DISSERTATION ON

“BILATERAL BREAST CANCERS – IS IT A SYSTEMIC MANIFESTATION OR NEW CONTRALATERAL DISEASE?”

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This is to certify that the dissertation entitled “BILATERAL BREAST CANCERS – IS IT A SYSTEMIC MANIFESTATION OR NEW CONTRALATERAL DISEASE?” is a bonafide original work of Dr. MURALIKANNAN M. J., in partial fulfilment of the requirements for M.S. Branch– I (General Surgery) Examination of the Tamil Nadu Dr. M.G.R. Medical University to be held in APRIL 2015 under my guidance and supervision in 2013-14.

Prof. Dr. R.A. PANDYARAJ M.S FRCS
Professor of General Surgery,
Guide and supervisor
Institute of General Surgery,
Madras Medical College,

Prof. Dr. P. RAGUMANIM.S
Director and Professor
Institute of General Surgery,
Madras Medical College,
Rajiv Gandhi Government General Hospital, Chennai – 600003.

Dr. VIMALA, M.D,
Dean
Madras Medical College &
Rajiv Gandhi Government General Hospital,
Chennai-3
DECLARATION

I hereby solemnly declare that the dissertation titled “BILATERAL BREAST CANCERS – IS IT A SYSTEMIC MANIFESTATION OR NEW CONTRALATERAL DISEASE?” is done by me at Madras Medical College & Rajiv Gandhi Govt. General Hospital, Chennai during 2013-14 under the guidance and supervision of Prof.Dr.R.A.PANDYARAJ M.S,FRCS The dissertation is submitted to The Tamilnadu Dr.M.G.R. Medical University, Chennai towards the partial fulfillment of requirements for the award of M.S. Degree (Branch-I)

in General Surgery.

Place: 
Date: 

DR.MURALIKANNAN M. J,
Post Graduate student ,
M.S., General Surgery,
Institute of General Surgery,
Madras Medical college,
Chennai-3.
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INTRODUCTION
Carcinoma Breast is considered to be one of that big list of cancers that could be very well treated if diagnosed early. The incidence of carcinoma breast is found to be on the rise probably due to the changing risk factor profile. The diagnosis of Breast cancers at an early stage is being made possible very often nowadays mainly due to extensive application of screening procedures and the widespread awareness among common public. This has paved way for the extensive talk on Breast Conservation procedures.

Bilateral breast cancers which used to form a very meagre percentage of cancer breast is also on the rise mainly because of the well established screening and investigational protocols available. Even then, the diagnosis of Bilateral breast cancer always remains a dilemma as there are no definitive protocols or literature reviews to support the establishment of the correct diagnosis as against a metastatic breast cancer. This is very important, rather must be very important, in view that, the second breast lump could very well be a second primary or a metastasis from the opposite breast.
In this study, we analyse about 20 patients who presented with bilateral breast cancers either synchronously or metachronously over a period of one year and discuss about how we arrived at the diagnosis and what should be actually done and a detailed literature review of the same. The most important aspect regarding distinguishing a bilateral breast cancer from a metastatic breast cancer is that the treatment strategy changes from being curative to being palliative. Thus, demonstrating the importance of the study.
REVIEW
OF
LITERATURE
REVIEW OF LITERATURE

HISTORICAL OVERVIEW:

The history of carcinoma breast dates back to around 3000 BC when Imhotep, the Egyptian physician – architect has mentioned about bulging tumors of breast in his description on soft tissue swellings of breast. The history of carcinoma breast then passed through various periods of ancient greek and roman and renaissance and finally in 19th century, Professor William S. Halstead from Germany who devised the procedure which later became the “Radical Mastectomy” where he used a tear drop incision. W.S.Halsted also demonstrated that the crux of the treatment is, “to remove in one piece, all of the suspected tissues”. This was considered the surgery of choice for the next 80 years.

Years Later, it was Prof.Hagenssens who gave the theory of inoperability to avoid and minimize unwarranted use of radical mastectomy among breast cancer patients.
It was the discovery of X-rays and the fact that breast cancers are hormone dependent were the key changes that brought in drastic changes in the treatment protocols of cancer breast. Few years later the discovery of X-rays it was found that, the X-rays not only helped in imaging but also killed cancer cells and thus evolved radiotherapy. X-rays were also used in mammography who later became the most significant screening tool. Hormonal dependence of carcinoma breast was first used to justify surgical oophorectomy for patients of carcinoma breast and later drugs were developed as adjunct therapies in the treatment of cancer breast based on this fact.

HALSTEDIAN VS FISCHERIAN CONCEPT:

Professor. Halstead had been propagating cancer breast as a local disease and that surgical removal will eliminate the disease. Recurrence if occurs, will be seen locally. Professor. Bernard Fisher was the one who proposed that carcinoma breast is a systemic disease whose course is determined by the interactions between the host and the tumor. This was validated from various control trials which demonstrated that, (i) any variation in the localised treatment of the disease does not alter the cure rates, (ii) the disease has to be tackled systemically, as it has already disseminated before or during the initial presentation itself. Supporting the Fischer’s concept, Umberto Veronessi from
Milan, Italy gave the concept of conservatism in breast cancer treatment. He proposed “breast conservation surgery” which included lumpectomy and postoperative radiation therapy. This was found to be well on par with the results of radical surgeries. It was later advocated as the treatment strategy for early breast cancers.

According to Halstedian concept, the dissemination of the tumor cells follow an orderly pattern depending on the anatomical considerations, Whereas the Fisherian concept states that there is haphazard dissemination of tumor cells. According to Halstedian concept, tumor cells reach the lymph nodes by traversing lymphatics and not by embolization as stated by Fisher and thus the Fisher’s concept challenges en bloc dissection of lymph nodes along with the breast tissue. Lymph nodal disease is not just a marker of disease spread, but a marker of tumor-patient relationship that allows metastasis.

Regional lymph nodes are considered as ineffective barriers that limit tumor spread by the Fisherian concept. Regional lymph nodes are not just of anatomically significant as stated by Halstedian concept, but are of Biological importance as stated by Fisher.
Apart from the lymph nodes, the blood stream is also considered to be an important source of disease spread according to Fisherian concept. In any operable tumor, the logo regional adjuvant therapy decides the outcome rather than the surgical clearance.

DEVELOPMENTAL ANATOMY:

The Development of Breast begins from the Milk line. The Breast tissue develops from the integument. It arises from the ventral surface of the embryo forming the milk line, which is a thickened line of ectoderm. The Ducts and the acini also develop from the ectoderm whereas the supporting tissues develop from the mesenchyme.

