PROSPECTIVE STUDY OF "CORRELATION OF PATHOLOGICAL RESPONSE AND HORMONE RECEPTOR STATUS AFTER NEOADJUVANT CHEMOTHERAPY IN CARCINOMA BREAST AND QUANTIFICATION OF HORMONE RECEPTOR STATUS FOR CHEMOTHERAPHY DOSE ADJUSTMENT"

M.S. DEGREE EXAMINATION

BRANCH I - GENERAL SURGERY

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CHENNAI, INDIA.

BONAFIDE CERTIFICATE

This is to certify that the dissertation entitled **"PROSPECTIVE STUDY OF CORRELATION OF PATHOLOGICAL RESPONSE AND HORMONE RECEPTOR STATUS AFTER NEOADJUVANT CHEMOTHERAPY IN CARCINOMA BREAST AND QUANTIFICATION OF HORMONE RECEPTOR STATUS FOR CHEMOTHERAPHY DOSE ADJUSTMENT" in Government Rajaji Hospital, Madurai.** Submitted by **Dr.KRISHNABHARATHI.R** to the Tamilnadu Dr.M.G.R. Medical University, Chennai in partial fulfilment of the requirement for the award of M.S. Degree Branch I (General Surgery) is a bonafide research work was carried out by her under the direct supervision and guidance.

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I, **Dr. KRISHNA BHARATHI.R** solemnly declare that the dissertation titled **"PROSPECTIVE STUDY OF CORRELATION OF PATHOLOGICAL RESPONSE AND HORMONE RECEPTOR STATUS AFTER NEOADJUVANT CHEMOTHERAPY IN CARCINOMA BREAST AND QUANTIFICATION OF HORMONE RECEPTOR STATUS FOR CHEMOTHERAPHY DOSE ADJUSTMENT"** is a bonafide work done by me in the Department of General Surgery at Government Rajaji Hospital during the period of October 2016 to September 2017.

I also declare that this bonafide work or a part of this work was not submitted by me or any other for any award, degree and diploma to any university, board either in India or Abroad. The dissertation is submitted to The Tamilnadu Dr.M.G.R. Medical University, towards partial fulfillment of requirement for the award of **M.S**. **DEGREE IN GENERAL SURGERY (BRANCH** I).

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CONTENTS

INTRODUCTION

Breast cancer, which is the most common malignancy in women was found to have association with oestrogen and progesterone. The discovery of oestrogen receptor and progesterone receptor produced vast changes in the management of cancer breast. It is an important prognostic marker on treating patient with carcinoma breast we are often found to how dilemma of how to identify those patients who are likely to most benefit from hormonal treatment. Oestrogen and progesterone receptor rich tumors respond well to hormone therapy. Tumors negative to hormone receptor respond well to chemotherapy. oestrogen and progesterone receptor status is the most important indicator in predicting response of advanced breast cancer.

Role of oestrogen and progesterone in development of breast Before puberty the breast is composed primarily of dense fibrous stroma and scattered ducts lined with epithelium. In the breast Hormone dependent maturation entails increase deposition of fat, formation of new ducts why branching and elongation, first appearance of lobular units. This process of growth and cell division is under the control of oestrogen, progesterone, adrenal hormones, bigotry hormones on the tropical effects of insulin and thyroid hormone. influence on breast is oestrogen. the initial immaturity of the

hypothalamic pitutary axis results in the anovulatory cycles for the first 1 to 2 years after mensus begin, subjecting the breast to effects of unopposed oestrogen and progesterone. It is during this period of unopposed oestrogen stimulation , considered an oestrogen window that the ductal growth phase occurs.

A potent mamogen, oestrogen primary stimulates ductal growth but also increases fat deposition and contributes to later phase of development. Impaired ductal growth have been demonstrated in what people lacking functional gene for the oestrogen receptor and progesterone receptor. Oestrogen receptor is thought to be the key mediator of oestrogen effects and in humans has only be documented in luminal epithelium.

Epidemiology of breast cancer

Insurance rates of best cancer increased in most countries through 1990s. After 1990 where was overall increase in insurance rates of approximately. 5 % annually recent data from SEER program reveal the decline in breast cancer incidence over the past decade and this is widely attributed to decrease use of hormone replacement therapy.

Breast cancer burden has well defined variations by geography, regional lifestyle and racial or ethnic background. In general both breast cancer incidence and mortality are relatively lower among the female populations of Asia and Africa . in contrast european and North American women and women from heavily industrialized or westernized countries have a substantially higher breast cancer burden. These International patterns are mirrored in breast cancer incidence and mortality rates.

Although often the factors that influence breast cancer incidence main Vary from doors that affect mortality. Incidence rates are heavily weighted with women who begin childbearing at young age and who often how multiple pregnancy is followed By prolonged lactation.

Breast cancer mortality rate should be lower in population that have lower insurance. But the mortality burden will simultaneously be adversely affected by the absence of screening programs for early detection and diminished access to multidisciplinary cancer treatment programs these features are likely to account much of the disproportionate mortality risk that are seen in underdeveloped Nations.

Signs and symptoms of breast cancer.

1. Mass or swelling in the breast
2. ulceration or fungating breast .
3. nipple ulceration.
4. nipple retraction.
5. Discharge

REVIEW OF LITERATURE

The value of adjuvant chemotherapy in treating breast cancer is well documented. The idea of neoadjuvant chemotherapy has been recently applied to breast cancer treatment and studies have shown the efficacy of neoadjuvant chemotherapy in down-staging the primary tumor. Before giving neoadjuvant chemotherapy hormone receptor status is analysed , based on which NAC is given.

The Milan Group, using a combination of doxorubicin and vincristine, achieved an 80% response rate with 15% of patients attaining complete clinical response. Tumor shrinkage by the neoadjuvant chemotherapy can be easily monitored clinically both by physicians and patients. For physicians, continuation of treatment is reasonably determined based on efficacy. For patients, compliance with the scheduled courses of chemotherapy is increased because they, themselves, experience the efficacy, which helps them mentally to overcome the unpleasant adverse effects. The pathological response to the neoadjuvant chemotherapy provides reliable prognostic information with increased overall (OS) and disease free survival (DFS).

The use of neoadjuvant chemotherapy in treating breast cancer has shown efficacy in downstaging primary tumors, and allows breast conservative surgery to be performed instead of mastectomy. This study aims to evaluate patterns of clinical and pathological response and hormone receptor status after neoadjuvant chemotherapy in patients with locally advanced breast cancer.

EMBRYOLOGY

At the fifth or sixth week of fetal development, two ventral bands of thickened ectoderm (mammary ridges, milk lines) are evident in the embryo. In most mammals, paired breasts develop along these ridges, which extend from the base of the forelimb (future axilla) to the region of the hind limb (inguinal area). These ridges are not prominent in the human embryo and disappear after a short time, except for small portions that may persist in the pectoral region. Accessory breasts (poly mastia) or accessory nipples (polythelia) may occur along the milk line ,when normal regression fails. Each breast develops when an ingrowth of ectoderm forms a primary tissue bud in the mesenchyme. The primary bud, in turn, initiates the development of 15 to 20 secondary buds. Epithelial cords develop from the secondary buds and extend into the surrounding mesenchyme.

Major (lactiferous) ducts develop, which open into a shallow mammary pit. During infancy, a proliferation of mesenchyme transforms the mammary pit into a nipple. If there is failure of a pit to elevate above skin level, an inverted nipple results. This congenital malformation occurs in 4% of infants. At birth, the breasts are identical in males and females, demonstrating only the presence of major ducts. Enlargement of the breast may be evident and a secretion, referred to as witch's milk, may be produced. These transitory events occur in

response to maternal hormones that cross the placenta

The breast remains undeveloped in the female until puberty, when it enlarges in response to ovarian estrogen and progesterone, which initiate proliferation of the epithelial and connective tissue elements. However, the breasts remain incompletely developed until pregnancy occurs. Absence of the breast (amastia) is rare and results from an arrest in mammary ridge development that occurs during the sixth fetal week. Poland's syndrome consists of hypoplasia or complete absence of the breast, costal cartilage and rib defects, hypoplasia of the subcutaneous tissues of the chest wall, and brachysyndactyly. Breast hypoplasia also may be iatrogenically induced before puberty by trauma, infection, or radiation therapy. Symmastia is a rare anomaly recognized as webbing between the breasts across the midline. Accessory nipples (polythelia) occur in <1% of infants and may be associated with abnormalities of the urinary tract (renal agenesis and cancer), abnormalities of the cardiovascular system (conduction disturbances, hypertension, congenital heart anomalies), and other conditions (pyloric stenosis, epilepsy, ear abnormalities, arthrogryposis). Supernumerary breasts may occur in any configuration along the mammary milk line but most frequently occur between the normal nipple location and the symphysis pubis. Turner's syndrome (ovarian agenesis and dysgenesis) and Fleischer's syndrome (displacement of

the nipples and bilateral renal hypoplasia) may have polymastia as a component. Accessory axillary breast tissue is uncommon and usually is bilateral

The breast is composed of 15 to 20 lobes, which are each composed of several lobules. Fibrous bands of connective tissue travel through the breast (Cooper's suspensory ligaments), insert perpendicularly into the dermis, and provide structural support. The mature female breast extends from the level of the second or third rib to the inframammary fold at the sixth or seventh rib. It extends transversely from the lateral border of the sternum to the anterior axillary line. The deep or posterior surface of the breast rests on the fascia of the pectoralis major, serratus anterior, and external oblique abdominal muscles, and the upper extent of the rectus sheath. The retromammary bursa may be identified on the posterior aspect of the breast between the investing fascia of the breast and the fascia of the pectoralis major muscles. The axillary tail of Spence extends laterally across the anterior axillary fold. The upper outer quadrant of the breast contains a greater volume of tissue than do the other quadrants. The breast has a protuberant conical form. The base of the cone is roughly circular, measuring 10 to 12 cm in diameter. Considerable variations in the size, contour, and density of the breast are evident among individuals. The nulliparous breast has a hemispheric configuration with distinct flattening above

the nipple. With the hormonal stimulation that accompanies pregnancy and lactation, the breast becomes larger and increases in volume and density, whereas with senescence, it assumes a flattened, flaccid, and more pendulous configuration with decreased volume.

BREAST

The breasts form a secondary sexual feature of females and are a source of nutrition for the neonate. In young adult females, each breast is a rounded eminence largely lying within the superficial fascia anterior to the upper thorax but spreading laterally to a variable extent**.** Breast shape and size depend on genetic, racial and dietary factors and on the age, parity and menopausal status of the individual. Breasts may be hemispherical, conical, variably pendulous, piriform or thin and flattened. In the adult female, the base of the breast, i.e. its attached surface, extends vertically from the second or third to the sixth rib, and in the transverse plane from the sternal edge medially almost to the mid-axillary line laterally. The superolateral quadrant is prolonged towards the axilla along the inferolateral edge of pectoralis major, from which it projects a little, and may extend through the deep fascia up to the apex of the axilla (the axillary tail of Spence). The trunk superficial fascial system splits to enclose the breast to form the anterior and posterior lamellae. Posterior extensions of the superficial fascial system connect the breast to the pectoralis fascia, part of the deep fascial system. The inframammary crease is a zone of adherence of the superficial fascial system to the underlying chest wall at the inferior crescent of the breast. The breast lies on the deep pectoral fascia, which in turn overlies pectoralis major and serratus anterior superiorly and external oblique and its aponeurosis

inferiorly, as the latter forms the anterior wall of the rectus sheath. Between the breast and the deep fascia, the loose connective tissue in the ‘sub mammary space’ allows the breast some degree of movement on the deep pectoral fascia.

Nipple areola complex

The epidermis of the nipple-areola complex is pigmented and is variably corrugated. During puberty, the pigment becomes darker and the nipple assumes an elevated configuration. During pregnancy, the areola enlarges and pigmentation is further enhanced. The areola contains sebaceous glands, sweat glands, and accessory glands, which produce small elevations on the surface of the areola (Montgomery's tubercles). Smooth muscle bundle fibers, which lie circumferentially in the dense connective tissue and longitudinally along the major ducts, extend upward into the nipple, where they are responsible for the nipple erection that occurs with various sensory stimuli. The dermal papilla at the tip of the nipple contains numerous sensory nerve endings and Meissner's corpuscles. This rich sensory innervation is of functional importance, because the sucking of the infant initiates a chain of neurohumoral events that results in milk letdown

Axilla:

The anatomical boundaries of the axilla represent a pyramidal compartment located between the upper extremity and the thoracic wall; this structure has four boundaries inclusive of a base and an apex. The curved oblong base consists of axillary fascia. The apex of the axilla represents an aperture that extends into the posterior triangle of the neck via the *cervico axillary canal.* Most structures that course between the neck and the upper extremity enter this anatomic passage. which is bounded anteriorly by the clavicle. medially by the first rib. and posteriorly by the scapula. The anterior wall of the axilla is composed of the pectoralis major and minor muscles and their associated fasciae. The posterior wall is formed primarily of the subscapularis muscle, located on the anterior surface of the scapula, and to a lesser extent by the teres major and latissimus dorsi muscles. The lateral wall of the axilla is the bicipital groove, a thin strip of condensed muscular tissue between the insertion of the musculature of the anterior and posterior compartments. The medial wall is composed of the serratus anterior muscle. The fascia of the pectoralis major and minor muscles are evident in two distinct planes: The superficial layer, called the *pectoral fascia,* invests the pectoralis major muscle, whereas the deep layer, called the *clavi pectoral* or *costo coracoid fascia.* Extends from the clavicle to the axillary fascia in the floor of

the axilla and encloses the subclavius and the pectoralis minor muscle. The costo coracoid membrane represents the upper portion of the clavi pectoral fascia and is pierced by the cephalic vein, the lateral pectoral nerve, and branches of the thoraco acromial trunk. The *medial pectoral nerve* does not penetrate the costo coracoid membrane, but enters the deep surface of the pectoralis minor and passes through the anterior investing fascia of the pectoralis minor to innervate the pectoralis major muscle. Caudal portions of the clavi pectoral fascia, which are anatomically inferior to the pectoralis minor are sometimes referred to as the *suspensory ligament of the axilla* or the *coraco axillary fascia.* Many surgeons refer to this anatomic landmark as *Halsted's ligament,* which represents a dense condensation of the clavi pectoral fascia that extends from the medial aspect of the clavicle, attaches to the first rib, and invests the subclavian artery and vein as each traverse the first rib. Within the axilla are the great vessels and nerves of the upper extremity, which, together with the other a:xillary contents, are encircled by loose connective tissue. These vessels and nerves are anatomically contiguous and are enclosed within an investing layer of fascia referred to as the axillary sheath.

