM + CT + RT + Tmx
41	M	55	Post	Rt	$T_{4b}N_1M_0$	III B	MRM + CT + RT + Tmx
42	G	50	Post	Lt	$T_{4c}N_1M_0$	III B	SM + CT + RT + Tmx

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