The Milk line otherwise referred to as the Mammary ridge, extends between the base of the forelimb and the hindlimb, i.e., axilla to groin. Except at the level of nipple, the milk line gets atrophied. This Mammary ridge development takes place at around 6th week of intrauterine life. The Nipple is formed by ectodermal ingrowth into 15–20 rods forming a rudimentary gland. Later, bulbous dilatation occurs at their ends, thus forming the alveoli. At
around 7\textsuperscript{th} – 8\textsuperscript{th} months, hollowing of ducts, differentiation as milk ducts, depression at the site of nipple becomes evident. At 9\textsuperscript{th} month, alveoli become canalised and finally at birth, mesenchymal proliferation occurs as a result of which, nipple everts and areola becomes pigmented.

At puberty, the breast has around 15-20 lobes each constituting 15-20 lobules. As the patient ages, the dense breast tissue gets replaced by fatty breast due to diminished number of lobules and increased numbers of fatty tissue.
The form and function of female breast tissue keeps on changing in response to various hormonal stimulations. Estrogen causes ductal growth and Progesterone causes lobular growth. As the patient enters the phase of postmenopause, progressive atrophy of the epithelial and connective tissue components occurs and the lobule becomes converted into ordinary stroma, which in the process of involution is replaced by fat. The Proportion of milk glands, ducts and fat in the breast keeps changing with age and thus, a breast of 20 year old will have more of ducts and milk glands whereas the breast of a 50 year old has more of fat. However, size of the breast doesn’t interfere in any way on the amount of breast milk production or breast feeding.
ANATOMY OF BREAST:

(including blood supply and lymphatic drainage)

Human Breast is a tear shaped gland. The Breast tissue is situated in the anterior chest wall between the 2\textsuperscript{nd} to 6\textsuperscript{th} ribs and between the lateral border of sternum medially and the mid-axillary level laterally where the axillary tail of spence ends. The cranio-caudal diameter averages about 12-15cm. It lies within the superficial fascia except for the axillary tail of spence which extends into the hiatus of langer in the deep fascia of medial axillary wall. The Superficial fascia enclosing the breast merges with abdominal fascia below, cervical fascia above and with the skin anteriorly.

The Nipple is located at the centre and is the Nipple-areolar complex is separated from the surrounding skin by its pink colour which is mainly due to the underlying blood vessels. The Nipple lies at the level of 4\textsuperscript{th} Intercostal space and thus innervated by the 4\textsuperscript{th} intercostal nerve. It consists of smooth muscles, both circular and longitudinal and serves to deliver milk in lactating women.
The Areola consists of hypertrophied sweat glands, the Montogomery’s glands which serves the purpose of lubrication during lactation.

The superficial fascia has connections with the deep fascia through the cooper’s ligaments which are primarily responsible for the shape of the breast. The pectoral fascia lies between the breast and the pectoral muscles.

The Internal anatomy of the breast consists of approximately 15-20 lobes in each breast. The milk secreted in each lobe is drained by their own lobules and then alveoli, ducts, ampulla, nipple in the order. The Glandular portion of the breast houses the lobules (which are the milk producing portions at the end of the lobes) and the ducts. Towards, each nipple, the duct dilates to form the ampulla.
Histologically, breast comprises of Glandular, connective / fibrous tissue, adipose tissues. Epithelial cells, myoepithelial cells and connective tissue elements form the cellular elements. The terminal duct unit comprises of the extralobular duct, intralobular duct and the duct sinus / acinus.
BLOOD SUPPLY:

The Arterial supply of Breast comes mainly from the subclavian artery and the axillary artery branches. The Internal Thoracic artery (medial mammary artery / internal mammary artery) arising from the 1\textsuperscript{st} part of axillary artery supplies the medial part of the breast along with perforating branches of the intercostal arteries. The Lateral thoracic artery (external mammary artery) arising from the 2\textsuperscript{nd} part of axillary artery supplies the lateral aspect of breast. The posterior part of breast tissue is supplied from the branches of acromio thoracic artery which arises from axillary artery. The Thoraco dorsal neuro vascular bundle comes in way of axillary dissection which lies deep in the axillary pad of fat and needs to be preserved.

The Venous drainage of breast follows the arteries. The internal mammary vein drains into subclavian vein and the lateral thoracic vein drains into axillary vein. The perforating veins drain into the intercostal veins which in turn drain into vertebral plexus, the batson’s plexus which are principally responsible for the bone metastasis in carcinoma breast.
NERVE SUPPLY:

The Nerve supply of the skin of breast comes from the anterior and lateral branches of 4\textsuperscript{th} – 6\textsuperscript{th} intercostal nerves. The nipple lies at the level of T4 and is extensively supplied by nerve plexus whereas the areola has few fine nerve endings.

LYMPHATIC DRAINAGE:

The Lymphatic nodes draining breast are classified into several group based on their location. They are: Pectoral(anterior), Subscapular(posterior), Medial, Lateral, Central, Apical. However, the universally accepted Berg’s Classification of lymph nodes of breast are on the basis of their location with respect to Pectoralis minor muscle. Accordingly, Level I nodes are those which lie lateral to the lateral border of pectoralis minor. Level II nodes lie behind the muscle whereas Level III nodes lie medial to the medial border of the Pectoralis minor. Level III denotes the infraclavicular nodes. The interpectoral group of nodes are called ‘Rotter’s nodes”. The internal mammary nodes and the supraclavicular nodes also drain the breast medially and superiorly respectively.
The metastasis to opposite breast occurs via the lymphatics across the sternum through the internal mammary nodes. Further, the subdiaphragmatic lymphatic channels spread the disease to the abdomen.

The peu-d’orange appearance of the skin of the breast occurs due to occlusion of the subdermal lymphatics of the breast.
APPLIED ANATOMY:

CLAVIPECTORAL FASCIA:

The Clavipectoral fascia lies underneath the Pectoralis minor muscle. It encircles the Pectoralis minor muscle. Above, it encloses the subclavius muscle and gets attached to inferior surface of clavicle. Posteriorly, it fuses with deep cervical fascia and axillary sheath. Laterally, it is thickened and it gets attached to coracoid process. Between 1st rib and coracoid process, it forms the costocorocoid ligament.

The Clavipectoral fascia is one of the routes of entry into axilla after doing mastectomy in modified radical mastectomy. The clavipectoral fascia is pierced by cephalic vein, lateral pectoral nerve and the thoracoacromian vessels. Pectoral major muscle is retracted to find the anterior leaf of clavipectoral fascia which is cut. Pectoralis minor muscle gets visualised now along with the posterior leaf of clavipectoral fascia, dividing which axilla can be entered.
AXILLA:

Axilla is a pyramidal space whose apex lies towards head and a broader base which lies towards the arm. The Axillary inlet has a bony margin. It includes, (i) lateral border of 1st rib forming the medial margin, (ii) posterior surface of clavicle forms the anterior margin, (iii) superior border of scapula forms the posterior margin. The anterior wall is made of the lateral part of the pectoralis major, pectoralis minor, subclavius and clavipectoral fascia. The medial wall is formed by the upper chest wall including the serratus anterior muscles. The lateral wall is narrow with the major part formed by the intertubercular sulcus. The complex posterior wall is formed by the costal surface of scapula and the muscles, viz., subscapularis, distal parts of latissimus dorsi and teres major and the proximal part of long head of biceps brachii. The Floor is formed by fascia which lies deeper, and the skin which lies superficially. However, it is supported by clavipectoral fascia.

