

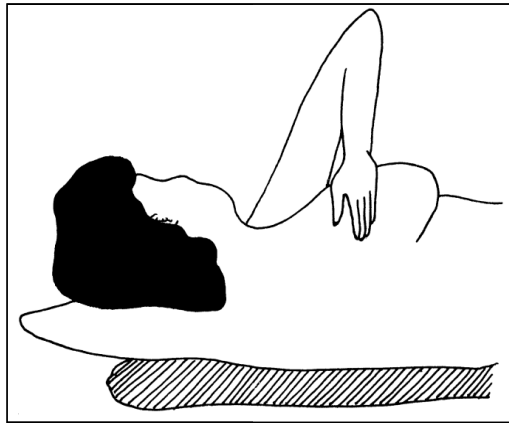
**Chapter 3**  
**Staging of Breast Cancer**  
**and end result of therapy**

**B**reast examination is an essential component of the evaluation of the patient with Breast Cancer.

### **The Technique of Breast Self-Examination**

The physician has to teach his patient, before anything else, the careful breast inspection at the mirror. Many women have inequality in the size of the breasts and they may discover it for the first time, when they inspect their breasts. Asymmetries of the contour, dimpling of the skin, chronic redness and thickening of the nipple epithelium or erosion of its surface have to be looked for. Nipple inversion, especially if difficult to be erected, is an important sign of malignancy, and the same for spontaneous serous or bloody discharge.

The woman should lie supine on bed, with a small pillow placed under the shoulder. This flattens her breast, making palpation of the lateral half much easier. At the supine position, palpation begins with the flat of the fingers of the opposite hand (Fig. 4.1). The whole extent of the inner half of the breast is explored by transverse movements; extending from the nipple line to sternal edge and from the clavicle to the inframammary fold.



**Figure 3.1.**

On examining the outer half, the examining hand starts at the inframammary fold ascending to the axilla and in transverse lines. It is better to discourage women to palpate their breasts in a sitting position. In the erect position, the lower dependent half is folded upon itself and small tumors might be masked.

Haagensen advised women who do not want to practice breast self-examination and are at a high risk of developing cancer (positive family-history, gross cystic disease, multiple intraductal papilloma and those who have had carcinoma in one breast) to go, regularly, every four months, to be breast-examined by a physician, who is skilled in that field.

## **PHYSICAL EXAMINATION OF THE BREAST**

### **Inspection of the Breast**

Good light is needed. Inspection has to be done first with the patient's arms at her sides and then high above her head. Redness, ulceration, edema, dilated veins and surface erosion have to be looked for.

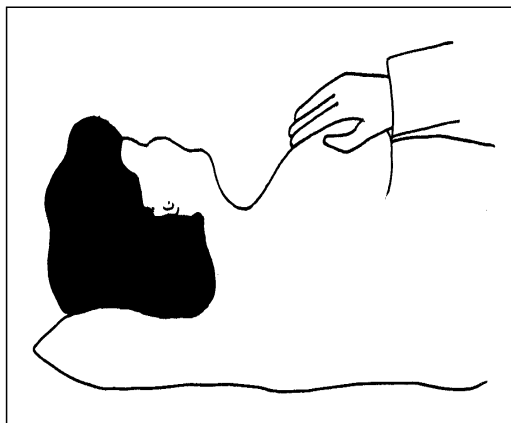
Changes in the nipples such as deviation, flattening, retraction and inversion are signs of diagnostic importance. The fibrosis in and about the lesion pulls on the duct system and tilts the nipple.

### **Palpation of the Breast**

The patient is asked to lie supine on the examining table. The nipple has to be examined first for thickening, redness or erosion. Sometimes, there is a pre-erosion stage that begins with slight reddening of its epithelium.

Next, place the nipple between your index finger and thumb and gently apply pressure to elicit discharge. Palpation has to be started over the medial half of the breast, better with the patient's arm above the head to tense the pectoral muscles (Fig. 4.2).

