Introduction
Cancer can be defined as a group of diseases that are characterized by uncontrolled cell proliferation and impaired differentiation. Although a variety of factors are known to play a role in the etiology of cancer, it appears that a cancer arises from a single altered cell. The initial change in a transformed cell is an alteration in a regulatory genes caused by a carcinogen. When one of these regulatory genes becomes altered and undergoes numerous mutations, it then has the capacity to contribute to the development of a malignant clone, called an oncogene. Oncogenes play a vital role in normal cellular proliferation, differentiation, and behavior (Yarbro JW et al 1997, Damjanov I et al 1996). The carcinogenesis is mainly divided in three steps viz. initiation, promotion and progression.

Initiation

Initiation is the process by which a carcinogen acts at the intracellular level. The initiation of carcinogen is usually classified as chemical, physical, viral, or familial. The initiating carcinogen causes an alteration in the molecular structure of the cellular DNA that is irreversible. If the DNA fails to repair itself prior to cell division, the cell has the potential to become neoplastic (Archer MC 1992).

Promotion

Promotion follows initiation and refers to the effect of the continued action of certain promotors. While the promoter itself does not cause the carcinogenic event, it does cause the cell that has undergone initiation to
become malignant (Yarbro JW et al. 1997). The promoting agent does this by causing cellular alterations during a long latency period (Archer MC 1992). It appears that promotion is a critical determinant in neoplastic transformation and one that can possibly be manipulated to prevent the development of cancer.

**Progression**

Progression is the phase of neoplastic growth in which a tumor undergoes changes causing it to increase in malignancy (Archer MC 1992). These changes are usually related to morphology or proliferation. Progression may result from the emergence of a heterogeneous subset of cells within a tumor that have the capacity to proliferate more rapidly or to metabolize at a faster rate (Damjanov I, 1996). The critical event in the progressive phase is local tissue invasion and metastatic spread to distant sites.

**Breast Anatomy**

The breasts of an adult woman are milk-producing, tear-shaped glands. They are supported by and attached to the front of the chest wall on either side of the breast bone or sternum by ligaments. They rest on the major chest muscle, the pectoralis major. The breast has no muscle tissue. A layer of fat surrounds the glands and extends throughout the breast.
The breast is responsive to a complex interplay of hormones that cause the tissue to develop, enlarge and produce milk. The three major hormones affecting the breast are estrogen, progesterone and prolactin, which cause glandular tissue in the breast and the uterus to change during the menstrual cycle. Each breast contains 15 to 20 lobes arranged in a circular fashion. The fat (subcutaneous adipose tissue) that covers the lobes gives the breast its size and shape. Each lobe is comprised of many lobules, at the end of which are tiny bulb like glands, or sacs, where milk is produced in response to hormonal signals. Ducts connect the lobes, lobules, and glands in nursing mothers. These ducts deliver milk to
openings in the nipple. The areola is the darker-pigmented area around the nipple (figure 1).

Figure 2 and figure 3 depict detailed information about breast anatomy.

**Figure- 2: Quadrants of the Breast**

"Clock" Positions, Quadrants and ICD-O Codes of the Breast

Note: C50.6 is the code for axillary tail or tail of breast.

Blood and lymph vessels form a network throughout each breast. Breast tissue is drained by lymphatic vessels that lead to axillary nodes (which lie in the axilla) and internal mammary nodes (which lie along each side of the breast bone). When breast cancer spreads, it is frequently to these nodes.
Breast Cancer: Incidence and Etiology

Breast cancer is the second most prevalent cancer among Indian women. One in 58 women are affected by breast cancer in the age group of 30-70 years and are mainly seen in the urban areas. The seriousness of the situation is apparent after going through recent data from Indian Council of Medical Research. The rise is being documented mainly in the metros, but it can be safely said that many cases in rural areas go unnoticed. It is reported that one in 22 women in India is likely to suffer from breast cancer during her lifetime. The incidence of breast cancer is rising in every country of the world especially in developing countries such as India. This is because more and more women in India working outside their home which allows various risk factors of breast cancer to come into play.

Breast cancer, like other forms of cancer, is considered to result from multiple environmental and hereditary factors.
1. Lesions to DNA such as genetic mutations. Exposure to estrogen has been experimentally linked to the mutations that cause breast cancer. Beyond the contribution of estrogen, research has implicated viral oncogenesis and the contribution of ionizing radiation.