The axillary artery can be divided into three anatomical segments within the axilla proper:

1. Located medial to the pectoralis minor muscle, the first segment gives rise to one branch, the *suprior thoracic,* which supplies the upper thoracic wall inclusive of the first and second intercostal spaces.

2. The *second* segment of this artery, located immediately posterior to the pectoralis *minor,* gives rise to two branches, the *thoraco acromial trunk* and the *lateral thoracic artery.* Pectoral branches of the thoraco acromial and lateral thoracic arteries supply the pectoralis major and minor muscles. Identification of these vessels during surgical dissection of the axilla is imperative to provide safe conduct of the procedure. The lateral thoracic artery gives origin to the lateral mammary branches.

3. The *third* segment of this vessel, located lateral to the pectoralis minor muscle, gives rise to three branches. These include the *anterior and posterior humeral circumflex artery* that supply the upper arm, and the *subscapular artery,* which is the largest branch within the axilla. After a short course, the subscapular artery gives origin to its terminal branches, the *subscapular circumflex* and the *thoracodorsal arteries.* The thoracodorsal artery, which courses with its corresponding nerve and vein, crosses the subscapularis muscle, providing its substantial blood supply, as *well* as that of the serratus anterior and latissimus dorsi muscles.

Tributaries of the axillary vein follow the course of the branches of the axillary artery, usually in the form of venae comitantes, paired veins that follow the course of the artery. The cephalic vein passes in the groove between the deltoid and pectoralis major muscles, and thereafter enters the axillary vein after piercing the clavipectoral fascia. Anatomically, the *axillary artery* is contiguous with various portions of the brachial plexus throughout its course in the axilla. The cords of the *brachial plexus* are named according to their structural and positional relationship with the axillary artery-medial, lateral, and posterior rather than their anatomic position in the axilla or on the chest wall.

The three nerves of principal interest to surgeons that are located in the axilla: The *long thoracic nerve,* located on the medial wall of the axilla, arises in the neck from the fifth, sixth, and seventh cervical roots (C5, C6, and C7) with entry in the axilla via the cervicoaxillary canal. This medially placed nerve lies on the lateral most surface of the serratus anterior muscle and is invested by the serratus fascia such that it might be accidentally divided together with resection of the fascia during surgical dissection (sampling) of lymphatics of the axilla. The long thoracic nerve, although diminutive in size, courses a considerable anatomic distance to supply the serratus anterior muscle, injury or division of this nerve results in the '"winging of scapula" deformity with denervation of the muscle group and the inability to provide shoulder fixation.

The *thoracodorsal nerve* takes origin from the posterior cord of the brachial plexus and innervates the laterally placed latissimus dorsi muscle. Injury or division is inconsequential to primary shoulder function; however, preservation of this nerve is essential to provide transfer survival and motor function preservation for the myocutaneous flap used for the latissimus dorsi musculocutaneous reconstruction. The *intercostobrachial nerve* is formed by the merging of the lateral cutaneous branch of the second intercostal nerve with the medial cutaneous nerve of the arm; this nerve provides sensory innervation of the skin of the apex and lateral axilla and the upper medial and inner aspect of the arm. A second intercostobrachial nerve may sometimes form an anterior branch of the third lateral cutaneous nerve.

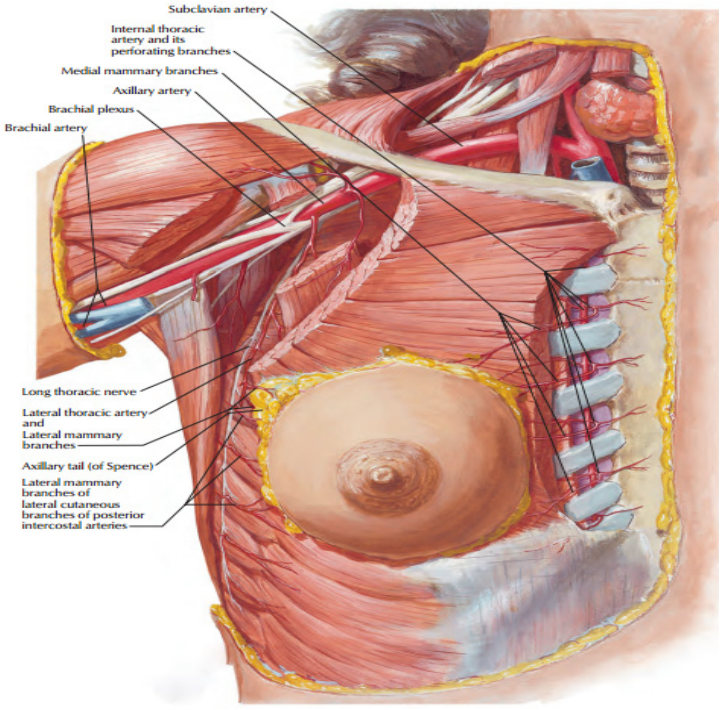
Blood Supply of Breast:

Blood supply to the mammary gland is derived from perforating branches of the *internal mammary artery,* lateral branches of the *posterior intercosta1 arteries,* and several branches of the *axillary* artery. The latter vessels include the highest thoracic, lateral thoracic, and pectoral branches of the *thoracoacromial artery*. Branches from the second, third, and fourth anterior perforating arteries pass to the breast as medial mammary arteries. The lateral thoracic artery branches allow perfusion to the serratus anterior muscle, both

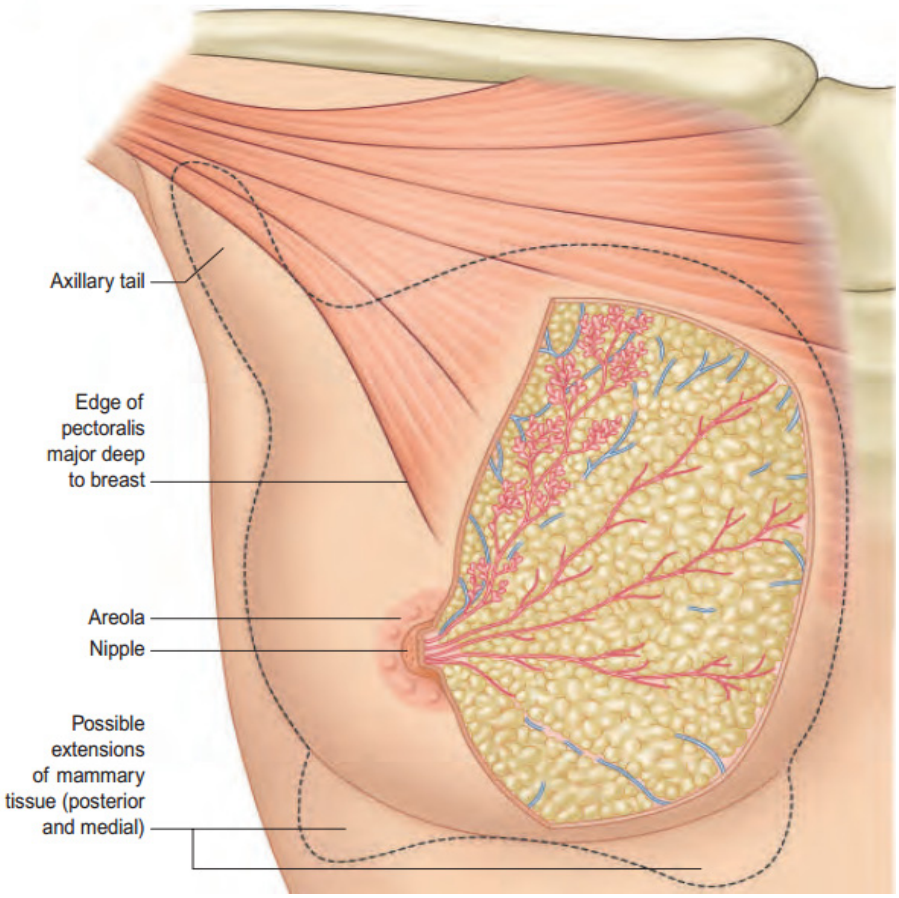
the pectoralis muscles, and the subscapularis muscle, and also supply the axillary lymphatics and supporting fatty tissues. The posterior intercostal arteries give rise to mammary branches in the second, third, and fourth intercostal spaces. Although the thoracodorsal branch of the subscapular artery does not contribute to the primary blood supply of the breast per se, *this* vessel *is* intimately associated with the central and scapular lymph node groups of the axilla. This *fact* should be taken into consideration during axillary node dissection, as bleeding *that* is difficult to control can result when penetrating branches of this vessel are severed.

Principal venous outflow of the gland has preferential directional flow toward the axilla, with the veins principally paralleling the path of the arterial distribution. The superficial venous plexus of mammary parenchyma has extensive anastomoses that may be evident through the overlying skin. Circumscribing the nipple, superficial veins form an anastomotic circle, the *circulus venosus. V*eins from this circle and from deeper aspects of the gland converge to drain blood to the periphery of the breast, and thereafter into vessels that terminate in the *internal mammary, axillary, and internal jugular yeins.* Venous return from the gland is derived from three principal groups of veins providing drainage of the breast and the thoracic wall and include (a)

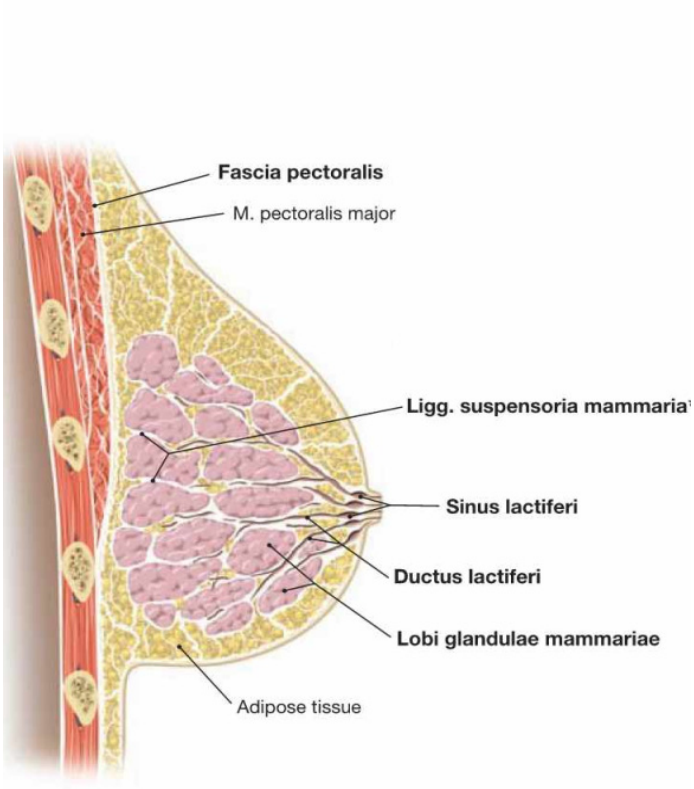
perforating branches of the *internal mammary vein,* (b) tributaries of the *axillary vein,* and (c) perforating branches of *posterior intercostal veins.* The posterior intercostal veins lie indirect continuity with the *vertebral plexus of veins (Batson's plexus)* that surround the vertebrae and extend from the base of the skull to the sacrum. Clinically, this plexus may provide an important pathway for hematogenous dissemination of breast cancer, and may physiologically account for metastases to the skull, vertebrae, pelvic bones, and centeral nervous system in the absence of pulmonary metastases.



Blood Supply



Topography of Breast



Breast – Sagittal View

INACTIVE AND ACTIVE BREAST

Each lobe of the breast terminates in a major (lactiferous) duct (2 to 4 mm in diameter), which opens through a constricted orifice (0.4 to 0.7 mm in diameter) into the ampulla of the nipple . Immediately below the nipple-areola complex, each major duct has a dilated portion (lactiferous sinus), which is lined with stratified squamous epithelium. Major ducts are lined with two layers of cuboidal cells, Whereas minor ducts are lined with a single layer of columnar or cuboidal cells. Myoepithelial cells of ectodermal origin reside between the epithelial cells in the basal lamina and contain myofibrils. In the inactive breast, the epithelium is sparse and consists primarily of ductal epithelium . In the early phase of the menstrual cycle, minor ducts are cord-like with small lumina. With estrogen stimulation at the time of ovulation, alveolar epithelium increases in height, duct lumina become more prominent, and some secretions accumulate. When the hormonal stimulation decreases, the alveolar epithelium regresses.