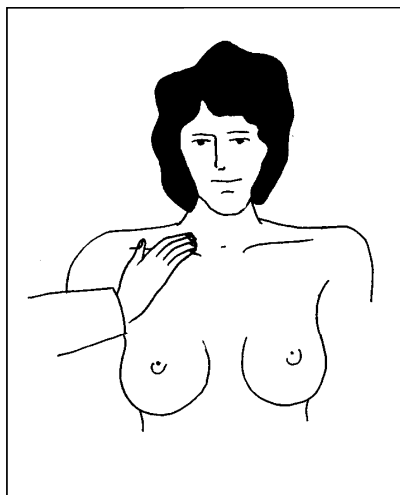
Palpation of the lateral half of the breast is best carried out with the patient's arm at her side, so it lies more caudal and its lateral half is more accessible to palpation. Note the general characteristics of the breast: smooth, granular or nodular. Any mass has to be recorded and checked whether it is fixed to the skin or pectoral fascia. Also press together the skin to elicit dimpling or flattening.



**Figure 3.2.**

**Supraclavicular and Axillary Regions**

The patient sits on the examining table, in front of the physician. He must search for the sentinel nodes at the confluence of internal jugular and subclavian veins; hidden deep behind the medial end of the clavicle. Laterally situated nodes are more superficial and usually involved by retrograde permeation from the sentinel nodes (Fig. 4.3).



**Figure 3.3.**

For examination of the axilla (Fig. 4.4), the examiner supports the patient's arm by his own hand to relax the pectoral muscles. The number, consistency and movability of axillary nodes should be noted; also their diameter in centimeters. In obese patients, axillary palpation is difficult. Palpation of both axillae is essential.

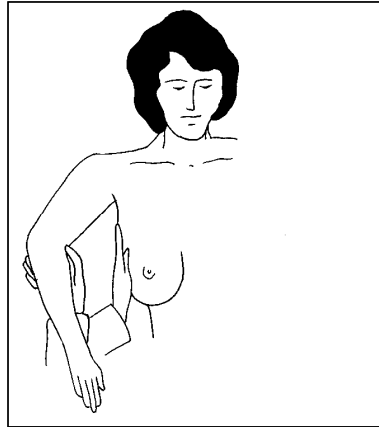


Figure 3.4.

### **DIAGNOSIS OF BREAST CANCER**

Different breast lesions commonly appear in patients in certain age groups. Cancer of the breast is unusual under the age of thirty. Nevertheless, all symptomatic women are suspect. The longer the delay in diagnosis and treatment of breast cancer, the more ominous is the outlook for survival.

Clinical examination remains indispensable for detection and clinical staging of breast cancer. Detectability increases with the increase in mass size and with care given in examination. The overall diagnostic accuracy of physical examination does not exceed 75%.

A lump or mass in the breast is the most common initial sign of mammary cancer. The mass is not always painless, Donegan, in 1979, reported that about 15% of cancers are painful. The upper outer quadrant of the breast is the most common site for mammary carcinoma.

Nipple discharge, particularly the serosanguineous type is an occasional sign. Nipple changes, including retraction, division, or elevation, can be due to benign lesions but are usually due to an underlying cancer. The changes known as Paget's disease can present a variety of appearances from moist and eczematoid to dry and psoriatic or it may appear as red granular erosion. The characteristic lesion may exist with or without a palpable tumor mass.

Skin retraction or dimpling was once considered diagnostic of mammary cancer, but some benign lesions can produce this change, notably fat necrosis, plasma cell mastitis and chronic infections. Skin changes including fixation to the skin, peau d'orange, edema, ulceration, satellite nodules, marked retraction of the entire breast and edema of the arm are signs of advanced malignancy.

Halsted in 1907 pointed out that enlarged axillary lymph nodes could be the only sign of occult mammary carcinoma, one per cent or less of all cases present in this fashion. Cancer is the probable etiologic factor if the axillary nodes are firm to hard, slightly irregular, matted, fixed, or larger than 2 cm. The presence of supraclavicular nodes, fixed axillary nodes or edema of the arm indicates an advanced regional disease. Complaints at distant sites may have their origin in the breast and represent metastasis to bones or viscera (e.g. liver or lung).