2. Failure of immune surveillance, which removes malignancies at early phases of their natural history.

3. Abnormal growth factor signaling in the interactions between stromal cells and epithelial cells, for example in the angiogenesis necessary to promote new blood vessel growth near new cancers.

4. Inherited defects in DNA repair genes, such as BRCA1, BRCA2 and p53.

5. Oxidative stress

Although many epidemiological risk factors have been identified, the cause of any individual breast cancer is often unknown. In other words, epidemiological research informs the patterns of breast cancer incidence across certain populations, but not in a given individual. Hereditary, hormonal and reproductive factors are associated with risk of breast cancer. Approximately 5% of new breast cancers are attributable to hereditary. Dietary influences have been proposed and examined, and recent research suggests that low-fat diets may significantly decrease the risk of breast cancer as well as the recurrence of breast cancer. Among
premenopausal women high intake of low-fat dairy foods was associated with reduced risk of breast cancer.

**Biology and scope of Present study**

In recent years significant advances have been made in the understanding of biology of breast cancer. The advent of advanced molecular biology techniques, mapping of the human genome and availability of high throughput genomic and proteomics strategies have opened new opportunities and will potentially lead to the discovery of novel biomarkers for early detection and prognostication of breast cancer. The primary prognostic factors for breast cancer still remain those determined by clinical or standard pathological approaches. These include axillary lymph node status, tumor size, histological or tumor grade, histological subtype and the presence or absence of metastatic disease. These pathological criteria have been used for decades for diagnosis and patient management. Currently many biomarkers, particularly the hormonal and epidermal growth factor receptors are being utilized for the breast cancer prognosis. Unfortunately, none of the biomarkers in use have sufficient diagnostic, prognostic and/or predictive power across all categories and stages of breast cancer. Biomarkers are materials of genetic origin that represent the molecular processes associated with biological mechanisms. When used in oncology, biomarkers are expected to provide information on the character, potential behavior of the tumor and disease outcome. The presence/absence or increased/decreased levels of such genetic
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materials in tumors typically predict the relative virulence of a particular tumor. The over or under expression of a strong and independent marker

1. have strong diagnostic, prognostic and/or predictive significance
2. Sensitive, selective and strongly associated with the disease;
3. Measurable via non-invasive or minimally invasive procedures;
4. Useful in the majority of the population

There are number of biomarkers that are currently being utilized or that may be useful for breast cancer diagnosis, prognosis, prediction of disease course, response to therapy and overall survival. The hormone receptors are routinely assessed on most breast cancer specimens, partly to identify patients that will benefit from hormonal therapy. Most reported biological markers mark the presence of metastatic disease or identify patients at high risk of disease progression or recurrence. Unfortunately, individual biomarkers do not have sufficient “predictive power” across all categories of patients. It is suggested that future cancer screening tests will combine the results of multiple diagnostic tests or biomarkers assays with prior testing histories and patient's specific risk factors for better management of cancer.

**Hormone related biomarkers:** The steroid hormone receptor-associated biomarkers are by far the most widely interrogated and reported breast cancer biological markers. The estrogen (ER) and progesterone (PR)
receptors, which provide prognostic and predictive information, are the most widely studied and utilized. Clinical studies indicate that ER negative and PR positive patients have lower grade tumors at diagnosis and show increased disease-free survival and increased overall survival compared to ER negative and PR negative patients. The exact mechanism by which PR interacts with ER remains largely unknown (Arciero et al Int. J. of Biological Markers 2003).

**Figure-4:** Schematic representation of interactions and pathways existing between hormone receptors (ER&PR), p53, cerbb2, bcl2, topo II alpha.

**Apoptosis** ("normal" or "programmed" cell death) is a physiological mechanism of cell loss that depends on both pre-existing proteins and *de novo* protein synthesis.
Figure-5: Morphological features of Apoptosis

(Source—Apoptosis wikiepedia online ). Apoptosis is a highly regulated process; one important regulator of apoptosis is Bcl2.

**Cellular activity related biomarkers: Bcl2** is a proto oncogene that is located on chromosome 18(18q21.33) and encodes a mitochondrial protein involved in multiple cellular functions, including the inhibition of programmed cell death. Bcl2 is expressed in approx. 80% of breast cancers derived from women with primary tumors. **Bcl2** a proto oncogene that is located on chromosome 18 (18q21.33) and encodes a mitochondrial protein involved in multiple cellular functions, including the inhibition of programmed cell death. The oncoprotein is a 26 KDa integral membrane protein localized to the membranes of the endoplasmic reticulum, mitochondria, and nuclear envelope. It can function to suppress or delay the induction of apoptosis in a number of systems, including prostate, skin, lymphoid tissues, and mammary gland.