The Contents of axilla are the large vessels of upper limb along with the nerves and lymphatics that drain the breast tissue.
EPIDEMIOLOGY:

The Global burden of breast cancer is on the rise mainly because of improved screening procedures. Even then, the toll is on the rise in developing countries and under developed countries because of the life style changes. The worldwide estimate of the disease is over a million of new cases every year with a deaths accounting for atleast of 12% of female cancer deaths. The same statistics holds good for india also where, breast cancer is still considered the most common cancer among females next to cancer cervix. The National programme for non-communicable diseases has framed in screening programmes for cancer breast at various levels of the health pyramid. This has lead to identification of early breast cancers amenable to better and definitive treatment involving surgery, chemotherapy, radiotherapy.

RISK FACTORS:

The Risk factors associated with carcinoma breast are:

(i) Age of the patient: As with any other malignancy, the incidence of cancer breast increases with the age of the patient until menopause, after which there is plateau phase in the incidence curve.
(ii) Ethnicity: With regard to the geographical distribution of the patient, the incidence varies mainly due to the environmental factors that are involved. It also predicts that the genetic factors play a role in influencing the environmental characteristics.

(iii) Age at Menarche / Menopause: The age at menarche and menopause also influence the risk of breast cancer incidence because they determine the duration of estrogen exposure. So, obviously, Early menarche and late menopause expose the patients for a higher exposure to estrogen in turn resulting in more incidence of breast cancer among them. Women who acquire menopause over 55 years of age are twice more likely to get cancer breast when compared with those who attain menopause before 45 years. Similarly, girls who attain menarche before 11 years are at a higher risk of cancer breast than those girls who attain menarche little later.

(iv) Age at first childbirth: Those women who have their child birth after 30 have a greater risk of cancer breast than those women who have their first child birth before 20.
(v) Family history of cancer breast: Around 10% of cancer breasts are familial genetic predisposition. The genes BRCA 1 & BRCA 2, located on chromosomes 17 & 13 are likely to be responsible for the genetic predisposition.

(vi) Previous Benign disease: Women with a previous history of a benign breast disease such as fibroadenosis or adenoma or cysts or proliferative changes have all been linked with increased risk of malignancy.

(vii) Radiation: Previous history of radiation exposure is also an important risk factor in the incidence of cancer breast.

(viii) Lifestyle: This includes diet, weight gain, alcohol intake, smoking. Each of these individually influence the incidence of cancer breast. A high fat diet, obesity and increased alcohol consumption has been associated with increased incidence of cancer breast.

(ix) Oral contraceptives / Hormone replacement therapy: Both these therapies exposes the patients to more estrogen which results in increased risk of cancer breast. However, increased risk is found in
patients who take estrogen + progesterone combination pills and the
cancers found to be associated with this is less advanced than that
occurred in other people.

PATHOGENESIS:

The Pathogenesis of Breast cancers is very complex. They may be either
Sporadic or Hereditary, according to the risk factors, Hormonal exposure and
Genetic alterations / mutations (germ-line) respectively.

SPORADIC BREAST CANCERS:

The Sporadic Breast cancers occur mainly due to the hormonal exposure,
mainly estrogen. The estrogen exposure can be either exogenous or endogenous.
Exogenous sources being OCPs, HRTs. Endogenous estrogen exposure depends
on the gender, age at menarche, age at first child birth, period of breast feeding,
age at menopause.

HEREDITARY BREAST CANCER:

Hereditary Breast Cancer occurs due to germline mutations and
inheritance of the susceptibility genes to next generations. The genes that are
most commonly involved are: BRCA 1, BRCA 2, ATM, P53, CHEK2.
CLASSIFICATION:

The Classification of Breast tumors is mainly based on their morphology and cell of origin. The Main types of breast carcinoma are the in situ and the invasive tumors. The in situ tumors which contribute around 15-30% of the total percentage of breast cancers, may be either Ductal carcinoma in situ (DCIS) or the Lobular carcinoma in situ (LCIS). DCIS constitutes around 80% whereas LCIS constitutes around 20%.
The invasive carcinoma constitutes the rest of 70-85%. It includes:

- Paget’s disease,
- invasive ductal,
- invasive lobular and other rare cancers.

Among invasive ductal, there are subtypes which includes the following:
- Invasive ductal with productive fibrosis (schirrous, simplex, NST, i.e., no special type),
- medullary,
- mucinous (colloid),
- papillary,
- cribriform (tubular).
Invasive ductal carcinoma
Invasive lobular carcinoma
The much more clinically valid classification is that of the “no special type” invasive ductal carcinoma. It may be classified as follows:

(i) Luminal A

This group consists of ER + and Her-2Neu negative tumors. They most commonly occur in postmenopausal women and are mostly well / moderately differentiated. As they are well differentiated, mostly they respond well to hormone therapy and are slow growing tumors. On the contrary, they respond poorly to standard chemotherapy regimens. Chemotherapy agents that work in these patients are still under study.

(ii) Luminal B / Triple Positive

These are “Triple positive” tumors, i.e., ER, PR, Her2-neu positive cancers which show a higher proliferative rate. These tumors have lymphatic spread and respond well to chemotherapy.
(iii) Normal Breast-like:

This group includes a group of well differentiated tumors that are ER + and Her2-neu negative

(iv) Basal like / Triple negative

This is notable that, these cancers lack all 3 receptors, viz., ER, PR, Her2-neu. This group includes Medullary cancers, metaplastic cancers and tumors with central fibrotic foci. These tumors are of higher grade and a higher proliferation rate. They are aggressive and frequently metastasize to viscera, especially brain and liver.

(v) Her2-neu positive

This group includes ER – and Her2-neu positive tumors. This group overexpresses Her2-neu gene. These tumors are poorly differentiated, have a higher proliferation rate and frequently metastasize to brain.
CLINICAL PRESENTATION:

The Clinical presentation of breast is very much variable. Off late, with good screening mammogram and awareness among public, early breast cancers are getting reported quite often. Depending on the presenting stage of the patient, they may be categorised either as early breast cancer, locally advanced breast cancer or advanced/metastatic breast cancer.

However, the most common presentation is that of a painless lump in breast though it is associated rarely with pain. Patients may also present with axillary lymph node swellings. In addition, patients also present with skin changes and nipple changes. Skin changes in carcinoma breast includes, peu de orange appearance, skin ulceration, satellite nodules. Peu de orange appearance occurs due to infiltration of the subdermal lymphatics by the tumor cells. Skin tethering may also be seen which occurs due to infiltration of the cooper’s ligaments. This becomes very evident by asking the patient to lift the hands above head.