Careful physical examination is the primary resource for evaluating the local and regional extent of the disease. Extensive preliminary investigations are not appropriate when it is unlikely that a lesion of the breast is cancer.

For practical purposes, the diagnosis and clinical staging of a patient without signs or symptoms suggesting dissemination might include a complete history and physical examination, a complete blood picture that may detect an anemia indicative of extensive bone marrow involvement and a roentgenogram of the chest, which may detect pulmonary metastasis in asymptomatic patients.

A radiographic survey of the skeleton, ribs, skull, spine, pelvis, femurs and humerus is generally unrewarding unless the patient has symptoms suggesting osseous metastasis.

Besides clinical palpation, the techniques of mammography, thermography, galactography ultrasonic examination of the breast and aspiration cytology have been used in the detection of early breast tumors.

It is to note that with the breast cancer detection screening, more and more cases (about 20% of cases in the country in which there is this type of program which concern only patients between 50 – 74 y.o.) are detected by mammography without any symptomatic disease.

Mammography has an accuracy of approximately 80-90%. Ultrasound mammography is somewhat useful as an ancillary procedure to mammography in selected patients for evaluating deep seated lesions, especially in premenopausal women whose dense glandular breasts may obscure masses on mammography. Mammary RMI can help to objective intramammary spread.(see chapter 6)

It is a useful advice that breast cancer should be considered as a systemic disease until proved otherwise. The methods for search for distant metastases can be broadly subdivided into physical techniques and biochemical methods.

Physical techniques include the conventional chest X-ray, , skeletal scans, hepatic scan, brain scan, computerized tomography scans and, now PET SCAN. The conventional chest X-ray should be a routine investigation for all cases with early carcinoma of the breast. The development of isotopic skeletal scanning has improved the accuracy for detecting bony metastases, followed by specific radiology for the areas of abnormal uptake. A negative scan would exclude, in the majority of cases, the presence of skeletal metastases.

However, a so called positive scan needs to be further evaluated since healing fractures, Paget's disease and areas of osteoarthritis can also show up as hot spots on the scan image. Having confirmed the presence of skeletal metastases by X-raying the area of abnormal uptake on the scan, the patient falls into the stage 4 category. There remains a considerable confusion as how to handle a group of patients who have an apparently early breast cancer with hot spots on their scan and no radiologically detectable metastases. It was advised that the optimum way of handling this problem would be to carry out a bone biopsy on suspicious areas shown up by the scan.

Haagensen in 1971 reported that approximately 35 to 65 per cent of autopsied patients with breast cancer have hepatic metastases. Ultra-sonic exploration or CT are the more common investigations. used to detect an hepatic lesion.

Positron Emission Tomography (PET) (associated or not with a CT Scan) is not used routinely. It can be of a great help for the diagnosis of an abnormal picture founded by an other imaging technique. The newly developed PET Mammo is

currently under evaluation with only one machine present in the world at Mazo Clinic.

All physical techniques for detecting metastases have a built-in limitation in that improvements in resolving power are bought at extreme costs with diminished returns.

Improvements in the detection of biochemical markers, which might be released by the tumor itself, can be of help. These markers might be released from normal parenchyma as a result of invasion and destruction by the tumor cells. Elevated liver enzymes, such as alkaline phosphatase are very crude estimates of hepatic invasion. If advanced laboratory facilities are available, additional investigations such as tumor markers [CA15.3, CEA, and MCA] can be considered.

### **Clinical Staging**

Since 1905, several systems of classification have been adopted. Steintal described the first pure clinical estimation of the stage or the extent of disease at the time of treatment.

In 1940, the four stage system for clinical evaluation was adopted at the Christi Hospital in Manchester. This classification was widely accepted, and is still in use in many centers all over the world.