**BAG-1** A multifunctional protein that regulate apoptosis, Proliferation, Transcription & Metastasis. It has multiple isoforms generated by alternate translation initiation from a single mRNA. BAG-1L and predominantly
nuclear localization of this isoforms. BAG-1 S largely located in cytoplasm and BAG-1 M between nucleus & cytoplasm.

**Figure-6:** Structure and Function of BAG-1

BAG-1 is a recently identified Bcl2-binding anti apoptotic protein that may play an important role in the pathogenesis of breast cancer. BAG-1 interacts with Bcl2 and enhanced the antiapoptotic activity of Bcl2 in invitro experiments. It also binds to hepatocyte growth factor receptor and enhances the protection from apoptosis by hepatocyte growth factor receptor. Over expression of BAG-1 resulted in sustained cell viability and proliferation, with minimal apoptosis and growth factor–independent state (Cutress et al 2002).
Cell cycle-related biomarkers

Cell cycle regulation is a critical phenomenon in all known biological systems. Cell cycle dysregulation is an important step that must occur in precancerous cells and that participates to carcinogenesis. Particularly the human epidermal growth factor receptor, p53, cyclinD1, topo II alpha and nm23-h1 are the most interrogated and evaluated as prognostic and/or predictive markers for breast cancer.

P53 tumor suppressor gene is the most frequently mutated and extensively studied gene associated with human cancers. The gene is located on chromosome 17 (17p13.1) and encodes a nuclear phosphoprotein that plays a role as a marker in breast cancer. The protein also plays a role in the inhibition of abnormal DNA replication and facilitation of apoptosis, blocking angiogenesis through binding to various parts of the genome, stimulating or inhibiting gene expression. The role of p53 in cell cycle regulation has been extensively characterized and it is believed that this gene regulates the transition from G1 to S-phase and G2 to mitosis. The p53 tumor suppressor gene is the most frequently mutated and extensively studied gene associated within human cancers.

P53 protein can be divided into three regions

1. The acidic amino terminus which contains the transactivational domain and which is the target for several protein partners of p53 such as TBP or mdm-2.
2. The central region of the protein, containing several very hydrophobic regions and very few charged amino acids, is involved in the specific DNA binding function of p53. Only this region has been explored by X-ray crystallography.

The LH domain is involved in the folding of several discontinuous regions in order to build a functional DNA binding domain. More than 95% of the mutations found in human cancer are localized in this central region. The immunodominant epitopes are localized in two well characterized discontinuous regions in the amino terminus and in a longer, less well defined region in the carboxy-terminus.

Figure-7: Structure of p53 protein

Topoisomerases II alpha is a 170 KD protein, which is considered a proliferation marker and is present only during the late S and G2 phases of the cell cycle belongs to the type-II enzymes and is represented in humans by two highly homologous isoforms, namely alpha (170kDa) and beta (180kDa). TOP2 alpha protein, which is encoded by a gene located on chromosome 17 (17q21.2) and positioned telomeric to the ERBB2 oncogene.

Proliferative activity biomarkers

Cell proliferation is controlled by

- Growth factors that bind to receptors
- Receptors on the cell surface that connect to signaling molecules.
- Signaling molecules (Signal Transduction pathway) that convey message from receptor to the nucleus where TF binds to DNA.
- Transcription factors bind to DNA, turning on or off the production of proteins that cause cells to continue dividing.

Proliferation is an important cancer-associated phenomenon that has been widely investigated in relation to breast cancer progression. The pathways associated with proliferation have been well studied and there are many reports that show that proliferative potential of breast tumors has both prognostic and predictive significance. Ki67 and bcl2 are reported to have significant clinical significance for breast cancer.
Ki67 antigen was the first immunohistochemically detectable marker of proliferating cells, Moab that recognizes a nuclear epitope present only in proliferating cells and expressed in cycling cells in G1, S, G2 phase and during mitosis but not in G0 phase.

Her2 and the three other members of the HER tyrosine kinase receptor family play important roles in regulation of cell growth, cell survival and cell differentiation. The CerbB2 gene is a proto-oncogene that encodes a 185 kDa transmembrane phosphorglycoprotein that has intracellular, transcellular and extracellular domains. The CerbB2 gene, also known as HER-2Neu, is located on chromosome 17 (17q11.2-q12). CerbB2 is over
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expressed in 25-30% of breast and ovarian carcinomas as well as in 40-60% of intra ductal breast carcinomas.

