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Early Breast Cancer

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Abstract: The management strategies for breast cancer have undergone revolutionary changes with increased frequency of early detection, thanks to advanced imaging modalities. The effort is more and more towards the preservation of form and function without a compromise in oncologic principles. Breast conservation surgery has evolved with the advent of newer adjuvant modalities. The concept of early breast cancer and its recommended management protocol is discussed in this overview on early breast cancer.

Keywords: *Early breast cancer, breast conservation therapy (BCT), axillary lymph node dissection, sentinel lymph node biopsy.*

Definition

According to AJCC staging system the term early breast cancer includes patients with breast cancer of

Stage I	T1N0M0	**Stage II**	T1N1M0
			T2N0M0
			T2N1M0

Why is this terminology needed?

As per the National Institute of Health consensus development conference on treatment of early breast cancer[1]; breast conservation (BCT) is an appropriate method of primary therapy for a majority of patients with early breast cancer. The recommended technique for BCT includes wide local excision of primary tumor with clear margins, at least level I and II axillary clearance and total breast irradiation. The scientific basis for BCT is based on the results of prospective randomized trials comparing BCT and total mastectomy with axillary clearance. These studies have demonstrated equivalent overall survival rates in both groups with maximum cosmetic results and maintenance of normal function in patients with BCT.

Surgical options

a) Breast conserving surgery i.e. wide local excision with axillary clearance
b) Modified radical mastectomy
c) Mastectomy with breast reconstruction
d) Partial mastectomy with reconstruction

Requirements for BCT

a) Patient's psychological acceptance with emphasis on cosmesis.
b) Breast tumor ratio should be such that in spite of wide excision of tumor, adequate breast tissue be present to give good cosmetic appearance. In general, tumor should be <5 cm in size for BCT.
c) Patient willing to take radiotherapy and come for regular follow-up. This is a very important factor in our setup, as follow-up rates at most centers (even with special breast cancer clinics) are unsatisfactory.

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Contraindication of BCT

Absolute Contra indications:

a) First or second trimester of pregnancy
b) Two or more tumors in separate quadrants of breast
c) Diffuse malignant micro calcification
d) History of prior therapeutic radiation to the breast region.

Relative contraindications:

a) Large tumor / breast ratio
b) History of connective tissue disorder
c) Large breast size
d) Tumor location beneath the breast nipple.

Controversies regarding contraindications

There is a controversy regarding whether certain clinical and pathological factors which indicate high recurrence rates should be considered as contraindications for BCT.

a) Younger the patient (<35 years), more aggressive the tumor.
b) Presence of extensive intraductal component (>25% within tumor) and focal positive margins after resection.
c) Breast that is difficult to evaluate by physical examination and mammography (large pendulous breast) should be considered a contraindication for BCT.

However, clinical and/or pathological positive axillary lymph nodes are not a contraindication for BCT.

Treatment of early breast cancer:

Evaluation of the patient

A. Clinical staging and
B. Evaluating for contra indications to Breast Conservative Surgery (BCS) or immediate breast reconstruction

Clinical staging should include:

1. Clinical evaluation and
2. Investigations

Most important components of clinical evaluation are:

(1) Breast mass (2) Skin changes (3) Nipple changes and (4) Nodes

In the breast mass it is important to exactly measure the size of the lesion, its location and distance from the nipple, consistency and fixation to skin, chest wall and pectoral muscles.

In the skin changes special examination is made about edema and erythema of skin, dimpling satellite nodules and ulceration.

In the nipple note should be made of its retraction, discoloration, erosion or any discharge (color, location of discharge).

In the nodes, the axillary, supraclavicular and infraclavicular nodes should be examined and mention be made of their size, number and fixation.