#### **The four stages are:**

*Stage 1:* The growth is confined to the breast; *Stage 2:* The growth is confined to the breast, but palpable, mobile lymph nodes are present in the axilla; *Stage 3:* The growth extends beyond the mammary parenchyma: (a) skin invasion or fixation over an area large in relation to the size of the breast or skin ulceration; (b) tumor fixation to the underlying muscle or fascia; axillary nodes, if present, are mobile. *Stage 4:* The growth extends beyond the breast area as shown by fixation or matting of the axillary nodes, complete fixation of the tumor to chest wall, deposits in supraclavicular nodes or in the opposite breast, or distant metastases.

In 1972, according to Denoix, and the committee of clinical staging of the UICC, the new method of clinical staging was widely used by different centers. This classification depends upon the T (Tumor Size), N (Regional Lymph Node Affection), and M (Distant Metastases).



**This classification adopted by the American Joint Committee on Cancer (AJCC) TNM system can be summarized as follows:**

**TNM Definitions**

Definitions for classifying the primary tumor (T) are the same for clinical and for pathologic classification. If the measurement is made by physical examination, the examiner will use the major headings (T1, T2, or T3). If other measurements, such as mammographic or pathologic measurements, are used, the subsets of T1 can be used. Tumors should be measured to the nearest 0.1 cm increment.

- TX: Primary tumor cannot be assessed
- T0: No evidence of primary tumor
- Tis: Intraductal carcinoma, lobular carcinoma *in situ*, or Paget disease of the nipple with no associated invasion of normal breast tissue
  - Tis (DCIS): Ductal carcinoma *in situ*
  - Tis (LCIS): Lobular carcinoma *in situ*
  - Tis (Paget): Paget disease of the nipple with no tumor. [Note: Paget disease associated with a tumor is classified according to the size of the tumor.]
- T1: Tumor not larger than 2.0 cm in greatest dimension
  - T1mic: Microinvasion not larger than 0.1 cm in greatest dimension
  - T1a: Tumor larger than 0.1 cm but not larger than 0.5 cm in greatest dimension
  - T1b: Tumor larger than 0.5 cm but not larger than 1.0 cm in greatest dimension
  - T1c: Tumor larger than 1.0 cm but not larger than 2.0 cm in greatest dimension
- T2: Tumor larger than 2.0 cm but not larger than 5.0 cm in greatest dimension
- T3: Tumor larger than 5.0 cm in greatest dimension
- T4: Tumor of any size with direct extension to (a) chest wall or (b) skin, only as described below
  - 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 to movable ipsilateral axillary lymph node(s)
- N2: Metastasis to ipsilateral axillary lymph node(s) fixed or matted, or in clinically apparent\* ipsilateral internal mammary nodes in the *absence* of clinically evident 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\* 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\* 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)

\* [Note: Clinically apparent is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination or grossly visible pathologically.]

### **Pathologic classification (pN)\***

- pNX: Regional lymph nodes cannot be assessed (e.g., not removed for pathologic study or previously removed)
- pN0: No regional lymph node metastasis histologically, and no additional examination for isolated tumor cells (ITC)

[Note: ITCs are defined as single tumor cells or small cell clusters not larger than 0.2 mm, usually detected only by immunohistochemical (IHC) or molecular methods but that may be verified on hematoxylin & eosin (H&E) stains. ITCs do not usually show evidence of malignant activity, e.g., proliferation or stromal reaction.]

- pN0(I-): No regional lymph node metastasis histologically, negative IHC
- pN0(I+): No regional lymph node metastasis histologically, positive IHC, and no IHC cluster larger than 0.2 mm
- pN0(mol-): No regional lymph node metastasis histologically, and negative molecular findings (RT-PCR)\*\*
- pN0(mol+): No regionally lymph node metastasis histologically, and positive molecular findings (RT-PCR)\*\*

\* [Note: Classification is based on axillary lymph node dissection with or without sentinel lymph node (SLN) dissection. Classification based solely on SLN dissection without subsequent axillary lymph node dissection is designated (sn) for sentinel node, e.g., pN0(I+) (sn).]

