Dissertation on

"PROSPECTIVE STUDY TO EVALUATE THE PROPHYLACTIC EFFECTS OF INJ.METHYL PREDNISOLONE AGAINST SEROMA FORMATION IN POST MODIFIED RADICAL MASTECTOMY PATIENTS"

BY
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CERTIFICATE

This is to certify that, the dissertation titled "**PROSPECTIVE STUDY TO EVALUATE THE PROPHYLACTIC EFFECTS OF INJ.METHYL PREDNISOLONE AGAINST SEROMA FORMATION IN POST MODIFIED RADICAL MASTECTOMY PATIENTS"** is the bonafide work done by DR.R.NIVASH MARAN during his M.S. General Surgery course 2014 – 2017, done under my supervision and is submitted in partial fulfillment of the requirement for the M.S. (BRANCH 1) – GENERAL SURGERY of the Tamilnadu Dr. M.G.R. Medical University, April 2017 examination.

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DECLARATION

I, **Dr.R.NIVASH MARAN,** certainly declare that this dissertation Titled ““**PROSPECTIVE STUDY TO EVALUATE THE PROPHYLACTIC EFFECTS OF INJ.METHYL PREDNISOLONE AGAINST SEROMA FORMATION IN POST MODIFIED RADICAL MASTECTOMY PATIENTS”** represents a genuine work of mine during 2015-16 under the guidance and supervision of **prof.Dr.K.RAMASUBRAMANIAN,M.S.** The contributions of any supervisors to the research are consistent with normal supervisory practice and are acknowledged.

I also affirm that this bonafide work or part of this work was not submitted by me or any others for any award, degree or diploma to any other university board, either in India or abroad.

This is submitted to the Tamilnadu Dr. M.G.R. Medical University, Chennai in partial fulfillment of the rules and regulations for the award of Master of Surgery degree Branch 1 (General Surgery).

Dr. R.NIVASH MARAN.

Date:
Place:

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CONTENTS

INTRODUCTION

"Post mastectomy seroma remains an unresolved quandary as the risk factors for its formation have still not been identified. Seromas of the axillary space following breast surgery can lead to significant morbidity and delay in the initiation of adjuvant therapy. Various techniques and their modifications have been practiced and published in English literature, but there seems to be no consensus. In this article, all aspects of seroma formation from pathogenesis to prevention including drug therapies have been discussed."

" Seroma is a collection of serous fluid in the dead space of post-mastectomy skin flap, axilla or breast following modified radical mastectomy (MRM) or breast conserving surgery (BCS) and is the commonest early sequel. However, there is inconsistency in the definition of seroma across published works. This presumed complication, albeit usually of minor consequence, may prolong recovery, length of hospital stay and over stretch health budget. The reported incidence of seroma formation varies widely between 15 and 18% . There are several factors implicated in seroma formation like the extent of lymph node clearance, number of positive nodes, the use of postoperative radiation and whether intraoperative lymphatic channel ligation was done or not, but opinion differs as to their individual role in its pathogenesis. The main pathophysiology of seroma is still poorly understood and remains controversial. The optimal ways to reduce the incidence of seroma formation are unknown."

This is a prospective study conducted at Rajiv Gandhi Government General Hospital, Chennai in patients admitted to all general surgical units over a one year period. All patients were managed according to standard guidelines. The role of inj methyl prednisolone against seroma formation in post MRM patients were studied. The distribution of age and other factors determining the seroma formation were also studied.

AIMS AND OBJECTIVES

1. Study to establish the prophylactic effects of inj Methyl prednisolone against seroma formation .

2. Study of factors determining seroma formation.

REVIEW OF LITERATURE

“Seroma formation is one of the troublesome complication after MRM.The pathogenesis of seroma has not been fully elucidated. Seroma is formed by acute inflammatory exudates in response to surgical trauma and acute phase of wound healing . Oertli et al believed that the fibrinolytic activity contribute to seroma formation. Petrek et al in a prospective randomized trial showed that the most significant influencing factors in the causation of seroma were the number and extent of axillary lymph node involvement. However, Gonzalez et al. and Hashemi et al. reported that the only statistically significant factor influencing the incidence of seroma formation was the type of surgery. They reported higher seroma rate in MRM than following wide local excision and axillary dissection (BCS). Factors such as age of the patient, obesity, tumor size and neoadjuvant therapy did not influence the incidence of seroma formation in the three mentioned studies. Extensive dissection in mastectomy and axillary lymphadenectomy damages several blood vessels and lymphatics and the subsequent oozing of blood and lymphatic fluid from a large surface area when compared with breast conserving surgery leads to seroma .”

“ Seroma accumulation elevates the flaps from the chest wall and axilla there by hampering their adherence to the tissue bed. It thus can lead to significant morbidity such as wound hematoma, delayed wound healing,

wound infection, wound dehiscence, prolonged hospitalization, delayed recovery and initiation of adjuvant therapy."

Prevention and Reduction of Seroma Formation:

There are several techniques in practice that have been reported to prevent or reduce seroma formation, but no single method has been shown to be consistently and reliably effective. They can be discussed as surgical techniques, (2) the use of sealants and sclerotherapy, (3) compression dressing, (4) the use of drains, (5) shoulder exercise (delayed vs early) and (6) the role of Octreotide

FEMALE BREAST

"The female breast has always been a symbol of beauty,fertility and femininity. In disease, however, it has challenged physicians since antiquity. Surgery, which ruled the roost for cancer therapy, inevitably caused disfigurement when the knife was applied to the breast. The history of breast cancer is a complex maze of attempts to understand the wily nature of this hormone-responsive cancer and the will of physicians to conquer it by physical removal (surgery), cell destruction (chemo-radiotherapy) or targeted therapy to cell receptors (biomodulation). It is also a saga of intense exploration to find the tools to enable early diagnosis. The story of the domination of surgery over two millennia and

its evolution from fatalistic choices to minimal damage is told in the succeeding paragraphs. The pathobiological basis of breast cancer that changed chirurgical practice from crudity to finesse is woven through the narrative."

Beliefs and Practices Through Antiquity:

" It is not surprising that written records and illustrations of breast cancer date back to antiquity since the location of the organ permitted easy identification. The Edwin Smith Surgical Papyrus, dating back to 3,000–2,500 B.C., and possibly attributable to Imhotep (the Egyptian physician-architect), provides authentic accounts of breast cancer. A case was deemed incurable if the disease was "cool to touch, bulging and spread all over the breast". In ancient Greece, a divinity was exhorted to offer relief from breast maladies, as evidenced by votive offerings in the shape of breasts in Greek temples that housed Asclepius, the god of medicine.Carcinoma (karkinoma), scirrhous (hard, Greek skirros) and cacoethes (malignant disease, Greek kakoethes) in the medical lexicon owe their origins to Hellenistic writings."

" Hippocrates' theory in c. 400 B.C. of the imbalance of humours (blood, phlegm, and yellow and black bile) as a cause of disease, and his classic descriptions of the progressive stages of breast cancer, represent early hypotheses on the cause of cancer.Leonides of Alexandria, in 1st

century A.D., preserving the Greek traditions, boldly and skillfully detailed his approach of incision and cautery. His stipulation of leaving a wide margin of excision and only removing tumours of limited extent, foreshadows the oncological principles of contemporary surgical practice.Galen, attributing breast cancer in A.D. 200 to the accumulation of black bile in the blood, concluded that it was a systemic disease.These ancient physicians postulated that the cessation of menstruation was somehow linked to cancer; in fact it probably had to do with the association of cancer with old age. In line with this theory, Galen allowed surgical wounds to bleed freely to get rid of the black bile and frowned on the use of ligatures. The word 'crab' for cancer was coined by him to illustrate the dilated veins radiating from the tumour."

Surgical Stagnation in the Middle Ages:

"Between 476 and 1,500 A.D. medical progress was inextricably intertwined with the emerging religious philosophies. Early Christian beliefs favoured faith healing and miracles over surgery, which was perceived as barbaric. Islamic emergence revived Greek medicine and, through meticulous translations, saved medical knowledge for posterity. Avicenna (Ibn Sina, Persia) and Albucasis (Abu Al-Qasim Al-Zahrawi, Spain) in the 10th century and Maimonides (Spain) in the 12th century were Arab physicians of renown, forming a trio of exemplars who spread

medical excellence to the boundaries of the expanding Islamic conquests. Albucasis was a strong advocate of the use of cautery in surgery. The use of caustic pastes to annihilate the tumour and render it operable, is reminiscent of the same logic for using chemotherapy for large breast cancers today. Unique instruments to aid in the rapid removal of breast tumours were introduced into the surgical armamentarium by Albucasis, Henri de Mondeville (‘father’ of French surgery, 13th century) and Guy de Chauliac (France, 14th century).”

Renaissance: A Celebration of emergence of surgery:

“The 16th to 18th centuries not only bred artistic creativity but proved to be the golden age for the emergence of surgery. The craft of surgery was unshackled from its previous conjoint status with the barber’s trade and grew on the shoulders of a strong anatomical exploration of the human body by Andreas Vesalius in 16th century Belgium. In 18th century England and France, respectively, Cooper’s eponymous ligaments of the breast and Sappey’s subareolar plexus of lymphatics ushered in an era that revisited the origins and spread of breast cancer. In the same era, John Hunter (the Scottish ‘father’ of investigative surgery) replaced ‘black bile’ with lymph as the cause of breast cancer. A multitude of theories ranging from inspissated milk, trauma, personality type, exposure to air and infection were fed into the cauldron of carcinogenesis. The observation of

the disease within families was naturally attributed to infection. Amidst this chaotic search for the truth, accounts of heroic surgeries from simple lumpectomies to radical removal of the pectoralis, enliven medical records.These are rendered more vivid and admirable when it is recalled that in the absence of anaesthesia, skill and speed were the sole attributes of a successful surgeon. It is also a grim reminder that surgery was the solitary modality for hope of relief with anecdotal incidences of cure. More conservative compatriots used ligatures or lead plates to strangulate the tumours, preferring them to the horrors of breast amputation."

Nineteenth Century: The golden age of surgery

"The surgical discipline rapidly grew on the bedrock of a spate of discoveries that rendered it safer with a good outcome for the patient. Disinfection and sterilisation and the use of sterile gloves were the first landmark events. General anaesthesia revolutionised the surgeon's ease (and indeed the patient's too!). Although in 1818 James Blundell attempted blood transfusion in postpartum haemorrhage, safe transfusions would be achieved only at the dawn of the 20th century with the discovery of blood groups by Karl Landsteiner. Against this background, seminal contributions to cancer came from the microscopic identification of normal cells and their cancerous brethren all the way from Hooke in 17th century England to Müller and Virchow in 19th century Germany. Müller

dismissed the humoral theory of the origin of cancer, declaring that cancers were composed of living cells and suggesting that metastasis was due to spread of these cells. The demonstration that breast cancer spread along the lymphatics to the guardian axillary nodes was to form the basis of a variety of excision techniques. Unique forms of spread leading to the clinical manifestations of carcinoma en cuirasse or peau d'orange and Paget's disease would demand alternative ways of approaching treatment."

"The middle years of the 19th century celebrated the newly acquired surgical freedom with bold and radical surgeries. The en bloc resections of Charles Moore in London, and Kuster and Volkmann in Germany ran a parallel course. Axillary lymph node dissections as part of the philosophy of extermination were performed in 1882 by William Banks in Liverpool, UK. While they may appear particularly mutilating today, they provided a unique opportunity to study the disease spread. Breast cancer surgery at the turn of the century came to be synonymous with the name of William S. Halstead, Professor of Surgery at Johns Hopkins hospital in Baltimore, USA. His radical mastectomy (first reported in 1894) with its emphasis on removing tissues in one piece to prevent spread and removal of the pectoralis major to prevent recurrence, became the undisputed path that generations of surgeons trod with diligence." "The suspected tissue should be removed in one piece, (1) lest the wound become infected by the

division of tissues invaded by the disease or of lymphatic vessels containing cancer cells, and (2) because shreds or pieces of cancerous tissue might readily be overlooked in the piecemeal extirpation."

These strict rules for non-violation of the tumour area precluded a preoperative biopsy to confirm whether the patient had a cancer at all: such was the strength of a skilled clinical diagnosis! Another ageold practice that came to a close was to leave the excised surgical wound open to granulate. The use of ligatures now allowed better wound healing through low infection rates.

Twentieth Century: Surgery reinvents itself

"The hormone dependency of breast cancer was initially hypothetical, through the observation that the disease was aggressive in younger women. Beatson ignited the era of endocrine surgery in 1906—long before the discovery of estrogen receptors by Jensen in 1967 and oopherectomy and adrenalectomy (to achieve castration) came in vogue. These rather drastic methods were gradually overtaken by estrogen receptor modulators, luteinising hormone-releasing agonists and aromatase inhibitors".

" Halstead's legacy was, for a while, preserved by Margottini and Veronesi in Milan who additionally removed internal mammary nodes and others

who extended the scope of ‘radicality’ to supraclavicular and mediastinal nodes. However, the late 19th and early 20th centuries gradually heralded the demise of the adage: big surgeons make big incisions (and hence perform big surgeries). Patey and Handley from London and Auchincloss Jr. of New York ushered in a movement that ‘modified’ the radical mastectomy and preserved the pectoralis major. Rapid advances in medical radiation as a means of killing cancer cells and new forms of chemotherapy that did the same, but also achieved medical castration or targeted mutated tumour receptors, forced a rethink of cancer management strategies. These were coupled with the burgeoning knowledge of the biological behaviour of breast cancer and the less-than-guaranteed success of surgery alone. Early cancer detection of smaller lesions by mammography added a new dimension to surgical management.”

“The clarion call to reorient to limited surgery came from the surgery fraternity. Bernard Fisher, Professor of Surgery at the University of Pittsburgh, revived Galen’s ancient belief that breast cancer was a systemic disease. Large randomised controlled clinical trials like the National Surgical Adjuvant Breast and Bowel Project (NSABP), published in 1989, provided scientific support.It is ironic that the disbandment of the radical Halstedian approach, the institution of trials and the acceptance of neoadjuvant therapy were the brainchildren of a surgeon!”

Veronesi from Italy and many others supported the notion of limited surgery complemented by adjuvants. Surgery reinvented itself to join hands with the other modalities. Since the close of the 20th century breast conservation and breast reconstruction—combined, where necessary, with sentinel node dissection—have held sway. The removal of only selected 'sentinel' nodes (those to which the tumour had spread) would relegate the swollen lymphoedematous arm, a distressing manifestation of axillary lymph node dissections, to the annals of surgical history.

Once surgeons lead the revolution towards minimising extirpation, the first faltering steps towards restoring cosmesis were taken by Verneuil, a French surgeon who transferred autologous tissue from the normal breast to the diseased one in 1887.This released the floodgates for a variety of innovative autologous and synthetic materials offering a restored shape that could even outdo nature's original creation. Muscle, myocutaneous flaps, lipomas and omentum were natural choices. The transverse rectus abdominis myocutaneous flap (TRAM) introduced in 1979 by Holmstrom has stood the test of time, undergoing several modifications in its evolution.Prosthetic and synthetic options brought industry and commerce into the fray: petroleum jelly, glass balls, ivory, rubber, polyvinyl alcohol sponge and silicone— the list is ever growing!

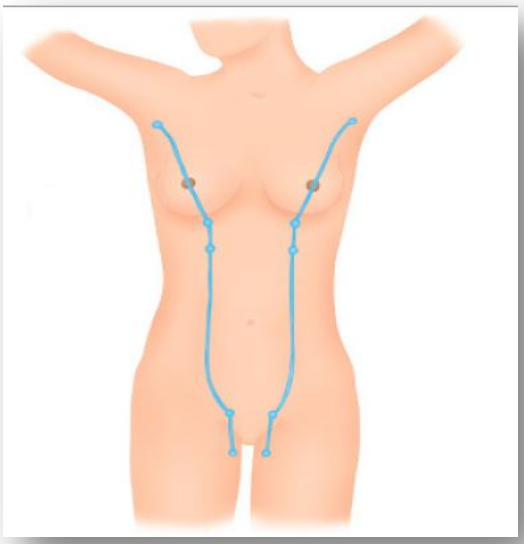
“Surgical domination over the treatment of breast cancer held sway for the millennia, ever since the first recorded medical literature. The hope for a cure by the radical removal of a diseased organ was always counterbalanced by fascinating and fearsome accounts of surgery sans anaesthesia as a physically and psychologically mutilating therapeutic option. While nowhere near its nadir, surgery remains at the heart of management in a multimodality setting. Instead of annihilation it now provides succour to the breast cancer survivor thus balancing cure and cosmesis”.

Lessons from the History of Surgery in Breast Cancer

“There are three lessons to be gained from the history of surgery in breast cancer. First, to delve into history is to rediscover buried insights: Galen’s perceptive assessment that breast cancer is a systemic disease was echoed two millennia later in Fisher’s 20th century observations. Second, the evolution of therapeutic weaponry raises the fortunes of medical disciplines (as antisepsis and anaesthesia did for surgery) or minimises their supremacy as stand-alone choices for panacea or cure (as chemoradiotherapy did for surgery). Third, stooping to conquer is the mark of survival in contemporary medical practice. Surgery has won the day by adapting and playing a complementary role in modern cancer management as a stylised, scientific and patient-friendly craft.”

EMBRYOLOGY

"The human breasts develop from the mammary ridges or milk lines which result due to thickening of the epidermis which usually appear first on the anterior surface of a 5 week old fetus that extends from the axilla to the upper and medial aspect of the thigh. These ridges continue to develop in the pectoral region and the remaining ridges disappear. The epithelial cells proliferate, enlarge and grow downward into the underlying mesenchymal tissue. By the end of the fifth month of gestation, 15 to 20 solid cords can be identified. These cords continue to grow downwards and branch, then slowly acquire lumina by hollowing in the last 8 weeks of the fetal life."



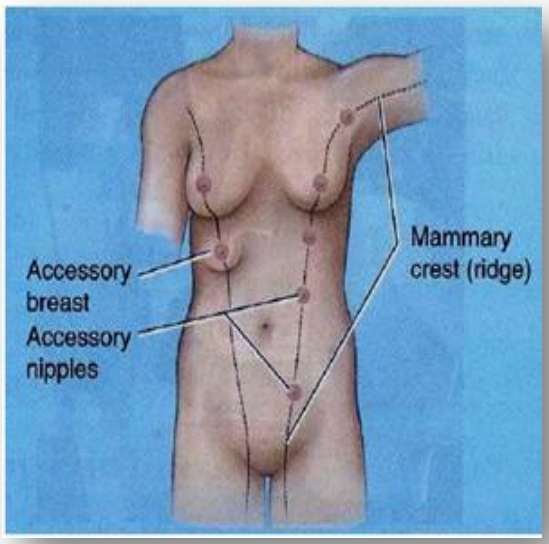


FIG:**Mammary Ridge & Breast Anomalies**
Ref: Taken from Moore's anatomy text book.

The previously elevated flat surface of the developing nipple develops a depression (the mammary pit) into which these lactiferous ducts open. At about the time of birth the mammary pit evaginates outwards to form the definitive nipple as a result of proliferating mesenchyme.

“The earliest stages development of the fetal mammary gland appears not to be depends on the steroid hormones, whereas actual development of breast structure after the 15th week is mediated by testosterone. In the last few weeks of gestation, fetal breast is usually responsive to placental and maternal steroid hormones and prolactin, that induce secretory activity in the fetal mammary ducts. This is the reason for secretion of colostrum immediately after birth and palpable breast bud enlargement. But due to disappearance of maternal hormones from infant's blood stream, the secretory activity subsides and ceases after birth within a month or two. The mammary gland shrinks and returns to an inactive state”.

In males mammary glands remain rudimentary throughout life but in most of the females, further breast development begin only after reaching puberty.