Nipple changes would include, nipple ulceration, nipple discharge (either serous / bloody single duct, spontaneous), nipple retraction. Nipple retraction occurs due to infiltration of the lobules/ducts just beneath the nipple areolar complex.
The patients who present with locally advanced tumor have a larger lump with any of the skin changes mentioned above with a matted or mobile node. They may present with a supraclavicular node or infraclavicular node. Clinical presentation with internal mammary nodes are very rare.

Patients presenting with metastasis may have bone pain, pathological fractures, hemoptysis or dyspnoea or liver metastasis. These produce lytic lesions in bone with cannon ball appearance in lung parenchymal secondaries.

Patients rarely present with huge inflammatory lesion of breast with a fungating skin ulcers representing inflammatory carcinoma which has a grave prognosis. Suppose, if the patient presents after a course of neo-adjuvant chemotherapy, lump or the node may be absent sometimes.
BILATERAL BREAST CANCERS – IS IT A SYSTEMIC MANIFESTATION OR A NEW CONTRALATERAL DISEASE?

Whenever a patient presents with bilateral breast cancer, either synchronously or metachronously, it could be either metastasis or a new primary. This Differentiation into metastasis and new primary is very important that, it decides the treatment as definitive or palliative. There are no adequate criteria available for this distinction. Some criterias available are Hagensen’s clinical criteria, robbins and berg pathological criteria, Chaudhary and mills pathological criteria. None of these criterias are considered to be standardized.

If the final diagnosis is metastasis, then the treatment would be palliative, whereas if the diagnosis is made as a new primary, then the treatment would be definitive, i.e., modified radical mastectomy followed by chemoradiotherapy and hormone therapy as required.

There is increasing rate of incidence of bilateral breast cancers mainly because of increasing awareness among the public, increased screening programmes and treatment results. In general, women diagnosed or treated with carcinoma breast in one breast are at a higher degree of risk of malignancy in opposite breast.
As discussed already, a patient with a breast cancer is always at risk of contralateral breast cancer. The second most common cancer in a women who already had a cancer breast is again cancer in the contralateral breast and nothing else. There is 2 – 6 % increased risk of breast cancer in the opposite breast when compared with the women in the general population. The incidence of bilateral breast cancers is around 3% worldwide. The various risk factors associated with the increased risk of contralateral breast cancer in a patient who had a primary in the other breast and underwent treatment are studied. They include:

(i) Early age at diagnosis:

Early age at diagnosis of the first cancer is an important factor that increased the probability that the patient may get a second cancer during the course of her life. Early age may be considered as premenopausal age group, i.e., <45 years of age.
(ii) Lobular architecture

In general, lobular architecture is associated with an increased risk of bilateral breast cancers as per literature. LCIS may be considered as a precursor and hence followed up. Lobular pattern malignancy frequently are multicentric and a lesion in opposite breast is often expected.

(iii) Family history of breast cancer

Family history of breast cancer in a first degree relative, irrespective of the type or grade of malignancy, is an established risk factor of a bilateral breast cancer. Moreover, the incidence of carcinoma breast in the new family member occurs at an early age than that occurred in the previous family member, thus supporting the genetic concepts underlying neoplasia.
(iv) Adjuvant treatment received – radiotherapy / chemotherapy / tamoxifen

Depending on which form of adjuvant therapy the patient received, the incidence of a second malignancy varies. This would more clearly be interpreted as, presence or absence of an adjuvant therapy can modify the outcome of the disease.
Age – specific incidence rates of unilateral and synchronous bilateral breast cancers
Kaplan Meir Kaplan-Meier estimates of breast cancer specific mortality of women diagnosed in 1991 among women having a 1st degree relative with breast cancer, stratified by proband’s cause specific outcome. Panel A- 1778
daughter’s with mother as proband. Panel B- 348 sister’s with older sister as proband.

This research aims helps define and predict patients who are at an increased risk of contralateral breast cancer, so that much efficient follow up protocol and appropriate preventive strategies could be formulated.

ADVANCED CARCINOMA BREAST:

Advanced Cancer breast is considered as stage iv disease which presents with distant metastasis. Metastasis in carcinoma breast mainly involves, nodes, liver, bones, peritoneal deposits, brain. The most important but still under studied metastasis is that of the opposite breast.

The route of metastasis to supraclavicular nodes is contiguous through the infraclavicular nodes and level I and II axillary nodes. The other distant metastasis occur through hematogenous spread. Opposite breast involvement can occur through the intercostal lymphatics In a similar manner, opposite axilla can also be involved.

Carcinoma Breast produces osteolytic lesions in the long bones like femur, in skull, pelvis and along the spine. The patient usually presents with bone pain or pathological fractures suggestive of malignant osteolytic deposits.
Metastasis to liver presents with jaundice and hepatomegaly at some instances. There can also be ascites as a result of metastasis liver or due to peritoneal metastasis.

Metastasis can also occur to brain. During such instances, patient presents with severe headache, vomiting, altered behaviour and other features of increased intracranial tension due to an intracranial SOL.

Termially ill patients due to carcinoma breast often present with brain metastasis or lung metastasis. Lung metastasis produces hematemesis, dyspnoea, cyanosis, clubbing. Death in patients with cancer breast can occur due to brain or lung metastasis or an axillary node eroding into axillary artery.

In case of Inflammatory carcinoma or disease with skin involvement of chest wall involvement and in patients with advanced disease, patients are always referred for neoadjuvant chemotherapy. This supports Fisher’s concept of “Breast cancer is a systemic disease” hypothesis strongly.
So, all the patients with advanced cancer breast are sent for neoadjuvant chemotherapy for 3 to 4 cycles. The drugs used are cyclophosphamide, 5-FU, paclitaxel. Taxane based chemotherapy is the most widely used ones as they are more effective and resistance is less common for unknown reasons. However, preoperative radiotherapy has a very minimal role in cancer breast hence it also try to tackle the local disease only and not the systemic one as done by the chemotherapy drugs.

In general, cancer breast becomes a systemic disease once the size of the tumor exceeds 5cm, i.e., crosses T2 clinical staging. Therefore, a lesion in opposite breast in early breast cancer is most probably a new second primary in the opposite breast rather than a metastatic lesion from the opposite breast. This is the basic criteria used to differentiate between a second primary in opposite breast and a metastatic disease. Also, a mammogram in a clinically palpable lump is mainly done to rule out impalpable lesions in opposite clinically normal breast tissue.
INVESTIGATIONS:

Investigating a cancer breast patient isn’t very complex. As for any case, thorough clinical examination stands first. The pathological and Radiological diagnostic tools come next. This constitutes the “Triple Assessment”. The significance of triple assessment is that, the sensitivity and specificity reaches 99% when the clinical examination, radiological examination (Sonomammogram) and Pathological examination(FNAC / Trucut biopsy) are all combined.
CLINICAL EXAMINATION:

Clinical examination of Breast is the most important tool in the diagnosis. Patient should be examined in 3 positions, i.e., in sitting position with the arms by the side and arm is raised above the head, lying down position, bending forward position. The symmetry of both the breasts is the most significant finding to be noted. Asymmetry between them is an important sign that gives a clue regarding the presence of a lump.