- pN1: Metastasis in one to three axillary lymph nodes, and/or in internal mammary nodes with microscopic disease detected by SLN dissection but not clinically apparent\*\*
  - pN1mi: Micrometastasis (larger than 0.2 mm but not larger than 2.0 mm)
  - pN1a: Metastasis in one to three axillary lymph nodes

- pN1b: Metastasis in internal mammary nodes with microscopic disease detected by SLN dissection but not clinically apparent\*\*
- pN1c: Metastasis in one to three axillary lymph nodes and in internal mammary lymph nodes with microscopic disease detected by SLN dissection but not clinically apparent\*\* (If associated with more than three positive axillary lymph nodes, the internal mammary nodes are classified as pN3b to reflect increased tumor burden.)
- pN2: Metastasis in four to nine axillary lymph nodes, or in clinically apparent \*\* internal mammary lymph nodes in the *absence* of axillary lymph node metastasis to ipsilateral axillary lymph node(s) fixed to each other or to other structures
  - pN2a: Metastasis in four to nine axillary lymph nodes (at least one tumor deposit larger than 2.0 mm)
  - pN2b: Metastasis in clinically apparent\* internal mammary lymph nodes in the *absence* of axillary lymph node metastasis
- pN3: Metastasis in ten or more axillary lymph nodes, or in infraclavicular lymph nodes, or in clinically apparent\* ipsilateral internal mammary lymph node(s) in the *presence* of one or more positive axillary lymph node(s); or, in more than three axillary lymph nodes with clinically negative microscopic metastasis in internal mammary lymph nodes; or, in ipsilateral supraclavicular lymph nodes
  - pN3a: Metastasis in ten or more axillary lymph nodes (at least one tumor deposit larger than 2.0 mm); or, metastasis to the infraclavicular lymph nodes
  - pN3b: Metastasis in clinically apparent\* ipsilateral internal mammary lymph nodes in the *presence* of one or more positive axillary lymph node(s); or, in more than three axillary lymph nodes and in internal mammary lymph nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent\*\*
  - pN3c: Metastasis in ipsilateral supraclavicular lymph nodes

**Distant metastasis (M)**

- MX: Presence of distant metastasis cannot be assessed
- M0: No distant metastasis
- M1: Distant metastasis

**AJCC Stage Groupings**

Stage 0

- Tis, N0, M0

Stage I

- T1\*, N0, M0

Stage IIA

- T0, N1, M0
- T1\*, N1, M0
- T2, N0, M0

Stage IIB

- T2, N1, M0
- T3, N0, M0

Stage IIIA

- T0, N2, M0
- T1\*, N2, M0
- T2, N2, M0
- T3, N1, M0
- T3, N2, M0

Stage IIIB

- T4, N0, M0

- T4, N1, M0
- T4, N2, M0

#### Stage IIIC\*\*

- Any T, N3, M0

#### Stage IV

- Any T, Any N, M1

However, these classifications did not satisfy all descriptive clinical conditions, as some of the tumors are biologically active and their clinical behavior differs irrespective of their original tumor measurements or apparent nodal affection. Consequently, an additive system of classification was adopted by the workers at Gustave-Roussy Cancer Institute in France. This system demonstrates staging according to the evolutionary phase PEV (Phase Evolutive).

#### **The Evolutionary Phase (PEV)**

The characteristics of the evolutionary phase were looked for in the tumor and the lymph nodes. They were present in varying degrees. Two elements: the signs of inflammation and the speed of growth as a function of time, distinguished the three degrees in decreasing severity.

**PEV 3** These are the worst cases, which correspond to the classical acute inflammatory type. The breast is hot, red, and presents diffuse edema of the dermis and subcutaneous tissues. There, almost always, exist a collateral circulation and most often greatly enlarged lymph nodes are hidden in the edematous tissues i.e. acute mastitis carcinomatosa involving the entire breast.