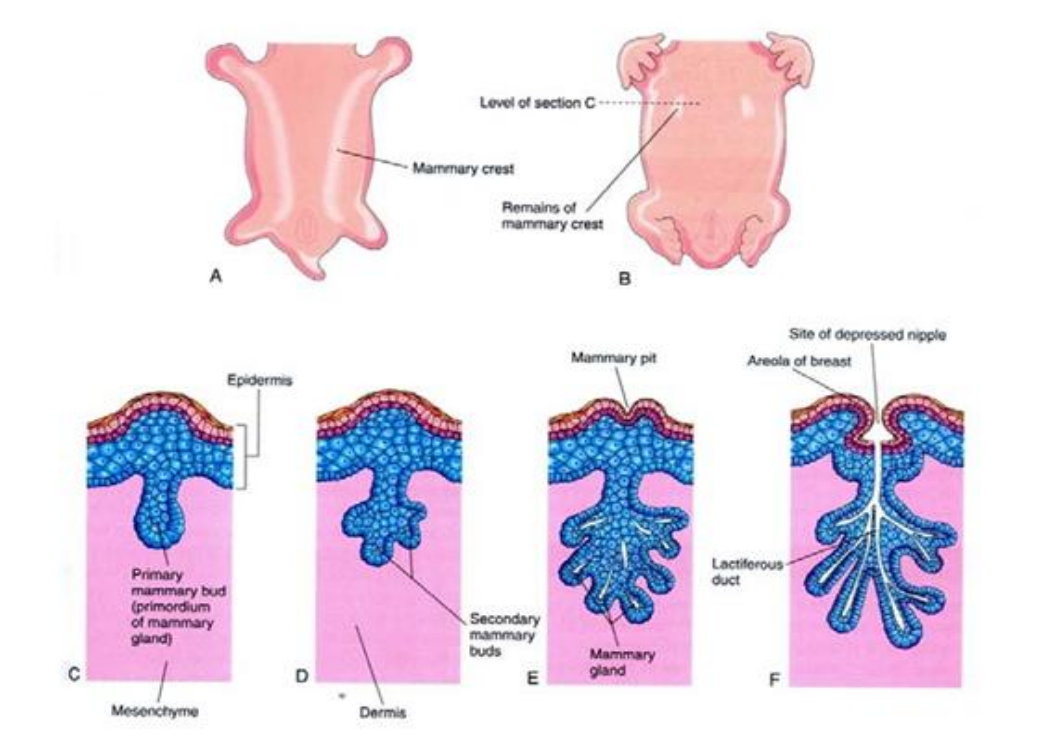


FIG - **Development of mammary glands**

A : 28 days embryo showing mammary crests. B : 6 weeks, showing remains of the crests.

C, D, E, F : successive stages in the development between 12th week and birth.

Ref: Taken from Moore's anatomy text book.

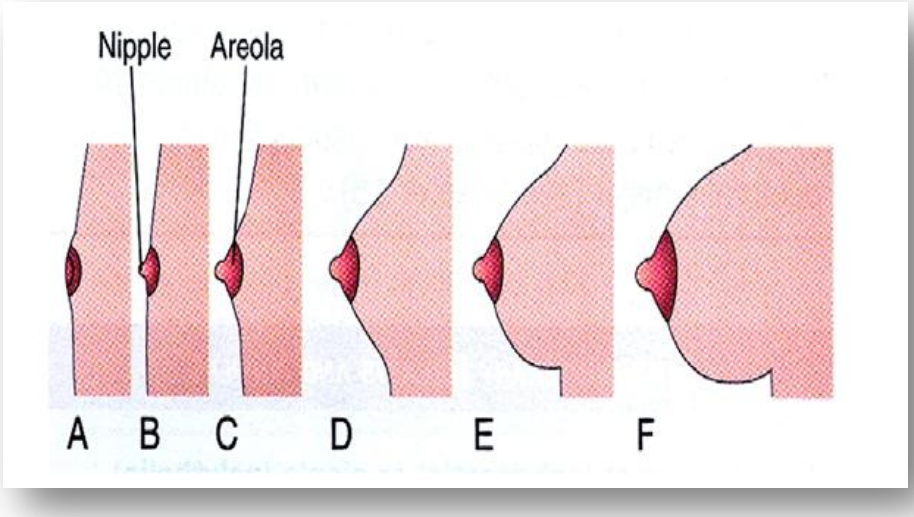


FIG - **Phases of Human Breast Development :**
Sketches showing progressive stages in the postnatal development of the breasts.
A-Newborn. B-Child. C-Early puberty. D-Late puberty. E- Young adult. F-Pregnant female.
Ref: Taken from Moore's anatomy text book

Female Breast Development & its Endocrine Control :

"Breast development commences with secretion of cyclical estrogen and the progesterone secretion at puberty. Estrogen is responsible for the differentiation of peri-ductal stroma and growth of the ducts that elongate and acquire a thickened epithelium. Growth hormone and gluco-corticoids also contribute to ductal growth.

Lobules are derived from solid masses of cells that form at the end of terminal ducts. Lobulo-alveolar differentiation and the growth during this puberty time are stimulated and increased primarily by insulin, progesterone and growth hormone . Though the greatest amount of breast

glandular differentiation occurs at puberty, the differentiation process continues into the second decade and is further enhanced by pregnancy. The evolution of breast from childhood to maturity has been divided into five phases by Tanner ."

Phase I (age: puberty) : Pre adolescent elevation of the nipple. No palpable glandular tissue or areolar pigmentation.

Phase II (age: 11.1 ± 1.1 yr) : Presence of glandular tissue in the sub areolar region of breast. The nipple and breast project as a single mound from the chest wall.

Phase III (age: 12.2 ± 1.09 yr) : Increase in the amount of readily palpable glandular tissue and enlargement of the breast with increased diameter and pigmentation of the areola. The contour of the breast and nipple remains in a single plane.

Phase IV (age: 13.1 ± 1.15 yr) : Enlargement of the size of areola and increased areolar pigmentation. The nipple and areola form a secondary mound above the level of the breast.

Phase V (age: 15.3 ± 1.7 yr) : Final adolescent development of a

smooth contour with no projection of the areola and nipple.

ANATOMY OF BREAST

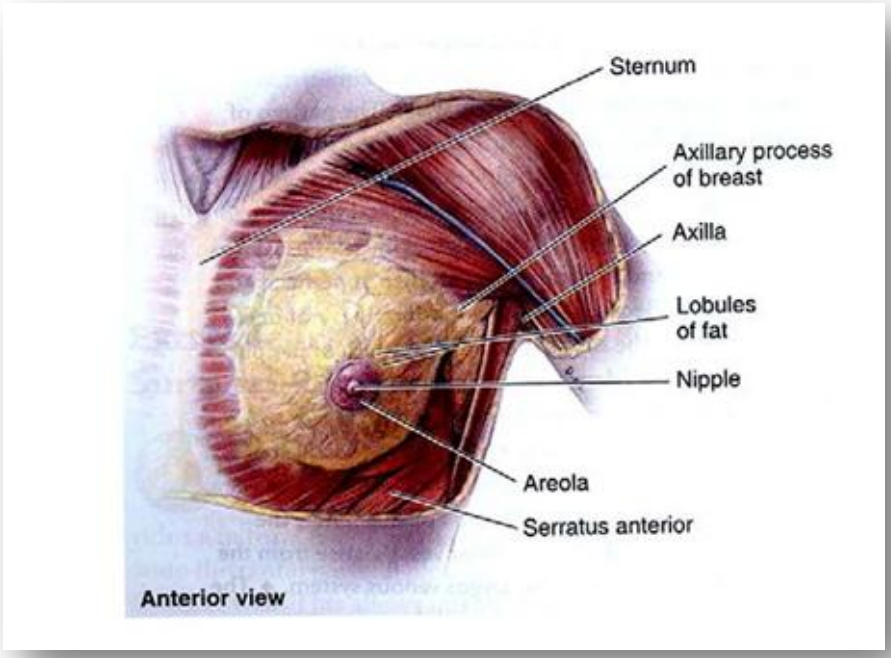


FIG - **Superficial dissection of female breast**

Ref: Taken from Moore's anatomy text book.

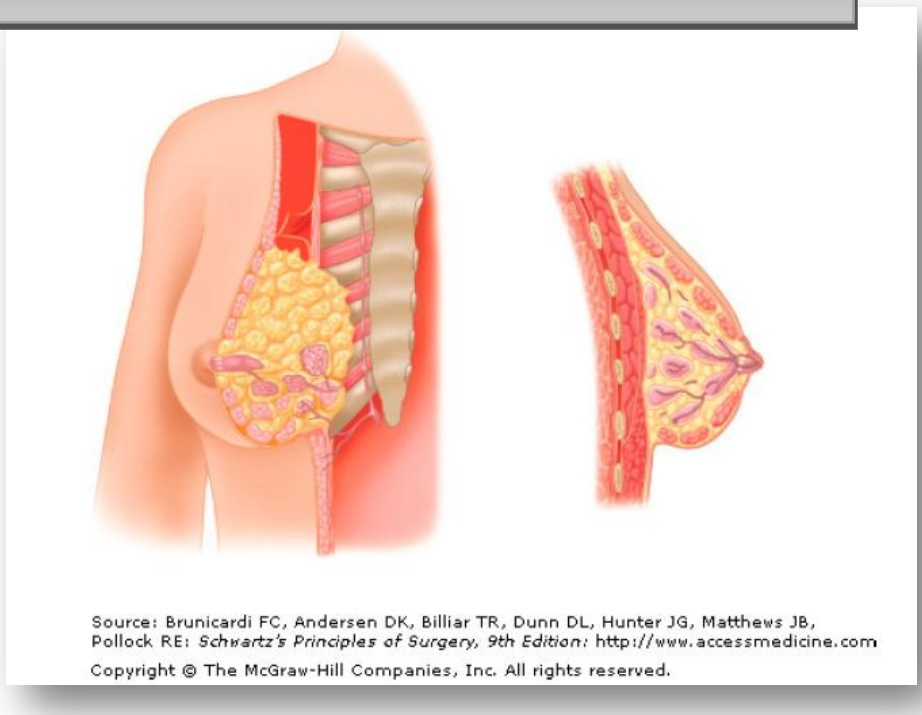


FIG - **Anatomy of the breast. Tangential and cross-sectional (sagittal) views of the breast and associated chest wall.**
(Ref: from Romrell et al,15 p 20. Copyright Elsevier)

The breast: basic structure and function

"The breasts or mammary glands are highly specialized modified sweat glands. The breasts consist of glandular tissue and supporting fibrous tissue embedded within fatty tissue matrix, together with blood vessels, nerve fibers, and lymphatic vessels. Both males and female have breasts: but breasts are normally well developed only in female".

The mammary glands are present in the subcutaneous tissue plane overlying the pectoralis major muscle and pectoralis minor muscle. At the greatest prominence of the breast is the nipple which is surrounded by a circular pigmented area, called the areola. A small portion of the mammary gland that extends along infero lateral edge of pectoralis major muscle towards the axillary fossa, forming the axillary process or the tail of Spence. About sixty percentage of cancer breast actually originates in the axillary tail, that is why it is an important part of clinical breast examination. [11]

Structure: The breast is formed by of 15-20 lobules of glandular tissue surrounded by the fat; the latter responsible for its smooth contour and most of the breast bulk. These lobules are separated individually by thin fibrous septa running from the subcutaneous tissue to the pectoralis fascia called the suspensory ligaments of Cooper. The breast is tightly

attached to the dermis of the skin, especially by substantial skin ligaments called (*L.retinacula cutis*), the **suspensory ligaments** (of Cooper). These suspensory ligaments particularly well developed in the superior part of the gland, help support the lobes and lobules of the breast.

Each lobule is drained by its lactiferous duct to the nipple, which is surrounded by pigmented areola. This areola and nipple are lubricated by the Montgomery's glands; which are large, modified sebaceous glands that may form sebaceous cysts which may, become infected.

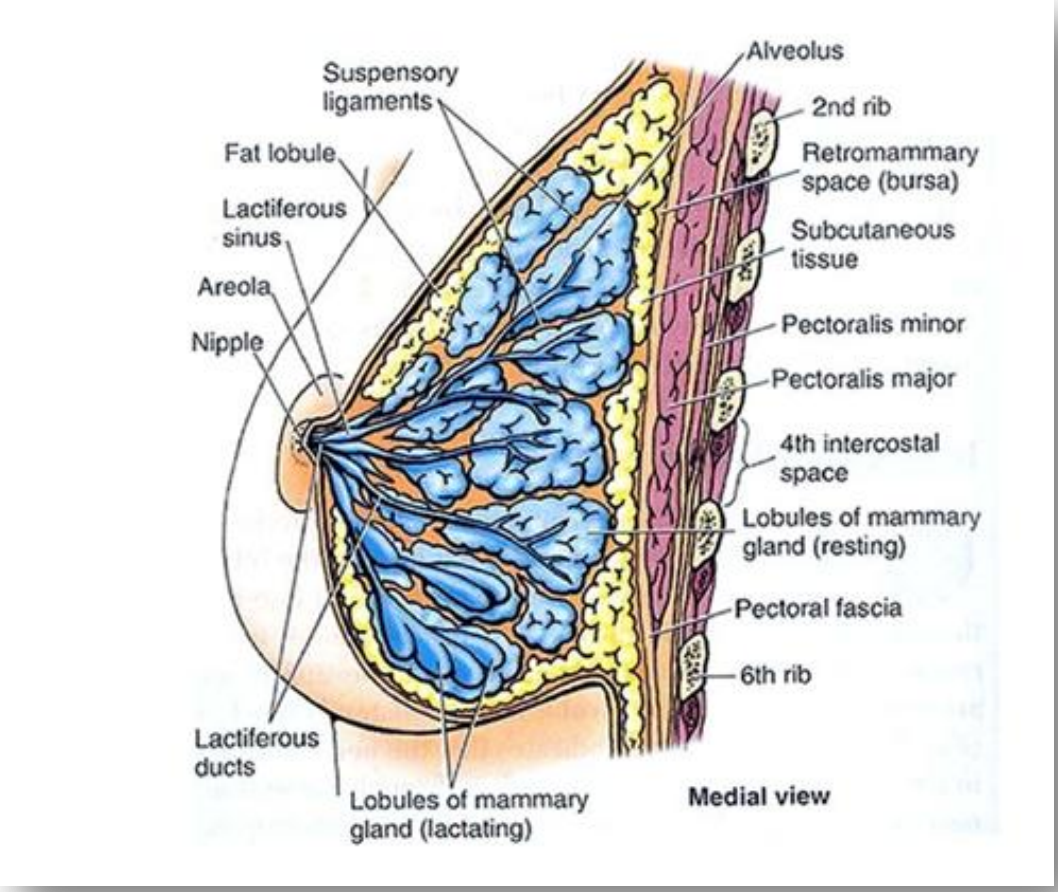


FIG - **Sagittal section of the female breast and anterior thoracic wall**
(Ref: Taken from Moore's anatomy text book.)

Anatomical extent

• medially upto Lateral border of sternum to the mid-axillary line laterally

• superiorly from Second to sixth rib inferiorly

Breast is located between the superficial and deep layers of superficial fascia of breast. Retromammary space is a thin layer of loose areolar connective tissue between the deep layer of superficial fascia and pectroralis fascia[12]. The breast can develop anywhere along the milk line, thus giving rise to accessory breasts or nipples.

Arterial supply

The Perforating branche of Internal thoracic/mammary artery

Lateral branches of Posterior Inter costal arteries

Superior thoracic artery

Lateral thoracic artery

Pectoral branches of thoraco-acromial artery

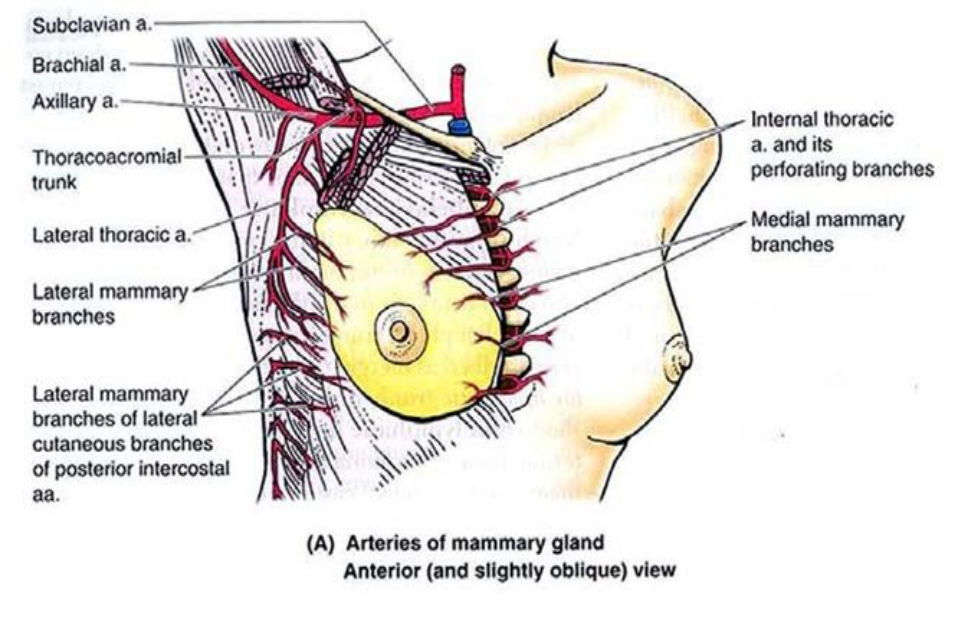


FIG - **Arterial supply of the mammary gland**
(Ref: Taken from Moore's anatomy text book..)

Venous drainage

"The venous return of the breast has both a superficial and deep system. Superficial veins of the breast are located just posterior to the superficial layer of the superficial fascia and can be seen by infrared photography. Around the nipple these veins form an anastomotic circle - *the circulus venous"*. The deep veins and veins of the superficial plexus can be classified into 3 principal groups as follows :

i) Internal mammary vein

ii) Tributaries of the axillary vein

iii) Posterior intercostal veins.

This system lies in direct continuity with the vertebral plexus of

veins (Batson's plexus)[13] that surround the vertebral column extending from the base of skull to the sacrum).

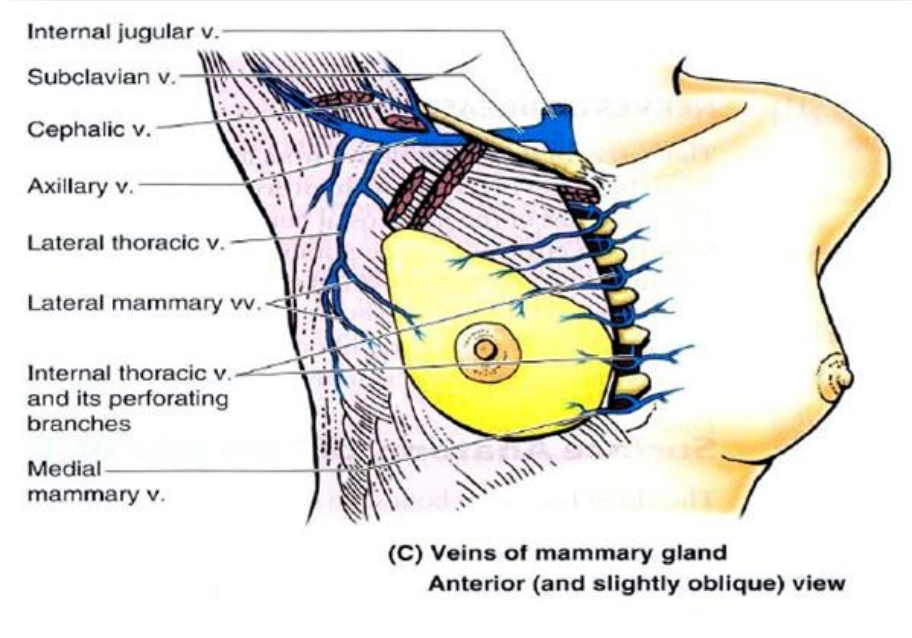


FIG - **Veins of the mammary gland**
(Ref: Taken from Moore's anatomy text book.)

Lymph Glands - Three routes for mammary lymphatic drainage have been identified:

I. Axillary Nodes are the most important and receives 75% or more of lymphatic flow. These range from 20 to 40 in number and have been classified by anatomists by their relationship to axillary structures in various groups 14 as follows :

1. Lateral group also called axillary vein group

2. External mammary group also called anterior or pectoral group

3. Posterior or subscapular group

4. Central group

5. Apical group

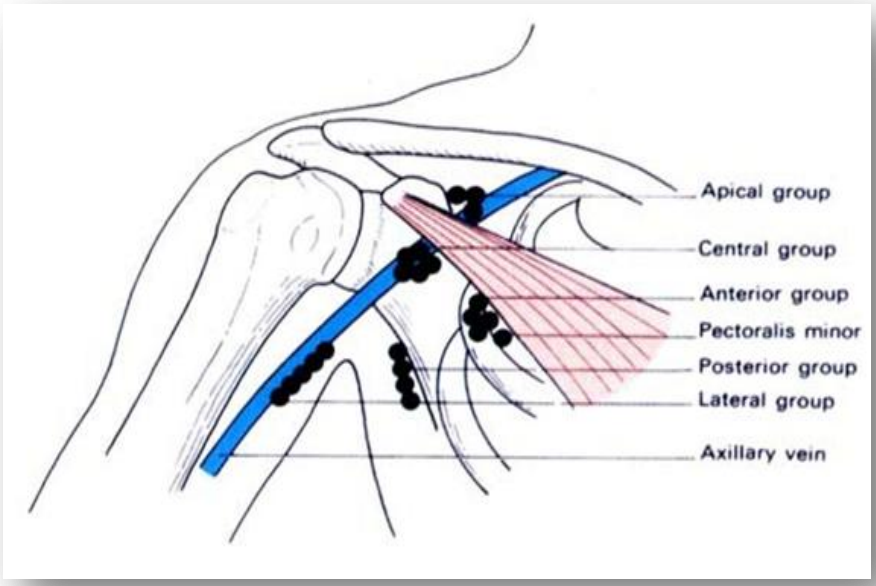
6. Interpectoral or Rotter's group

Axillary lymph nodes are divided into three levels according to its relation of lymph nodes to the pectoralis minor muscle :

Level I - Those are located at the lower border of pectoralis minor muscle.