EPIDEMIOLOGY

"Worldwide, breast cancer is the most common type of cancer and the most common cause of cancer-related mortality among women. In women, breast cancer accounts for 26% of new cases of cancer and 15% of cancer deaths, second only to lung cancer as a cause of cancer-specific death. Approximately 1% of breast cancers occur in males and 90% are estrogen receptor (ER)-positive. Incidence rates continued to increase until 2002, likely reflecting the increase in use of mammographic screening, but recently have been reported to be declining. Part of that decline may be due to a decrease in the use of postmenopausal hormone replacement therapy. Although incidence rates (all races combined) are substantially higher for women age 50 and older (375.0 per 100,000) compared with women younger than 50 years (42.5 per 100,000), approximately 23% of breast cancers are diagnosed in women younger than 50 years, because those women represent 73% of the female population."

RISK FACTORS

Dietary and Lifestyle Factors:

“Observational studies suggested that high-fat diets were associated with higher rates of breast cancer than low-fat diets. However, a meta-analysis of eight prospective epidemiologic studies failed to identify an association between fat intake and breast cancer risk in adult women in developed countries. Consistent with these findings, a randomized dietary modification in 48,835 women in the Women’s Health Initiative study did not result in a statistically significant reduction in breast cancer incidence after 8 years of follow-up. Breast cancer risk increases linearly with the amount of alcohol consumed.

Obesity is associated with both an increased risk of breast cancer development in postmenopausal women and increased breast cancer mortality. Women with a body mass index of ≥31.1 have a 2.5-fold greater risk of developing breast cancer than those with a body mass index of ≤22.6.23 Weight and weight gain appear to play an important but complex role in breast cancer risk.

Environmental Factors:

Exposure to ionizing radiation increases breast cancer risk, and the increase is particularly marked for exposure at a young age. This pattern has been observed in survivors of the atomic bombings, those undergoing multiple diagnostic X-ray examinations, and in women receiving therapeutic irradiation.

A markedly increased risk of breast cancer development has been reported in women who received mantle irradiation for the treatment of Hodgkin lymphoma before age 15 years.

Hormonal Factors:

The development of breast cancer in many women appears to be related to female reproductive hormones, particularly endogenous estrogens. Early age at menarche, nulliparity or late age at first full-term pregnancy, and late age at menopause increase the risk of developing breast cancer. In postmenopausal women, obesity and postmenopausal hormone replacement therapy (HRT), both of which are positively correlated with plasma estrogen levels and plasma estradiol levels, are associated with increased breast cancer risk. Most hormonal risk factors have a relative risk (RR) of ≤ 2 for breast cancer development. The age-specific incidence of breast cancer increases steeply with age until menopause, and then plateaus. There is substantial evidence that estrogen deprivation via iatrogenic premature menopause can reduce breast cancer risk. Premenopausal women who undergo oophorectomy without hormone replacement have a markedly reduced risk of breast cancer later in life, with an increasing magnitude of risk reduction as the age at oophorectomy decreases. Data from women with *BRCA1* and *BRCA2* mutations suggest that early oophorectomy has a substantial protective effect on breast cancer risk in this

population also. Age at menarche and the establishment of regular ovulatory cycles are strongly .ed to breast cancer risk; the total duration of exposure to endogenous estrogens seems important. There appears to be a 20% decrease in breast cancer risk for each year that menarche is delayed. Of note, hormone levels through the reproductive years in women who experience early menarche may be higher than in women who undergo a later menarche. Additionally, late onset of menarche results in a delay in the establishment of regular ovulatory cycles, which may contribute to protective effects.

Nulliparous women are at greater risk for the development of breast cancer than parous women, with a RR of about 1.4. Breastfeeding, particularly for longer duration, lowers the risk of breast cancer diagnosis. The combined effects of reproductive history and breastfeeding may account for substantial fractions of the difference in breast cancer risk between developed and developing nations.

Familial Factors:

A family history of breast cancer has long been recognized as a risk factor for the disease, but only 5% to 10% of women who develop breast cancer have a true hereditary predisposition. Overall, the risk of developing breast cancer is increased 1.5-fold to 3 fold if a woman has a mother or sister with breast cancer. Mutations in the breast cancer susceptibility genes BRCA1 and BRCA2 are

associated with a significant increase in the risk of breast and ovarian carcinoma, and account for 5% to 10% of all breast cancers. These mutations are inherited in an autosomal dominant fashion and have varying penetrance."

Non-modifiable Risk Factors	Modifiable Risk Factors
Gender and age	Body weight
Personal cancer history	Physical activity
Family cancer history and genetics	Alcohol use
Early menstruation and late menopause	Smoking
Breast density	Exposure to hormones: the Pill, IVF, and HRT
Breast conditions	Pregnancy and breastfeeding
	Radiation exposure

WHO Classification of Tumors of the Breast

- **Epithelial tumors**
  - Microinvasive carcinoma

- **Invasive breast carcinoma**
  - Invasive carcinoma of no special type (NST)
    - Pleomorphic carcinoma
    - Carcinoma with osteoclast like stromal giant cells
    - Carcinoma with choriocarcinomatous features
    - Carcinoma with melanotic features
  - Invasive lobular carcinoma
    - Classic lobular carcinoma
    - Solid lobular carcinoma
    - Alveolar lobular carcinoma
    - Pleomorphic lobular carcinoma
    - Tubulolobular carcinoma
    - Mixed lobular carcinoma
  - Tubular carcinoma
  - Cribiform carcinoma
  - Mucinous carcinoma

- Carcinoma with medullary features
  - Medullary carcinoma
  - Atypical medullary carcinoma
  - Invasive carcinoma NST with medullary features
- Carcinoma with apocrine differentiation
- Carcinoma with signet ring differentiation
- Invasive micropapillary carcinoma
- Metaplastic carcinoma of no special type
  - Low-grade adenosquamous carcinoma
  - Fibromatosis like metaplastic carcinoma
  - Squamous cells carcinoma
  - Spindle cell carcinoma
  - Metaplastic carcinoma with mesenchymal differentiation
    - Chondroid differentiation
    - Osseous differentiation
    - Other types of mesenchymal differentiation
  - Mixed metaplastic carcinoma
  - Myoepithelial carcinoma
- Rare types
  - Carcinoma with neuroendocrine features

        - Neuroendocrine tumor, well differentiated
        - Neuroendocrine carcinoma, poorly differentiated (small cell carcinoma)
        - Carcinoma with neuroendocrine differentiation
    - Secretory carcinoma
    - Invasive papillary carcinoma
    - Acinic cell carcinoma
    - Mucoepidermoid carcinoma
    - Polymorphous carcinoma
    - Oncocytic carcinoma
    - Lipid rich carcinoma
    - Glycogen rich clear cell carcinoma
    - Sebaceous carcinoma
    - Salivary gland / skin adnexal type tumors
        - Cylindroma
        - Clear cell hidradenoma

- **Epithelial-myoepithelial tumors**
    - Pleomorphic adenoma
    - Adenomyoepithelioma

        - Adenomyoepithelioma with carcinoma
    - Adenoid cystic carcinoma

- **Precursor lesions**
    - Ductal carcinoma in situ
    - Lobular neoplasia
        - Lobular carcinoma in situ
            - Classic lobular carcinoma in situ
            - Pleomorphic lobular carcinoma in situ
        - Atypical lobular hyperplasia

- **Intraductal proliferative lesions**
    - Usual ductal hyperplasia
    - Columnar cell lesions including flat epithelial atypia
    - Atypical ductal hyperplasia

- **Papillary lesions**
    - Intraductal papilloma
        - Intraductal papilloma with atypical hyperplasia
        - Intraductal papilloma with ductal carcinoma in sit

        - Intraductal papilloma with lobular carcinoma in situ
    - Intraductal papillary carcinoma
    - Encapsulated papillary carcinoma
        - Encapsulated papillary carcinoma with invasion
    - Solid papillary carcinoma
        - In situ
        - Invasive

- **Tumors of the nipple**
    - Nipple adenoma
    - Syringomatous adenoma
    - Paget disease of the nipple

- **Malignant lymphoma**
    - Diffuse large B cell lymphoma
    - Burkitt lymphoma
    - T cell lymphoma
        - Anaplastic large cell lymphoma, ALK negative
    - Extranodal marginal-zone B cell lymphoma of MALT-type
    - Follicular lymphoma

- **Metastatic tumors**
- **Tumors of the male breast**
    - Gynaecomastia
    - Carcinoma
        - Invasive carcinoma
            - In situ carcinoma

- **Clinical patterns**
    - Inflammatory carcinoma
    - Bilateral breast carcinoma

AJCC STAGING

Primary tumor (T) 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 Carcinoma in situ

Tis (DCIS) Ductal carcinoma in situ

Tis (LCIS) Lobular carcinoma in situ

Tis (Paget's)

Paget's disease of the nipple with no tumor (NOTE: Paget's disease associated with a tumor is classified according

to the size of the tumor)

T1 Tumor 2 cm in greatest dimension

T1mic Microinvasion 0.1 cm or less in greatest dimension

T1a Tumor >0.1 cm but not >0.5 cm in greatest dimension

T1b Tumor >0.5 cm but not >1 cm in greatest dimension

T1c Tumor >1 cm but not >2 cm in greatest dimension

T2 Tumor >2 cm but not >5 cm in greatest dimension

T3 Tumor >5 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—Clinical (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 Metastases in ipsilateral axillary lymph nodes fixed or matted, or in clinically apparenta 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

N3 Metastasis only in clinically apparenta ipsilateral internal mammary nodes and in the absence of clinically evident

axillary lymph node metastasis; metastasis in ipsilateral infraclavicular lymph node(s) with or without axillary lymph node involvement, or in clinically apparenta 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

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

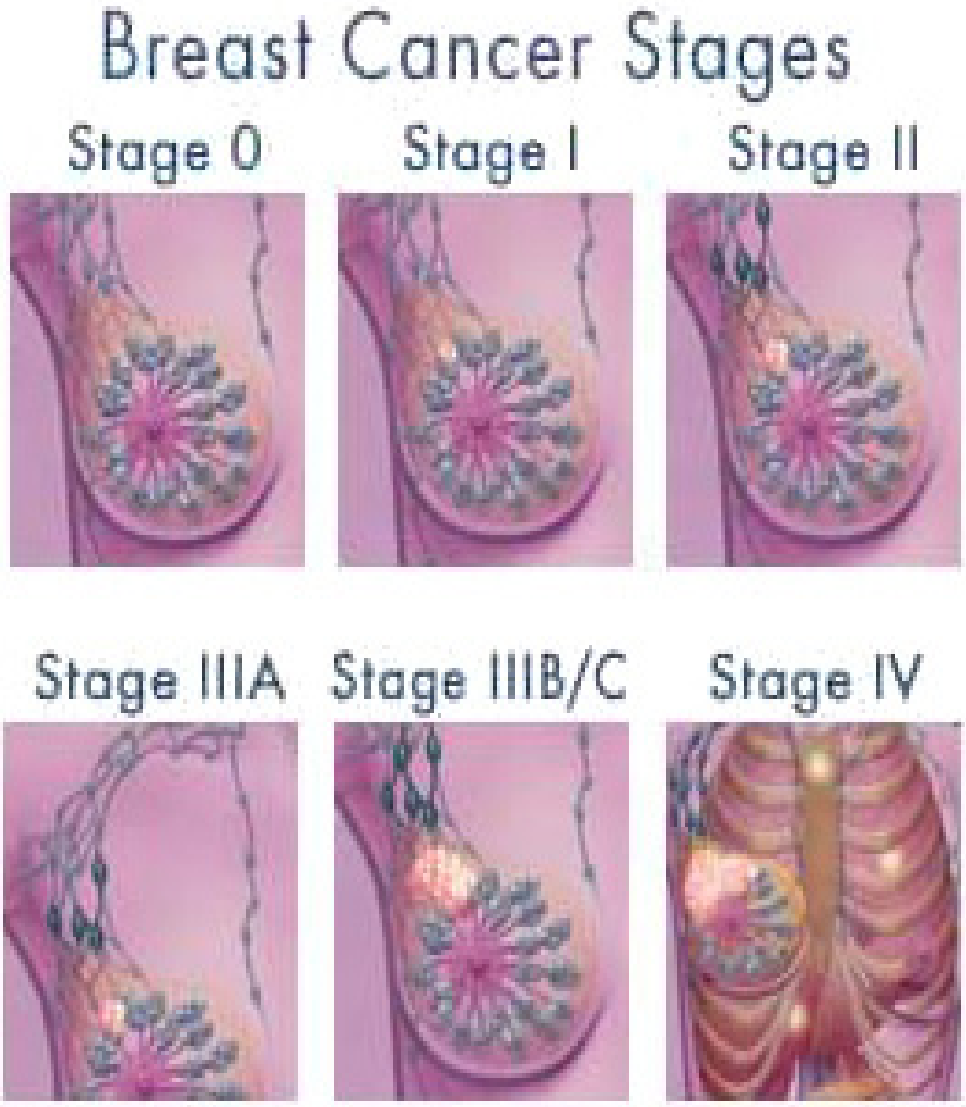
N3c Metastasis in ipsilateral supraclavicular lymph node(s)

M0 No clinical or radiographic evidence of distant metastases

cM0(i+) No clinical or radiographic evidence of distant metastases, but deposits of molecularly or microscopically detected tumor cells in circulating blood,

bone marrow, or other non-regional nodal tissue that are no larger than 0.2 mm in a patient without symptoms or signs of metastases"

M1 Distant detectable metastases as determined by classic clinical and radiographic means and/or histologically proven larger than 0.2 mm"


Breast Cancer Stages
Stage 0
Stage I
Stage II
Stage IIIA
Stage IIIB/C
Stage IV

ANATOMIC STAGE/PROGNOSTIC GROUPS:

Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T0 T1	N1mi N1mi	M0
Stage IIA	T0 T1 T2	N1 N1 N0	M0
Stage IIB	T2 T3	N1 N0	M0
Stage IIIA	T0 T1 T2 T3 T3	N2 N2 N2 N1 N2	M0
Stage IIIB	T4 T4 T4	N0 N1 N2	M0
Sage IIIC	Any T	N3	M0
Sage IV	Any T	Any N	M1

"Inspection of arm and thorax: Edema of the arm may be due to lymphatic obstruction of axillary nodes by malignant cells spreading from carcinoma breast. Edema begins from distal to proximal and more prominent distally (*brawny edema*). Venous obstruction can also cause edema arm. Here edema is more prominent proximally in the arm and is having bluish discolouration over the skin. It is commonly due to infiltration and often by compression of lymph nodal metastatic disease onto the axillary vein. It needs urgent radiotherapy to axilla or chemotherapy otherwise venous gangrene of upper limb may develop. Arm edema may be seen after mastectomy also. Multiple nodules with skin thickening over the arm and chest wall due to carcinomatous infiltration is called as '*cancer en cuirasse'*as it looks like armor coat.