**PEV 2** These are the cases of moderate severity, which correspond to the sub-acute pseudo-inflammatory forms involving only a part of the breast. However, peritumoral and cutaneous edema is more often to be found beyond the limits of the tumor, even though at times, it is difficult to precise its limits. The enlarged lymph nodes are often matted together, and attached to the tumor by an indurated cord of “neoplastic lymphangitis”.

**PEV 1** These are the cases which are apparently the least serious but also the most difficult to define. They are differentiated from the usual “chronic” type of breast cancer by one essential and unique characteristic “the rapid rate of growth”.

**PEV 0** These are the cases, which correspond to the classic “chronic” type of breast cancer but they lack the previously-mentioned activity signs.

It is therefore admitted that any tumor with its apparent volume doubled in 6 months is to be considered in evolution (progressive). The determination of this characteristic is based on the interrogation of the patient and thus, its appreciation is subjective. Such evaluation is impossible for recently discovered tumors. However, skin biopsy for involvement of skin lymphatics by tumor cells is a more reliable method to assess the stage of evolution.

### **Inflammatory Carcinoma**

Inflammatory carcinoma of the breast was described by Lee as a distinct entity. This disease form is reported to account for 1% to 10% of breast malignancies and can be divided into two types: the primary type, in which inflammatory changes appear simultaneously with the carcinoma in an otherwise normal breast, and the secondary type in which the inflammatory manifestations appear in a breast with long standing carcinoma. The common factor in all such cases is the unusual appearance of widespread redness and edema in the skin, usually without any increase in the patient’s temperature and with no change in the white blood count. This inflammatory type corresponds to types PEV3 and PEV2 mentioned above.

### **End Results of Therapy (National Cancer Institute, Cairo)**

A Follow up study was conducted on a total of 408 female patients with operable breast cancer treated in National Cancer Institute, Cairo (NCI) during the period January 1980-December 1983. All patients except 6 were subjected to radical mastectomy at that time; 224 patients received adjuvant postoperative radiotherapy and 73 patients were treated by adjuvant CMF combination for 6 courses. This adjuvant regimen was conducted in relation to tumor size and lymph node affection. In June 1987 multivariate analysis was carried out where multiple stepwise regression analysis was done on the various prognostic factors to elicit the prognostic index. In our study, age had no effect on survival similar to the results obtained by Rosen et al. and Muscolino et al. This was in disagreement with the results of Palmer et al. who found a better survival rate of patients ranging from 40-49 years of age than older patients in stage I and II of the disease.

Staging had a strong effect on survival as evidenced by the different rates of survival in relation to tumor extent. T1 lesions, had survival of 60.7% in contrast to 19.6% for T4 lesions and clinical nodal affection (N) N0 66.9%; N1a 54.6%, N1b 25.9% and N2 3.5%. The first 3 years were the critical period for patients especially those with T4 lesions and N2 category. Using stage grouping as a prognostic discriminator, it was noticed that Stage I was far better than Stage II which was better than IIIa and IIIb, while 5% of Stage I patients died during the first 6 months; 19.7% of the poorest prognosis group (Stage IIIb) continued alive and free of recurrence for the first 3.5-5 years. Either this was due to the biological heterogeneity effect proven by many reports as Isaacs', or that staging was not sufficient to predict prognosis. This result was also supported by the multivariate analysis, which showed no independent prognostic effect for the clinical staging. Although PEV showed a significant prognostic value, yet their discriminating power was not like that of staging. This was in agreement with what Contesso et al. and Chevallier had reported.