Investigations

1. Bilateral 2 view diagnostic mammograms of both breasts.
   Medio lateral oblique (MLO)
   Cranio caudal(CC)
2. Metastatic workup includes LFT and CXR.
3. DCIS patients do not require metastatic workup
4. Bone scan—In stage I and Stage II – only 5% of patients have occult bony metastasis; hence the value of a bone scan is questionable[2,3]. In stage III – 20% of patients have occult bony metastatic, hence a bone scan is recommended in stage III[4,5].
5. Liver scan yield is even lower than bone scan in early breast cancer. Liver scan is advised if LFT's are abnormal[6,7].
6. Pre-operative serum markers are of no value[8].

Halsteadian era (1900-1950) believed that breast cancer spreads in a systematic manner and that lymph nodes were primary filters before blood borne metastasis occurred. [(19)] Hence more and more radical surgeries including extended radical and supraradical mastectomies were later carried out. These showed no change in 10 yrs overall survival but added to the morbidity. In these operations the breast and the underlying pectoralis muscles are sacrificed and regional lymph nodes along with axillary vein to the Halstead's ligament (costoclavicular ligament) are removed.

Fisher[9,10] (from 1950 and onwards) in laboratory animals showed that there were venous lymphatic communications in breast cancer and that microscopic systemic disease is present at the time of presentation, and hence variations in local and regional treatment was unlikely to influence long term cure. The mortality of breast cancer was mainly due to distant spread and that to control distant metastatic disease there was need for adjuvant chemotherapy.

As it became widely known that treatment failure after breast cancer surgery was usually due to systemic dissemination of cancer cells before surgery and was not due to inadequate local operation. Modified Radical Mastectomy came into existence in 1960 & 1970. From 1970 onwards retrospective and prospective studies showed no difference in the overall survival with Radical Mastectomy or Modified Radical Mastectomy. Two forms of MRM are in use by the surgeons the Patey procedure and modifications described by Scanlon & the procedure described by Auchincloss. Patey developed a procedure that preserves the underlying pectoralis major muscle and sacrifices the pectoralis minor muscle to remove axillary lymph nodes. Scanlon modified the Patey's procedure by dividing and not removing the pectoralis minor muscle allowing removal of lateral pectoral nerves to the major muscle. Auchincloss procedure allows ALND by retracting the pectoralis minor muscle.

NSABP (National Surgical Adjuvant Breast Project) trial of Fisher, of patients with mastectomy with or without axillary node dissection, showed that overall survival in both groups was the same even though a large number of patients without axillary nodal treatment presented with axillary metastasis. This presented the first evidence that systemic disease is likely to be present before surgery is performed and doesn't arise from incompletely dissected axillary nodes.

This formed the basis for breast conservative surgery (BCS).

Occult breast cancer

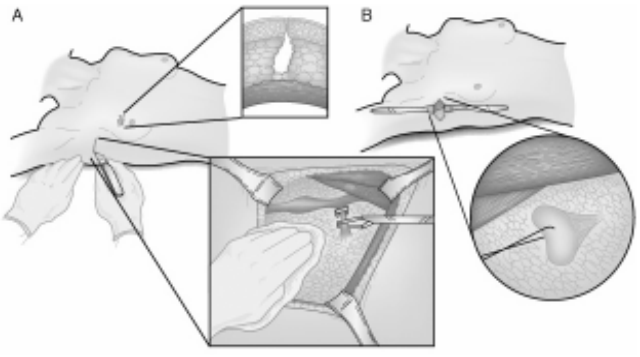
On rare occasions, a breast cancer may present with large axillary glands but without any evidence of primary in the breast. Lloyd and Nash[11] made a retrospective review of T0NIM0 cases at their clinic. They found that in six cases there was evidence of occult breast cancer. Neither mammogram nor ultrasound scans had shown any evidence of suspicious lesion in either breast. Neither patient had undergone MRI of breast. In 1997, at Rotterdam[12], it was concluded that true occult breast cancer is rare in incidence and MRI is investigation of choice in such cases.