Level II -Lymph nodes that are located deep to the pectoralis minor muscle.

Level III -Lymph nodes along the medial border of pectoralis minor muscle.



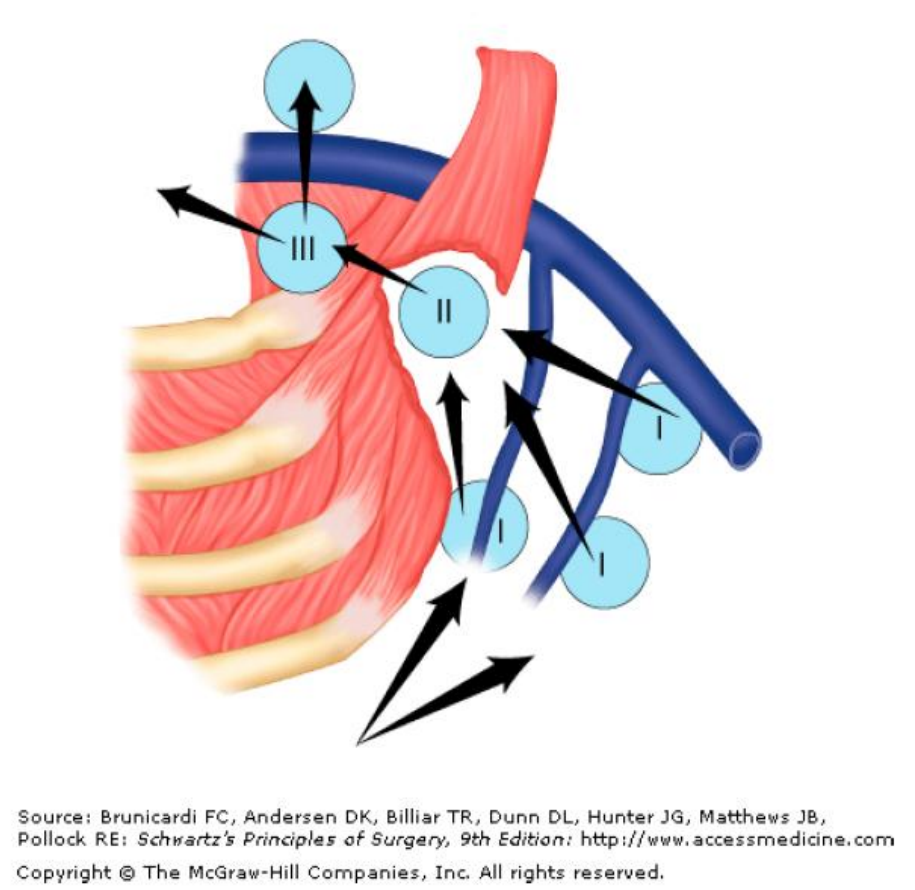


FIG - **Lymphatic drainage**
(Ref: Taken from Moore's anatomy text book..)

II. Internal Mammary Lymph nodes (around 8-10 nodes) : Lymphatics from the medial edge of the breast pierce through the pectoralis major muscle and intercostal muscles to drain into the internal mammary lymph nodes - located along the sternal border of the internal thoracic trunk. This group accounts for 25% or less of lymph flow from the breast. The internal thoracic lymph trunks drain into right lymphatic duct or thoracic duct. These lymph nodes cannot be palpated, rather they are percussed or detected by imaging studies.

III. Posterior Intercostal lymph nodes - The third route for lymphatic

drainage is via the posterior intercostal lymphatics to posterior intercostal lymph nodes where the ribs and vertebrae articulate. There is enough evidence that lymphatic drainage from any given region is not limited to any one of the foregoing pathways. Nonetheless correlation of patterns of lymph node metastasis with the location of primary tumors in the breast suggests that preferential pattern of lymphatic flow does exist in the breast.

B. Lymphatic Vessels

a) There are few channels which drain the overlying skin excluding nipple and areola. The integumental lymphatics pass in a fan like radial manner and drain into surrounding lymph nodes. Lymphatic trunks from skin drain a separate portion and there is no communication between adjacent territories.

i) From the outer part - terminate at the axillary group of lymph nodes.

ii) The skin of upper part - drained by vessels which enter into the supra-

clavicular lymph nodes.

iii) The skin over the inner part of gland - drain into internal mammary chain of lymph nodes.

The cutaneous lymphatic channels communicate across the midline with

those of opposite breast.

b) Lymphatics of the parenchyma of the breast including nipple & areola

i) A plexus of lymphatic vessels that lie in the inter-lobular connective tissue and freely communicates with a sub areolar lymph plexus around the nipple called subareolar plexus of Sappey. The Efferent vessels pass from the breast tissue from the anterior axillary fold to the pectoral group of axillary lymph nodes. Some lymph channels may pass directly for the sub scapular group of lymph nodes. The Efferent vessels drain from the superior part of the breast may drain directly to apical group of axillary lymph nodes sometimes may be interrupted by small inter-pectoral and infra-clavicular lymph nodes. These lymphatic channels run on the deep fascia.

ii) Lymphatics from both medial and lateral part of the breast enters into the thorax along the anterior perforating branches of the internal thoracic artery and along the lateral perforating branches of the posterior inter-costal vessels. Eventhough most of this lymphatics reaches the internal mammary chain a small group of lymphatics may pass to the posterior inter-costal lymh nodes lying near the heads of the ribs.

iii) Lymphatics from the deep part of the breast pass through the

pectoralis major muscle on draining into the axillary or internal mammary lymph nodes.

iv) The plexus of deep fascia consists of fine lymphatic vessels. They do not act as a normal pathway for lymphatics from the breast into the regional lymph nodes. Fine lymphatics connect the right and left internal mammary chains behind the manubrium sterni and small glands may be found there.

Lymphatics from the nipple, areola & the lobules of the gland drains into the sub areolar lymphatic plexus of Sappey.

From this plexus:

- Most lymphatics (>75%), from lateral quadrants of breast tissue drains to axillary lymph nodes, first into the anterior/ pectoral lymph nodes. However, some lymphatics may drain directly into the other axillary group of lymph nodes or even to the inter pectoral rotter's nodes, delto pectoral nodes, supra clavicular nodes, or the inferior deep cervical lymph nodes.
- Most of the remaining lymphatics, particularly from medial breast quadrants, drains into para sternal lymph nodes within 2 cm of the latereal sternal border or into the contralateral breast, whereas lymphatics from inferior quadrants of breast may pass deeply into the sub

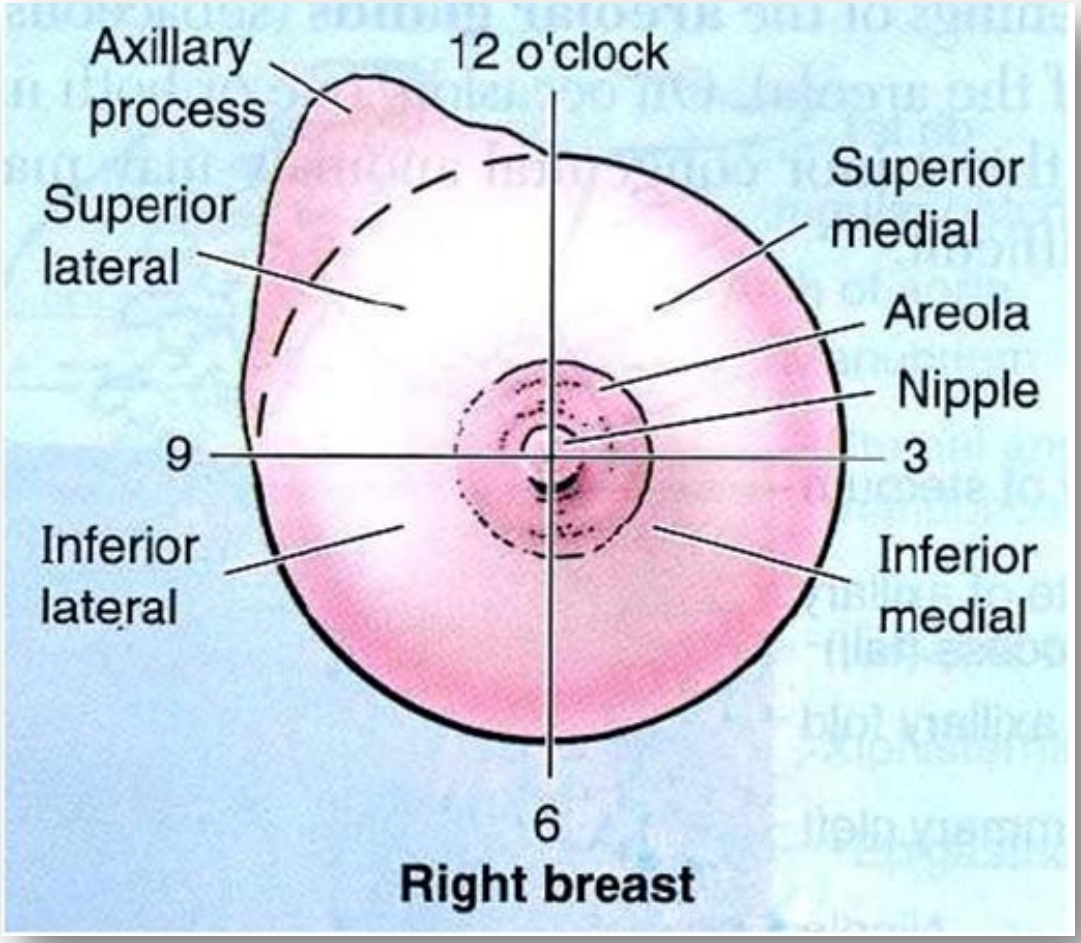
diaphragmatic inferior phrenic lymph nodes in the abdomen.

"Lymphatics from the breast skin, except the nipple and areola complex drains to ipsi lateral axillary nodes, inferior deep cervical nodes, and the infra clavicular group of lymph nodes and into para sternal lymph nodes of both sides of breast within 2 cm of the lateral border of sternum.

Lymphatics from the axillary nodes drains into the level III clavicular (infra clavicular and supra clavicular) lymph nodes and from them into the subclavian lymphatic trunk, which also drains lymphatics from the ipsilateral upper limb. Para sternal nodes drain into bronchomediastinal lymphatic trunks."

Breast Quadrants :

The surface of breast is divided into 4 quadrants for the purpose of location



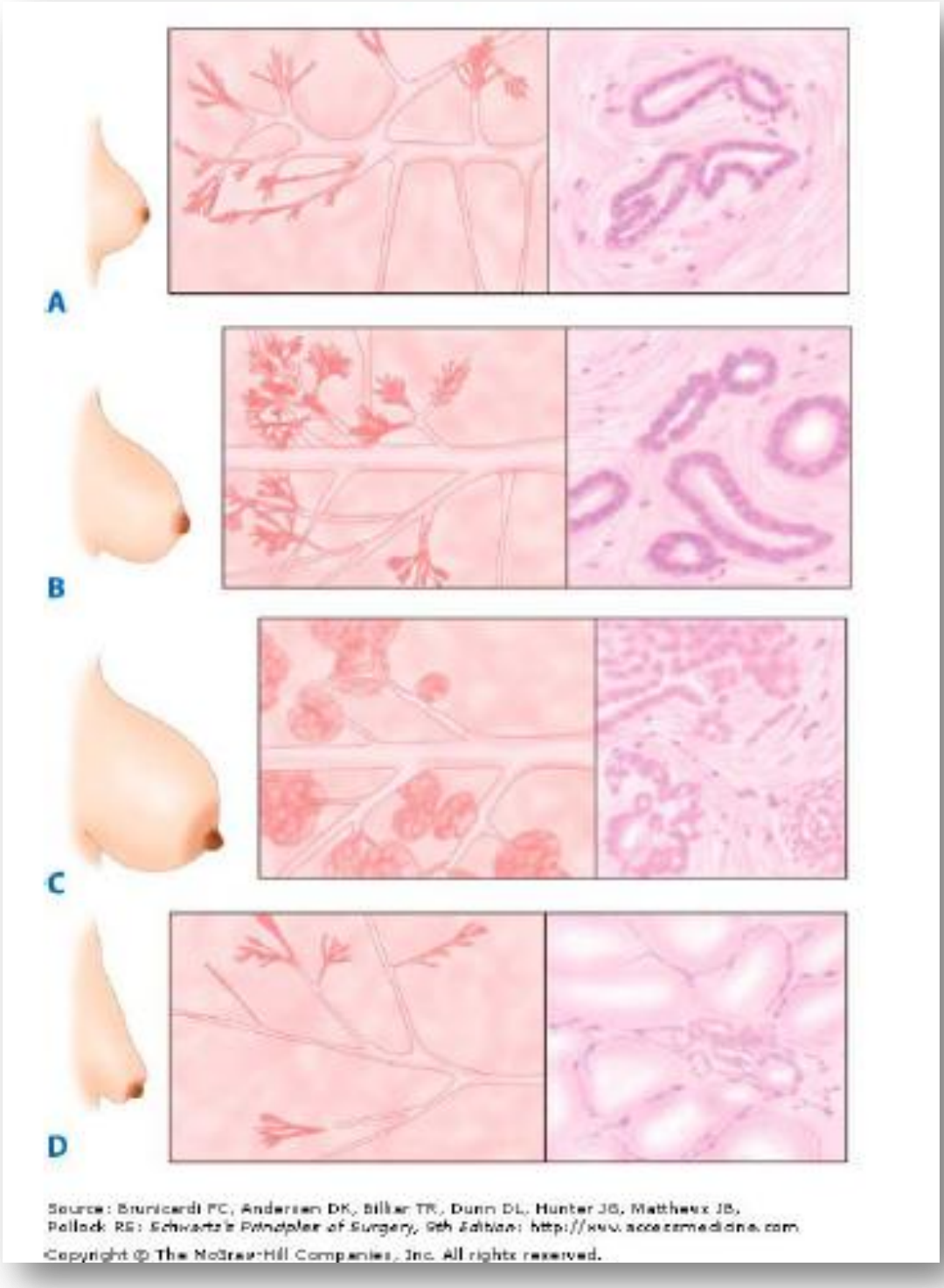


FIG - **Physiological changes in Breasts**
The breast at different physiologic stages. The central column contains three-dimensional depictions of microscopic structures.
A. Adolescence. B. Pregnancy. C. Lactation. D. Senescence
(Ref: Ref: Taken from Moore's anatomy text book.)

Physiological changes in Breasts

"From birth until puberty, there is no difference in the breast tissue of both male and female. The breast tissue is made up of connective tissue & mammary glands . But physiological changes occur in the female breast with puberty, during every menstrual cycle and then pregnancy and menopause. During puberty, increased hormones such as estrogens stimulate the secondary sexual characters, including the development of breast parenchyma. The breasts grow in both size and amount of the mammary glands & of fatty and connective tissues deposited in the breast."

"In females, with each menstrual cycle hormone fluctuations occur which are important forth e developing breast tissues. After every ovulation, the female body prepares for pregnancy and thus a change in the hormone pattern is noted. One of the purpose of this preparation is to stimulate growth of the mammary glands to make the breast glands ready for milk production if the female became pregnant. The increase in size is responsible in some women to feel breast tenderness during part of their menstrual cycle called cyclical mastalgia, During menstruation, the hormone levels drop to low level and the breast glands decrease to their normal size."

"During pregnancy, increased estrogen stimulates breast growth,

both increasing the size & number of glands and the fatty tissue amount in the breasts as part of the body's preparedness for lactation and breast feeding. Prolactin & the placental hormones stimulate milk production during pregnancy, but milk secretion is prevented by the high levels of oestrogen & progesterone. But at child birth, the oestrogen and progesterone levels drop to very low levels so that milk secretion can starting to occur."

"After menopause, the levels of oestrogen levels in the female body reduces and the breast tissue is no longer stimulated. Thus, the breast content changes from mostly of glands & dense connective tissue to fatty tissue mostly. The dense breast tissue of younger women is responsible for difficulty to see through on mammographic study, that is why screening mammograms are not ideal in femaels under 40 yrs of age, as masses may be missed.

As the fat content in the breast tissue increases with age, it became easier to detect lumps and changes consistent with malignancy on mammogram. Branchig of the lactiferous ducts occur in the breast tissues during menstruation and pregnancy. Eventhough breast is prepared for secretion by mid pregnancy, breasts do not produce milk before the baby is born."

"Colostrum is a yellowish or white colored pre milk fluid, which is

secreted from the nipples during the last trimester of pregnancy and during initial few days after child birth. Colostrum is especially rich in proteins, immune antibodies, and a growth factors acting on the infant's intestines for proper development. The elderly female breasts are small because of the decreasing fat content and the atrophic changes of glandular tissue".

RISK FACTORS OF CARCINOMA BREAST

Etiology of the cancer breast remains unknown till. Epidemiological data suggest the well defined factors show an increased likelihood of developing the disease. Risk factors for cancer breast can be classified according the following:

Relative risk <2	Relative risk 2-4	Relative risk >4
Early Menarche	breast cancer in a first degree relative	Mutation BRAC1 Or BRCA 2
Late menopause	CHEK2 mutation	Lobular carcinoma in situ (LCIS)
Nulliparity	Age >35yrs for first child birth	Atypical hyperplasia
Estrogen plus progesterone Hormone Replacement Therapy	Proliferative breast disease	Radiation exposure before 30 yrs age
Diet and Alcohol use	Mammographic breast density	
Post menopausal obesity		

TABLE 1- **Magnitude of risk for known breast cancer risk factors**
(Ref: Taken from Devita principles and practice of oncology 10th edition)

Risk assessment models :

Breast cancer risk can be predicted by two risk assessment models currently. *Gail's* model, which incorporates age at onset of menarche, total number of breast biopsies, age at 1st child birth and total number of breast cancer in first degree relatives .Gail's model is most frequently used. It predicts the total cumulative risk of cancer breast according to decade of life.

The other frequently used model developed by *Calus* and colleagues which is based on high penetrance breast cancer susceptibility genes. The Calus model (when Comparing with the Gail model) incorporates more information about family history.

EPIDEMIOLOGY

"Breast cancer is the most common cancer in the females and is the leading cause of death from cancer for women of age group forty to forty four years. It totally accounts for about one third of all female cancers and is responsible for about one fifth of the cancer related deaths in women."

"Until 1985 Breast cancer was the leading cause of death, then it was crossed by the lung cancer as the leading cause of death. There is a ten fold variation in cancer breast incidence among various countries worldwide. England and Wales having the highest age adjusted mortality for breast cancer while South Korea having the lowest. Females living in less developed countries have a lower incidence of cancer breast comparing to women living in well developed countries".

NATURAL HISTORY OF BREAST CANCER

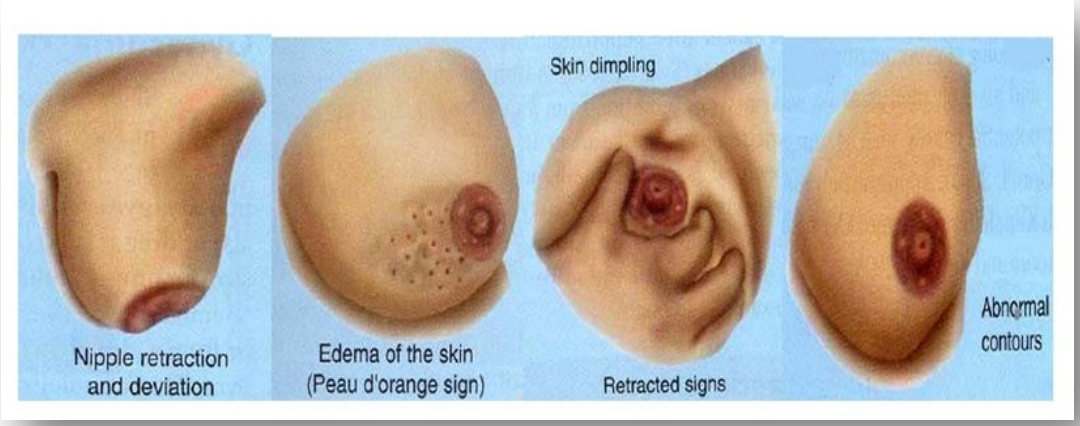
"Natural history of breast cancer described by Bloom and colleagues is based on records of 250 females with untreated cancer breast who were treated on charity hospital wards in Middlesex Hospital, London.