On the other hand, tumor size showed a prognostic effect on survival, which seems to be indirect through the lymph node metastasis and not through the tumor grades. This, was supported by the non significant relationship detected between tumor size and tumor grade. These results were in agreement with those of the American College of Surgeons in 1979 and Lee who found that the larger the tumor, the more the number of lymph nodes involvement with metastasis, thus the greater would be the tumor relapse and mortality rates. The histopathologic types (favorable and unfavorable) and grade gave significant discrimination, which was indirect through nodal metastasis. It was found that the favorable group had a lower incidence of nodal metastasis in comparison to the unfavorable group (56.0% vs. 70.6%). Also patients with grade 1 had a survival rate of 65% while those of grade II and III were 30%. This was in accordance with the results of Davis et al. and Fisher et al.

Axillary lymph node metastasis showed the most significant prognostic power of the whole prognostic factors. Our results indicated that patients with (4-9) and (>9) nodes were far worse. These results are supported by those of Fisher et al. and Contesso et al. Capsular invasion was also a powerful prognostic factor in multivariate analysis done. The clinical diagnostic accuracy for axilla nodes was 66.6% and 78.4% for the clinically negative and clinically positive lymph nodes respectively.

A more recent series was conducted at the same institute between 1994 and 1998, and included 400 patients. The median age of this group of patients was 46 years (range 21-76 years). Of these 400 cases, 261 (65%) were postmenopausal, and 139



(35%) were premenopausal. While all cases in the older series conducted between 1980-1984 had modified radical mastectomy as their primary treated option followed by adjuvant radiotherapy in 55% and chemotherapy in 24% of those cases, in the recent series (1994-1998), modified radical mastectomy was the primary treatment option in 333/400 (83%) and conservative surgery was done for the remaining 67 cases (17%). Adjuvant radio-chemotherapy was given to 85% of these cases. Tumor size was below 2 cm in 13%, between 2-4 cm in 54% and >4 cm in 33% of cases. Pathological axillary lymph node involvement was absent in only 14/400 (3.5%) cases examined, while 1-3, 4-6, 6-10, and >10 positive nodal affection was present in 16.5%, 11%, 13%, and 56% of cases respectively.

At a median observation time of 49 months, the 5-year disease free survival rate was 60.1% for the patients included in 1994-1998 series, compared to 37.2% for those reported in 1980-1984 series. Survival rate was significantly adversely affected by postmenopausal status, tumor size more than 2 cm in diameter, grade III tumors, positive axillary lymph nodal affection, and being ineligible for conservative surgery as primary treatment.

In another study using high dose adjuvant chemotherapy with autologous peripheral blood stem cell transplantation in node positive breast cancer, fifty-three premenopausal patients with node positive ( $\geq 6$ ) breast cancer were randomly allocated to receive one cycle of high-dose cyclophosphamide 6 gm/m<sup>2</sup> divided on 3 days, etoposide 1500 mg/m<sup>2</sup> divided on 3 days and carboplatin 800 mg/m<sup>2</sup> divided on 2 days (CVCb regimen) versus six cycles of conventional-dose cyclophosphamide 600 mg/m<sup>2</sup>, epirubicin 75 mg/m<sup>2</sup> and fluorouracil 600 mg/m<sup>2</sup>, all given IV day one, and repeated every 21 days (CEF regimen). The high-dose regimen used peripheral blood stem cells as a stem cell rescue. HDC (n=27) and CEF arms (n=26) were almost comparable with respect to different prognostic factors. In HDC arm, the mean times to neutrophil and platelet recovery were 10.29 and 11 days respectively. The mean time of empiric antibiotic therapy was 8.59 days. The complications of the HDC regimen were mild (grades 2 and 3) and were mainly gastrointestinal (vomiting, diarrhea and mucositis). In both arms of the study, there were no life-threatening complications or treatment-related mortality. At a median follow up period of 30 months, the 3-year disease-free survival of the HDC group (50.5%) was better than that of the CEF group (29.4), but the difference did not reach statistical significance ( $p = 0.137$ ). The 3-year overall survival of HDC arm (82.8%) was slightly higher than that of the CEF arm (76.9%), but the difference was also statistically insignificant ( $p=0.763$ ). So, it was concluded that further follow-up and additional studies are required to evaluate the role of high-dose adjuvant chemotherapy in high-risk breast cancer patients.