**Epithelial biomarkers and tumor-associated antigen biomarkers**

These have become important because they have been found useful as sensitive markers for distant metastasis of epithelial origin and nodal status of patients with breast cancer. Although many epithelial biomarkers and tumor-associated antigens are known, cytokeratin19, mammaglobin and muc1 are the most widely evaluated as biomarkers for breast cancer.

**Table-1:** TNM definitions for Breast Cancer

<table>
<thead>
<tr>
<th>Tumor size (T)</th>
<th>Nodal involvement</th>
<th>Metastasis (M)</th>
</tr>
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<tbody>
<tr>
<td>Tis in situ</td>
<td>N0 nodal metastasis</td>
<td>M0 No distant metastasis</td>
</tr>
<tr>
<td>T1 &lt;2 cm</td>
<td>N1 Movable axillary nodes</td>
<td>M1 Distant metastasis</td>
</tr>
<tr>
<td>T2 2-5 cm</td>
<td>N2 Fixed axillary nodes</td>
<td></td>
</tr>
<tr>
<td>T3 &gt;5 cm</td>
<td>N3 Internal mammary nodes</td>
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<tr>
<td>T4 extension to chest wall</td>
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These TNM categories are combined to give the stage (eg. Stage I = T1N0 M0; Stage II = T2N1M0)

Numerous sub-classification and variations exist with the TNM system

**Tumor staging**

Anatomic tumor staging is performed to determine “to extent of disease” it is related to the size of the primary tumor mass, extent of local spread,
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nodal involvement, and the systemic spread (metastasis) of disease. The
TNM classification system is commonly used to stage many cancers. The
system is such that $T =$ primary tumor size and/or extent of invasion, $N =$
nodal involvement, and $M =$ presence or absence of metastases.
Table I shows the simplified depiction of the TNM classification for breast
cancer.