The Primary Breast Cancer: More than eighty percentage show fibrosis involving the stromal & epithelial tissues of breast. With growth of cancer the Cooper's ligaments are shortened and skin dimpling occurs which is classic of cancer breast. Localized dermal edema , otherwise called peau d orange appearance develops when drainage of lymphatic fluid from skin is blocked. With continued growth of cancer cells invading the skin and ulceration occurs in upto 75% of untreated cases. Small satellite nodules appear near primary ulceration as new areas of skin are involved.

Locoregional recurrences occur in general upto 20% of breast cancer, among them more than 60% are distant and 20% both loco-regional and distant."

Axillary lymph node metastases: "As size of the breast cancer increases some cells started to shed into cellular spaces, which are then transported via lymphatics to ipsilateral regional axillary lymph nodes. Lymph nodes containing cancer are first soft but later become firm or hard

with continued growth. The nodes adhere each other and form a fixed matted mass.”



“Involvement of Axillary lymph nodes occuring sequentially from the level I to central level II group and then to the apical level III group. While distant metastases are responsible for cancer related death in more than 95% women , axillary lymph node status is the most important prognostic factor correlate for disease free survival in cancer breast . About 30% risk of recurrence in node negative women whereas around 70% risk for node positive women” .

Distant Metastases:

The breast cancers acquire their own blood supply approximately twentyth cell doubling time. Thereafter cancer cells shed into

systemic veins -→ pulmonary circulation → lung

Axillary and intercostals veins → Batson's plexus of veins→ vertebral columns. Successful implantation of the metastatic foci from cancer breast

can occur after the primary cancer size exceeds 0.5cm in diameter. Within 24 months of treatment 60% of women develop distant metastases but metastases may become evident as late as twenty to thirty years after treatment of primary cancer.

Distal metastases:
Bone,
Lung,
Pleura,
Soft tissues and
Liver

Skeletal metastases
Lumbar vertebra,
Femur,
Thoracic vertebra,
Ribs and
Skull .

HISTOPATHOLOGY OF BREAST CANCER

FIG 22- **Nonlactating (inactive) mammary gland**
(Ref: Stain: hematoxylin and eosin, medium magnification left side and right side, high magnification. Taken from, Eroschenko VP; diFiore's Atlas of Histology.)

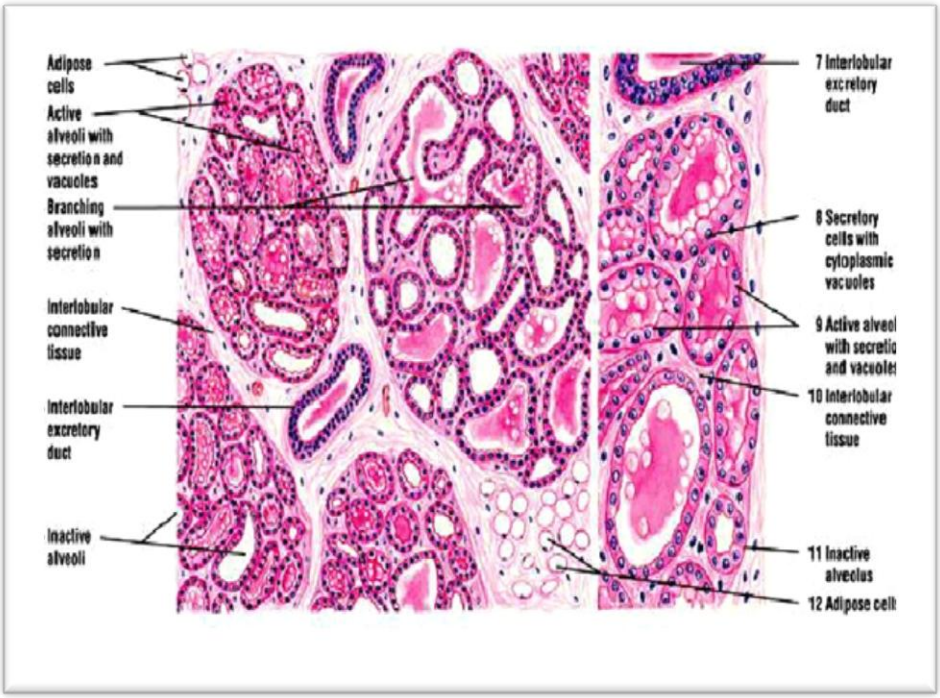


FIG 23- **Mammary gland during lactation**
(Ref: Stain: hematoxylin and eosin, left side, medium magnification and right side, high magnification. Taken from, Eroschenko VP; diFiore's Atlas of Histology.)

anywhere from the nipple end of major lactiferous ducts upto the terminal duct unit in the breast lobule.

Classification of Primary Breast Cancer:

Non-invasive Epithelial Cancers :

- LCIS →Lobular carcinoma in situ
- DCIS→ Ductal carcinoma in situ or intra ductal carcinoma

Invasive Epithelial Cancers :

- Invasive lobular carcinoma (10-15%)
- Invasive ductal carcinoma (50-70%)
- Tubular carcinoma (2-3%)
- Mucinous or colloid carcinoma (2-3%)
- Medullary carcinoma (5%)
- Invasive cribriform (1-3%)
- Invasive papillary (1-2%)
- Adenoid cystic and metaplastic carcinoma (2%)

Mixed Connective & Epithelial Tumors :

Cystosarcoma Phyllodes,

benign and malignant carcinosarcomas and

angiosarcomas.

Non-Invasive Epithelial cancers: Non-invasive neoplasms are divided into two: LCIS and DCIS (or Intraductal carcinoma).

	LCIS	DCIS
Age (years)	44–47	54–58
Incidence[a]	2–5%	5–10%
Clinical signs	None	Mass, pain, nipple discharge
Mammographic signs	None	Microcalcifications
Premenopausal	2/3	1/3
Incidence of synchronous invasive carcinoma	5%	2–46%
Multicentricity	60–90%	40–80%
Bilaterality	50–70%	10–20%
Axillary metastasis	1%	1–2%
Subsequent carcinomas:		
Incidence	25–35%	25–70%
Laterality	Bilateral	Ipsilateral
Interval to diagnosis	15–20 y	5–10 y
Histologic type	Ductal	Ductal

TABLE 2- **Ductal (DCIS) and Lobular (LCIS) Carcinoma insitu of the Breast**
(Ref: Taken from Devita principles and practice of obcology 10th edition and Schwartz text book of surgery 9th edition)

Histologic Subtype	Determining Characteristics		
	Nuclear Grade	Necrosis	DCIS Grade
Comedo	High	Extensive	High
Intermediate[a]	Intermediate	Focal or absent	Intermediate
Noncomedo[b]	Low	Absent	Low

TABLE 3- **Classification of Breast Ductal Carcinoma in situ (DCIS)**
(Ref: Taken from Devita principles and practice of obcology 10th edition and Schwartz text book of surgery 9th edition)

Invasive ductal carcinoma:

"Invasive ductal carcinoma is the most common presentation of cancer breast, accounting for fifty to seventy percentage of invasive breast cancers in the India. When there is no special features, it is called as infiltrating ductal carcinoma nothing otherwise specified (NOS). About sixty percentage of cases, IDC-NOS can present with microscopic or macroscopic axillary lymph node metastases. IDC-NOS usually presents in peri-menopausal or postmenopausal females in the 5^{th} to 6^{th} decades of their life as a firm solitary lump. It has ill defined margins and the cut surface will show areas of central stellate configuration with chalky white or yellow streaks that are extending to surrounding breast parenchyma. Histologically the tumor consists of anaplastic duct lining cells disposed in solid nests ,cords, gland masses and mixture of all these. The cells are often arranged in small clusters, disseminated in fibrous stroma".

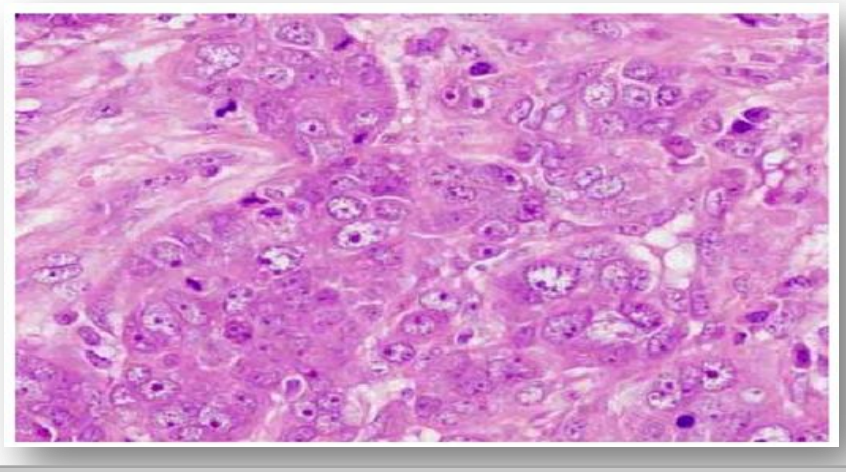


FIG 24- **Slide showing features of Infiltrating Ductal Carcinoma**
(Ref:. Taken from, Eroschenko VP; diFiore's Atlas of Histology.)

CLINICAL PRESENTATION:

"Breast cancer can arise from any portion of the breast, including the axillary tail, it is found most frequently around sixty percentage in upper and outer quadrant of the breast which is due to increased amount of breast tissue in that particular area. This is followed by the upper inner quadrant and retro areolar while lower half of the breast accounts for the rest of occurrence."

Symptoms caused locally by tumor

Lump: In about thirty three percentage of breast cancer cases, the woman presents with a lump in her breast often when discovered during some household activities like bathing.

Pain: Pain is an uncommon symptom, except for vague pricking sensation in the breast pain is often suggestive of a benign condition. If present it suggests aggressive type of malignancy.

Nipple retraction: Usually present in later part of the disease process. Recent onset of nipple retraction in an elderly female patient is highly suggestive of malignancy.

Nipple discharge: Present in 3-11% of cases, blood stained discharge usually indicates a intraductal carcinoma, Paget's disease or the tumor has grown into a major duct.

Nipple erosion: It is the commonest mode of presentation in Paget's disease, also seen in advanced intra ductal carcinomas. Skin involvement

which include peau d'orange, or frank ulceration or skin satellite nodules are the signs of locally advanced disease. Fixation to the chest wall is described as cancer-encuirasse. About twenty percentage of breast cancers in developing countries present in locally advanced stage.

Symptoms caused due to metastases :

Lymphatic spread:

Patients may present with swelling in the axilla or supraclavicular region, which may be mobile or fixed. Swelling of arm due to lymphatic or even venous obstruction in the axilla either due to nodal metastases or following radiotherapy or node dissection, is an uncommon but significant presentation.

Hematogenous spread*:*

Respiratory symptoms like cough, breathlessness due to pulmonary metastases. Low back pain is a common symptom, caused by secondary infiltration and collapse of lumbar vertebrae, with nerve root pains radiating to both the legs. A pathological fracture may be the first indication of the presence of the disease due to bone metastases.

Cerebral metastases may cause a fit or behavioral abnormality. Mass in the right upper abdomen, jaundice may be caused due to liver metastases. The general symptoms commonly associated with cancer, including malaise, weight loss and cachexia, are rare in patients with cancer breast.

CLINICAL EXAMINATION :

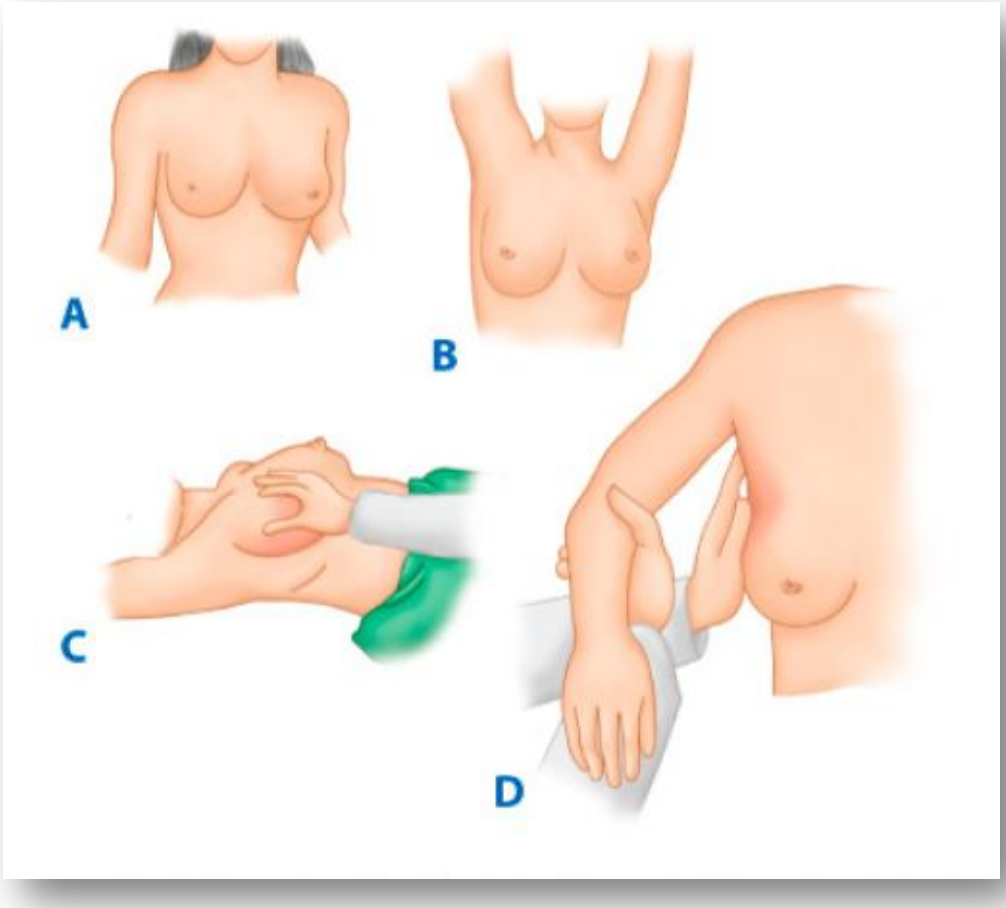


FIG 25- **Examination of the breast.**
A. Inspection of the breast with arms at sides. B. Inspection of the breast with arms raised.
C. Palpation of the breast with the patient supine. D. Palpation of the axilla.
(Ref: Schwartz text book of surgery 9th edition)

Examination of breast in 3 positions

1. Arms by the side.

2. Arms straight up in the air and

3. Hands on her hips.

INVESTIGATIONS

Triple assessment: In UK, suspected cases receive triple assessment which includes 1) History and physical examination;

2) Diagnostic imaging by mammography or Ultrasonography and 3) pathological examination - Cytology or histology.

Sensitivity ranges from 85% to 95%.[29]

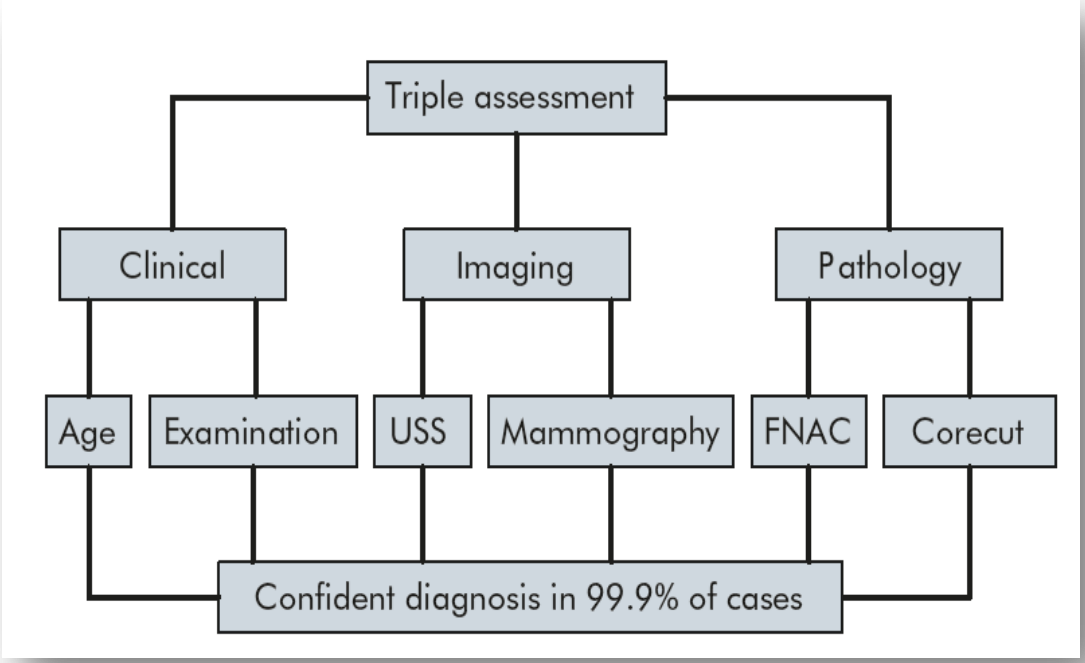


FIG 26- **Triple assessment**
(Ref: Bailey & Love 26th edition)

Breast imaging and image guided diagnostic techniques

Non-palpable lesions are frequently diagnosed using Image guided breast biopsies . Ultrasonography and mammography assisted techniques have been used to a variable extent in different hospitals

Ultrasonography of breast

"The use of breast ultrasound was first described by Wild and Neal, who investigated the usefulness of ultrasound for defining the normal breast as well as breast masses. Most procedures are done using hand held 7.5 MHz to 10 MHz probes with a penetration depth of 4 to 6 cm. Benign lesions are characterized by smooth, well-defined margins, homogenous internal echo pattern, symmetric posterior enhancement and compressibility. Suspicious lesions show irregular, fuzzy or jagged margins, irregular internal echoes, irregular posterior shadowing and show no compressibility."

Indications :

• Breast ultrasound can be primarily used to differentiate between solid and cystic lesions of breast with an accuracy of 96% to 100%.

• Ultrasound is the first choice for evaluating mammographically benign appearing lesions.

• Pregnant women having suspicious lesions.

• Ultrasound is part of evaluation and work up of patients with abnormal nipple discharge.

Ultrasound guided biopsy techniques :

• Ultrasound guided needle biopsy.

• Ultrasound guided cyst aspiration- if contents are clear no need for

cytological examination.

• Ultrasound guided FNAC and Core biopsy.

Ultrasound guided, Vacuum assisted breast biopsy (VAB): Uses the handheld VAB device. Less patient discomfort caused by multiple needle repositioning.

• Ultrasound guided, vacuum assisted excisional biopsy: Ensures both biopsy specimen as well as complete removal of lesions under ultrasound guidance.