NSABP Guidelines for Breast Conservative Surgery (BCS)

Major goal of BCS is to have cosmetically acceptable breast with resection of tumor and reasonable amount of normal breast tissue around it so as to get negative microscopic margins.

Incision and Flaps

- Incision should generally be placed directly over the tumor even for a mammographically detected lesion.
- Circumareolar incisions shouldn't be used.
- Incisions should be curvilinear or transverse both in the upper and lower quadrants. There is no need to remove the skin except for superficial tumors.
- Subcutaneous fat should be preserved.
- Haemostasis should be adequate to avoid distortion and follow up evaluation.
- Best cosmetic results are obtained by not putting in a drain.
- Incision should preferably be closed by a subcuticular stitch.



Breast - conserving surgery. A, Incisions to remove malignant tumors are placed directly over the tumor, without tunneling. A transverse incision in the low axilla is used for either the sentinel node biopsy or the axillary dissection. The axillary dissection is identical to the procedure in a modified radical mastectomy. The boundaries of the operation are the axillary vein superiorly, the latissimus dorsi muscle laterally, and the chest wall medially. The inferior dissection should enter the tail of Spence (the axillary tail) of the breast. The *inset* shows the excision cavity of the lumpectomy; no attempt is made to approximate the sides of the cavity, which fills with serous fluid and shrinks gradually. **B,** In the sentinel node biopsy, a similar transverse incision is made (it may be located by percutaneous mapping with the gamma probe if radiolabeled colloid is used) and extended through the clavipectoral fascia and the true axilla entered. The sentinel node is located by virtue of its staining with dye or radioactivity, or both, and dissected free as a single specimen.

Preoperative Needle Biopsies and Localization

Subclinical architectural deformities are removed with the aid of preoperative radiograph localization. If a preoperative needle core biopsy is not possible it is better to manage these abnormalities as if they were carcinomas.

1. If after wide local excision, the margins are negative there will be no need for a second procedure. After excision the specimen is sent for radiography to see the adequacy of excision.
2. If margins are positive, the proper markings and handling of the specimen by the pathologist will enable the surgeon to revise the excised area with little sacrifice of further tissue.

Radiation therapy

As stated earlier, BCS involves wide lumpectomy followed by ERT. Radiotherapy with linear accelerator is considered ideal with limited radiation to lung volume. Whole breast dose is in the range of 45-50 Gy given at 1.8- 2 Gy / day.

To boost or not to boost?

Delivery of boost dose to primary site increases the probability of local tumor control. Recht and Harris[13] discussed the rationale for administration of a boost dose to a limited volume of the breast that could reduce the incidence of local recurrence. Tumor bed boost can be administered to all patients undergoing BCT except those with tumor <1 cm with tumor free margins of 2 cm or following Quadrantectomy. Doses range between 10-20 Gy depending the tumor size and status of excision margins. Tumor bed boost can be administered by electron beam therapy or interstitial brachytherapy.

Preoperative Chemotherapy

NSABP trial of B-18[13] where preoperatively Adriamycin and Cyclophosphamide was given to one arm confirmed that the preoperative chemotherapy would shrink the tumor to make BCS possible more frequently and that lymph node involvement was down staged no difference was demonstrated in disease free survival or overall survival.

Summary of Breast Conservative Surgery (BCS)

The 1992 NIH Consensus Development Conference reported that "Breast Conservation Treatment is an appropriate method of primary therapy for the majority of women with stage I and II breast cancer and is preferable because it provides survival equivalent to total mastectomy and axillary dissection while preserving the breast"[15].

Surgeons should balance the cosmetic factors with techniques required for good local control. The primary concern should be adequate removal of the primary tumor with histologically negative margins.

Adjuvant Systemic Therapy

Most data indicate that adjuvant CT and or hormonal therapy in stages I and II diminish local recurrence rates compared to those not receiving adjuvant treatment. But that long term survivals and distant metastasis is not affected whether women had BCS or mastectomy.