An invisible lump on normal examination becomes very obvious on raising the hands above the head. Skin changes like peu d’orange, skin ulcerations, satellite nodules may also be seen. Nipple changes include nipple retraction, nipple ulceration or nipple discharge. A spontaneous discharge from a single duct that is bloody in most instances is considered significant and requires exclusion of malignancy.

The Axilla should be examined for the nodal status. The anterior, posterior, lateral, central, apical groups of axillary nodes should be examined. Also the infraclavicular and supraclavicular groups of nodes should be examined. However, the most important aspect is examination of opposite breast and axilla. Abdomen should be palpated for any hepatomegaly.
Skin changes identified by classical examination in cancer breast
Peu d’orange appearance
MAMMOGRAM:

Mammogram is the most important radiological tool that is used in the diagnosis of carcinoma breast. Mammogram is usually done to rule out multicentricity in the ipsilateral breast and to look for any impalpable lump in the contralateral breast. Two views, craniocaudal (CC) and mediolateral oblique (MLO) are usually taken.

Mammographic features of carcinoma include density changes and microcalcifications. Density changes include architectural alterations and discrete mass. Microcalcifications may be either clustered or speculated.

Mammogram is at most instances combined with ultrasound to do the sonomammogram. The results are depicted as BI-RADS score. BI-RADS stands for ‘Breast Imaging – Reporting and Data system’ . The BI-RADS scoring is as follows:
BI-RADS GRADE

0 - Incomplete assessment
1 - Normal / Negative findings
2 - Benign
3 - Probably benign
4 - Probably malignant
5 - Highly suspicious of malignancy
6 - Biopsy proven malignancy

If BI-RADS score is 3, then the patient can be followed up with a repeat mammogram after 6 months. If there is any suspicious of malignancy, be it, mild or moderate or high, immediate work up is required. The next work up may be in the form of a biopsy either FNAC or Trucut.
Mammographic and ultrasound images in breast cancer
FOLLOW UP / INTERVENTION FOLLOWING BI-RADS:

BI-RADS Score

0  -   needs further imaging evaluation

1  -   Repeat mammogram after 1 year

2  -   Repeat mammogram after 1 year

3  -   Short term follow up required

4  -   followed up with biopsy

5  -   Appropriate action is mandatory

6  -   Appropriate action is mandatory
MRI is also used in breast imaging. The various indications for the use of MRI in breast diseases are as follows:

1. Dense breast / young breast
2. Implants
3. Inconclusive mammography (malignant nodes with impalpable lump or not diagnosed by mammography)
PATHOLOGICAL EXAMINATION:

The pathological diagnosis is however the final and conclusive diagnosis that directs treatment. The Pathologist will the lump as either DCIS, LCIS, Invasive ductal or lobular. The grade of the tumor is also important, for it determines the prognosis of the tumor.

The tool used for the pathological examination is the FNAC or the Trucut biopsy.

FNAC vs TRUCUT BIOPSY:

The need for a pathological specimen from the breast lump is mandatory. This is usually obtained either by an FNAC or Trucut biopsy, both of which are outpatient procedures. FNAC gives cytology whereas Trucut biopsy gives tissue for histology. Therefore, trucut biopsy gives a better picture and more tissue for the hormone receptor status. However, FNAC may be considered sufficient in early breast cancers. Trucut biopsy is considered mandatory in patients who are sent for neoadjuvant chemotherapy. This is mainly because, after the neoadjuvant chemotherapy, the lump might disappear and even the MRM specimen may not contain tissues representative of the original malignancy. Hence, hormone receptor study could not be conducted. Therefore, it is always advisable to get a trucut biopsy done before sending a patient to neoadjuvant
chemotherapy, whereas FNAC is sufficient in cases taken up for upfront surgery.

FNAC:

Fine Needle aspiration cytology is done in cases of breast lump, be it, benign or malignant. It is usually done with a 22 gauge needle on a 10ml syringe. The needle is inserted into the breast lump with a constant negative pressure and then removed after releasing the suction and then smeared on to a slide. The slide is fixed with 95% ethyl alcohol and air dried and viewed under microscope to find out the presence of malignant cells and their type if present. The advantage of FNAC is that, the results can be obtained in an hour or so. Unwanted open biopsies could be avoided. The disadvantage of FNAC is that, it just comments on the presence or absence of malignant cells and doesn’t differentiate between insitu and invasive malignancy.

FNAC differentiates solid from cystic masses. The colour of the fluid aspirated also gives a clue of the malignancy. FNAC may however be postponed until a mammogram gets done as it can cause artefacts during the mammogram imaging of the breast.

The sensitivity and specificity of FNAC approaches near 95% in a clinically suspicious malignant lump.
CORE-NEEDLE BIOPSY:

This core needle or trucut biopsy is also considered as an outpatient procedure and is usually done using a 14 gauge needle. Automated trucut biopsy guns are also available. The procedure is carried out under local anaesthesia. The specimen obtained is placed in formalin and later paraffin blocks made out of it. The false negative results are very low for core-needle biopsy specimens when compared to the FNAC as more quantity of tissue is available with core-needle biopsy.

However, a positive FNAC or Trucut biopsy specimen is significant but a negative FNAC or trucut biopsy report doesn’t rules out malignancy. When the biopsy report is negative, an incisional or an open biopsy should be considered before tailoring the treatment option for the patient.
FNAC
TRUCUT BIOPSY NEEDLE
RECENT TRENDS:

The recent in the management of cancer breast is directed mainly towards early detection. Therefore screening procedures have improved. Though screening mammography is already available, various modifications of the mammography have come that has helped in better sensitivity and specificity in cancer breast. Some of the newer available:

- Digital mammography
- Computer aided detection
- Tomosynthesis
- PET – CT / combined with tomosynthesis
- Ductography / Ductoscopy / Lavage
- MR elastography
- Optical imaging / coherence tomography
- Hair diffraction
SCREENING MRI:

MRI has been used as a tool in the diagnosis of carcinoma breast from a long time. But still, the cost effectiveness of using MRI as screening tool has always been a matter of conflict. This is because, MRI is considered superior to Mammography as an imaging method. The various indications for MRI as a screening tool in breast cancer are as follows and this is in accordance with the American cancer society guidelines.