**Histologic types of Breast Cancer**

**Invasive Carcinoma** – Tumors included in this category are all those in
which stromal invasion is detectable, whether an insitu component is
identifiable or not and regardless of the relative proportion of the two
components. Divided into two major categories: - **Ductal and Lobular**
(Rosen PP, 2001). Invasive ductal carcinoma are divided into two major
criteria Cycoarchitecture and pattern of spread. The morphologic
variations in the Ductal carcinoma represent a small, but important, group
of pre invasive breast cancers that can almost always be cured by local-
regional therapy. Only 1% of these early cancers are associated with
metastasis to axillary nodes, and almost all 98% are cured by local-
regional therapy regardless of their size, systemic adjuvant therapy is
unnecessary. Invasive carcinoma carries with it the clear potential for
metastasis and a diminished opportunity for cure. The term "microminvasive"
is loosely used to describe the process of invasion in its earliest
beginnings and to suggest that a tumor is still highly curable and a group,
invasive carcinomas 5mm or less in diameter have widely divergent rates of metastasis to regional lymph nodes ranging from 3-28%. A number of additional histologic features of invasive ductal and lobular carcinomas have prognostic value when considered in isolation. They include histologic grade, nuclear grade, tumor borders as stellate or circumscribed, peritumoral lymphatic and blood vessel invasion and necrosis within the tumor. Histologic grade is currently based on the degree of tubule formation, number of mitosis, and nuclear pleomorphism in routine sections. These are combined as the Bloom-Richardson (BR) grade or Scarff-Bloom-Richardson grade. Grades from 1-3 indicate progression from well differentiated (Low or good) to poorly differentiated (high or poor grade). Histologic and nuclear grade are subordinate to node status and tumor size as prognostic features, but both are significant predictors of overall mortality for node - positive and node- negative patients. Poor histologic and nuclear grade may indicate responsiveness to adjuvant chemotherapy. Adjuvant chemotherapy has been observed to produce a greater improvement in prognosis among node positive and node negative patients with poorly differentiated tumors than among such patients with well-differentiated tumors. Among node negative patients, the prognostic influences of nuclear and histologic grades are clearly evident. There are ductal carcinoma in situ, lobular carcinoma in situ, invasive lobular carcinoma, invasive ductal carcinoma, non-invasive-solid, comedo, cribriform, papillary carcinoma, vascular and lymphatic invasion. Tumors with the classical Comedo carcinoma appearance (or the grade 3 ductal
carcinoma insitu of other classification) are characterized by aneuploidy, positivity for hormone receptors, metallothionein expression cerbb2 over expression and a high frequency of p53 expression. In solid form of ductal carcinoma, the glandular lumen is filled by the proliferation of medium sized cells, which are smaller and more uniform than those of comedo carcinoma. A feature of diagnostic important is common to all forms of DCIS are the appearance of the luminal content. Lobular carcinoma in situ. is known as lobular neoplasia, has no distinguishing features on gross examination and is usually found incidentally in breasts removed for other reasons. In general atypia, pleomorphism, mitotic activity and necrosis are minimal or absent Tubular carcinoma has also been designated as well differentiated carcinoma but the latter term is not advisable because it has also been used for other well differentiated tumors with other patterns of growth. The average age of patients is about 50 years. Grossly tubular carcinoma suggests malignancy by virtue of its poorly circumscribed margins and had consistency it is characteristically small with a mean diameter of about 1 cm. Cribriform carcinoma is a rare form of breast malignancy closely related to tubular carcinoma and sharing with it as excellent prognosis. The tumor has cribriform appearance similar to that seen in the more common in situ counterpart, but it also exhibits stromal invasion. Mucinous carcinoma also known as mucoid, colloid gelatinous carcinoma usually occurs in postmenopausal women. Grossly, it is well circumscribed, crepitant to palpation and formed by a current jelly like mass held together by delicate septa. Microscopically it is often
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described as a small clusters of tumor cells "floating in a sea of mucin. This cluster may be solid or exhibit acinar formation. The mucin is almost entirely extracellular. Medullary carcinoma usually appears in patients under 50 years of age and is said to be particularly common in Japanese women. Grossly it is well circumscribed and may become large; it can be mistaken clinically & grossly for a fibroadenoma. Apocrine carcinoma is a very rare form of breast malignancy (1-4%) of all cases. The large tumor cells have an abundant acidophilic, somewhat granular cytoplasm, which may contain eosinophilic or golden brown granules that are strongly PAS positive. The nuclei are vesicular & nucleoli are prominent. Glandular differentiation is usually found, the luminal portion of tumor having a characteristic bulbons expansion ("apocrine snout"). Metaplastic carcinoma is a generic term for breast carcinoma of ductal type in which the predominant component of the neoplasm has an appearance other than epithelial and glandular and more in keeping with another cell type. Papillary carcinoma is a very distinct type, thought to arise from large ducts and makes up only a small percentage of breast carcinomas.

The word tumor is derived from the Latin word tumere meaning, "to swell". At one time, the word was used to indicate any type of swelling (traumatic, inflammatory, neoplastic). Today, its meaning often is used synonymously with the term "neoplasm". Composed of two terms, neo (new) and plasma (formation), the word neoplasm refers to an abnormal growth of tissue whose cells usually have rapid growth. Neoplasia is the
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The pathologic process that results in the formation and growth of a neoplasm (tumor) (Devita 7th edition). A tumor can be either benign or malignant.

**Benign Tumors**

The word benign means nonmalignant and suggest that such tumors are harmless. But a benign tumor can lead to death if it grows in critical area of the body, such as the brain. Also, over a period of time, some benign tumors do become malignant.

- A benign tumor usually is encapsulated by a well-defined fibrous cover (like the skin of an orange) separating the mass from surrounding tissue.
- A benign tumor neither invades surrounding tissue nor metastasizes (spreads via the blood and lymphatic systems), but remains within the site of origin.
- Benign tumor cells exhibit a lesser degree of anaplasia (loss of structural organization and useful function) than do cells of a malignant tumor. Therefore, benign tumor cells resemble normal cells; they are said to be typical of the cells or tissues of origin.
- Benign tumors usually grow slowly. (This is a generalization; some malignant tumors such as breast cancers, also grow slowly, while some benign tumors, such as leiomyomas, grow rapidly.)
- Benign tumors do not progress in a uniform manner. Their growth may be slow, stationary, or they may even regress.
- Finally recurrence is rare after simple surgical removal.
Thus benign tumors are generally less dangerous to the patient than malignant tumors.

**Malignant Tumors**

The word malignant means to have the property of local invasion and destructive growth and metastasis, and is derived from a Latin term meaning, "wicked". The distinguishing features of malignant tumors make it clear why this type of tumor was so named.