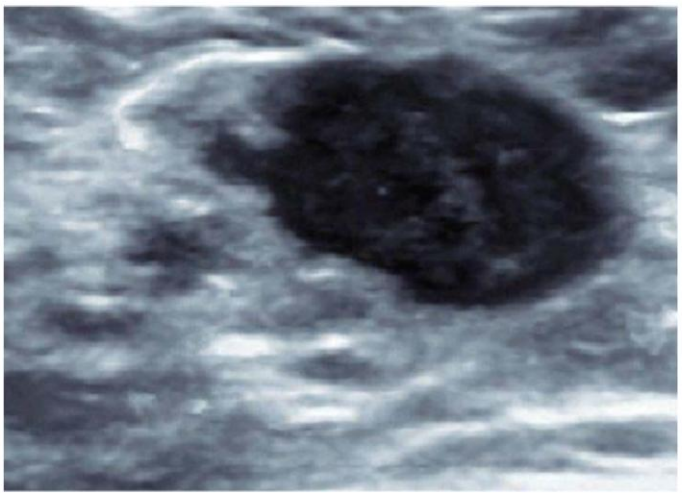


FIG 27- **Ultrasound of the breast for a case of carcinoma breast showing the lesion in the centre**
(Ref: Bailey & Love 26th edition)

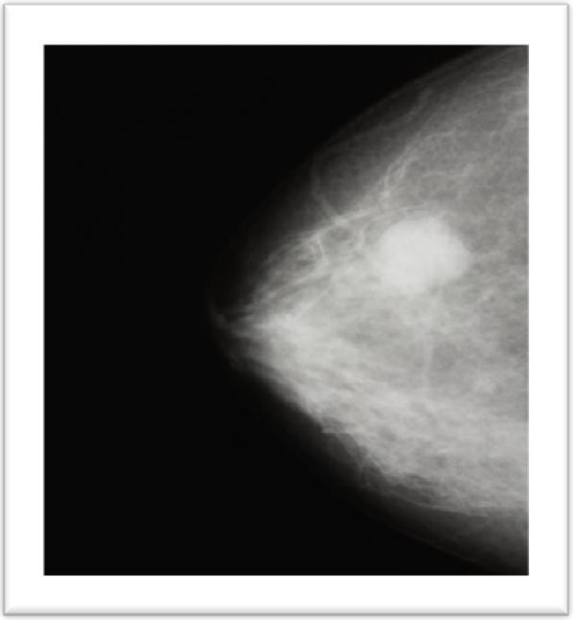


FIG 28- **Mammogram of the breast for a case of carcinoma breast showing the lesion in the centre**
(Ref: Bailey & Love 26th edition)

Since 1960s Mammography has been used in the North America Radiation dose of Conventional mammography is of 0.1 centigray (cGy) per study. One chest x-ray delivers twenty percentage of this dose. However there is no increased risk of cancer breast associated with this radiation dose.

Screening Mammography:

It is used to detect unexpected cancer breast in asymptomatic women. **craniocaudal (CC)** and **mediolateral oblique (MLO)** are the two views of the breast taken in screening. Upper Outer quadrant and axillary tail is best viewed in the MLO view. Medial aspect of breast is best viewed in the CC view provides better visualization and permits greater breast compression.

At present screening mammography should be offered:

1. Annually to women aged 50 and older.

2. At least biennially in women aged 40 to 49.

3. Annually in younger women with significant family history, or a history of prior breast cancer or histological risk

Diagnostic Mammography

It is used in the diagnosis of women presenting with cli features such as a breast lump, bloody of serous nipple discharge, or an abnormality on screening mammography. It includes magnification and compression imaging in addition to MLO and CC views. The additional views are 90^{0} lateral and spot compression views. Compression device used here minimizes the motion artifact, improves the picture definition, separates overlying breast tissues and decreases the amount of radiation dose. Magnification (x1.5) improves better visualization of margins.

Diagnostic mammography may be offered to:

1. Evaluate the opposite breast.

2. To evaluate the questionable or ill defined mass or other suspicious changes in breast.

3. To search for any occult cancer in patients with positive nodal status.

4. When women is undergoing conservative breast surgery to detect concomitant lesion in the same breast.

Mammographic abnormalities suggestive of malignancy can be divided into:

• ***Density abnormalities***-masses, architectural distortion and asymmetries.

• ***Micro calcifications***-The presence of fine, stippled, clustered calcium in and around a suspicious breast lesion is highly suggestive of malignant breast lesion, especially in younger women.

Breast biopsy techniques

1. **Fine needle aspiration cytology**:

“Fine needle aspiration of a palpable breast lump is easily performed in an out-patient setting as a painless procedure. A 1.5 inch, 22 or 23 guage needle attached to a 10 ml syringe is commonly used. The surgeon performing the procedure to control the syringe using a syringe holder with one hand while positioning the breast lump with the opposite hand. After placing the needle inside the lump, suction is applied while the needle is moved back and forth with the lump for six passes”.

“The cellular material expressed inside the needle hub is put onto microscope slide. Both air-dried and ethanol or cytofix used for fixing microscopy slides for analysis. The sensitivity and specificity approaches

100% when the breast mass is clinically or mammographically suspicious. The false negative rate is 5% and false positive rate is 2%.

Disadvantages

a. Cannot differentiate between in situ and invasive cancer.

b. No histological detail is obtained as compared to a tissue biopsy.

c. False negative results are high due to sampling errors.

d. Requires expert and specialized pathological interpretation"

2. **Core biopsy:**

"Core biopsy can be performed on palpable breast masses with a 14 gauge needle. A variety of techniques instruments can be used to provide a core or tissue such as manual biopsy needle or automated biopsy guns which has replaced FNAC in many departments. This technique is performed under local anaesthesia. Tissue specimens from the biopsy guns are placed in formalin and then processed to paraffin blocks for analysis. The only disadvantage is because of sampling errors.

Advantages :

a. Produces excellent histological detail rather than cytological specimen.

b. In situ cancers can be differentiated from infiltraive cancers.

c. Grading of tumors is possible.

d. Identification of estrogen receptors is also possible".

3. **Open surgical biopsy**:

"Biopsy is required when FNAC or core biopsies have failed to demonstrate malignant disease in a clinically suspicious lumps. It has the *disadvantage* of hospital admission, even majority of patients can be treated and discharged the same day. Main *advantage* of this is that it provides a definitive method of proving or excluding malignant breast disease. Open surgical excision biopsy can occasionally be done under local anesthesia but more easily under general anesthesia"

4. **Open surgical biopsy and frozen section:**

"This procedure can be done at the time of definitive surgery. But this is outdated. Modern surgical practice should avoid the outdated approach of performing mastectomy on the basis of frozen section.

5. **Incisional biopsy**: For cases presenting with an ulcer or lump >4 cm size, this method was used. Not used routinely and has been replaced by FNAC".

6. **Breast imaging and image guided diagnostic techniques**

Non-palpable lesions are usually diagnosed using Image guided breast biopsies. Ultrasonography and mammography assisted techniques have been used to a variable extent in different hospitals.

Mammography assisted biopsy techniques :

1. Needle Localization Breast Biopsy:

Until 1990, this was the only method to evaluate non-palpable Mammographic abnormality, which included surgical excision of breast masses marked with preoperative wire localization

2. Large core needle biopsy (LCNB):

"It can be either performed under ultrasound or mammographic guidance. Mammographic calcifications are sampled using stereotactic capabilities. Histological detail can be obtained. Stereotactic LCNB involves the patient lying prone on core biopsy table with breast in compression. computer analysis of triangulated mammographic images helps a robotic arm and automated biopsy gun to take specimen."

Other investigations

Xeroradiography These techniques are semilar to those of mammography but the exception that it provides a positive image rather than a negative one, which allows easy interpretation, good visualization. It requires less irradiation and is carried out in lighted rooms.

Ductography: The primary indication is nipple discharge, when the

discharge fluid is blood stained. Contrast media is injected into one or more major lactifrerous ducts and CC and MLO mammography views are obtained. Intraductal papillomas appear as small filling defects, but malignant lesions appear as irregular masses or as multiple filling defects. Ductal lavage and cytology using microcatheters is used in women with increased breast cancer risk.

Thermography: Malignant lesions are hotter than normal and benign lesions due to increased vascularity and increased metabolism. It has 85% diagnostic accuracy.

Magnetic Resonance Imaging: MRI can be used to screen the breasts of high-risk women especially younger women and of women with a newly diagnosed cancer breast.

1. It can be useful to differentiate scar due to previous surgery from recurrence in females who have had previous breast conservation therapy.
2. Gold standard investigation for imaging breasts of females with implants.
3. useful in screening of pregnant female breast

Investigations to assess the metastases

- **Liver function tests**: Enzyme levels may be elevated in hepatic metastases.
- **Serum calcium**: elevated in patients with bony metastases.

- **Chest X-ray**: Features suggestive of secondaries include coin lesions, interstitial infiltration, mediastinal widening, pleural effusion and rib secondaries.
- **Bone X-rays**: Usually present with osteolytic lesions while some lesions are rarely osteogenic.
- **Bone Scan**: Technetium Tc99 labeled bone scans are more sensitive than X-rays. They are most helpful when strong suspicion of skeletal metastases is present.
- **Ultrasound scan of abdomen** is used to asses liver metastases, lymph nodes, free fluid in abdomen, ovarian secondaries or any pelvic deposits.

HORMONE RECEPTORS

"The laboratory discovery and subsequent measurement of estrogen receptors (ERs) and progestin receptors (PRs) in breast tumors have given the physician useful tools to aid in the treatment of women with breast cancer. The ER and PR belong to a large class of nuclear receptor proteins, are present in normal breast, and other tissues and are expressed in up to 60% to 70% of breast cancers. In both normal and tumor cells, estrogen binds to the ER, which is a large protein molecule located in the cytoplasmic and nuclear fractions of the cell. The receptor hormone

complex results in gene activation and transcription of mRNA and cell proliferation."

"The blockade of estrogen inhibits protein translocation, cell proliferation, and leads to initiation of cell death. One method of reducing estrogen levels is with direct blockade of ER with drugs like tamoxifen. Synthesis of progestin receptors is a product of estrogen action on cells, it is an estrogen dependent process. Hormone receptors can be routinely identified by a variety of immunohistochemical staining of the breast tissue. Specimen may be obtained by core cut needle biopsy, open biopsy or postoperative specimen of breast tissue".

Hormonal therapy should be recommended to patients whose breast cancer contains ER or PR, regardless of age, menopausal status or involvement of axillary nodes. Benefit of hormonal therapy in receptor negative tumors is very less.

Estrogen receptor	**Progesterone receptor**	**Response % to hormonal therapy**
+	+	78
+	-	34
-	+	45
-	-	10

TABLE 4- **Response rate to hormonal therapy**

Methods of Measurement of steroid Receptors :

1. **Titration method** : Where the sample is incubated with increasing amounts of labelled steroid with and without the presence of unlabelled inhibitor.

2. **Biochemical assays** :

a. Dextran coated charcoal (DCC) method first described by Korenman and Dukes in 1970.45

b. Sucrose density gradient analysis.

c. High performance liquid chromatography.

3. **Immunoflourescence** : Flourescein labelled steroid is bound to tissue steroid receptors. Amount of bound steroid is visualized by fluorescent microscopy.

4. **Enzyme linked immunoassays** : Sandwich assay with immobilized monoclonal antibody to receptor.

5. **Immunohistochemistry (IHC)** : Monoclonal antibody specific to steroid receptor binds to tissue steroid receptor. Second Ab labeled with peroxidase is used to localize first Ab binding, visualization of receptor in tissue with substrates in peroxidase stain.

6. Cloning of steroid receptor genes and generation of specific complementary DNA and hybridization analysis of the generated complementary DNA**.**

7. In-situ hybridization of hormone receptor mRNA levels in histological sections.

HER-2/neu oncoprotein

"The 185 KD oncoprotein HER-2/neu is a mimicker of the tyrosine kinase receptor family,which is a type of growth factor receptor with fifty % homology to the epidermal growth factor receptor EGFR, and has surface membrane, transmembrane, and cytoplasmic domains. The cytoplasmic domain to which antibodies for immunohistochemical studies have been derived that has activating phosphorylation and transcription initiating functions, The activating ligand for the HER-2 receptor is unknown.

Since the initial reports describing the association of HER-2 amplification with poor clinical outcome, the gene product has been the subject of at least 48 prognostic research studies involving 15,000 patients with cancer breast".

The techniques used to evaluate HER-2/neu status in breast cancer

Gene-based assays such as southern and slot blotting,

PCR- Polymerase chain reaction methods, and

more recently in-situ hybridization featuring both flouorescent and nonfluorescent techniques - FISH

Qualitative and quantitative measurements of HER-2/neu protein have been performed by IHC on frozen and archival tissues, western blotting and enzyme immunoassays (ELISA).

BIOMARKERS

"Breast cancer biomarkers are of several types.. These include BRCA-1, BRCA-2 and other germline mutations. Exposure biomarkers include measurement of carcinogen exposure. Biomarkers are biologic alterations in breast tissues that occur between initiation and cancer development. These biomarkers are used in short term chemoprevention trials, include histologic changes and indices of proliferation. Drug effect biomarkers (serum glutathione reductase activity, ornithine decarboxylase activity) are used to monitor biochemical effect of drugs".

Prognostic and predictive biomarkers in cancer breast include:

1. **Indices of proliferation:** such as Proliferating cell nuclear antigen (PCNA), a nuclear protein, which is over expressed in tumor with high mitotic index, high histologic grade.

2. **Indices of apoptosis**: Bcl-2 family proteins appear to inhibit apoptosis. The death signal protein bax induced by the growth factor deprivation. The bax:bcl- 2 ratio represent intracellular regulatory mechanism with prognostic implications.

3. **Indices of angiogenesis:** vascular endothelial growth factor (VEGF) and angiogenesis index.

4. **Growth factor receptors and growth factors:** Such as Human epidermal growth factor (HER)-2/neu and epidermal growth factor receptor (EGFr). Over expression is associated with receptor negative, p53 positive tumors. Anti HER2/neu therapy is now an important breast cancer therapy.

5. p53 overexpression correlates with high histologic grade of tumor, high proliferative fraction, aneuploidy, HER2/neu overexpression and ER/PR negative tumors.

IMMUNOHISTOCHEMISTRY

"Immunohistochemistry is one of the powerful ancillary methods used in pathology today which has revolutionized the study of disease and its prognosis. The most profound method today has been of Immunohistochemistry (IHC) – which is a powerful and cost effective tool applicable in light microscopy. IHC is an aesthetic component to the practice of histology, which validates the morphologic judgements pathologists make".

"Immunohistochemistry (IHC), also called as immunocytochemistry, is a method for localizing specific antigens in body tissues or cells based on antigen-antibody recognition or reaction; IHC

seeks to exploit the specificity provided by the binding of an Ab with its Ag at a light microscopic level."

VIRTUES OF IHC :

- It works in routine (less than ideal) conditions.
- It is compatible with standard fixation and embedding procedures.
- Studied under light microscope.
- Permanent slides can be prepared which can be stored.
- It can be performed retrospectively on archival material.
- It is sensitive and specific and is applicable to almost any immunologic molecule.
- It is interpreted in morphologic context.
- It does not require fluorescent microscope.

MAIN USES OF IHC :

- Classifying undifferentiated tumors, lymphomas, neuroendocrine and soft tissue tumors.
- Detection & accurate assay of the tumor biologic factors of predictive & prognostic values such as hormone receptors (ER, PR) and HER-2/neu in breast cancer.
- Detection of metastatic tumor cells in bone marrow, lymphnodes & serous fluids when the cell groups are too less or confusing.
- Additionally, immune histochemistry is being increasingly used in

the characterization of the underlying agent in many infectious diseases applying specific antibodies to bacterial, viral or fungal antigens like in HIV,HCV,HSV,HPV,TB bacilli and leprabacilli.

The validity of immunohistochemistry in diagnostic histopathology depends on the quality of immunostains used. In addition to antibody quality,3 other factors have a major impact on immunohistochemistry.

1. Tissue fixation and processing.
2. Unmasking of epitopes.
3. Sensitivity of the detection system.

Formaldehyde is the most popular fixative used in great part because of its low cost, easy of preparation, & because it preserves morphologic details with few artifacts. However, formaldehyde fixation results in a variably reversible loss of immune reactivity by its masking or damaging some antibody binding sites.

The different methods of detection are:

Enzyme bridge technique: hardly used these days

PAP (peroxidase anti-peroxidase) method devised by Sternberger et al in 1970

Biotin avidin procedure devised by Heitzman and Richards in 1974

Avidin-Biotin Conjugate procedure (ABC) This procedure improved sensitivity was devised by Hsu et al.

Biotin streptavidin system (B-SA)

Alkaline phosphatase and anti-alkaline phosphatase method (APAAP) of Cordell et al

Protein A method is not much in use.

EnVision systems

TNM STAGING OF CARCINOMA BREAST

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

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 apparent[a] 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 apparent[a] 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 apparent[a] ipsilateral internal mammary lymph node(s) and in the presence of clinically evident axillary lymph node metastasis; or metastasis in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement
N3a	Metastasis in ipsilateral infraclavicular lymph node(s)
N3b	Metastasis in ipsilateral internal mammary lymph nodes(s) and axillary lymph node(s)
N3c	Metastasis in ipsilateral supraclavicular lymph node(s)

pN0(i–)	No regional lymph node metastasis histologically, negative IHC results
pN0(i+)	No regional lymph node metastasis histologically, positive IHC results, no IHC cluster >0.2 mm
pN0(mol–)	No regional lymph node metastasis histologically, negative molecular findings [reverse-transcriptase polymerase chain reaction (RT-PCR)]
pN0(mol+)	No regional lymph node metastasis histologically, positive molecular findings (RT-PCR)
pN1	Metastasis in 1 to 3 axillary lymph nodes, and/or in internal mammary nodes with microscopic disease detected by sentinel lymph nodes dissection, not clinically apparent[c]
pN1mi	Micrometastasis (>0.2 mm, none >2.0 mm)
pN1a	Metastasis in 1 to 3 axillary lymph nodes
pN1b	Metastasis in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection, not clinically apparent[c]
pN1c	Metastasis in 1 to 3 axillary lymph nodes and in internal mammary lymph nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent[c] (if associated with >3 positive axillary lymph nodes, the internal mammary nodes are classified as pN3b to reflect increased tumor burden)
pN2	Metastasis in 4 to 9 axillary lymph nodes, or in clinically apparent[a] internal mammary lymph nodes in the absence of axillary lymph node metastasis
pN2a	Metastasis in 4 to 9 axillary lymph nodes (at least one tumor deposit >2.0 mm)
pN2b	Metastasis in clinically apparent[a] internal mammary lymph nodes in the absence of axillary lymph node metastasis
pN3	Metastasis in ≥10 axillary lymph nodes, or in infraclavicular lymph nodes, or in clinically apparent[a] ipsilateral internal mammary lymph nodes in the presence of 1 or more positive axillary lymph nodes; or in >3 axillary lymph nodes with clinically negative microscopic metastasis in internal mammary lymph nodes; or in ipsilateral supraclavicular lymph nodes
pN3a	Metastasis in ≥10 axillary lymph nodes (at lease one tumor deposit >2.0 mm), or metastasis to the infraclavicular lymph nodes
pN3b	Metastasis in clinically apparent[a] ipsilateral internal mammary lymph nodes in the presence of ≥1 positive axillary lymph nodes; or in >3 axillary lymph nodes and in internal mammary lymph nodes with microscopic disease detected by sentinel lymph node dissection, not clinically apparent[c]
pN3c	Metastasis in ipsilateral supraclavicular lymph nodes

Distant metastasis (M)

MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

TNM STAGE GROUPING – CARCINOMA

Stage 0	Tis	N0	M0
Stage I	T1[a]	N0	M0
Stage IIA	T0	N1	M0
	T1[a]	N1	M0
	T2	N0	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T0	N2	M0
	T1[a]	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
Stage IIIB	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
Stage IIIC	Any T	N3	M0
Stage IV	Any T	Any N	M1

[a] T1 includes T1mic.

TREATMENT OF BREAST CANCER

Once diagnosed of caner breast , the type of treatment offered to a patient is determined by clinical stage of the disease. But before any therapy is started, the doctor must discuss the plan of treatment and all the complications with the patient and the attenders.

In Situ Breast Cancer (Stage 0)

Lobular carcinoma in situ (LCIS):

The current treatment protocol is either observation alone with or without hormonal therapy using Tamoxifen. The goal of the treatment is to prevent or detect at an early stage the invasive cancer that develops subsequently in 25% to 35% of females.

Ductal carcinoma in situ (DCIS):

Total Mastectomy is done for women with DCIS and evidence of extensive disease while Lumpectomy and radiation therapy is done for women with limited disease. Lumpectomy alone is enough for women with lesion less than 0.5 cm.

Early Invasive Breast Cancer (Stage I, IIa, or IIb):

Currently,

a. MRM - Mastectomy with axillary lymph node dissection or

b. Breast conservation BCS (lumpectomy with assessment of axillary lymph node status and radiation therapy) are considered gold standard for

treatment of early cancer - stages I and II of breast cancer.

Indications of Total Mastectomy in early Breast Cancer :

- When Tumour is more than 4 cms
- Multicentric tumour
- Poorly differentiated tumour
-Tumour margin is not clear of tumour after breast conservation surgery

Axillary lymphadenopathy or metastatic disease in SLN sentinel lymph node necessitates an axillary lymph node dissection. Traditionally axillary clearance is done upto level II in early stage breast cancers. If the SLN sentinel lymph node cannot be identified or is found to harbor metastatic disease, then axillary lymph node dissection is performed.

Systemic therapy for early stage breast cancer

Adjuvant chemotherapy:

i. Considered for all node positive breast cancers.

ii. Cancers size larger than 1cm .

iii. Node negative cancers - size more than 0.5 cm in with adverse prognostic features such ass vessel invasion, high nuclear grade, high histologic grade, with negative harmone status and HER2/neu over expression.