Annual Screening MRI (based on Evidence)

1. Positive BRCA mutation
2. BRCA Carrier – in a first degree untested relative
Molecular predictors of outcome:

The prognosis of cancer breast is evaluated by various factors, though there are some important molecular factors which help us determine the prognosis more accurately. These factors have a higher degree of association with cancer breast, thus influencing its outcome. They are as follows:

Steroid receptors:

The estrogen and progesterone receptor positivity is considered as an independent risk factor and predictor that correlates with the prognosis. It also helps in choosing the adjuvant therapy with regard to the hormone treatment.

Her-2neu:

The overexpression of Her-2neu in cancer breast has found to be an important factor associated with outcome as more overexpression, poorer the prognosis. However, targeted therapy with Trastuzumab (Herceptin) has been found to be useful in altering the course of the disease in such patients.
P53:

The most important factor in determining the prognosis is the P53 mutations which is the most common mutations seen in cancer breast, mainly in sporadic cases.

When P53 mutations co-exist with her2-neu overexpression, the prognosis is still poorer. Definite P53 mutations could be recognised by specific genetic tests like the genetic signature testing / molecular profiling (Oncotype Dx, Mammoprint)

uPA – Uroplasminogen activator / PAI-1 – Palsminogen activator inhibitor:

The overexpression of these have been found to associated with a poor prognosis, especially in early breast cancers.
Ki-67:

This Ki-67 is a nuclear marker of cellular proliferation whose overexpression is associated with a poor prognosis in cancer breast. This nuclear marker is also highly associated with triple negative cancers.
AIMS & OBJECTIVES
AIMS & OBJECTIVES

The Aim of this study, “Bilateral breast cancers – is it a systemic manifestation or a new contralateral disease?” is mainly to study the clinical profile of patients with bilateral breast cancers.

The primary aim of the study is to study the clinical profile of bilateral breast cancers. However, the secondary aim or the objective of the study is to identify if the second breast cancer is a metastasis from the first primary or is it a new second primary lesion. This distinction is very important in that, it decides the treatment protocol and the prognosis of the patient.

The treatment of a metastatic breast cancer is palliative chemotherapy or radiotherapy. But, the treatment of a new second primary is definitive, i.e., either direct surgical management or surgery following neoadjuvant chemotherapy.
There is no standard protocol in literature regarding the distinction between the second primary and a metastatic lesion of opposite breast. Though some criteria are available, they are not standardized and are not universally followed.

This study tries to bring out the criteria that is more feasible and more factors that is associated with the development of bilateral breast cancer.
METHODOLOGY
The cases included in the study are patients admitted with a breast mass. The inclusion criteria include:

1. Patients with Bilateral breast mass at initial presentation

2. Patients who have underwent Mastectomy and now presenting with breast mass or axillary node on opposite breast.

3. Patients who have underwent Chemotherapy and now presenting with breast mass or axillary node.

The Exclusion include:

1. Patients having Breast Mass with Skin Nodules

2. Patients having Breast mass with Bone Metastasis Clinically.

Patients admitted with the breast mass are selected for the study according to the inclusion and the exclusion criteria. The patients are subjected to the routine blood investigations. The patients are also examined clinically thoroughly, and are subjected to Mammogram, USG breast, Trucut biopsy, receptor study (ER, PR, Her2-neu), CT chest, LFT, skeletal survey (in advanced carcinoma breast).

The patients are clinically evaluated using the Hagensen’s clinical criteria for the distinction between the metastasis or the new second primary.
The Rationale of the study is as follows. Breast Cancer is one of the leading causes of death worldwide. Bilateral breast cancers are on the raise mainly because of the higher degree of follow up and various upcoming investigational modalities.

The approximate incidence of Bilateral Breast cancers is around 1 – 3.2 %. The diagnosis of bilaterality is becoming a challenge as there is no clear literature reviews regarding the same and the non-availability of molecular based investigations required for accurate distinction between the metastasis and primary breast cancer.

The significance in distinction of a breast or axillary lesion to be a metastasis or second primary is that, the treatment modality changes from palliation to definitive treatment. Though there are quite some criterias like Hagensen’s clinical criteria, Robbins & berg pathological criteria, Chaudary & millis clinical criteria, none of them is accepted universally and not much studies have been published to demonstrate the validity of these criterias.

The bilateral breast lesions may be either synchronous or metachronous. The time duration for their differentiation is a variable and if the bilateral lesion occurs within 6 months it is considered synchronous and if the lesion occurs beyond a time period of 6 months, it is considered to be metachronous lesion.
So in this study, I chose to assess the Patients with bilateral breast cancer and investigate them to find if the breast mass is a metastasis or second primary using the routine breast cancer workup and metastasis workup and review the literature regarding the newer molecular based investigations available.
OBSERVATION & RESULTS
A total of 19 patients were included in the study and the patients were evaluated by triple assessment. It included clinical examination, radiological examination (Mammogram), Pathological examination. Either FNAC or Trucut biopsy is taken from the breast lump. Pathological examination of the FNAC or Trucut biopsy specimen is done. Receptor study is also done. Then, the patients were subjected to USG abdomen, LFT, skeletal survey.

The results were tabulated and depicted in the master chart. The results in graphical representation in the following charts. Patients were analysed for their age, incidence, chronicity, histological diagnosis, clinical staging, receptor status, age at diagnosis of first cancer.
Out of the total 700 patients of carcinoma breast followed up in this retrospective study, around 19 patients were found to be bilateral breast cancer patients. The incidence of Bilaterality in RGGGH is therefore, around 3%. This corresponds to the universal incidence rates around 2.7 – 3%.
FREQUENCY TABLE for AGE / SEX of the patients

<table>
<thead>
<tr>
<th>Age / Sex</th>
<th>Frequency</th>
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<th>Valid Percent</th>
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The age of the patients were plotted against the no. of patients in each age group approximately. The minimum age of the patient was 38 years and the maximum age was 67 years. It was found that the patients mostly affected were of <50 years of age (69%). The remaining patients were within the 50-60 year range. This shows that the earlier the age at diagnosis, more is the incidence of bilateral breast cancers.
# AGE AT THE DIAGNOSIS OF FIRST CANCER

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<th>Age at diagnosis of 1st cancer</th>
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<td>Total</td>
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</tbody>
</table>
The age at the diagnosis of the first cancer is plotted against the number of patients. The results are: Number of patients who developed bilateral breast cancer with the age at the diagnosis of first cancer < 45 years are 11 (57.8%). The rest of the patients were over 45 years.
## Frequency table - Interval between the 2 cancers

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MENOPAUSAL STATUS

Menopausal status

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</table>
Of the patients who were found to have bilateral breast cancers, the menopausal state also influenced the incidence. The incidence of bilateral breast cancer in premenopausal patients was found to be higher than in the postmenopausal age group. The incidence was around 63% in premenopausal age group whereas it was around 37% among the postmenopausal age group.
Family history