Palpation

Normal breast tissue is firm, lobulated with fine nodularity. Often it can be soft and smooth also. Palpation is also done between thumb and fingers. All quadrants should be palpated along with nipple areola complex and axillary tail of Spence.

During palpation one should look for raise in temperature over the breast (observed in mastitis but also can occur in vascular tumor like medullary carcinoma and sarcoma), tenderness, nature of the swelling—its size, shape,

extent, surface, margin, consistency (carcinoma is hard/stony hard and irregular), fixity to breast tissue (swelling will not have independent/differential mobility), fixity to skin (by pinching the skin), fixity to pectoral fascia (by tethering), fixity to pectoralis major muscle/serratus anterior muscle/latissimus dorsi muscle. Palpate ulcer if present—look for tenderness, its edge and base for induration, bleeding on palpation. Nipple and areola should be palpated for tenderness, eversion, induration and discharge.

Local rise of temperature: It is checked with dorsum of fingers. Breast is warm in mastitis and so also sarcomas can be warmer. Aggressive carcinoma also can be warm due to increased vascularity.

Tenderness: Breast is tender to palpate in acute mastitis and abscess. Carcinoma is non tender initially but becomes tender once skin is involved or when chest wall infiltration occurs.

Number, size and shape: Carcinoma of breast is solitary; fibro adenosis can be multiple. Fibro adenoma is usually solitary but multiple fibro adenomas are known to occur occupying entire breast tissue.

Opposite breast also can be involved especially in fibro adenosis. Size is important in staging the (T staging) carcinoma breast and so it should be measured using a tape (in cm).

Margin: Margin is well-defined and regular in fibro adenoma; well-defined and irregular in carcinoma; ill-defined in fibro adenosis.

Surface: It may be nodular or granular or uneven in carcinoma. Smooth surface is seen in benign condition like fibro adenoma.

Consistency: Fibro adenoma is firm swelling; carcinoma is stony hard; fibro adenosis is firm or diffuse India rubber consistency. Sarcoma is variable with soft or firm or hard in texture.

Fluctuation: When swelling is soft, fluctuation test is done. It is done by examiner standing or sitting behind the patient. Two hands of the examiner are placed above the shoulders of the patient. Swelling is held with one hand and with index finger of the other hand summit of the swelling is pressed/indented. Fluid displacement can be appreciated with yielding of the finger. Cystic swelling, localised abscess can be fluctuant."

"**Fixity of the lump to breast tissue:** It is checked by holding the breast tissue in one hand and moving the lump in other hand. If lump is fixed to breast tissue, then breast tissue moves along the lump. Carcinoma breast is fixed to breast tissue. Fibro adenoma shows free mobility (differential mobility) within the breast tissue and so is called as 'breast mouse'.

Skin tethering can be demonstrated by moving the lump one side. It is due to inward puckering of the skin following involvement of the elastic Cooper's

ligament which becomes inelastic. Dimpling of skin appears which can be demonstrated by raising the arms above the shoulder level. When skin tethering occurs lump can be moved in the arc anywhere without moving the overlying skin whereas lump cannot be moved at all without moving the skin in skin fixation.

Fixity to skin: When tumor directly infiltrates the skin, fixity occurs. Here skin will not be moved separately over the lump. Skin thickening and hard nodules are felt. Peau d' orange can be better seen by holding the skin between thumb and fingers. Whether benign or malignant, when tumor lies beneath the nipple, it is fixed to it. But tumor beneath the areola may or may not be fixed to it as it depends on presence or absence of infiltration to areola.

Fixity to pectoralis major muscle: It is checked in sitting position. Patient is asked to keep her hands on her waist. Lump is moved along the direction of the muscle and also perpendicular to the direction of the muscle. Patient is asked to hold the hands tightly pressed over the waist to contract the pectoralis major muscle (action of the muscle is flexion of the shoulder) which is confirmed by feeling the taut muscle. Lump is again moved along the direction and perpendicular to the direction of the muscle. Mobility along the line of muscle fibers will be restricted totally if lump is adherent to the pectoralis major

muscle. It becomes T3 stage tumor."

Fixity to latissimus dorsi muscle: It is checked in sitting position with examiner standing by the side of the patient. Latissimus dorsi is an extensor of the shoulder joint. Initially mobility of the lump is checked and then arm is extended against resistance with elbow flexed 90° to contract the latissimus dorsi. If now mobility of the lump is restricted, it confirms that lump is fixed to latissimus dorsi muscle

Fixity to serratus anterior muscle: It is checked by checking the mobility of the lump before and after contracting the serratus anterior. Contraction of serratus anterior is achieved by pushing both the outstretched hands against resistance over the wall or over the examiner's shoulders and checking for restriction of mobility of the lump. It signifies involvement of chest wall—stage T4.

Chest wall fixity: It can be assessed by absence/ presence of mobility of the mass; and breast with mass will not fall forward if it is fixed to underlying chest wall; and on raising the arm above shoulder breast with mass will not raise upward. Chest wall fixity means fixity to ribs and intercostal muscles.

"**Palpation of nipple:** It is equally important to palpate the nipple. Tenderness, thickening, hardness, mobility should be checked. Tumor underneath nipple is

usually fixed to nipple. Retraction of nipple may be confirmed by palpating it. Discharge can be better appreciated while palpatin g the lump in the breast or other part of breast tissue or nipple itself. Colour, content (serous, blood, pus, greenish milk) of the discharge can be found. Discharge should be collected for cytology or culture or AFB staining. In retracted nipple, gentle pressing of the base of the nipple is done to evert it. If it is due to congenital or of benign cause, retracted nipple can be everted by pressing at the base. If retraction is due to carcinoma, it cannot be everted at all. Retraction is circumferential in carcinoma; slit like in duct ectasia.

Palpation of areola: Areola should be palpated for nodularity, thickening, ulcer, destruction. Paget's disease can cause destruction of areola.

Examination of an ulcer over breast: Ulcer if present over the breast lump, should be examined like any ulcer with inspection of floor, margin, edge, discharge; palpation for tenderness, induration, mobility, fixity.

Examination of ipsilateral, regional axillary lymph nodes.

Anterior/pectoral, central/medial, posterior, lateral, apical lymph nodes should be examined.

Supraclavicular lymph nodes should be examined.

Examination of opposite breast opposite axilla:

Opposite axillary nodes are also examined. It may get involved through

retrograde spread from internal mammary nodes or through cutaneous lymphatics"

Palpation of Axillary Lymph Nodes

"**Anterior/pectoral group** of nodes are commonly involved nodes. Patient will be in sitting position. Raise the patient's arm high and inspect the axilla. Place the patient's forearm over examiner's forearm. Palpate the relaxed axilla over pectoralis major muscle for any lymph nodes. Examiner will use his left hand to examine the nodes (of right axilla) and his right hand will be over patient's left shoulder to support.

Interpectoral nodes (Rotter's) are also palpated similarly by insinuating the fingers between the two pectori. It signifies retrograde spread of the tumor. It is often difficult to palpate.

Central/medial group of nodes are palpated in similar way like pectoral nodes but hand in the axilla is directed medially over the lateral chest wall and with gentle rolling movements using pulp of the finger.

Lateral/humeral group of nodes are palpated with examiner's right hand (for right axilla) with left hand placed over same side shoulder.

Posterior/subscapular nodes are palpated with patient in sitting position and examiner standing behind the patient. By raising the arm and forearm of the patient from opposite side the posterior axillary fold is palpated between thumb

and fingers.

Apical nodes are palpated (for right axilla) with left hand of the examiner placing high in the axilla with right hand supporting over the shoulder and supraclavicular region of the same side of the axilla. It is often difficult to palpate.

Supraclavicular nodes are palpated using fingers over supraclavicular fossa by standing behind the patient who is asked to shrug the shoulder. **Axillary nodes on opposite side are also examined**.

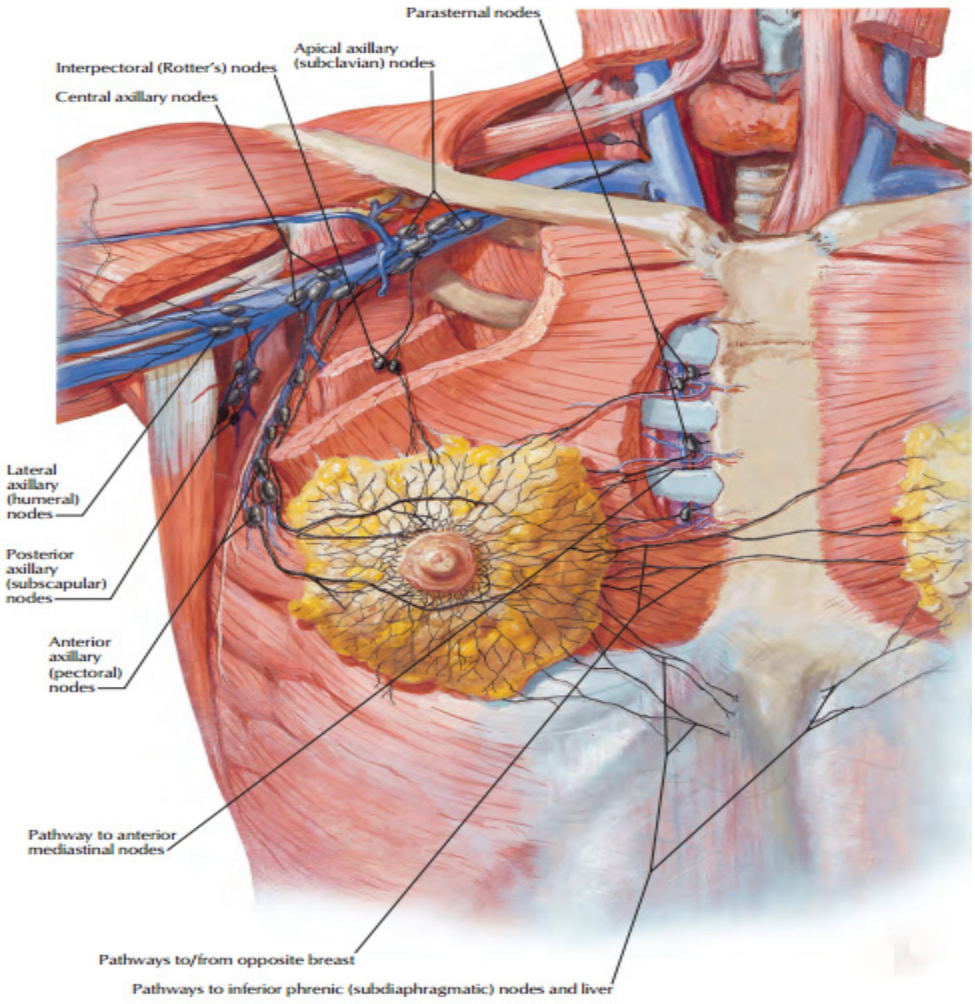
Opposite axilla can be examined by examiner standing on the same side by leaning over the patient or can be examined by standing on the opposite side. Its involvement signifies stage IV disease."

Levels of the axillary nodes (Berg's levels):

Level I—Below and lateral to the pectoralis minor muscle—anterior, lateral, posterior

Level II—Behind the pectoralis minor muscle—central

Level III—Above and medial to pectoralis minor muscle—apical


Parasternal nodes
Apical axillary (subclavian) nodes
Interpectoral (Rotter's) nodes
Central axillary nodes
Lateral axillary (humeral) nodes
Posterior axillary (subscapular) nodes
Anterior axillary (pectoral) nodes
Pathway to anterior mediastinal nodes
Pathways to/from opposite breast
Pathways to inferior phrenic (subdiaphragmatic) nodes and liver

“**Axillary tail of the Spence:** It is the extension of the upper outer quadrant of breast across foramen Langer deep to deep fascia. Foramen Langer is an opening in deep fascia over outer aspect of the breast which allows part of breast tissue to extend under deep fascia. Axillary tail is located adjacent to outer border of the pectoralis major muscle. When it is involved by carcinoma it should be differentiated by pectoral node enlargement. Axillary tail will move along with main breast tissue whereas pectoral node will not move when breast is moved as it has got independent mobility. Axillary tail often extends over the lateral edge of the pectoralis major muscle up to axilla.