Tamoxifen therapy: Considered for hormone receptor positive (ER/PR) females with cancers larger than 1 cm in size.

Radiation therapy: All conservative breast surgeries need radiation to chest wall. If lymph node status is N0 then no radiation to axilla is needed. If N1 and less than 3 nodes are positive, no radiation to axilla is given (plus axillary dissection). If N1 and more than 3 nodes radiation is mandatory to axilla (plus axillary dissecti `

MASTECTOMY:

Implies to surgical removal of entire breast parenchyma

Skin sparing mastectomy (SSM): Includes the resection of the nipple/areola complex including existing biopsy scar, and removal of whole breast parenchyma. If indicated a sentinel lymph node biopsy or axillary can also be performed. The types of incisions can be used are 1. periareolar, 2.tennis racquet,3. reduction mammoplasty and 4.modified elliptical.[41]

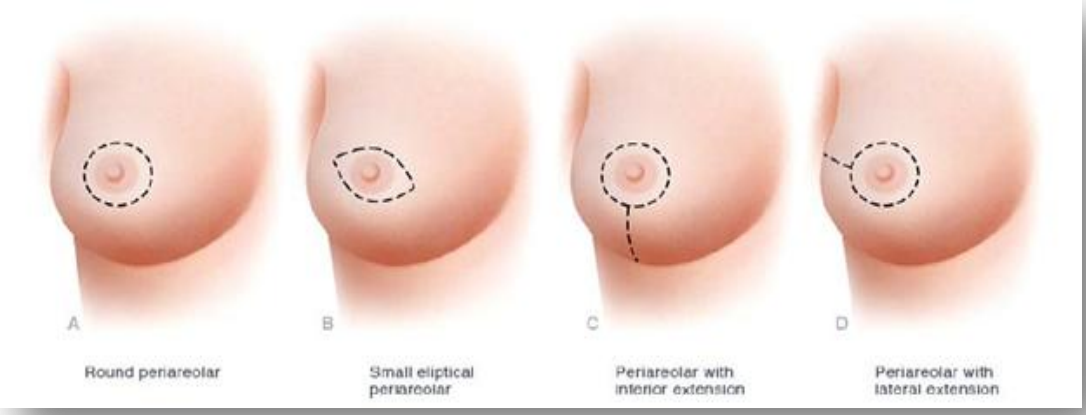


FIG 29- **Types of skin sparing mastectomy**

Advantages: Minimal skin is harvested, thus generous skin envelope remains after mastectomy, thus cosmetic results are excellent. It affords improved symmetry with the other breast when compared with traditional modified radical mastectomy. Can be done in early breast cancers but contraindicated in inflammatory carcinoma, locally advanced cancers and multifocal disease. There is a recurrence rate of less than two percentage when Skin Spaing Mastectomy is used for T1 to T3 cancers.

Simple mastectomy: A simple or total mastectomy removes all of the breast tissue, the nipple areola complex, and the skin. A transverse elliptical incision is taken on either sides of the breast and mastectomy is performed.

Extended simple mastectomy : Removes all of the breast tissue, the nipple-areola complex, skin, and the level one and level two axillary lymph nodes.

Radical Mastectomy:

William Stewart Halsted and Meyer descried radical mastectomy in 1894, which removes all of the breast tissue & skin, the nipple-areola complex, the pectoralis major muscle and pectoralis minor muscles and

the level one, two and three axillary lymph nodes. Preservation of the axillary vein, cephalic vein and long thoracic nerve of Bell was made. Good loco regional control is obtained in this procedure. But it is no longer indicated as it causes excessive morbidity with no increased survival benefit. The word radical is not completely true as it ignores internal mammary chain of lymph.

Modified Radical Mastectomy:

Patey's Modified radical mastectomy (MRM) preserves both the pectoralis major and pect minor muscles, allowing removal of the level one and level two axillary nodes but not level three or apical lymph nodes.

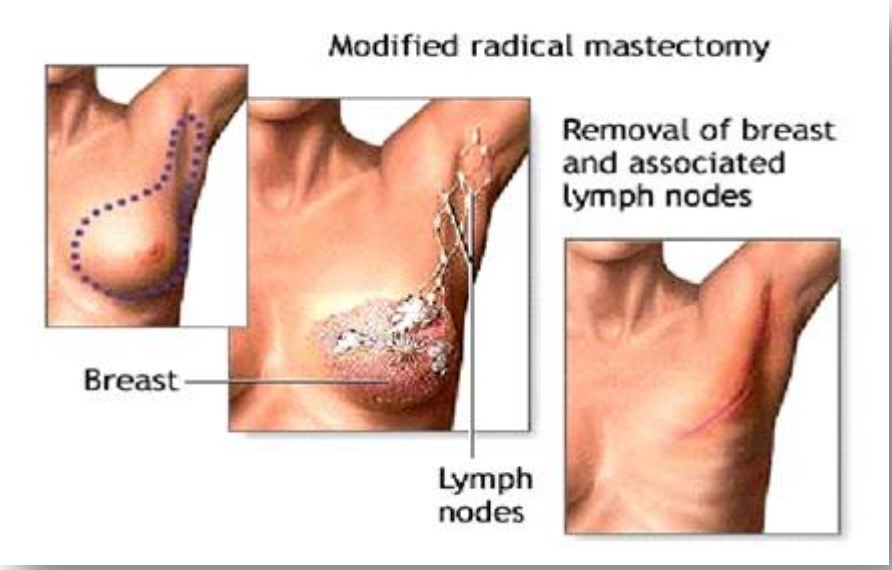


FIG 30- **Modified Radical mastectomy**

Operative Procedure

Anesthesia: This procedure is performed under General Anesthesia.

Access:

Place the patient in supine position, with arm on operating side extended on an arm board.

Prepare the skin and place towels to allow access to breast and axilla.

With skin marking pen draw a transverse elliptical incision (Stewart's) and encompass approximately 5cm of skin around the lesion and also the nipple.

Ensure that you will be able to approximate the wound edges after surgery.

Elevate the skin flaps in the plane between subcutaneous fat and breast tissue.

PROCEDURE

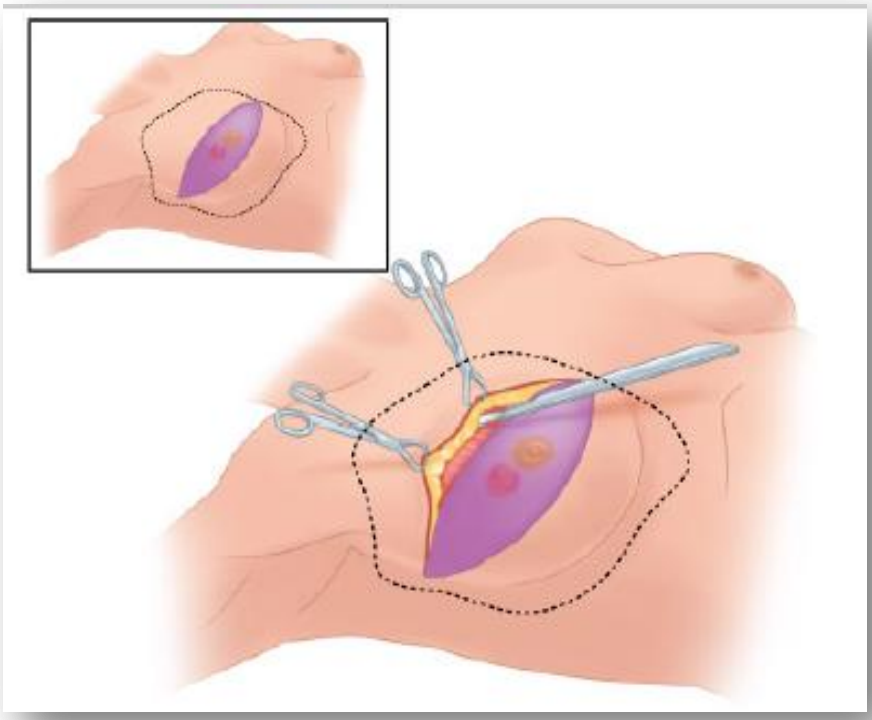
"Ensure the flaps (7-8mm) are not too thin, no breast tissue is left behind. Raise the upper flap to the upper limit of breast tissue that is 2-3 cm below lower border of clavicle. Raise the lower flap to the lower limit of breast, upto infra-mammary fold. Dissect down until pectoralis fascia is reached, introduce a finger covered by a swab and find a submammary plane between the fascia and the breast. Proceed dissection in this plane, the anatomical boundaries are the anterior border of the latissimus dorsi muscle laterally; to the midline of the sternum medially; superiorly the subclavius muscle & the caudal extension of the breast two to three cm inferior to the inframammary fold inferiorly. Preservation of the medial pectoral nerve is made in this procedure."

Axillary dissection:

"The axillary lymph nodes are removed as a part of modified radical mastectomy. The axilla is opened by an incision in axillary fascia, the most lateral limit of the axillary vein is identified and the areolar tissue of the lateral axillary space is lifted as the vein is cleared on its anterior and inferior surfaces. The cephalic vein should be preserved as it is an important collateral if main axillary vein is injured. Using combination of sharp and blunt dissection lateral border of pectoralis major and anterior border of latissimus dorsi are identified; these landmarks form limits of

axillary dissection. The level I nodes at the junction of axillary vein and anterior border of latissimus dorsi are cleared. For level II nodes pectoralis minor beneath pectoralis major is pulled out and retracted forwards and medially.

If level III clearance is desired, both borders of pectoralis minor should be defined and divided at its insertion to coracoid process. The thoracodorsal bundle, the long thoracic nerve is preserved.. Finally the whole breast and the axillary contents are removed from the surgical bed as en masse and sent for pathologic assessment after labelling the margins. Then the wound is closed in two layers with a closed system suction drainage.”



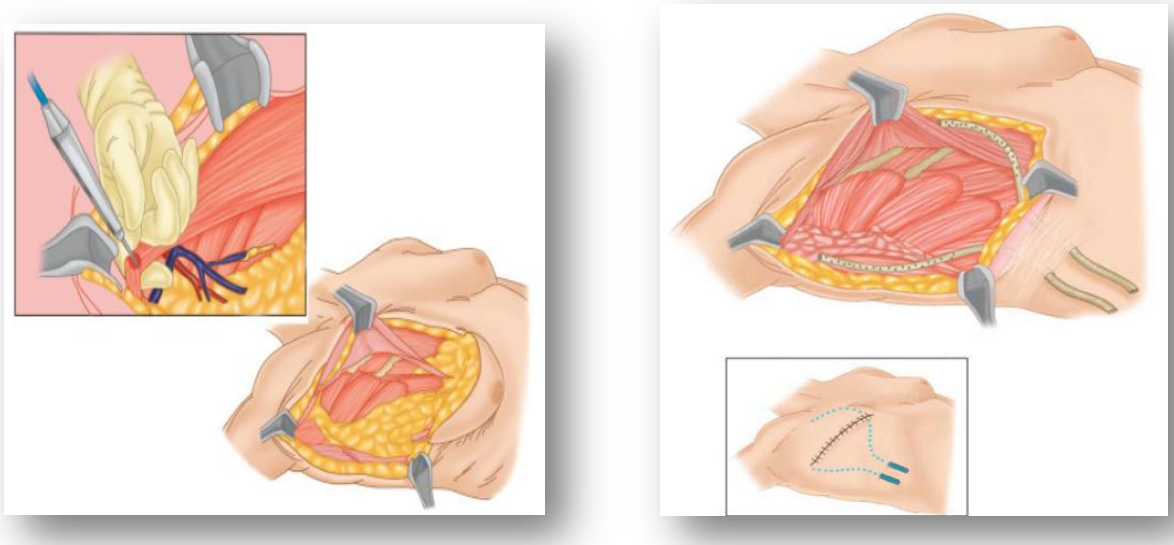


FIG 30- **Steps of Modified Radical mastectomy**

Locally advanced breast cancer (Stage IIIa or IIIb):

Stage IIIa with operable disease: Auchincloss MRM - Modified radical mastectomy followed by adjuvant CT chemotherapy followed by adjuvant RT radiation therapy. Chemotherapy is used to maximize the distant disease free survival while radiation therapy is used to maximize locoregional contol and disease free survival. Neoadjuvant chemotherapy can be given in selected cases of IIIa cancers to reduce the size of the tumor.

Stage IIIa (inoperable) and IIIb: Neoadjuvant chemotherapy plus Modified radical mastectomy plus adjuvant chemotherapy plus adjuvant radiation therapy.

Distant metastases (Stage IV):

It is the blood spread of cancer into bones, lungs, pleura, liver, soft tissues,

brain and adrenals. Breast lump is evaluated by FNAC/ incision biopsy, chest CT, LFT, USG abdomen, CT abdomen, whole body scanning, CT brain, and tissue study for ER/PR/Her- 2 neu receptor status for starting chemotherapy

Treatment options :

To improve quality of life

To relieve pain of secondaries like bone, lungs

To relieve neurological problems like convulsions, space occupying cranial problems

Other symptomatic relief

Treatment strategies in metastatic carcinoma of the breast includes :

1. Chemotherapy : CMF, CAF, Taxanes in combination.

2. High dose of CT using cyclophosphamide, cisplatin, carmustine, melphalan.

3. Haemopoetic growth factor - enhance cell kill with less bone marrow toxicity.

4. Radiotherapy - used in bone metastasis, brain secondaries

BREAST CANCER PROGNOSIS

Five year survival rate for breast cancer in

stage one I → 94%.

stage IIa → 85%

stage IIb → 70- 52%,

stage IIIb → 48%; and

stage IV → 18%.

PREVENTION OF BREAST CANCER

"Prevention is always better than cure. Hence based on the concept that detecting and treating small cancers and precancerous lesions could save lives, breast screening and more recently chemoprevention of breast cancer in high-risk groups have been started to reduce the mortality". The three commonly used screening methods are:

1. **Breast self examination**
2. **Clinical breast examination**
3. **Screening Mammography**

MATERIALS AND METHODS

PLACE OF STUDY:

Rajiv Gandhi Government General Hospital and Madras Medical College, Chennai.

TYPE OF STUDY:

prospective randomized control trial.

PERIOD OF STUDY:

March 2016 to September 2016.

INCLUSION CRITERIA:

All patients admitted in RGGGH with

1.Age>18 yrs

2.Female Patients

3.Primary breast cancer

EXCLUSION CRITERIA:

- Previous axillary surgery(<4 months)
- Diabetic patients
- Recent steroid treatment(<1 month)

- Pregnancy
- Immunosuppression

SAMPLE SIZE:

70 cases; control group:35, Test group:35

METHODOLOGY

This will be a hospital based time bound study. All those cases which satisfy the inclusion criteria will be included in this study. All patients will be taken into the study after obtaining written informed consent. They will be subjected to baseline investigations (CBC, LFT, RFT, blood grouping and typing) and specific investigations namely ultrasound breast. Data will be collected in the form of detailed history, clinical examination and investigations (radiological investigations), intra operative findings and ultimate outcome of the patients.

ASSESSMENT OF PARAMETERS:

- 24 hr seroma volume.
- Age
- Intraoperative findings. • Postoperative outcome.

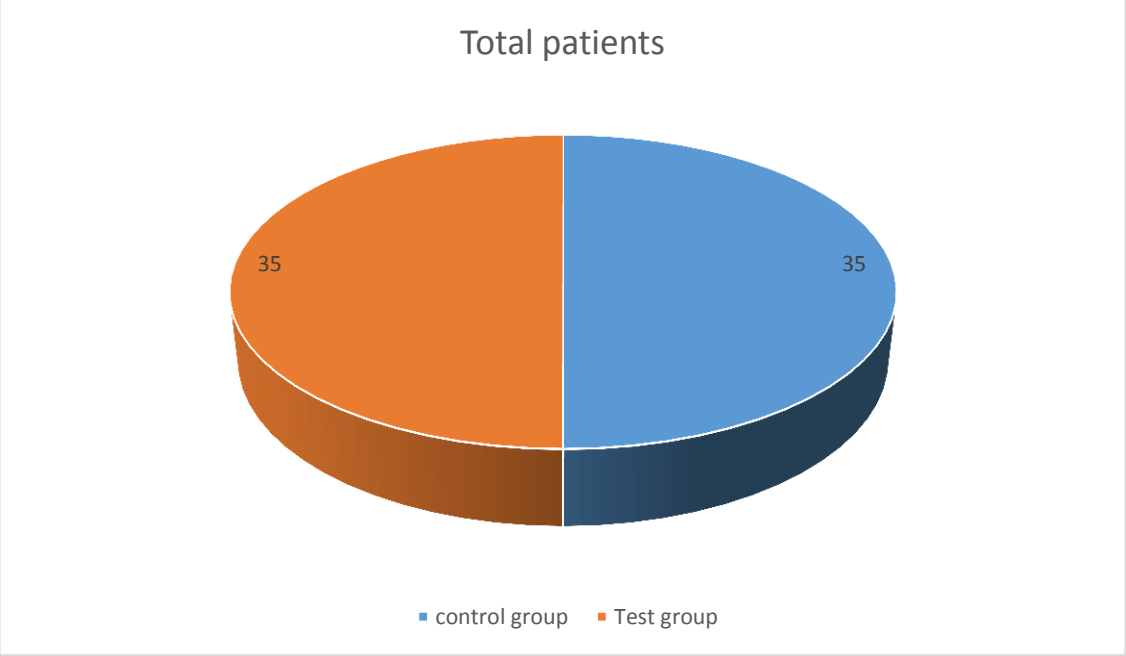
· Total cases → 70

· No. of patients in control group → 35

· No. of patients in study group → 35

The study group were given inj methyl prednisolone 80mg locally into the wound cavity for first two days after surgery and the other group had a normal dressing.

24hr seroma collection in the DT was measured both in study and control groups for 1 week till DT removal and it was compared between these two groups.