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SYNCHRONOUS / METACHRONOUS

### Synchronous

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CLINICAL STAGE OF 1\textsuperscript{st} CANCER

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## CLINICAL STAGE OF 2\textsuperscript{nd} CANCER

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</table>
HISTOLOGY

Histology of the two cancers were compared. In all the patients, it was found to be infiltrating ductal carcinoma. Though the literature says, there is increased incidence of bilateral breast cancer in lobular type of breast cancer, in this study, all the 19 patients had infiltrating ductal type of malignancy in both the breasts, though the grade of the tumors was different in different lesions.
ADJUVANT TREATMENT (if any)

The adjuvant treatment received also has some influence on the incidence of bilateral breast cancers. The adjuvant treatment may be in the form of chemotherapy or chemoradio therapy. The etiology of the relationship between the bilateral breast cancers and the adjuvant therapy may be either linked directly to the type of adjuvant therapy or due to compliance of the patients receiving the therapy. The defaulters from the adjuvant therapy may either develop a metastasis or a second new primary in the opposite breast.
The Receptor status of the bilateral breast cancers also play an important role in the incidence of bilateral breast cancers. The majority of the cancers were Triple negative tumors (Luminal B).
DISCUSSION
DISCUSSION

Bilateral breast cancers is a rare entity universally. But, still the incidence of bilateral breast cancers is on the raise mainly because of the following possible reasons:

1. Increased survival of breast cancer patients
2. Better screening programmes

Bilateral breast cancers can be either a metastasis from the opposite breast or it may be new second primary. The distinction between the new primary and a metastasis is very important because the treatment protocol may differ accordingly. The treatment of metastasis is palliation whereas the treatment of a second primary is definite., modified radical mastectomy.

RARITY OF BILATERAL BREAST CANCERS:

As already mentioned, bilateral breast cancers is a rare entity. The Incidence is however, around 1-3 % of breast cancer patients. In our study, the incidence was found to be 2.7%. It is because of this rarity that it has been very minimally studied in literature.
DIAGNOSIS OF BILATERAL BREAST CANCERS:

The Diagnosis of bilateral breast cancers is a real challenge in that no standard protocols have been devised that is universally accepted. Each criteria or the method has its own advantages and disadvantages. The various criteria available are the following:

1. Hagensen’s clinical criteria
2. Robbins and Berg pathological criteria
3. Chaudary and millis pathological criteria

Though several other criterias have been proposed, there is no standardised protocol available for the distinction between a bilateral breast cancer as metastasis or second primary.

These criterias have not been validated by any randomized control trials in the literature. This study which included 19 patients of bilateral breast cancers were diagnosed using the Hagensen’s clinical criteria.
The Hagensen’s clinical criteria includes the following:

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<th>Factors</th>
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<th>Primary</th>
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</thead>
<tbody>
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<td>Spread across midline of chest to second breast</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Number of lesions</td>
<td>multiple</td>
<td>Solitary</td>
</tr>
<tr>
<td>Distant metastases</td>
<td>Present</td>
<td>Absent</td>
</tr>
</tbody>
</table>
According to the clinical criteria of Hagensen’s, the bilateral breast cancers were evaluated and diagnosed. The most important part of the Hagensen’s criteria is the evaluation of the presence or absence of distant metastasis. Also, the number of lesions is also important. If the number of lesions is multiple, the lesion is more probably considered as metastatic. However, if the lesion is solitary, then the lump is considered as a second primary.
The Robbins and berg pathological criteria is as follows:

<table>
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<tr>
<th>Factors</th>
<th>Metastatic</th>
<th>Primary</th>
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<tbody>
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<td>Location</td>
<td>In the fat surrounding the breast</td>
<td>Within the breast parenchyma</td>
</tr>
<tr>
<td>Histology</td>
<td>Expansile</td>
<td>Infiltrating and histologically dissimilar</td>
</tr>
<tr>
<td>Contiguous INSITU component</td>
<td>Absent</td>
<td>Present</td>
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</table>
The Robbins and berg pathological criteria is a subjective criteria and variations may be due to observer bias. The location of the tumor, if in the fat surrounding the breast, the lump is more likely to be a metastasis. If the location is within the parenchyma, then the lump is considered as a second primary. Histologically, expansility is considered as metastasis whereas histologically different tumors are considered as second primary.

A contiguous insitu component is present in all cases of primary tumors whereas they are absent in metastasis. These pathological criterias as proposed by Robbins and Berg, are also considered for the diagnosis of bilateral breast cancers.
Chaudary and millis clinic - pathological criteria has also been quoted universally in several literature. The various criteria included in it are:

1. Insitu change in the contralateral tumor
2. The second tumor is histology different from the first
3. The degree of histological differentiation is different from the first
4. No evidence of local, regional, distant metastasis from the cancer in ipsilateral breast.

This chaudary and millis criteria is based on both clinical findings and pathological findings. The histology of both the breast lumps may be same but still, the grade of differentiation may be higher or different which is suggestive more of a metastasis rather than a primary.

There should be no evidence of local, regional or distant metastasis clinically. Supraclavicular nodal involvement, lung metastasis, liver metastasis, bone secondaries may be considered as the distant metastasis.
WHAT NEXT?

Except for these criterias, there are several factors which could be taken into account. Some of them are:

1. Lag period
2. Status of the primary (in case of metachronous lesions)
3. Molecular imaging
4. Genetic fingerprinting

LAG PERIOD:

This refers to the time interval between the 2 cancers. In general, oncology principles state that, in any cancer, any lesion in the same site after a period of 3 or 5 years after complete treatment of the primary tumor is considered again as a new primary tumor and not as a metastasis or recurrence. But, this is not the case with bilateral breast cancers. The Lag period between the 2 cancers helps differentiate between the two. If the Lag period is say, within 6 months the tumor is considered as synchronous and if it is beyond 6 months, it is considered as metachronous lesions.
STATUS OF THE PRIMARY:

Whenever a patient presents with bilateral breast lump, there arises the question of which is primary and which is secondary. This is elicited to some extent from the patient with regard to the duration of the lump.

The next most important factor regarding the status of the primary is that, a T1 tumor in one breast and a T2 lesion in another breast could most probably be 2 separate primaries rather than a metastatic lesion from 1 breast. In a similar fashion, a T4 lesion in one breast and a T1 lesion in another has a very high probability of being a metastatic one.

This common sensed factor may also be considered in making a diagnosis of a bilateral breast cancer as a new primary or metastasis.
MOLECULAR IMAGING:

The Molecular imaging technique that is available at present is the FDG-PET scan. This scan is at present considered only in recurrent lesions. But the trick is that it also detects fibrosis of tissues and hence is of no use in recently operated patients.