Examination of arms for venous edema or lymphedema:

Venous edema may be due to axillary vein compression by nodal mass. Lymphedema may be due to lymphatic block following nodal involvement. Lymphedema is mainly distal. It is gradual in onset and progressive. Venous edema is sudden in onset, with bluish discolouration over the skin, uniform in both distal and proximal aspect of the upper limb (forearm and arm).

Examination for mediastinal node involvement: It is done by percussion. Initially percussion for liver dullness. Percussion is done one space above from lateral to medial, to look for widened mediastinal border. Mediastinal nodes are common in middle mediastinum.

Examination of respiratory system: It is done for secondaries—altered breath sounds, features of consolidation or pleural effusion are looked for. **Examination of abdomen:** To look for palpable nodular liver, Krukenberg tumor in ovaries in menstruating age group, and ascites. It is completed with digital examination of rectum (P/R), and per vaginal examination. **Examination of pelvis, spine, long bones for any swelling**/ tenderness/pathological fracture/restricted movements of spine, hips, etc.

Examination of central nervous system to look for any neurological deficits following metastatic disease in the brain"

“Diagnosis:

The presence or absence of carcinoma in a suspicious clinically or mammographically detected abnormality can only be reliably determined by tissue biopsy. An abnormal MRI does not reliably indicate the presence of cancer, and a non-worrisome MRI does not reliably exclude carcinoma. Available biopsy techniques include fine needle aspiration (FNAC), core needle biopsy, and excisional biopsy. Needle biopsy techniques (FNAC or core biopsy) are preferred because they are more cost-effective than surgical excision, and because most breast lesions are benign, they avoid a surgical scar and potential cosmetic deformity. FNAC is easily performed, but requires a trained pathologist for accurate specimen interpretation and does not reliably distinguish invasive cancer from DCIS, a particular drawback for non-palpable abnormalities, which are often DCIS. Core-cutting needle biopsy has many of the advantages of FNAC, but provides a histologic specimen suitable for interpretation by any pathologist, and facilitates ER, PR, and HER2 testing.”

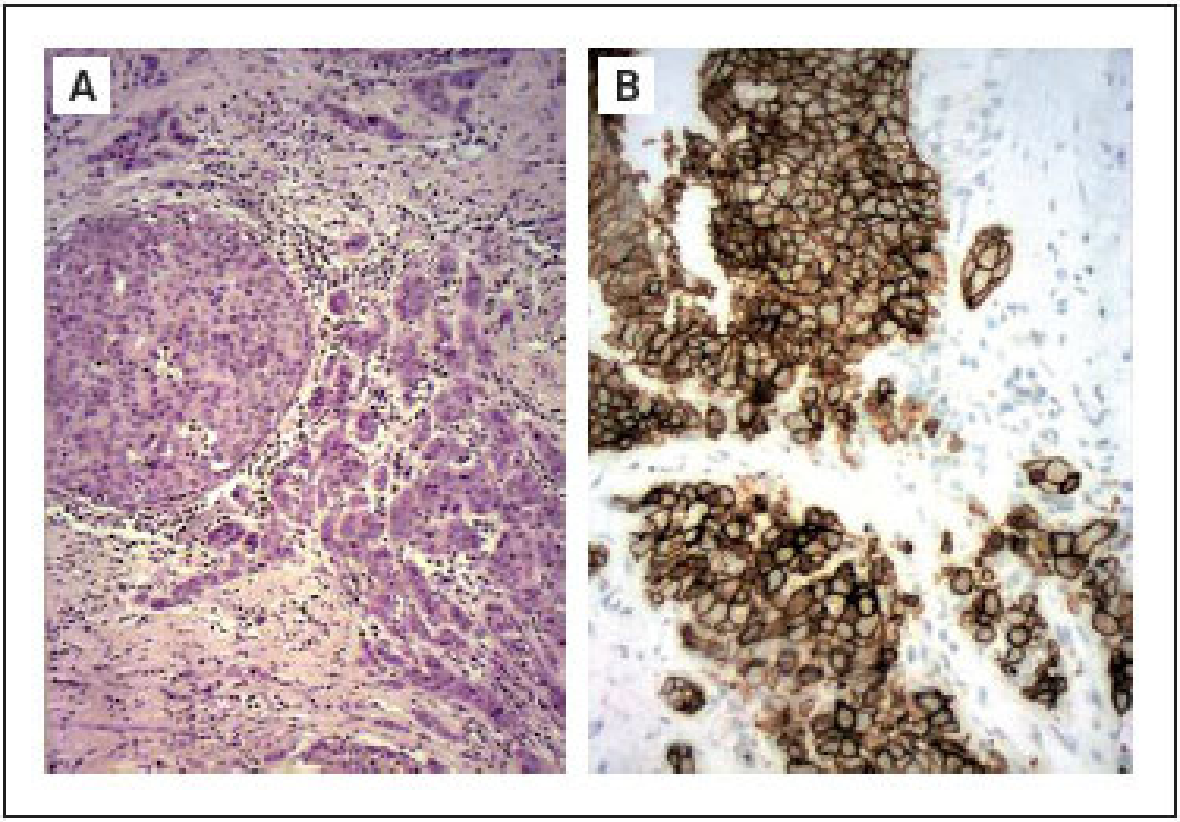


Figure 2. HER2 score 3+ in DCIS (A) and invasive carcinoma (B), both components nuclear grade 3.

Biomarkers

Breast cancer biomarkers are of several types. Risk factor biomarkers are those associated with increased cancer risk. These include familial clustering and inherited germline abnormalities, proliferative breast disease with atypia, and mammographic densities. Exposure biomarkers are a subset of risk factors that include measures of carcinogen exposure such as DNA adducts. Surrogate endpoint biomarkers are biologic alterations in tissue that occur between cancer initiation and development. These biomarkers are used as endpoints in short-term chemoprevention trials and include histologic changes, indices of proliferation, and genetic alterations leading to cancer. Prognostic biomarkers provide information regarding cancer outcome irrespective of therapy, whereas predictive biomarkers provide information regarding response to therapy. Candidate

prognostic and predictive biomarkers and biologic targets for breast cancer include (a) indices of proliferation such as proliferating cell nuclear antigen (PCNA) and Ki-67; (b) indices of apoptosis and apoptosis modulators such as bcl-2 and the

bax:bcl-2 ratio; (c) indices of angiogenesis such as vascular endothelial growth factor (VEGF) and the angiogenesis index; (d)

growth factors and growth factor receptors such as human epidermal growth

factor receptor 2 (HER-2)/neu, epidermal growth factor receptor (EGFr), transforming growth factor, platelet-derived growth factor, and the insulin-like growth factor family; (e) the steroid hormone receptor pathway; (f) the cell cycle, cyclins, and cyclin-dependent kinases; (g) the proteasome; (h) the COX-2 enzyme; (i) the peroxisome proliferator-activated receptors (PPARs); (j) tumor-suppressor genes such as p53; and (k) the mammalian target of rapamycin (mTOR) signaling pathway.

Neoadjuvant chemotherapy (NCT) was initially used to treat inflammatory and locally advanced breast carcinoma and to improve local control, and if possible patient survival. More recently, this strategy has been extended to the management of patients with operable disease, eligible for mastectomy, mainly in order to increase the rate of breast conservation. Nowadays, it is established that positive hormone receptor (HR) status acts as a favorable prognostic factor, and also as a strong predictor of response to adjuvant hormonal therapy. However, in contrast to stable parameters such as human epidermal growth factor receptor (HER)-2 status modifications in HR status have been described in the literature. Aromatase levels and progesterone receptor (PR) levels have been shown to be modified in residual disease after induction chemotherapy in breast cancer treated by NCT (docetaxel) . Arpino et al. have shown that HR status of contralateral breast cancer is independent of the receptor status of the first primary in the absence of adjuvant tamoxifen. Moreover, Lower in a retrospective study, found a discordant HR status in 30% of cases between the primary and metastatic tumors from the same individual. This discordance in HR status had an impact on the overall survival (OS) of these patients. Nicolini found, in 10%–30% of cases, a conversion rate from estrogen receptor $(ER)^{+}$ to ER^{-} and from ER^{-} to ER^{+} between the primary tumor and the metastatic relapse.

The purpose of this study was to investigate the concordance rate of HR status between the initial biopsy and the tumor remaining after NCT.

Patient and tumor characteristics according to type of neoadjuvant chemotherapy

The absence of distant metastasis was confirmed by chest x-ray, bone scan, and liver ultrasound. HR status was re-evaluated, before and after NCT.

Treatment Modalities

NCT breast cancer has already been summarized in detail from prospective phase II clinical trials; for most patients treatment was with protocols: AVCF (doxorubicin, Taxobel (docetaxel). Changes in pathological prognostic factors have been described .Patients received a median number of six cycles of NCT. Chemotherapy was administrated i.v. at 21- or 28-day intervals. After treatment, patients underwent appropriate surgery according to the size of their residual tumor.

Determination of HR Status

Tumor samples were compared when available for the analysis of HR status of the tumor. The first biopsy was a needle core performed before NCT. The second came from the remaining tumor at surgery. A centralized comparative evaluation of ER and PR status was realized by immunohistochemistry (IHC).

To ensure homogeneity of the HR results, HR status was retested on a new section for all patients. HR status was then reevaluated in a blinded fashion by two pathologists, on 420 patients.

Scoring System for HR Status

The HR status was considered as positive if either the ER or PR status, or both, were positive. The HR status was considered negative when both the ER and PR status were negative

The 10% cutoff system is currently used and recommended in France. The cutoff value for positivity was 10% of invasive tumor cells with stained nuclei.

Survival results were last updated in March 2006. Disease-free survival (DFS) was defined as the elapsed time between the date of first diagnosis and the date of first relapse (local, contralateral, and distant event), whatever this relapse might be. OS was the time between the date of initial diagnosis and the date of the last status report, with the patient being alive or dead, whatever the cause of death. Survival curves were established according to the Kaplan–Meier method.

The log-rank test was used for univariate comparisons of survival endpoints. A stepwise Cox regression procedure was carried out to assess the relative influence of prognostic factors on OS and DFS.

Scarff-Bloom-Richardson (SBR) Grading

- Tubule Formation
  - Majority of tumor (>75%) – 1 point
  - Moderate degree (10-75%) – 2 points
  - Little or none (<10%) – 3 points
- Nuclear pleomorphism (compare to adjacent normal epithelium)
  - Small, regular uniform cells – 1 point
  - Moderately increased size and variability – 2 points
  - Marked variation – 3 points
- Mitotic Count (must adjust for microscope field)
  - Low – 1 point
  - Moderate – 2 points
  - High – 3 point

Elston-Ellis modification of Scarff-Bloom-Richardson grading system

- Formation of tubules
- Degree of anaplasia
- Number of mitoses

3-5 points: Low grade
6-7 points: Intermediate grade
8-9 points: High grade

HISTORY OF NEOADJUVANT CHEMOTHERAPHY

Historically, women diagnosed with breast cancer were first recommended local therapy, with emphasis on surgical removal of breast tissue and loco-regional lymph nodes. Subsequently, results of multiple randomized clinical trials have demonstrated unequivocally that adjuvant chemotherapy improves disease-free and overall survival. Adjuvant chemotherapy is commonly recommended to women with stage 2 or 3 breast cancer and to those with high risk stage 1 disease. Given the improvements in survival outcomes observed with adjuvant chemotherapy, investigators from the National Surgical Adjuvant Breast and Bowel Project (NSABP) led by Dr. Bernard Fisher hypothesized that, compared to adjuvant chemotherapy, the administration of the same regimen in the neoadjuvant setting would improve survival outcomes by early elimination of micro metastatic systemic disease. Indeed, the hypothesis was supported by early animal studies demonstrating superior outcomes in mice receiving systemic therapy prior to surgical removal of a tumor .

One of the initial clinical trials testing the hypothesis, designated NSABP Trial B-18, was designed to determine whether the neoadjuvant combination of 4 cycles of doxorubicin and cyclophosphamide (AC) would more effectively prolong disease-free and overall survival than the same chemotherapy given in

the adjuvant setting. Another objective was to determine if the neoadjuvant chemotherapy would permit a more conservative breast surgery and reduce the incidence of ipsilateral breast tumor recurrence by minimizing the tumor size. Survival outcomes were identical among the two groups, with hazard ratio (HR) 0.93 (95% confidence interval [CI], 0.81 to 1.06; P=0.27) for disease-free survival and 0.99 (95% CI, 0.85 to 1.16; P=0.90) for overall survival. Although neoadjuvant chemotherapy did not improve disease-free and overall survival, a higher proportion of women who received neoadjuvant therapy were able to undergo breast conserving surgery compared to the adjuvant group (68% and 60%, respectively, P=0.001). Therefore, a main goal of neoadjuvant chemotherapy is to enhance surgical options and breast conservation. Dozens of trials have demonstrated similar results and the administration of neoadjuvant chemotherapy has become an attractive approach to women with stage 2 or 3 breast cancer who are not candidates for breast conservation.