- Malignant tumors usually infiltrate or invade surrounding tissue. This peculiar characteristic may be why the term cancer (meaning “crab”) was chosen, because certain types of breast cancer resemble a crab with claw-like processes extending deep into breast tissue. Cancer almost never are encapsulated. Although an occasional, slowly expanding malignant tumor may appear to develop an enclosing fibrous membrane, histologic examination may reveal tiny crab-like penetrations through such encapsulation.

- Malignant tumors frequently metastasize, which refers to the spread of primary tumor cells to distant body sites, generally via the lymphatic system and blood stream.

- Malignant tumor cells usually are atypical of the cells of their tissue of origin and have a greater degree of anaplasia than those of a benign tumor. Because some similarities usually remain, the cell of origin can generally be determined.
Malignant cells exhibit a unique trait called autonomy. Autonomy is the ability of tumor cells to grow in an essentially unrestrained manner in the host.

Malignant tumors, unlike benign tumors, recurrence is more common after surgical removal because cells have invaded surrounding tissue or have metastasized and are not removed or destroyed by treatment.

Cancer cells are genetically unstable and contain or later develop abnormal numbers of chromosomes.

Malignant tumor invades surrounding tissues, usually produces metastases, is likely to recur after attempted removal, and in most cases causes death unless adequately treated.

**Breast Cancer Treatment**

Treatment of breast cancer is among the most widely studied of all cancer therapies. New approaches to therapy and refinements in accepted regimens are constantly being evaluated and may rapidly become part of standard treatment protocols. Geographic practices also influence what is considered standard. Users should continually update their knowledge of cutting edge and standard treatment patterns.

Local control of the cancer occurs more often when the tumor is small and can be completely removed by surgery. In the most advanced stages, breast cancer treatment begins with excision of the tumor or destruction of the tumor by radiation therapy. Surgery is frequently accompanied by
some type of adjuvant treatment -- radiotherapy, chemotherapy, hormonal therapy, immunotherapy, and other therapies

Treatment Options by Stage

Intraductal Carcinoma

Total mastectomy; excisional biopsy with radiation therapy

Lobular Carcinoma in situ

Unilateral or bilateral total mastectomies with or without low axillary dissection

Stage I (negative nodes)

Excisional biopsy/lumpectomy or segmental/wedge/partial breast resection with separate axillary node dissection and radiation to breast; modified radical or total mastectomy with axillary dissection. Adjuvant chemotherapy for estrogen receptor negative patients; adjuvant tamoxifen for estrogen receptor positive patients.

Stage II

Excisional biopsy/lumpectomy or segmental/wedge/partial breast resection with separate axillary node dissection and radiation to breast; modified radical or total mastectomy with axillary dissection; radical mastectomy (if needed to accomplish complete resection of tumor). Adjuvant chemotherapy (CMF, CAF, CA+/tamoxifen, L-PAM + 5-FU, L-PAM, 5-FU + tamoxifen, PAF, CMFVP, tamoxifen alone)

Stage IIIA (operable)

Modified radical mastectomy or radical mastectomy with either radiation or chemotherapy. Radiation could be preoperative external beam radiation or
postoperative external beam radiation with a booster dose to primary site. Chemotherapy could be CMF, CA, CAF, CMFP, CMFVP, L-PAM and 5-FU with or without tamoxifen

**Stage IIIB (inoperable, including inflammatory)**
Incisional biopsy plus external beam radiation to primary and regional nodes, followed by boost to local area plus interstitial implants to primary. Mastectomy thereafter if technically feasible, followed by chemotherapy or endocrine manipulation. Chemotherapy could be CMF, CAF, CMFP, CA, CMFVP. Endocrine therapy could include oophorectomy, tamoxifen, progesterone or androgens.

**Stage IV**
Biopsy followed by external beam radiotherapy to primary or mastectomy to control local disease. Hormonal therapy if estrogen receptor positive (oophorectomy, tamoxifen or progestational agent). Chemotherapy (CMF, CAF, CMFP, CMF VP, CA)

Considering significance of the biomarkers in breast cancer, the major aim of the study was to evaluate clinical importance of Bcl2, BAG-1, p53, Topoisomerase II alpha and ki67 in breast tumors by Immunohistochemistry and PCR. The biomarkers were assessed their correlation with established clinicopathologic prognostic factors and disease outcome.
In a set of circumstances, the proper course of action is determined by subsequent events........

Murphy's law