Indications for Post op Radiation therapy

Postoperative Radiation refers to the irradiation of chest wall and / or draining lymph nodes regions used as an adjuvant treatment following definitive mastectomy.

Aim of radiation therapy is to prevent loco regional recurrence, which can be hazardous to the patient in two ways

1. psychologically; 2. recurrence besides being the persistent site for cancer can also be the source of distant metastasis.

Note:- (1) Though RT is routinely not indicated in patients with uninvolved axillary nodes except when there is a clear evidence of positive margins especially at the depth. A recent trial (16) concludes that omission of radiotherapy was associated with a increase in risk of ipsilateral breast tumor recurrence and with a small increase in patient mortality. (2) In patients with involved axillary nodes especially when more than 4 nodes are involved, ERT will greatly reduce the incidence of local recurrence and may improve overall survival in premenopausal patients. (3) Patients with 10 or more positive nodes treated with high dose chemotherapy routinely receive post operative ERT following completion of chemotherapy. This is to reduce a high early local failure rate when patients were not irradiated.

Management of Axilla in early breast cancer

Axillary dissection of lymph nodes has following benefits:

a) To stage the disease accurately
b) Local control of tumor in the axilla
c) Prognostic significance
d) To provide a rational basis for subsequent systemic therapy.
e) To increase the likelihood of cure —→ ? Survival benefit.

Axillary dissection is principally a prognostic rather than therapeutic procedure. A number of studies were undertaken to determine the extent of axillary surgery needed to determine

whether nodes were positive. Many of the studies examined likelihood of skip metastasis i.e. involvement of level III nodes in the absence of involvement of level I or II and involvement of level II nodes in the absence of involvement of level I. The conclusion from these studies is that removal of both level I and II is required as it is effective in providing local control in the axilla and provides enough nodes for prognosis[17].

Note:- (i) 5 years probability of an axillary recurrence is about 20% in patients with no nodes examined and about 10% when one or two negative nodes are removed. It is thus recommended that more than ten nodes be removed to avoid misclassification and to void local recurrence. This normally would involve level I and II axillary nodal clearance. (ii) Axillary nodal clearance at level I and II, also called 'partial axillary lymph node dissection' (ALND), involves removal of axillary nodes superior to the level of the axillary vein, lateral to the latissimus dorsi muscle and medially to the medial border of the pectoralis minor muscle. Long thoracic nerve, which supplies serratus anterior, should be saved. Thoracodorsal nerve with its vein and artery should also be preserved if possible.

Complications of ALND

Major complications of injury or thrombosis of axillary vein for ALND are few. Minor complications of seroma formation, shoulder dysfunction, loss of sensation in the underarm and upper arm, and edema of the arm and breast are common.

Recent developments have led to the change in philosophy of axillary dissection under some special circumstances. Breast cancer with low risk of axillary involvement could be spared the axillary dissection. Tumors with microinvasive cancers, tubular cancers and DCIS have axillary metastasis in less than 5%. At present DCIS, DCIS with microinvasive element and pure tubular cancers less than 1 cm can be spared the axillary dissection.

Sentinel lymphnode biopsy (SLNB) (18)

Sentinel node technique has the potential to allow the axillary dissection to be carried out in those with positive nodes and leave out the ones with negative nodes. Morton described the 'Sentinel node' as the first lymph node to receive lymphatic drainage from a tumor. Sentinel lymph node is the first lymph node in the ipsilateral axilla or internal mammary chain to drain the tumor in the breast. The sentinel lymph node is usually located by the injection of technetium radio labeled sulfur colloid, isosulfan blue dye, or both. If radio labeled colloid is used, the node in the axilla is located using a handheld gamma detector. If only blue dye is used then the node is detected by meticulous dissection into the axillary space until a blue stained node or afferent lymphatic is located. Several studies have shown that SLNB reliably predicts the status of axillary nodes. If histopathological examination is negative then axillary dissection can be spared. But in the presence of positive sentinel lymph node current medical practice dictates additional treatment to axilla. This is most commonly performed with a completion level I & Level II axillary dissection. In a recent randomized control trial (19) the efficacy and safety of sentinel lymph node biopsy was tested. A total of 516 patients with primary breast cancer in whom T < 2 cm in diameter were randomized either to sentinel lymph node biopsy and total axillary dissection or to sentinel lymph node biopsy followed by axillary lymph node dissection only if it is positive for metastasis. The authors concluded that sentinel lymph node biopsy is a safe and accurate method of screening the axillary nodes for metastasis in women with small breast cancer.