Importantly, the response to therapy is a powerful individualized prognostic factor. Women who achieve a pathological complete response in the breast following neoadjuvant chemotherapy are expected to experience excellent disease-free and overall survival compared to women with large residual disease. In B-18, women achieving a pathological complete response in the breast had superior disease-free survival (DFS) and overall survival (OS)

compared to those who did not achieve a pathological complete response (DFS HR=0.47, P=0.0001; OS HR=0.32, P=0.0001)).

Different groups have used varied definitions of pathological complete response which may have indicated absence of invasive disease in the breast, or both in the breast and lymph nodes . Others have proposed more continuous definitions such as a residual stage or combination of anatomical and histopathological features. Regardless, in each of these reports, absence of disease in both the breast and lymph nodes provides the best overall outcome.

Investigations of neoadjuvant chemotherapy over the years have produced additional value by both providing data regarding selection of agents or combinations and the appropriate identification of patient populations most likely to benefit from the approach.

Women should be observed closely during treatment and if there is a concern for progressive disease they should be transitioned to an alternative regimen or to a local treatment. Finally, the neoadjuvant treatment approach has become an important vehicle for new drug and biomarker investigation. Response can be assessed clinically or with standard and functional imaging. Moreover, access to tumor tissue is relatively non-invasive and allows both for

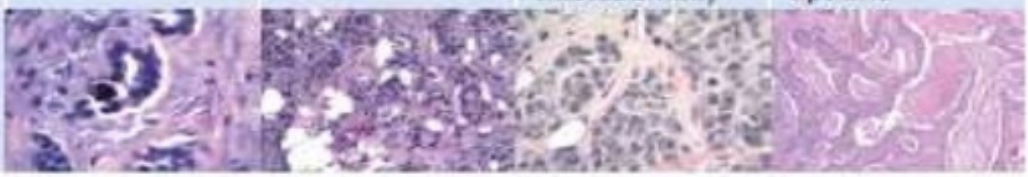
assessment of biomarker modulation following standard or novel treatment and the study of drug mechanism of action.

Women should be informed that neoadjuvant chemotherapy may be associated with potential disadvantages. Initial studies raised concern that breast conserving surgery was associated with increased loco regional recurrence risk. However, newer studies suggest that with adequate free margins, the risk of loco regional recurrence is not higher in women administered neoadjuvant chemotherapy compared to those receiving the same regimen in the adjuvant setting. Another concern is that the inability to determine an accurate pathological stage may be a disadvantage of neoadjuvant chemotherapy. However, the knowledge of residual disease may provide a more personalized prognostic value.

Since disease-free and overall survival are equivalent when the same regimen is administered in the adjuvant or neoadjuvant setting, discussions with an individual woman should focus on the potential benefits and possible disadvantages she may encounter. Once neoadjuvant chemotherapy is initiated, women should be well informed of the goals of treatment, the required preoperative assessment, monitoring response, local treatment considerations, and post-treatment evaluation

SELECTION OF PATIENTS

Members of an International Consensus Expert Panel have suggested that neoadjuvant chemotherapy should be considered in any individual for whom adjuvant chemotherapy is indicated .Once a decision has been made to administer chemotherapy, the entire recommended chemotherapy regimen should be ideally delivered prior to the local therapy. Therefore, a careful staging evaluation must take place prior to initiation of treatment to assess the extent of the disease within the breast and regional lymph nodes, to exclude distant metastatic sites of disease, and to characterize the tumors, as described in Section 4. Initial clinical trials of neoadjuvant chemotherapy have generally included women with stage 2 or 3 disease regardless of their tumor characteristics. More recent understanding of tumor biology has led to refinement of the criteria of women who should be considered for neoadjuvant chemotherapy based on the likelihood of achieving a pathological complete response. Improvements in disease-free survival in those achieving pathological complete response were observed in luminal B/HER2-negative, HER2-positive/non-luminal, and triple-negative breast cancer; but not in luminal A, or luminal B/HER2-positive tumors . Importantly, pathological complete response in HER2-positive (non-luminal) and triple-negative tumors was associated with excellent overall outcome.

Intrinsic Type	Luminal A	Luminal B	HER2 Enriched	Basal Type
Histological Grade	Low to intermediate	Intermediate to high	High	High
Breast Carcinomas, %	40	20	20–30	~ 15
Most Common Marker Results	ER positive PR positive HER negative Low Ki67	ER (weaker) positive PR positive or negative HER2 positive or negative Higher Ki67	ER negative PR negative HER2 positive	ER negative PR negative HER2 negative CK5/6 positive EGFR positive
Prognosis	Good	Intermediate Mutations in *TP53* High risk of relapse	Poor	Poor High frequency of *BRCA1* mutations
Targeted Treatment	Hormonal therapy	Hormonal therapy	HER2-targeted therapies (eg, trastuzumab)	No targeted treatment options
Tumor Histology				

CK = cytokeratin, EGFR = epidermal growth factor receptor, HER2 = human epidermal growth factor receptor 2.

Women with stage 2 or 3 disease whose tumors do not express ER/PR or whose tumors are HER2-positive should be considered for neoadjuvant chemotherapy. Women whose tumors are low grade with a high expression of the hormone receptors and that are HER2-negative are less likely to respond to cytotoxic therapy and should be considered for primary surgery, especially when the nodes are clinically negative. Those women may not require chemotherapy or may be recommended a less aggressive systemic regimen. Women with a limited number of positive nodes may also be eligible for clinical trials randomly assigning them to chemotherapy versus no chemotherapy based on molecular characteristics. For example, in the S1007 trial (RxPONDER) women with hormone receptor-positive, HER2-negative breast cancer with 1–3 positive nodes and a recurrence score of 25 or less are randomly assigned to standard adjuvant endocrine therapy with or without adjuvant chemotherapy). Of note, women with large hormone receptor-positive cancers may be candidates for neoadjuvant hormone therapy, an approach discussed elsewhere in this issue.

ROLE OF NEOADJUVANT CHEMOTHERAPHY

Neoadjuvant chemotherapy has traditionally been recommended to women with locally advanced breast cancer, being employed predominantly to downstage inoperable tumors and allow for definitive surgery. Current consensus opinion for use of preoperative chemotherapy recommends anthracycline- and taxane (paclitaxel)-based therapy. This recommendation is based on data from several prospective trials which suggest that neoadjuvant anthracycline- and taxane-based therapy is associated with the highest response rates . Multidisciplinary management of patients undergoing neoadjuvant therapy by an experienced team is essential in order to optimize the selection of patients, choice of systemic therapy, management of the axilla and surgical approach, as well as the decision to administer adjuvant radiation therapy.

As similar survival benefits have been demonstrated for the administration of chemotherapy before or after surgery, this approach is more frequently recommended to women with primary operable stage 2 or 3 disease.

1. The preoperative period has been accepted as an important setting for evaluation of surrogate biomarkers for both response to therapy and the prediction of clinical outcome.. Tumor response to therapy can be assessed determination pathological response or by exploiting biochemical or

radiologic changes in malignant tissue prior to, during, and following neoadjuvant therapy.

2. The most utilized surrogate predictor of long term outcome in neoadjuvant clinical trials is pathological complete response. Despite the varied definitions in trials completed to date, it has been consistently demonstrated that pathological complete response is associated with superior disease-free and overall survival. Women without residual invasive and noninvasive tumor cells in the breast and axillary nodes have substantially improved outcomes compared to women with similar stage and tumor characteristics and extensive residual disease.

3. Standard clinical & pathologic factors such as age, estrogen receptor or HER2 status, grade, and proliferation index are already used routinely in clinical practice to determine the choice of therapy for those with breast cancer . Chromosomal instability and PTEN loss modules were associated with an increased rate of pathological complete response with anthracycline with or without taxane-based neoadjuvant chemotherapy in ER-negative/HER2-negative and ER-positive/HER2-negative cancers

PATHOLOGICAL RESPONSE

4. pCR is defined as the absence of residual invasive cancer on hematoxylin and eosin evaluation of the complete resected breast specimen and all sampled regional lymph nodes following the completion of neoadjuvant systemic therapy (ie, ypT0/Tis ypN0 in the current AJCC staging system) or
5. pCR is defined as the absence of residual invasive and in situ cancer on hematoxylin and eosin evaluation of the complete resected breast specimen and all sampled regional lymph nodes following the completion of neoadjuvant systemic therapy (ie, ypT0 ypN0 in the current American Joint Committee on Cancer [AJCC] staging system).

luminal A–like tumors.

ER positive and/or PR positive, HER2 negative, grade 1 or 2.

Luminal B/HER2-negative–like tumors.

ER positive and/or PR positive, HER2 negative, grade 3.

Luminal B/HER2-positive–like tumors.

ER positive and/or PR positive, HER2 positive, all grades.

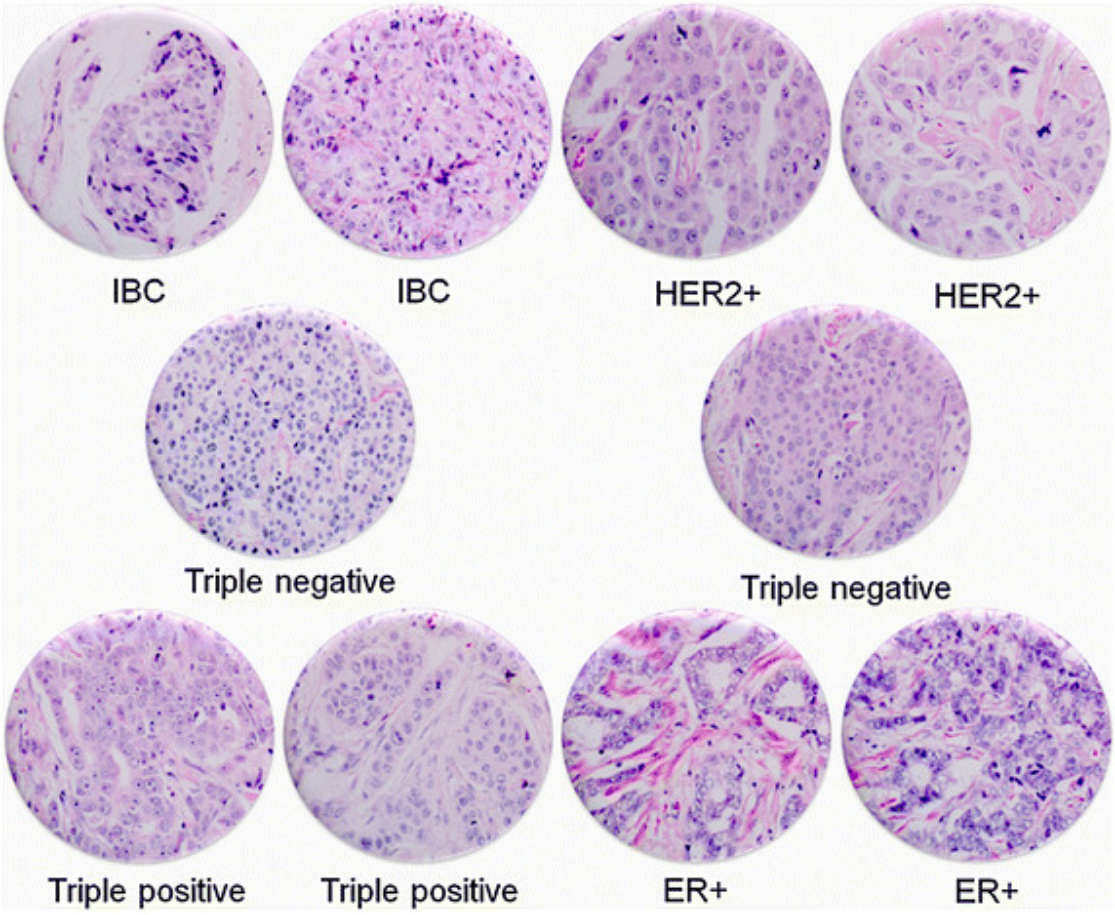
HER2-positive (nonluminal) –like tumors.

ER negative and PR negative, HER2 positive, all grades.

TN tumors.

ER negative, PR negative, HER2 negative, all grades.