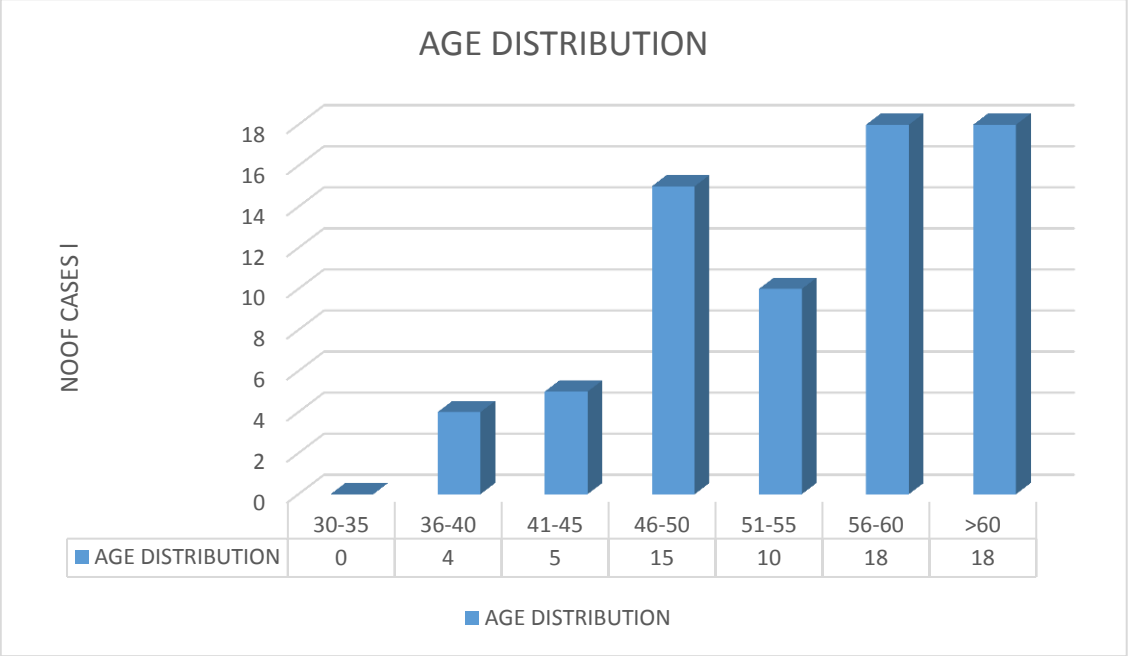


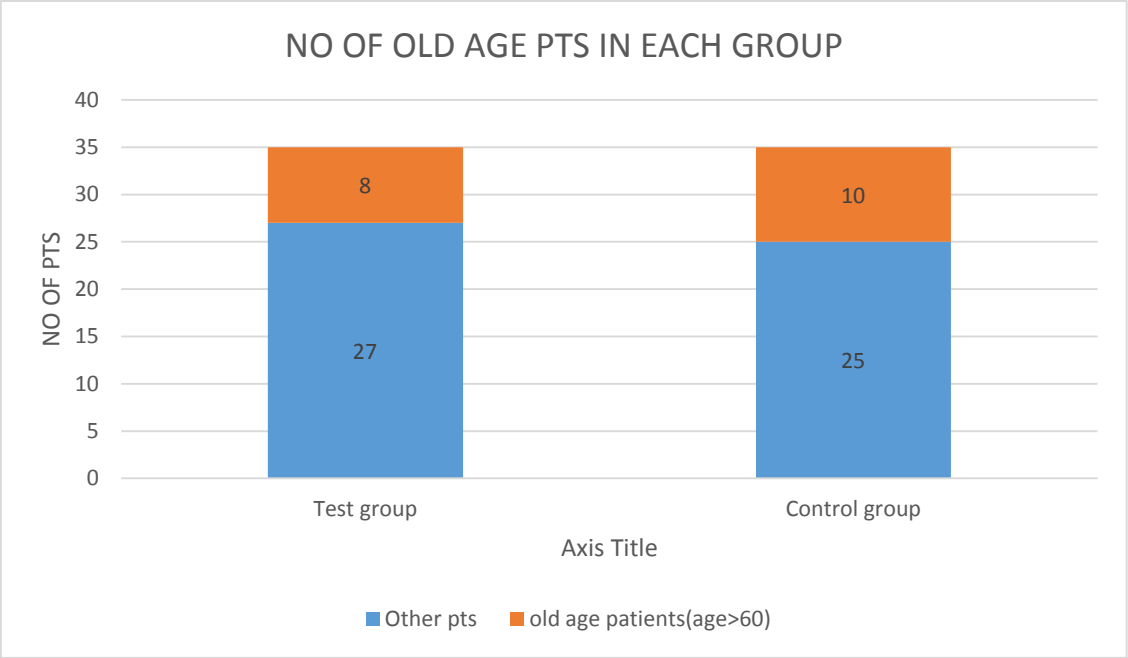
RESULTS

AGE DISTRIBUTION

AGE GROUP (YRS)	No of patients
30-35	–
36-40	4
41-45	5
46-50	15
51-55	10
56-60	18
>60	18

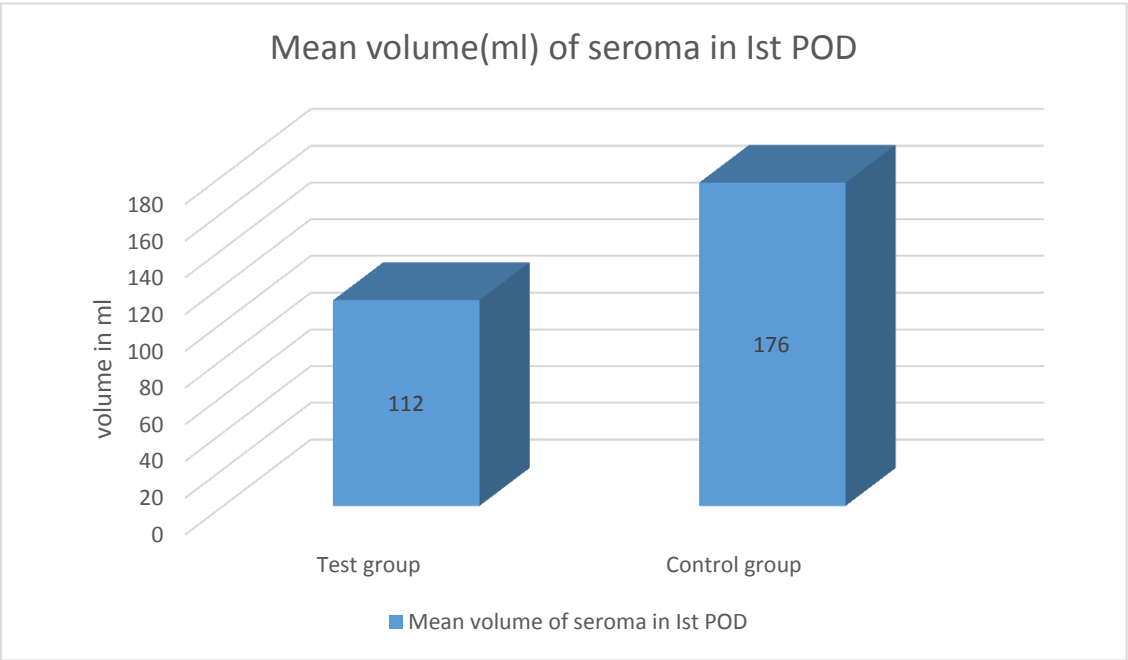
Majority of the patients belong to older age group, early with the highest being in the age group 56-60 followed by >60 age group. So breast cancer is most common ib older age group patients.



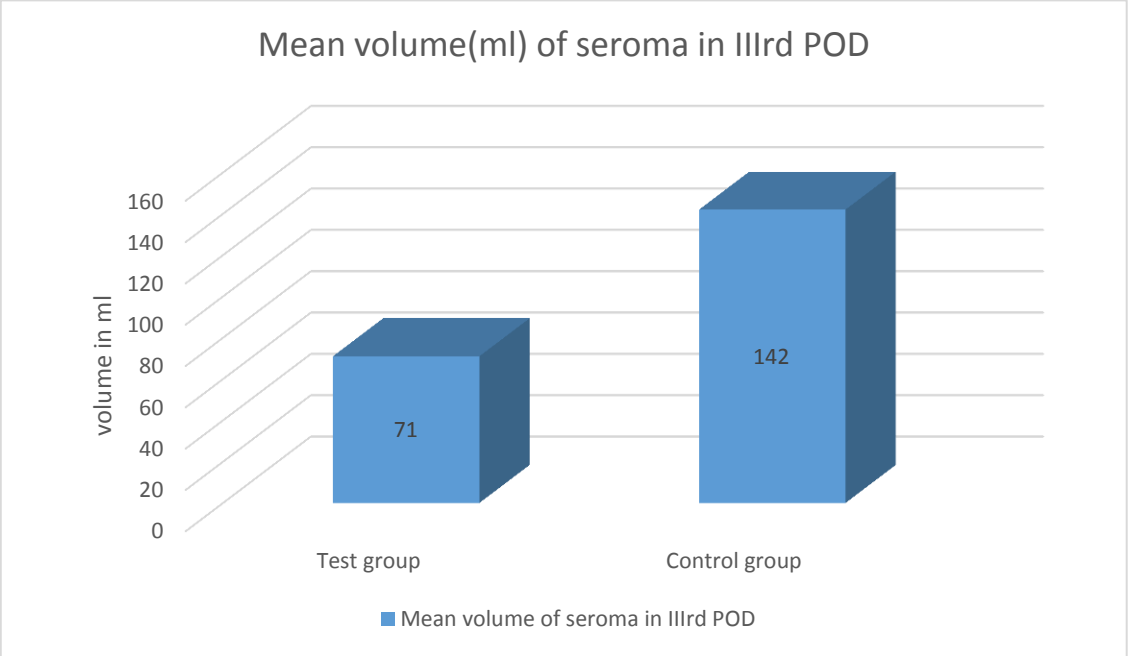


MEAN VOLUME OF SEROMA

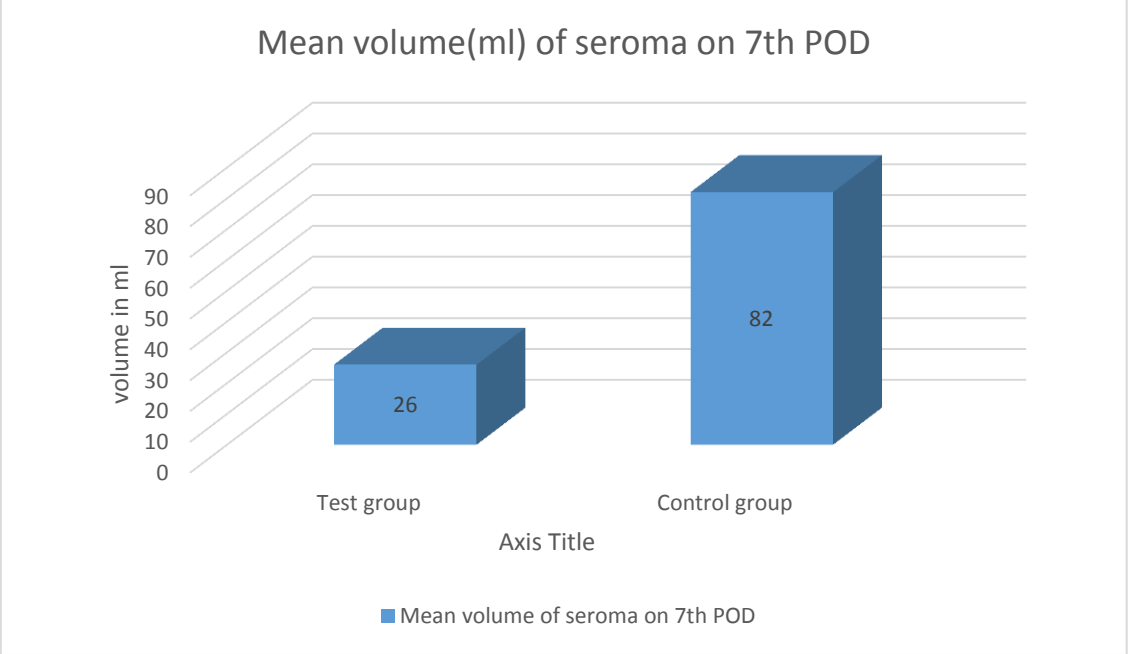
i) I st POD:



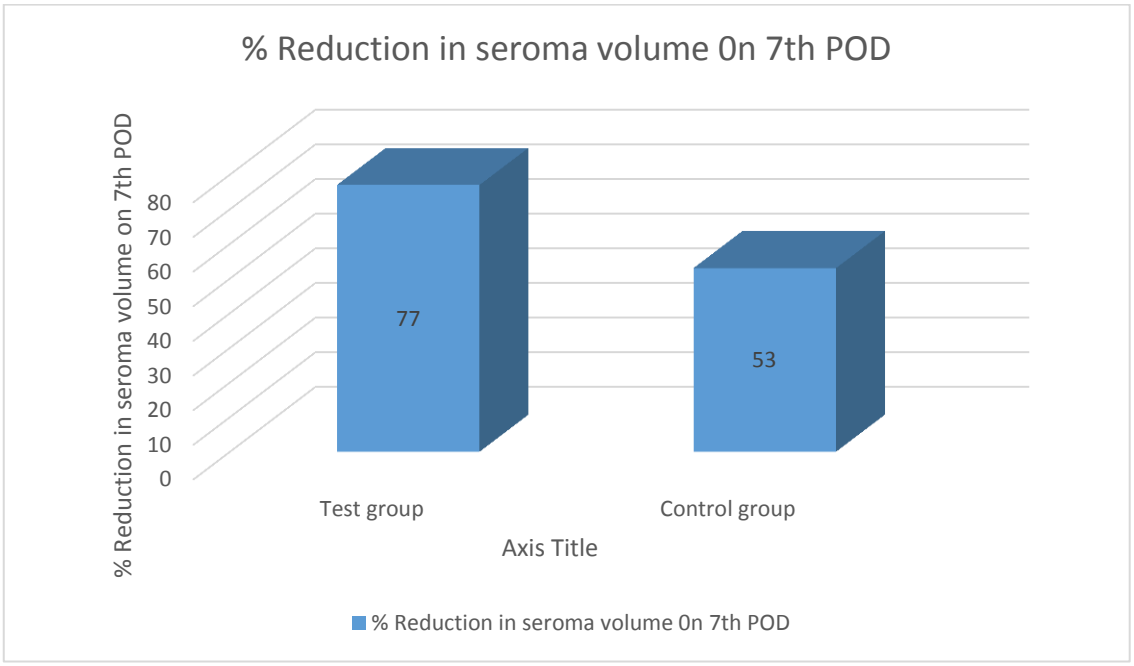
ii) IIIrd POD:

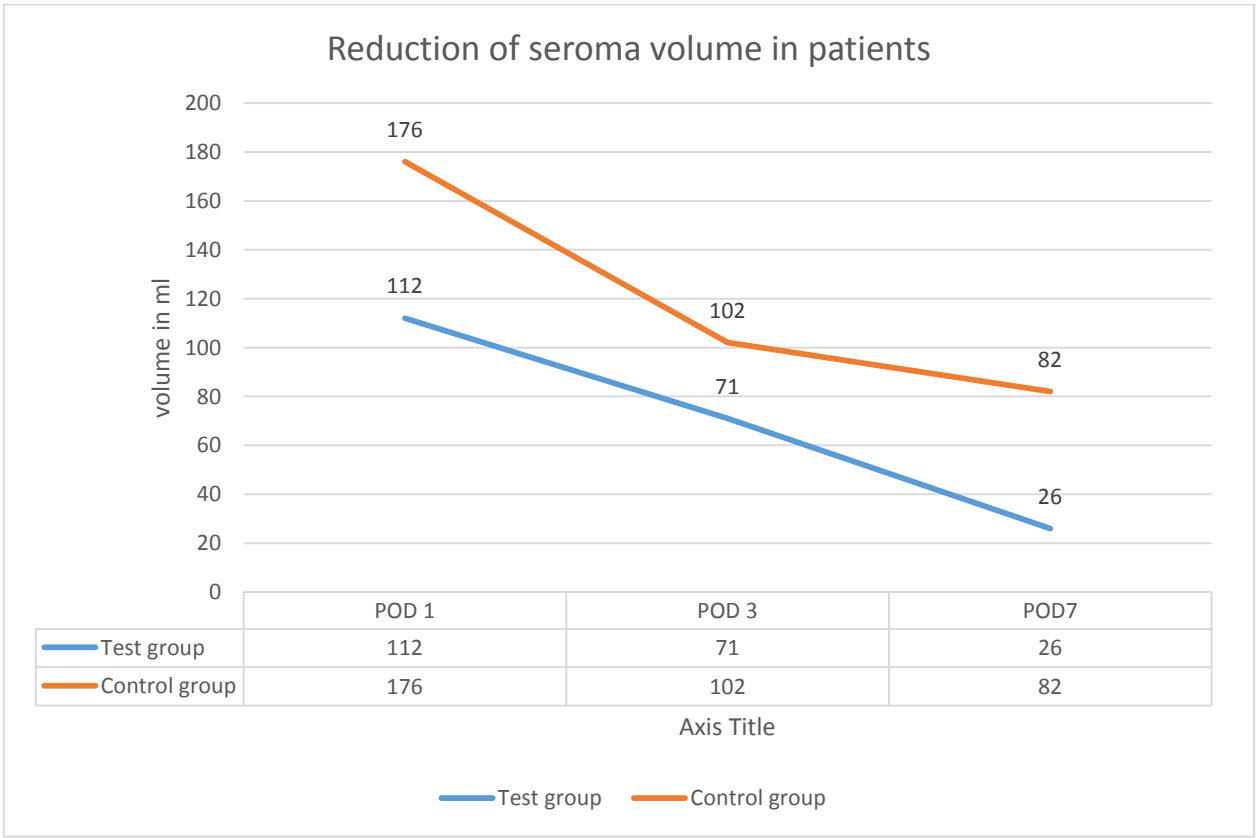


iii) VII POD:

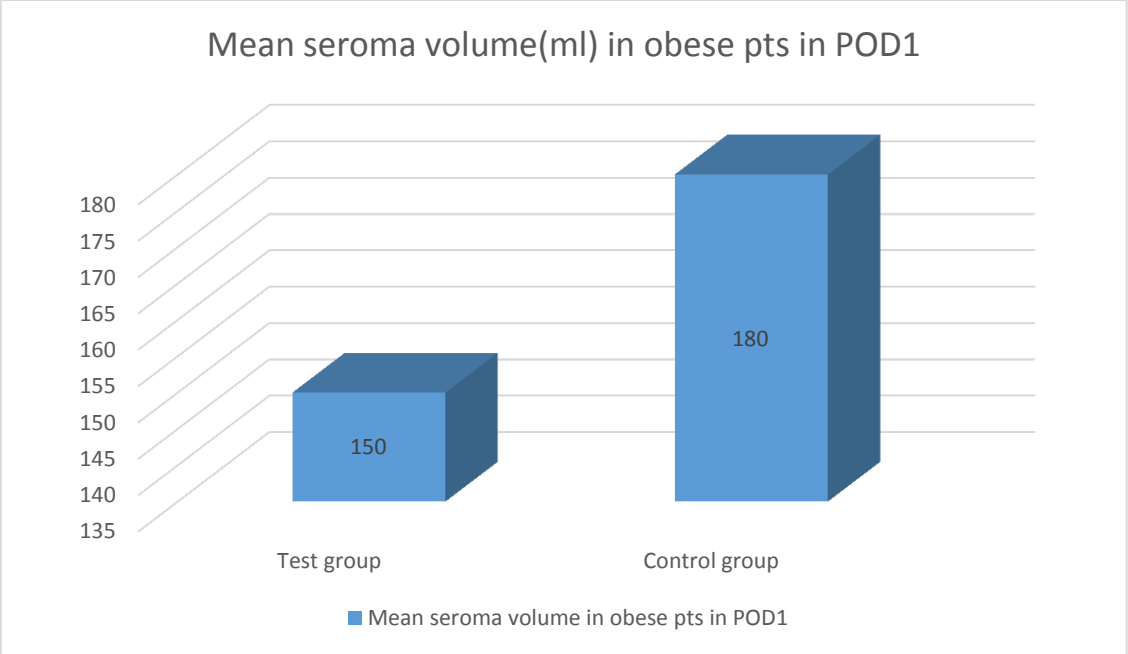


PERCENTAGE REDUCTION IN SEROMA

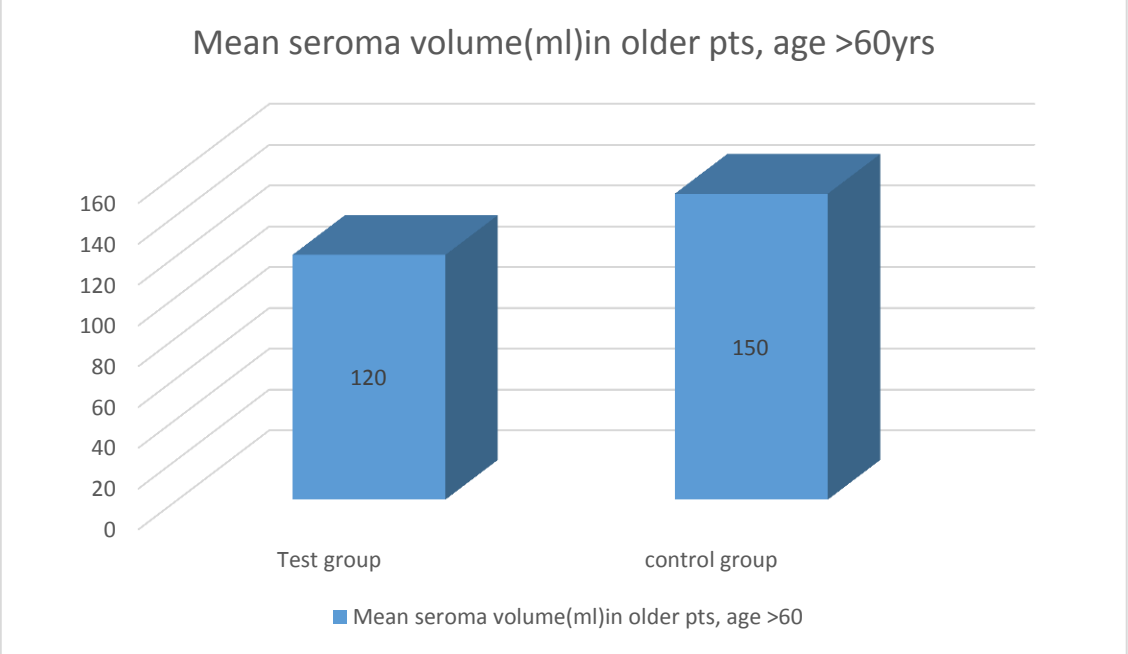




MEAN SEROMA VOLUME IN OBESE PATIENTS



MEAN SEROMA VOLUME IN OLDER PATIENTS



DISCUSSION

“Breast cancer is one of the most common malignancy in women. Surgery is the mainstay treatment. Modified radical mastectomy with or without reconstruction or breast preservation in addition to axillary node dissection are common surgical procedures in breast cancer”.