Contraindications for SLNB

1. Palpable axillary lymphadenopathy
2. Prior axillary surgery
3. Locally advanced disease
4. Pregnant & lactating woman

Aim of SLNB is to minimize the complications & side effects of ALND.

False negative rates: - A review of the published data by Cox and colleagues found a world wide false negative rate of 3.1%.

Interpretations Nodal metastasis is termed macro metastasis if the tumor deposit is larger than 0.2cm and micro metastasis if the deposit is 0.2 cm or smaller. If each node is sliced every 0.2 to 0.3 cm, and then stained with Hematoxylin & Eosin (H&E), all macro metastasis are detected though micro metastasis may be missed. This is the method currently recommended by the college of American Pathology.

In the future axillary dissection might be avoided in patients who have no metastatic involvement of the sentinel node.

Radiotherapy to the axilla

A total dose 30 to 70 Gy is generally used. The mean dose is usually 50 Gy. Most fractionation schemes employ daily doses of 1.8 – 2 Gy over six weeks. Axillary RT is generally considered a treatment option only for the patient with clinically impalpable nodes. NSABP B-04[21] and Institute Curie[20] trials have compared Radical Mastectomy, Mastectomy with RT to axilla/chest, and Mastectomy alone. At 10 years there was no significant difference between the groups that did and did not receive RT with respect to overall survival or local recurrence in the axilla. This study suggested that ALND and RT are equally effective treatment options in clinically node negative patients. The trial also suggested that delayed treatment of the axilla does not adversely affect breast cancer survival. These trials assert that "Axillary lymph node metastasis are an expression of bad prognosis rather than a determinant of overall survival". The biggest disadvantage of treating the axilla with ERT is that the prognostic significance of axillary nodes is lost forever.

35 to 40% of patients with clinically detected invasive breast cancer proved to be node positive following ALND. Although the extent of ALND seems to have no effect on breast cancer mortality, it does influence the risk of axillary relapse. Greater the extent of ALND, lesser the risk of axillary relapse. Following a level I and II dissection the risk of recurrence is reduced to 1-2 % while for level I ALND the risk of recurrence is more than

10%.

Summary of axillary treatment

Treatment of axilla with either ALND or radiotherapy remains an integral part of the management of patients with invasive breast cancer. The issue of survival benefit of axillary treatment remains controversial. Axillary node dissection is an effective staging procedure and is essential for local control of disease in the axilla.

With breast cancer awareness, routine mammography and early detection of cases, less and less number of patients is node positive and hence many undergo unnecessary nodal dissection and the associated morbidity. Hence SLNB may eventually prove to be a preferred alternative to routine ALND. It must first be demonstrated that SLNB (without completion ALND) doesn't adversely affect out come.

Patients with DCIS, DCIS with micro invasion and pure tubular carcinomas less than 1 cm in size need not have axillary dissection. All other patients require level I and II axillary dissection to prognosticate, to design adjuvant chemotherapy and to change the type of chemotherapy and to enter into high dose and newer chemotherapy trials.