Histologic type, tumor grade, and ER, PR, and HER2 status were assessed in the primary tumor core biopsy

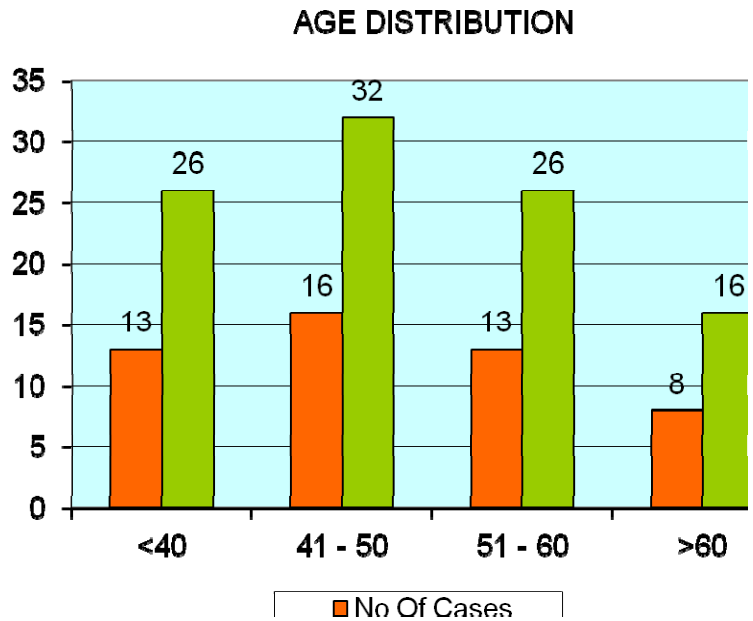

IBC
IBC
HER2+
HER2+
Triple negative
Triple negative
Triple positive
Triple positive
ER+
ER+

Neoadjuvant chemotheraphy

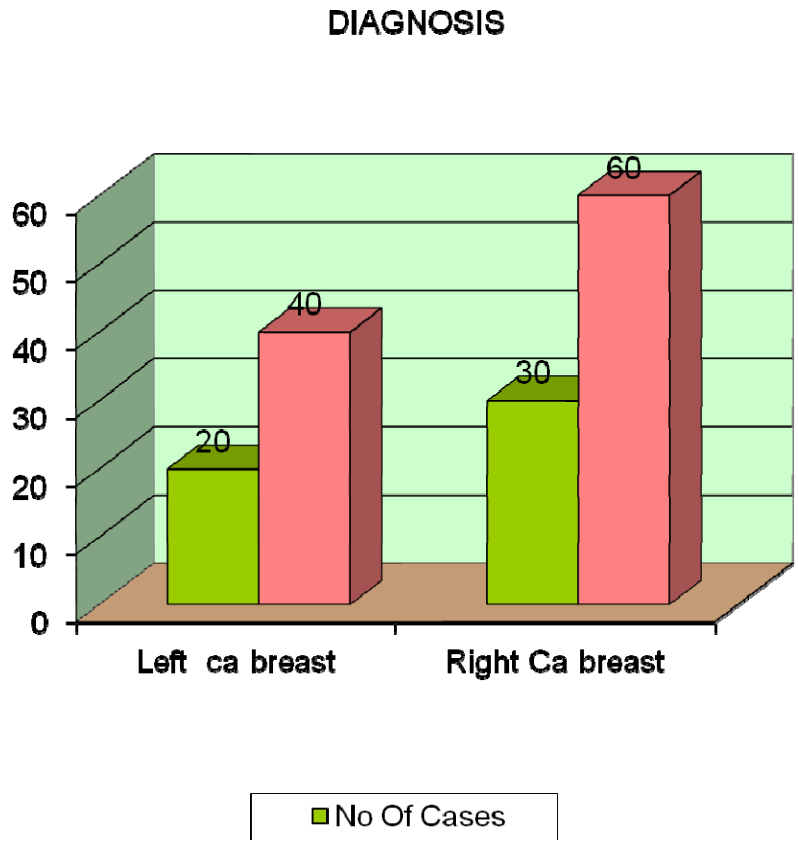
Neoadjuvant chemotherapy has traditionally been recommended to women with locally advanced breast cancer, being employed predominantly to downstage inoperable tumors and allow for definitive surgery. Current consensus opinion for use of preoperative chemotherapy recommends anthracycline- and taxane (paclitaxel)-based therapy. This recommendation is based on data from several prospective trials which suggest that neoadjuvant anthracycline- and taxane-based therapy is associated with the highest PCR rates .

RESULTS

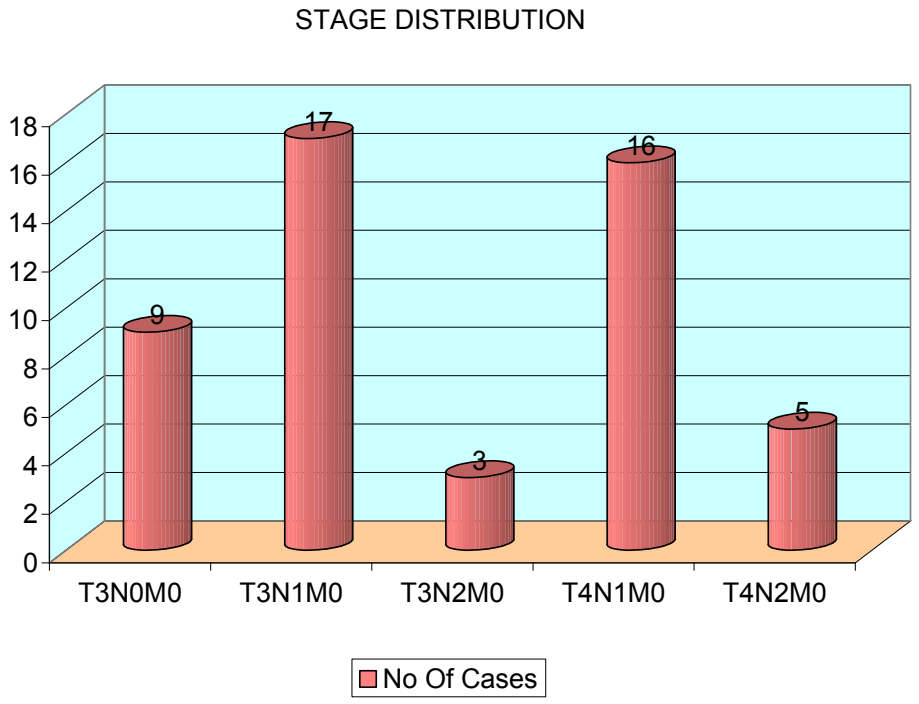
AGE	No Of Cases	Percentage
<40	13	26
41 – 50	16	32
51 – 60	13	26
>60	8	16
Total	50	100



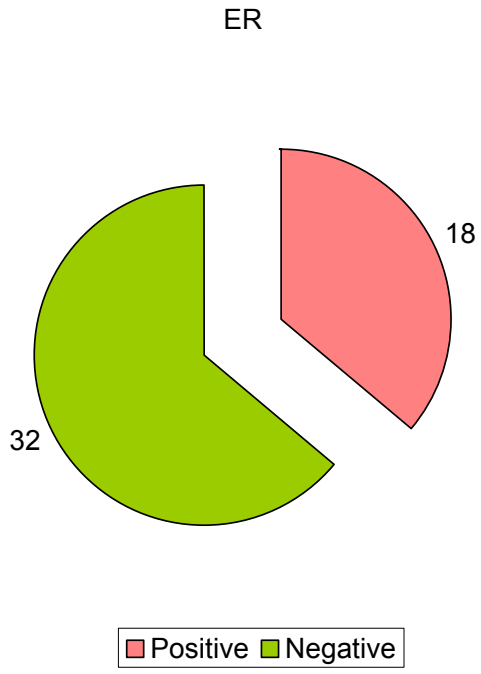
Diagnosis	No Of Cases	Percentage
Left ca breast	20	40
Right Ca breast	30	60
Total	50	100



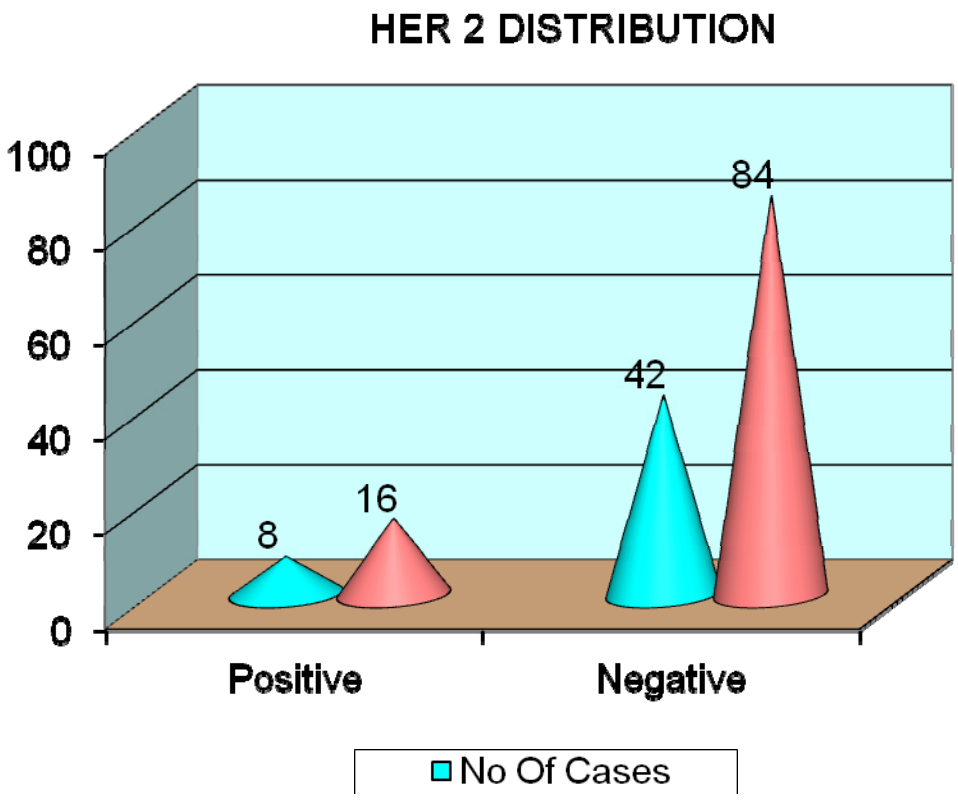
Stage	No Of Cases	Percentage
T3N0M0	9	18
T3N1M0	17	34
T3N2M0	3	6
T4N1M0	16	32
T4N2M0	5	10
Total	50	100



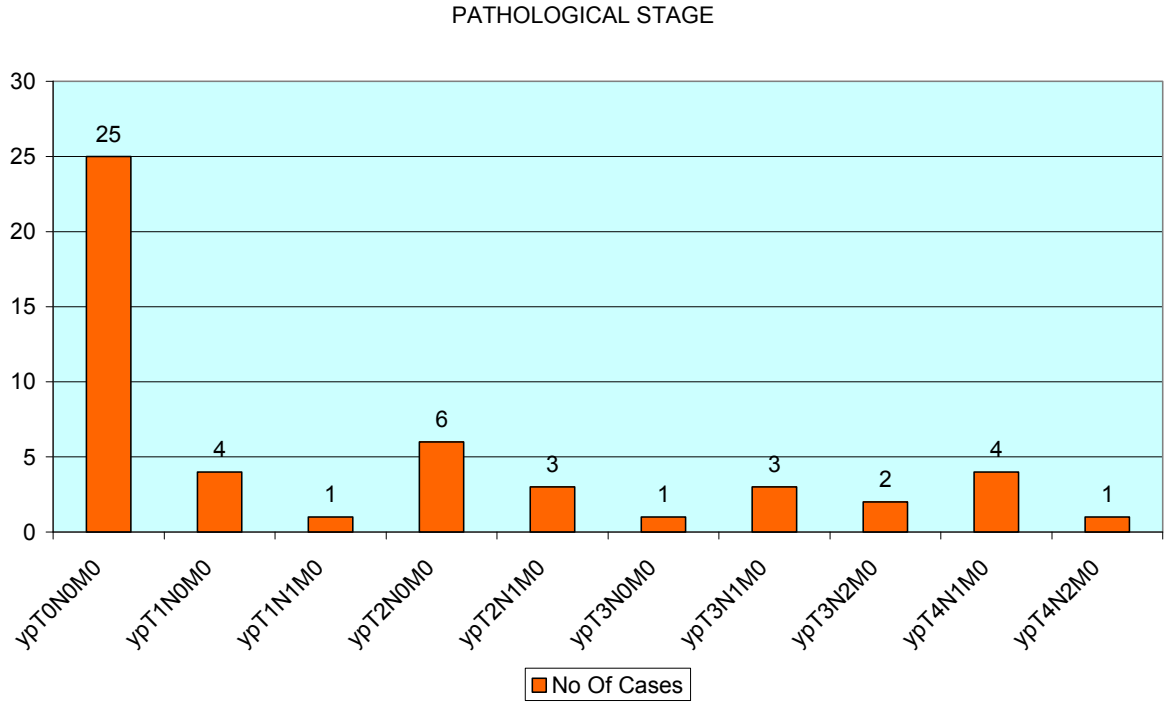
ER / PR	No Of Cases	Percentage
Positive	18	36
Negative	32	64
Total	50	100



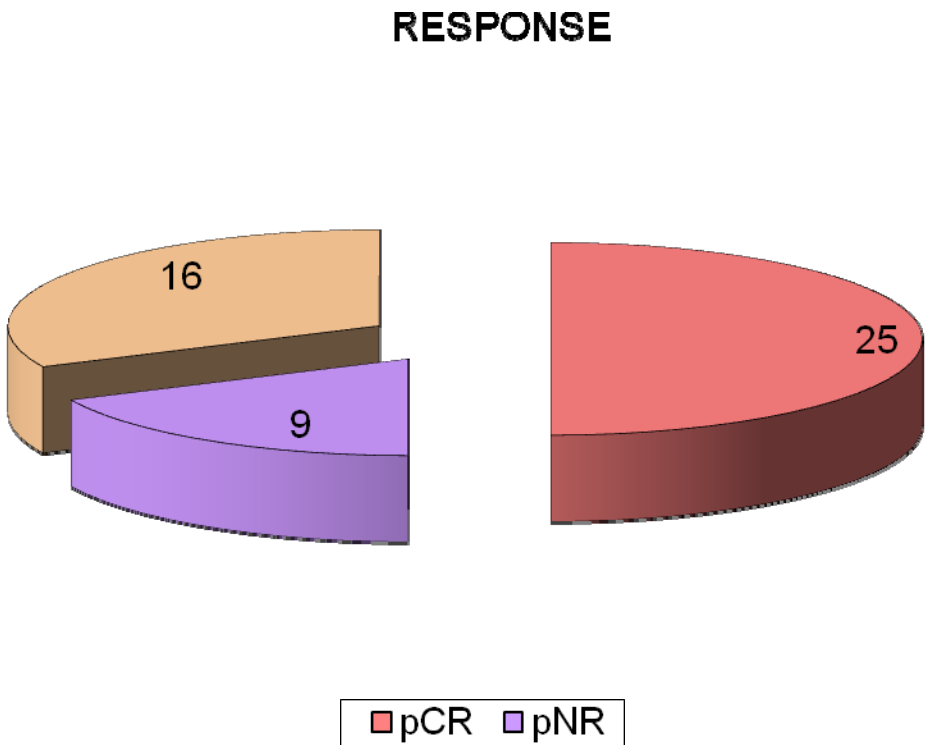
HER 2	No Of Cases	Percentage
Positive	8	16
Negative	42	84
Total	50	100