The advantage of this FDG-PET (fluoro deoxy glucose – Positron emission tomography) is that it is a functional imaging unlike other MRI, CT which are considered as anatomical imaging. Therefore, the advantage is that even very small lesions which get missed in MRI / CT can be picked up by a FDG-PET scans.

This is mainly used in patients who have a contralateral axillary node positivity to rule out an impalpable lump in the opposite breast.

Suppose, if there is a patient with a lump and an axillary node in one breast and an axillary node in opposite axilla, the patient will be labelled as a case of metastatic breast disease. Rather, if a PET scan is done and it detects a lesion in opposite breast which was clinically normal, then the diagnosis becomes second primary and therefore the treatment can be curative.
GENETIC FINGERPRINTING:

Genetic fingerprinting is the latest and the best possible tool available to differentiate between the two cancers. In this case, the tissue specimen from the two cancers are analysed for the type of mutation involved. The following table depicts the analysis.

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<thead>
<tr>
<th>S.No.</th>
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<th>Grade</th>
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<th>P53 fingerprinting</th>
<th>P53 fingerprinting</th>
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<td></td>
<td>Left</td>
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<td>2</td>
<td>E+P+</td>
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<td>8 bp deletion</td>
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CONCLUSION:

The final conclusion of this study is very simple and observational rather than interventional. However, it helps us to differentiate a bilateral breast cancer into a metastatic one or a second primary.

1. The differentiation of a bilateral breast cancer into a metastasis or a second primary, i.e., systemic manifestation or a new contralateral disease is possible by Hagensen’s clinical criteria. The use of robbins and berg criteria or the chaudary and millis criteria are subjective.

2. A definite relationship has been established between the bilateral breast cancers incidence and the triple negativity of breast cancers, i.e., Basal-like group of invasive ductal NST cancers.
### BIBLIOGRAPHY

8. 2. Furth, J. Influence of host factors on the growth of neoplastic cells, Cancer Res. 23:21-34,
Differential expression of E-cadherin in lobular and ductal neoplasms of the breast and its biologic and diagnostic implications.


SCIENTIFIC REPORTS | 3 : 2590 | DOI: 10.1038/srep02590


Contralateral breast cancer: molecular differentiation between metastasis and second primary cancer.

Vienna, Vienna, Austria
ABBREVIATIONS

ER – Estrogen receptor
PR – Progesterone receptor
FNAC – Fine needle aspiration cytology
DCIS – Ductal carcinoma in situ
LCIS – Lobular carcinoma in situ
MRM – Modified radical mastectomy
CT / RT – chemotherapy / Radiotherapy
BILATERAL BREAST CANCERS - IS IT A SYSTEMIC MANIFESTATION
OR NEW CONTRALATERAL DISEASE?

PROFORMA

Name: Age/Sex:

Address: Occupation:

SYMPTOMS:

Bilateral Breast Mass

Post MRM, mass in opposite breast or axilla

Post adjuvant Chemo, mass in opposite breast or axilla

PAST HISTORY:

Previous h/o surgery or chemotherapy for breast mass

PERSONAL HISTORY:

Smoking

Alcohol

High fatty diet

Menstrual History
GENERAL EXAMINATION:

VITAL SIGNS:

   PR-
   BP-
   RR-

LOCAL EXAMINATION:

Examination of Both Breast and axilla
Examination of spine and cranium

INVESTIGATIONS:

MAMMOGRAM

USG BREAST

USG ABDOMEN
## ASSESSMENT SHEET / MASTER SHEET:

<table>
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<tr>
<th>Age</th>
<th>Interval of 2 cancers</th>
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<th>Histology</th>
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<td></td>
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<td></td>
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<td>2nd ER PR Her 2 - Neu</td>
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**TRUCUT BIOPSY**

**LFT**

**CT CHEST**

**SKELETAL SURVEY**
PATIENT CONSENT FORM

Study Detail: “BILATERAL BREAST CANCERS - IS IT A SYSTEMIC MANIFESTATION OR NEW CONTRALATERAL DISEASE?”

Study Centre: Rajiv Gandhi Government General Hospital, Chennai.

Patient's Name:

Patient's Age:

Identification Number:

Patient may check (v) these boxes

a) I confirm that I have understood the purpose of procedure for the above study. I have the opportunity to ask question and all my questions and doubts have been answered to my complete satisfaction.

b) I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving reason, without my legal rights being affected.

c) I understand that sponsor of the clinical study, others working on the sponsor’s behalf, the ethical committee and the regulatory authorities will not need my permission to look at my health records, both in respect of current study and any further research that may be conducted in relation to it, even if I withdraw from the study I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from this study.

d) I agree to take part in the above study and to comply with the instructions given during the study and faithfully cooperate with the study team and to immediately inform the study staff if I suffer from any deterioration in my health or well being or any unexpected or unusual symptoms.

e) I hereby consent to participate in this study.

f) I hereby give permission to undergo detailed clinical examination and blood investigations as required.

Signature/thumb impression

Patient's Name and Address: Signature of Investigator
## MASTER CHART

<table>
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<tr>
<th>S. No</th>
<th>Name</th>
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<th>Interval between the 2 cancers</th>
<th>Age at diagnosis of 1st cancer</th>
<th>Famil y history</th>
<th>Menopausal status</th>
<th>Adjuvant treatment (if any received)</th>
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அரஞ்சி கோளிய நாள்

இரட்டையாக பிருந்து காண்பது பயன்படுத்துவதற்கு இருந்து பிறந்து பிருந்து நேர அரஞ்சி கோளிய நாளால் மாறியது.

இருந்து பிறந்து பிருந்து நேர அரஞ்சி வழியாக பயன்படுத்துவதற்கு இருந்து பிறந்து நேர அரஞ்சியின் வழியாக பயன்படுத்துவதற்கு இருந்து பிறந்து நேர அரஞ்சியின் வழியாக பயன்படுத்துவதற்கு இருந்து பிறந்து நேர அரஞ்சியின் வழியாக பயன்படுத்துவதற்கு.

இருந்து பிறந்து பயன்படுத்துவதற்கு இருந்து பிறந்து நேர அரஞ்சியின் வழியாக பயன்படுத்துவதற்கு இருந்து பிறந்து நேர அரஞ்சியின் வழியாக பயன்படுத்துவதற்கு.

ஆரஞ்சி வழியாக பயன்படுத்து வழியாக பயன்படுத்து.

இன்னை:
ஆரம்பத் கோளத்தில்:

இது மாட்டு புது விள்ளையான புரிந்த ஆரம்பம்.

இப்பக்த மாட்டு புது விள்ளையான புரிந்த ஆரம்பம்.

இப்பக்த மாட்டு புது விள்ளையான புரிந்த ஆரம்பம்.

முனைவரின் பந்துவரும் சிற்றுடன் பரிசாரகம் நிறைவுகொண்டது புரிந்து ஆரம்பம்.

சுருக்கம்
INTRODUCTION