“Most common complication after breast cancer surgery is wound seroma.The exact etiology of seroma formation is controversial. several interventions have been reported with the aim of reducing seroma formation including fibrin glue,fibrin sealant,bovine thrombin application and altering surgical technique to close dead space.However,it has been suggested that although the use of these interventions might reduce the risk of seroma formation ,further studies are needed to verify the real impact on long term morbidity of such techniques.”

“Several studies have been performed to investigate factors related to post surgical seroma.These studies have observed that the early removal of drains might led to increased incidence of seroma whereas others have shown that drains removal time had no influence on seroma formation”.

“The findings from our study also indicated that the length of time drains are left did not influence the seroma rate. Similar observation was reported by a recent study where the use of drains did not prevent seroma

formation on the other hand it is associated with along postoperative hospital stay and more pain after surgery for breast cancer.compression dressing to prevent seroma rate is a common method used by many surgeons.A study demonstrated that use of pressure garments to reduve postoperative drainage after axillary lymph node dissection for breast cancer is not warranted. However we think that the use of pressure garments and prolonged limitation of arm activity not only reduces seroma formation but also may increase the incidence of seroma formation after removal of drain and even might cause shoulder dysfunction."

"A seroma survey failed to identify any significant independent risk factors for seroma formation. Obesity, Modified radical mastectomy and a large drainage volume during the first three postoperative days were associated with an increased risk, although these findings were not significant. None of the following could be identified as risk factors: duration of drainage, hormone receptor status, immobilization of the shoulder, nodal status or lymph node metastases, number of lymph nodes removed, number of drains, previous biopsy, type of drainage, use of fibrin sealant. Other authors have found that obesity, age, hypertension, and the use of electrosurgery predispose to seroma formation."

“The mechanism behind the formation of a seroma is not known in detail. It was concluded that a seroma was not just an accumulation of serum, but probably formed part of the postoperative inflammatory response involved in wound healing. Steroids inhibit the inflammatory response through inhibition of cytokine function. An increased complication rate after surgery in patients treated with a single dose of glucocorticoid has not been demonstrated”

In the study group, it was tested whether a single dose of glucocorticoid (methylprednisolone) given locally inside the wound cavity on day of surgery and day 1 postoperatively was effective against seroma formation after mastectomy and axillary dissection. The drainage volume during the first two postoperative days, total seroma volume during days 1-7 were reduced, but not significantly. There were no differences in wound healing time or rate of infectious complications between the groups . The temporary immunosuppression induced by postoperative glucocorticoid infusion may, theoretically, be a risk factor in this study. In general, the same factors that stimulate wound healing also stimulate malignant cell growth. Inflammation stimulates the production of cytokines, as do tumour cells. It is estimated that steroids probably do not stimulate, but may have an inhibitory effect on the growth of unrecognized micro-metastases left by cancer surgery.

CONCLUSION

The results of this study suggest that,

1. Seroma formation is one of the important post operative complication after MRM
2. More common in patients who undergo MRM
3. Highest incidence is among older age groups and obese patients.
4. Local injection of methyl prednisolone 80mg into the wound cavity significantly has some prophylactic effects against seroma formation in post MRM patients.
5. During this study there is no adverse reactions in patients by injection of methyl prednisolone.
6. The use of inj methyl prednisolone ,as indeed of every new therapeutic modality ,should not be practiced alone but be incorporated in a holistic strategic approach.

ABBREVIATIONS

MRM	Modified radical mastectomy
LCIS	Lobular carcinoma insitu
DCIS	Ductal carcinoma insitu
BCS	Breast conserving surgery
FNAC	Fine needle aspiration cytology
ER /PR	Estrogen/Progesterone receptor

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PATIENT PROFORMA

DATA COLLECTION SHEET

1.**Patient particulars**:

Name: Age: Sex:

IP No. : Address:

DOA: DOS: DOD: Occupation:

2.**Diagnosis:**

3.**Chief complaints**(with duration)

A.lump B.pain/ discharge C.other complaints

PAST HISTORY:

PERSONAL HISTORY:

EXAMINATION:

INVESTIGATIONS:

MANAGEMENT:

COURSE DURING THE STUDY

24hr Seroma volume

Day1	Day2	Day3	Day 4	Day5	Day6	Day7	

COMORBIDITIES:

CONDITION ON DISCHARGE

FOLLOWUP:

Case details of Test group:

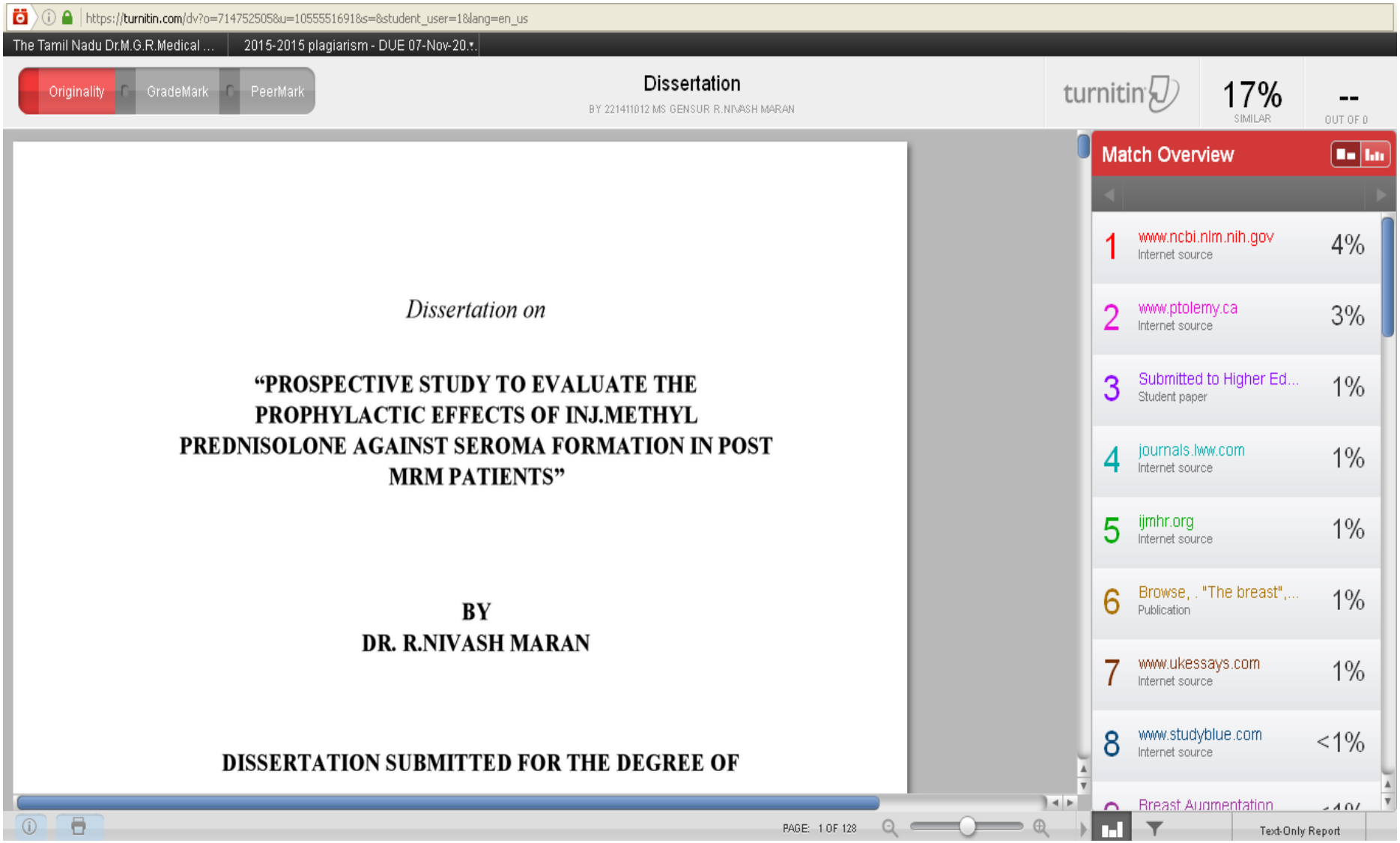
S.NO	NAME	AGE/ SEX	PROCEDURE DONE	STAGE	WEIGHT	DT DRAIN (ML)						
						DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	DAY 6	DAY 7
1	SHANTHI	65/F	MRM	T2N1M0	55KG	100 ml	75ml	70ml	50ml	50ml	30ml	<30ml
2	LAKSHMI	56/F	MRM	T2N1M0	52KG	110ml	80 ml	80ml	70 ml	50ml	30ml	<30ml
3	PARVATHY	54/F	MRM	T2N1M0	58KG	70ml	70ml	50ml	50ml	30ml	30ml	<20ml
4	SAVITHRI	47/F	MRM	T2N1M0	49KG	75ml	70ml	50ml	50ml	50ml	30ml	30ml
5	KASIAMMAL	56/F	MRM	T2N1M0	60KG	200ml	150ml	120ml	100ml	75ml	70ml	50ml
6	VANAJA	58/F	MRM	T2N1M0	62KG	150ml	100ml	70ml	50ml	50ml	30ml	30ml
7	KALYANI	46/F	MRM	T2N1M0	48KG	100ml	70ml	70ml	60ml	50ml	30ml	<30ml
8	CHITHRA	38/F	MRM	T2N1M0	55KG	80ml	75ml	50ml	50ml	30ml	<20ml	DT removed
9	KAVERI	48/F	MRM	T2N1M0	64KG	120ml	100ml	100ml	70ml	70ml	50ml	30ml
10	LEELAVATHY	49/F	MRM	T2N1M0	53KG	150ml	100ml	100ml	70ml	50ml	50ml	30ml
11	KUPPAMMAL	50/F	MRM	T2N1M0	58KG	100ml	70ml	70ml	50ml	30ml	<30ml	<30ml
12	MAYAVATHY	51/F	MRM	T2N1M0	68KG	160ml	120ml	100ml	80ml	70ml	50ml	50ml
13	RAJALAKSHMI	61/F	MRM	T2N1M0	51KG	110ml	80ml	70ml	70ml	50ml	30ml	30ml
14	BHAVANI	42/F	MRM	T2N1M0	58KG	80ml	75ml	50ml	40ml	30ml	<30ml	20ml
15	SIVAGAMI	53/F	MRM	T2N1M0	70KG	150ml	100ml	70ml	50ml	50ml	30ml	<30ml
16	MUNIAMMAL	58/F	MRM	T2N1M0	66KG	100ml	80ml	75ml	50ml	50ml	30ml	<30ml
17	GANGESHWARI	64/F	MRM	T2N1M0	69KG	110ml	90ml	70ml	50ml	50ml	30ml	30ml
18	SAROJA	57/F	MRM	T2N1M0	57KG	100ml	70ml	50ml	50ml	30ml	30ml	<30ml
19	THANGAMMAL	70/F	MRM	T2N1M0	54KG	75ml	60ml	50ml	50ml	30ml	<20ml	DT removed
20	VIJAYA	47/F	MRM	T2N1M0	71KG	100ml	80ml	70ml	50ml	50ml	30ml	<30ml
21	KURUVAMMAL	56/F	MRM	T2N1M0	60KG	90ml	75ml	75ml	50 ml	30ml	30ml	<20ml
22	CHELLATHAI	68/F	MRM	T2N1M0	50KG	80ml	50ml	50ml	30ml	30ml	<20ml	DT removed
23	GOWRI	45/F	MRM	T2N1M0	65KG	100ml	90ml	75ml	60ml	50ml	50ml	30ml

S.NO	NAME	AGE/ SEX	PROCEDURE DONE	STAGE	WEIGHT	DT DRAIN (ML)						
24	LOGAMMAL	66/F	MRM	T2N1M0	68KG	100ml	90ml	80ml	50ml	50ml	30ml	<30ml
25	MALLIGA	59/F	MRM	T2N1M0	74KG	110ml	100ml	70ml	70ml	50ml	40ml	40ml
26	KAMALA	58/F	MRM	T2N1M0	62KG	120ml	100ml	100ml	70ml	50ml	50ml	30ml
27	JEGATHAMBAL	47/F	MRM	T2N1M0	67KG	200ml	150ml	120ml	100ml	70ml	50ml	50ml
28	GIRIJA	53/F	MRM	T2N1M0	62KG	120ml	100ml	75ml	60ml	50ml	50ml	30ml
29	JEYANTHI	64/F	MRM	T2N1M0	59KG	150ml	100ml	80ml	60ml	50ml	30ml	<20ml
30	RAJESHWARI	51/F	MRM	T2N1M0	55KG	110ml	100ml	80ml	60ml	50ml	50ml	30ml
31	MYTHILI	46/F	MRM	T2N1M0	66KG	100ml	80ml	60ml	50ml	50ml	30ml	30ml
32	KANIMOZHI	52/F	MRM	T2N1M0	49KG	90ml	60ml	60ml	50ml	30ml	<30ml	<20ml
33	MALA	36/F	MRM	T2N1M0	58KG	75ml	70ml	50ml	30ml	30ml	<30ml	DT removed
34	VANAJA	63/F	MRM	T2N1M0	56KG	150ml	120ml	100ml	80ml	50ml	50ml	30ml
35	NITHYA	44/F	MRM	T2N1M0	60KG	100ml	80ml	50ml	50ml	30ml	30ml	<20ml

Case details of control group:

	NAME	AGE/SEX	PROCEDURE	STAGE	WEIGHT	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	DAY6	DAY 7
1	SHANTHA	59/F	MRM	T2N1M0	58kg	170ml	150ml	150ml	130ml	120ml	100ml	80ml
2	PRABAVATHY	46/F	MRM	T2N1M0	56kg	190ml	160ml	150ml	150ml	130ml	110ml	100ml
3	VIDHYA	39/F	MRM	T2N1M0	49kg	150ml	150ml	130ml	120ml	100ml	80ml	50ml
4	JOTHI	56/F	MRM	T2N1M0	60kg	180ml	170ml	150ml	120ml	120ml	100ml	70ml
5	CHELLAMMAL	64/F	MRM	T2N1M0	57kg	200ml	180ml	160ml	140ml	120ml	100ml	100ml
6	AMUDHA	58/F	MRM	T2N1M0	48kg	120ml	100ml	100ml	90ml	70ml	50ml	30ml
7	UMA	49/F	MRM	T2N1M0	53kg	160ml	150ml	120ml	100ml	100ml	70ml	50ml
8	GANGAIYAMMAL	65/F	MRM	T2N1M0	59kg	140ml	120ml	100ml	100ml	90ml	70ml	70ml
9	VALLIYAMMAL	64/F	MRM	T2N1M0	56kg	160ml	150ml	150ml	130ml	100ml	100ml	90ml
10	THENANDAAL	61/F	MRM	T2N1M0	50kg	170ml	150ml	150ml	130ml	120ml	100ml	80ml
11	THAMARAI	58/F	MRM	T2N1M0	65kg	160ml	150ml	140ml	140ml	130ml	120ml	100ml
12	ROJA	43/F	MRM	T2N1M0	63kg	200ml	190ml	170ml	150ml	130ml	100ml	100ml
13	AYESHA	53/F	MRM	T2N1M0	55kg	120ml	120ml	100ml	90ml	80ml	50ml	30ml
14	SASIKALA	46/F	MRM	T2N1M0	59kg	150ml	150ml	100ml	100ml	90ml	80ml	60ml
15	AMBIKA	54/F	MRM	T2N1M0	55kg	170ml	160ml	160ml	150ml	130ml	130ml	110ml
16	RANI	41/F	MRM	T2N1M0	55kg	120ml	120ml	100ml	80ml	70ml	50ml	30ml
17	SORNAM	59/F	MRM	T2N1M0	51kg	220ml	200ml	200ml	180ml	150ml	150ml	120ml
18	MATHI	56/F	MRM	T2N1M0	62kg	250ml	220ml	200ml	190ml	170ml	150ml	130ml
19	MALAR	47/F	MRM	T2N1M0	66kg	220ml	200ml	200ml	190ml	160ml	150ml	150ml
20	ANNAPOORNI	66/F	MRM	T2N1M0	54kg	170ml	160ml	160ml	150ml	120ml	100ml	80ml
21	ARUNA	52/F	MRM	T2N1M0	62kg	140ml	150ml	120ml	100ml	100ml	80ml	60ml
22	CHANDRIKA	59/F	MRM	T2N1M0	58kg	200ml	180ml	170ml	140ml	120ml	100ml	80ml
23	CHARULATHA	57/F	MRM	T2N1M0	66kg	190ml	180ml	150ml	150ml	160ml	150ml	120ml

	NAME	AGE/SEX	PROCEDURE	STAGE	WEIGHT	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	DAY6	DAY 7
24	FATHIMA BEGUM	69/F	MRM	T2N1M0	57kg	170ml	150ml	150ml	130ml	120ml	110ml	100ml
25	LAKSHMI	48/F	MRM	T2N1M0	59kg	160ml	150ml	150ml	140ml	130ml	100ml	70ml
26	MANJULA	52/F	MRM	T2N1M0	49kg	140ml	120ml	110ml	90ml	70ml	50ml	30ml
27	PADMINI	49/F	MRM	T2N1M0	52kg	130ml	130ml	110ml	100ml	100ml	75ml	50ml
28	SAROJAMMAL	70/F	MRM	T2N1M0	55kg	250ml	220ml	180ml	180ml	150ml	130ml	120ml
29	NIRMALA	58/F	MRM	T2N1M0	56kg	220ml	200ml	180ml	170ml	140ml	120ml	100ml
30	VALLIYAMMAI	69/F	MRM	T2N1M0	60kg	200ml	200ml	170ml	150ml	140ml	120ml	90ml
31	PAULINE	37/F	MRM	T2N1M0	51kg	180ml	160ml	150ml	150ml	120ml	100ml	80ml
32	GEETHA	50/F	MRM	T2N1M0	55kg	160ml	140ml	140ml	110ml	80ml	60ml	40ml
33	KARMEGAKUZHALI	64/F	MRM	T2N1M0	56kg	260ml	220ml	200ml	160ml	150ml	150ml	120ml
34	BHAVANI	55/F	MRM	T2N1M0	71kg	170ml	150ml	150ml	140ml	120ml	100ml	100ml
35	RAJESHWARI	65/F	MRM	T2N1M0	58kg	190ml	170ml	170ml	150ml	120ml	100ml	80ml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BY
DR. R.NIVASH MARAN
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CERTIFICATE OF APPROVAL

To
Dr.R.Nivash Maran
Post Graduate in M.S.General Surgery
Madras Medical College & RGGGH
Chennai 600 003

Dear Dr.R.Nivash Maran,

The Institutional Ethics Committee has considered your request and approved your study titled **"PROSPECTIVE STUDY TO EVALUATE THE PROPHYLACTIC EFFECTS OF METHYL PREDNISOLONE AGAINST SEROMA FORMATION IN MRM PATIENTS"- NO. 04042016.**

The following members of Ethics Committee were present in the meeting hold on **05.04.2016** conducted at Madras Medical College, Chennai 3

1.Dr.C.Rajendran, MD.,	:Chairperson
2.Dr.Isaac Christian Moses,MD.Ph.D.Dean(FAC)MMC,Ch-3	:Deputy Chairperson
3.Prof.Sudha Seshayyan,MD., Vice Principal,MMC,Ch-3	: Member Secretary
4.Prof.B.Vasanthi,MD., Prof.of Pharmacology.,MMC,Ch-3	: Member
5.Prof.P.Raghumani,MS, Prof. of Surgery,RGGGH,Ch-3	: Member
6. Prof.Md.Ali,MD.,DM.,HOD-MGE, MMC,Ch-3	: Member
7.Prof.Baby Vasumathi, Director, Inst. of O&G,Ch-8	: Member
8.Prof.K.Ramadevi,MD, Director,Inst.of Bio-Chem,MMC,Ch-3	: Member
9.Prof.M.Saraswathi,MD.,Director, Inst.of Path,MMC,Ch-3	: Member
10.Prof.Srinivasagalu,Director,Inst.of Int.Med.,MMC,Ch-3	: Member
11.Tmt.J.Rajalakshmi, JAO,MMC, Ch-3	: Lay Person
12.Thiru S.Govindasamy, BA.,BL,High Court,Chennai	: Lawyer
13.Tmt.Arnold Saulina, MA.,MSW.,	:Social Scientist

We approve the proposal to be conducted in its presented form.

The Institutional Ethics Committee expects to be informed about the progress of the study and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

22/4/16

Member Secretary - Ethics Committee

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE
CHENNAI-600 003