Sequencing of systemic and radiation therapy in patients with mastectomy

The integration of adjuvant chemotherapy and RT is also controversial. Initial RT may inhibit the ability to administer full doses of chemotherapy hence modification of drug doses is required as RT reduces lymphocytic counts significantly and also causes cardiac toxicity. RT given after chemotherapy reduced the risk of local recurrence to a level comparable with that seen with immediate post-operative RT. Hence there is support for the use of RT after completion of adjuvant chemotherapy. **Hence post operative RT is not indicated in patients with uninvolved axillary lymph nodes except when there is evidence of disease extending beyond the deep margins of resection.**

Follow - up

It is extremely important to closely monitor patients treated with BCT, because early detection of a local recurrence may allow for another wide excision or a total mastectomy, without significantly comprising the overall survival of the patient. The follow-up protocol followed at most centers is 3 monthly visits to the hospital for the first two years, six monthly till 5 years and yearly thereafter. During the visit clinical evaluation is performed to detect any loco regional or systemic disease. Periodic self examination during the intervening period should also be emphasized. The optimal interval for follow-up mammography is not clear. But most centers recommend a baseline mammogram within 6 months after completion of treatment and bilateral mammograms every 6 months or yearly for the first 2-3 years and yearly thereafter. If there is strong evidence of suspicious micro calcification or masses, or architectural distortions of the breast after BCT, a biopsy should be performed to rule out recurrence. At times, these patients are difficult to evaluate. Post treatment hematomas, fat necrosis, seromas, cysts, and scar tissue pose difficult diagnostic dilemmas. Close coordination between surgeon, radiologist and pathologist is essential for optimal management.

In conclusion, careful clinical examination and mammography are critical in the post treatment evaluation of patients of early breast cancer who have undergone BCT. At least yearly evaluation is mandatory even 10 years after therapy because of possibility of late breast recurrences and occasional distant metastasis.

Prevention of Breast cancer

Efforts in the primary prevention of breast cancer will increase as promising information becomes available from prospective studies.

Various drugs available are

a) *Tamoxifen* the real value and its role in the prevention of breast cancer remains unclear because of variations in the outcome of different trials carried out on healthy women. One Italian trial has demonstrated a small risk reduction in favour of Tamoxifen but IBIS[22] study did not demonstrate a difference for invasive breast cancer. It is unfortunate that selection criteria for entry into these studies varied thus explaining the differences in outcome. A meta-analysis[23] of these studies concluded that Tamoxifen if taken for five years is followed by a significant reduced risk of developing breast cancer. Tamoxifen has been authorized by FDA for this purpose.

b) *Raloxifene* Like tamoxifen, raloxifene is a selective oestrogen receptor modulator (SERM). If taken for eight years [24] it reduces the risk of breast cancer in women with osteoporosis, the group in which it was studied. In one trial 1% of the women on raloxifene developed breast cancer during that time compared with 1.6% of women on placebo group showing a risk reduction by 59%.

Genetic Predisposition and prophylactic surgery

Although it seems certain that prophylactic mastectomy and/or oophorectomy will not be the ultimate answer in preventing cancer in these organs for people carrying gene mutations, it is likely that these surgeries will be carried out in the foreseeable future where the indications for such interventions becomes better defined. At present criteria for gene testing include a family history in which (1) Three cases of breast or ovarian cancer have been identified in the first degree relatives, one of whom has been diagnosed when under 50 years of age (2) Where two cases of breast or ovarian cancer have been identified in the first-degree relatives, one of whom was under 40 years of age at diagnosis. (3) Where breast or ovarian cancer occurs in a woman under 30 years of age.

Various probability models have been described for BRCA 1 or BRCA 2 mutations[25,26] the risk of cancer developing by the age of 70 years in mutation carriers with BRCA 1 is 65% for breast cancer and 39% for ovarian cancer. For carriers of BRCA 2 the risk of developing breast cancer is 45% and is 11% for ovarian

cancer by the age of 70 years. The risk is larger if the index cancer patient is younger than 35 years. In a prospective study of BRCA 1 carriers with and without prophylactic mastectomy followed for five years, 187 patients underwent a surveillance policy and 23 of them developed breast cancer and two of them died[27].

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