Pathological Stage	No Of Cases	Percentage
ypT0N0M0	25	50
ypT1N0M0	4	8
ypT1N1M0	1	2
ypT2N0M0	6	12
ypT2N1M0	3	6
ypT3N0M0	1	2
ypT3N1M0	3	6
ypT3N2M0	2	4
ypT4N1M0	4	8
ypT4N2M0	1	2
Total	50	100



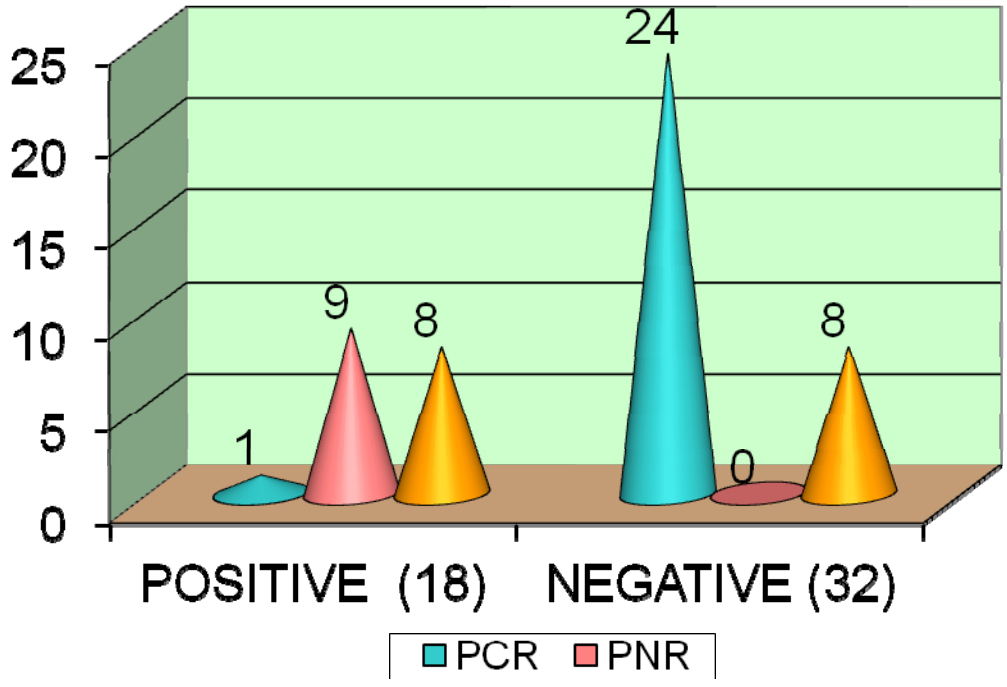
Response	No Of Cases	Percentage
pCR	25	50
pNR	9	18
pPR	16	32
Total	50	100



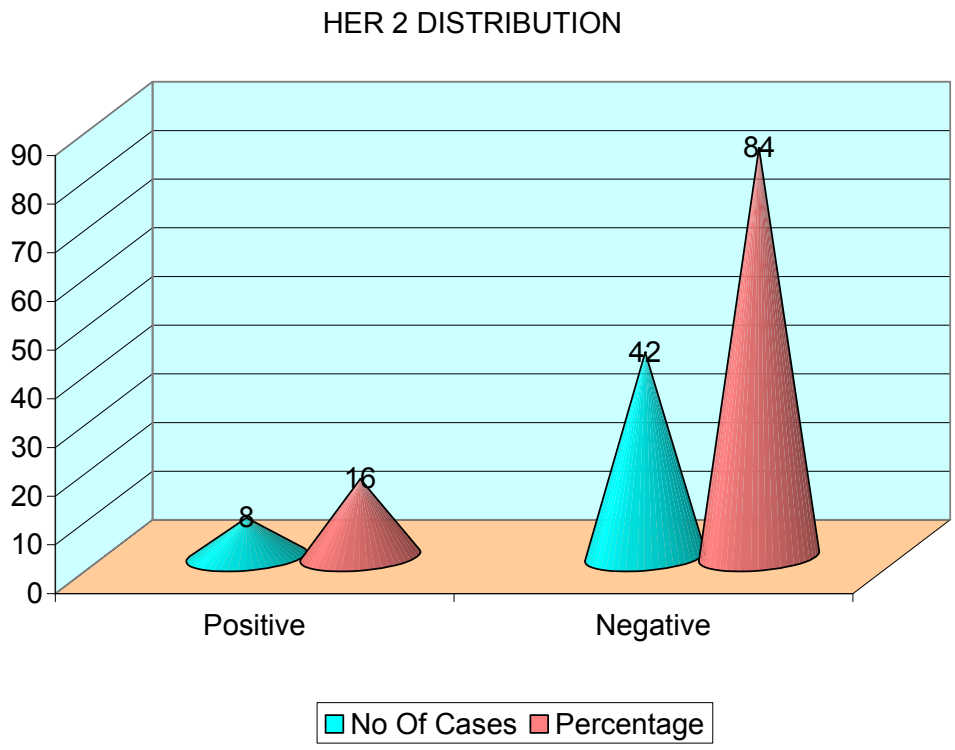
ER / PR VS RESPONSE

ER / PR VS RESPONSE	PCR	PNR	PPR
POSITIVE (18)	1	9	8
NEGATIVE (32)	24	0	8
TOTAL	25	9	16

ER / PR VS RESPONSE



HER2 VS RESPONSE	PCR	PNR	PPR
Positive	2	5	1
Negative	23	4	15
Total	25	9	16



RESEARCH PROPOSAL

AIM &OBJECTIVES

To know the association between hormone receptor status and pathological response in carcinoma breast after neo adjuvant chemotheraphy.

To quantify receptor status for chemotheraphy dose adjustment

1. **ELIGIBILITY CRITERIA :**

- **INCLUSION CRITERA : 1.**PATIENTS OF REPRODUCTIVE AGE GROUP(20-60 YRS) DIAGNOSED AS CARCINOMA BREAST

2. LUMP SIZE MORE THAN 5CMS

3. NO DISTAL METASTASIS

4. PATIENTS CONSENTED FOR INCLUSION IN THE STUDY ACCORDING TO THE DESIGNATED PROFORMA

- **EXCLUSION CRITERIA : 1.**ALL THE PATIENTS PRESENTING WITH LUMP SIZE LESS THAN 5CM

2.AGE MORE THAN 60 YEARS

3.WITH METASTASIS PATIENTS

4.PREGNANCY

ARE NOT CONSENTED FOR INCLUSION IN THE STUDY

3.SOURCE OF DATA : ALL PATIENTS DIAGNOSED TO HAVE CARCINOMA BREAST DISEASE COMING UNDER THE INCLUSION CRITERIA AT GOVT RAJAJI HOSPITAL, MADURAI

4.METHOD OF COLLECTION OF DATA : DETAILS OF CASES, FULL HISTORY, CLINICAL EXAMINATION & SIGNS AND SYMPTOMS OF PATIENTS COMING UNDER THE INCLUSION CRITERIA & THEIR ER/PR STATUS

CLINICAL APPLICATION

Patient selected for study was undergone trucut biopsy and sent for HPE and ER/PR STATUS .

Quantification of hormone receptor status

After confirming that its malignancy, neoadjuvant chemotheraphy is given

After neoadjuvant chemo patient is taken for surgery

Post op HPE is studied

- Good clinical response is absence of residual tumor cells in specimen.
- Partial response is down staging of tumor (ductal to carcinoma in situ)
- Equcivocal response no response or no change in status.
- Poor response tumor size increased

DISCUSSION

Nowadays, Neo adjuvant therapy remains the most efficient adjuvant treatment for HR-negative breast cancer, with a gain in DFS of around 15% at 15 years in a meta-analysis database. Patients treated with this therapy are traditionally selected by an assessment of their HR status. It is generally accepted that an HR negative status predicts response to neo adjuvant therapy.

50 patients with breast cancer included in this study, preoperative core needle biopsy done and hormone receptor status assessed . neoadjuvant chemotheraphy given after hormone receptor status.

Right breast involved in 60 % of cases and upper outer quadrant most commonly involved. Infiltrating ductal carcinoma was the underlying pathology in all cases.

Hormone receptor negativity was seen in more no of patients . Dose adjustments in chemotheraphy is done . After completing chemotheraphy patient is taken for surgery depending upon residual tumor. ER+PR-HER2+, ER-PR+HER2+ and ER-PR+HER2-. In the neoadjuvant setting the pathological complete response (pCR) to primary chemotherapy (PC) is associated to negativity for ER and PR receptors, and in patients (Patients) with HER2 + BC, the addition of trastuzumab to PC increasing the rate of pCR. The aims of this study were to determine the pCR of PC with anthracyclines (A) and

taxanes (T) in Patients with LABC grouped according to ER, PR and HER2 status.

Methods: Patients with LABC treated with PC including A and T were grouped according to ER, PR and HER2 status, and the pCR rate were analyzed using the chi-squared test and correlations with a p value of ≤0,05 were considered statistically significant

.

CONCLUSION

We conclude that pCR is associated with highly favorable outcome. ypN+ residuals only are associated with increased relapse risk and should therefore no longer be considered as pCR. Extent of residual disease and evidence of regression provide helpful additional prognostic information. pCR is a suitable surrogate end point for patients with HER2-positive (nonluminal), TN, and luminal B/HER2-negative tumors but not for luminal B/HER2-positive and luminal A tumors.

In this study 50 post mastectomy specimens were collected hormone receptor negativity is seen in most patients . Pathological response assessed. Dose adjustment in chemotheraphy is also done.

pCR is seen 50% of patients

pPR is seen in 32% of patients

pNR is seen in 18% of patients

We conclude that neoadjuvant chemotheraphy is recommended for patients with hormone receptor negative status , which gives pCR . Thereby enhances patients OS & DFS.

Standard chemotheraphy dose should be administered to patients otherwise response will be poor .

In patients with LABC to group Breast Cancer according to ER, PR and HER2 status can help to predict pCR to Primary Chemotheraphy

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PROFORMA

Name :

Age/sex :

Address :

Occupation :

Phone no :

Diagnosis :

Staging : T

N

M

CHIEF COMPLAINTS:	DURATION
LUMP	
PAIN	
ULCER	
AXILLARY NODE	

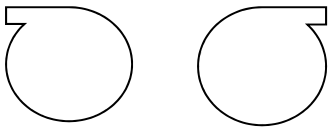
HPE;

FNAC-

TRUCUT-

HISTOLOGY;

R **L**



ESTROGEN RECEPTOR

PROGESTERONE RECEPTOR

HER-2 STATUS

RADIOLOGICAL EXAMINATION;

LUMP SIZE;

PATTERN

AXILLA

INVESTIGATION;

HB-

RBS-

UREA-

CREATININE-

Sr.electolytes;

ECG/ECHO:

NAME:

WEIGHT:

DIAGNOSIS:

IST CYCLE OF CHEMOTHERAPHY:

REGIMEN;

CLINICAL EXAMINATION;
%reduction in size

NAME:

WEIGHT:

DIAGNOSIS:

3rd CYCLE OF CHEMOTHERAPHY:

REGIMEN;

CLINICAL EXAMINATION;

%reduction in size

NAME;

WEIGHT;

DIAGNOSIS

CLINICAL EXAMINATION AFTER CHEMOTHERAPHY
CyT N M

RADIOLOGICAL EXAMINATION;
CyT N M

ON TABLE EXAMINATION;
Yp T N M

PATHOLOGICAL LUMP SIZE;

RESPOND TO CHEMOTHERAPHY;
PATHOLOGICAL RESPONSE-

NO RESPONSE-

PARTIAL RESPONSE-

COMPLETE RESPONSE-

MADURAI MEDICAL COLLEGE
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(Affiliated to The Tamilnadu Dr.MGR Medical University, Chennai, Tamil Nadu)

ETHICS COMMITTEE CERTIFICATE

Name of the Candidate : Dr.R.Krishna bharathi

Course : PG in MD., General Surgery

Period of Study : 2015-2018

College : MADURAI MEDICAL COLLEGE

Research Topic :

Correlation of pathological response and hormone receptor status after neoadjuvant chemotherapy in carcinoma breast and quantification of hormone receptor status for chemotherapy dose adjustment.

Ethical Committee as on : 17.03.2017

The Ethics Committee, Madurai Medical College has decided to inform that your Research proposal is accepted.

Member Secretary Chairman Dean / Convenor

Madurai Medical College
Madurai-20

Prof Dr V Nagaraajan
M.D., MNAMS, D.M., Dsc.,(Neuro), Dsc (Hon)
CHAIRMAN
IEC - Madurai Medical College
Madurai

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