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Bilateral Breast Cancer: A Comprehensive Review of Classification, Diagnosis, Management, and Prognosis

Gede Angga Janardana[1], Timmy Yonatan Nangoy[2], Ida Ayu Diah Wedawati[3], Michele Yoselin[4], I Made Adi Narendranatha Komara[5]

[1, 2, 3, 4, 5]Wangaya Hospital, Denpasar, Bali, Indonesia
Corresponding author email: *anggajanardana[at]gmail.com*

Abstract: ***This literature review provides a comprehensive overview of bilateral breast cancer, a rare malignancy that affects both breasts. The article discusses the classification, risk factors, pathophysiology, diagnosis, management, and prognosis of the disease. The review aims to enhance understanding of bilateral breast cancer and contribute to improved patient care.***

Keywords: Bilateral Breast Cancer, Synchronous Bilateral Breast Cancer, Metachronous Bilateral Breast Cancer, Risk Factors, Diagnosis, Management, Prognosis

1. Introduction

Bilateral breast cancer is a malignancy that grows in both breasts, occurs when cell proliferation is uncontrolled in breast cells.[1] The incidence of bilateral breast cancer is very rare, around 1 - 14% and data on this disease are very few. The risk of bilateral breast cancer varies from age, family history, use of oral contraceptives and hormone replacement therapy, obesity, smoking and alcohol consumption.

Bilateral breast cancer is divided into two types based on the time interval, namely synchronous bilateral breast cancer (sBBC) and metachronous bilateral breast cancer (mBBC).[4] Kilgore in 1921, who defined synchronous carcinoma as one in which both tumors were diagnosed at the same time. In 1971, Haagensen introduced the concept of the time interval between the appearances of the two tumors. The length of this time period is set arbitrarily by different authors, from one month to 5 years. In Argentina, Uriburu defined bilateral tumors as synchronous if diagnosed within the first 12 months and metachronous after that period.

Before diagnosing as bilateral breast cancer, it must be distinguished first, whether this is a new primary tumor or a contralateral metastasis using Chaudary's criteria.[6] Appropriate anamesis, physical examination and careful supporting examinations such as breast ultrasound, mammography and biopsy can establish the correct diagnosis.[7] The management of sBBC and mBBC in mammary glands is generally no different, surgery, radiotherapy or chemotherapy can be performed.[8]

Purpose:
The purpose of this review is to provide a comprehensive overview of bilateral breast cancer, including its classification, risk factors, pathophysiology, diagnosis, management, and prognosis, with the aim of enhancing understanding and contributing to improved patient care.

Significance:
This review is significant as it provides a comprehensive overview of bilateral breast cancer, a rare type of cancer. The review can contribute to the body of knowledge in the field and potentially improve patient care by enhancing understanding of the disease.

2. Comprehensive Reviews

Definition
Breast cancer is known as bilateral (ca mammae bilateral) when a primary carcinoma grows into the other breast. This occurs when uncontrolled cell proliferation in breast cells

Classification
Bilateral breast cancer is divided into two, namely synchronous bilateral breast cancer (sBBC) and metachronous bilateral breast cancer (mBBC) based on the time interval for the growth of the cancer. The definitions of the two types of bilateral breast cancer differ in several literatures. The first series was published by Kilgore in 1921, who defined synchronous carcinoma as one in which both tumors were diagnosed at the same time. In 1971, Haagensen introduced the concept of the time interval between the appearance of the two tumors. The length of this time period is set arbitrarily by different authors, from one month to 5 years. In Argentina, Uriburu defined bilateral tumors as synchronous if diagnosed within the first 12 months and metachronous after that period.

Table 2.1: Time interval for division into sBBC and mBBC

Time Intervals	Expert
The same time	Kilgore10; Robins and Berg11; Leis12
1 month	Prior and Waterhouse13; Healey14; Gollamudi15; Yeatman16
3 months	Carmichael17; Intra18; Hartmann19
68 days	Mose20
6 months	Haagensen21; McCredie22; De La Rochefordiere23; Broets24; Verkooijen25
1 year	Al - Jurf26; Uriburu27; Hislop28; Heron29; Kaas30; Quan31
5 years	Bloom32

Risk Factor

Several risk factors for the development of bilateral mammary glands, including:

a) Age
Young people who are diagnosed early with breast tumors tend to have a higher risk of experiencing bilateral mammary cancer. A study in Sweden, women aged 30 - 34 years have a higher risk of contralateral cancer than postmenopausal women.

b) Family history
A positive family history of breast cancer is the most widely recognized risk factor for bilateral breast cancer. The lifetime risk is up to 4 times higher if a mother and sister are affected, and about 5 times greater in women who have two or more first - degree relatives with breast cancer. The risk is also greater among women with breast cancer in one first - degree relative, especially if the relative was diagnosed at an early age (≤50 years), as well as a BRCA1 or BRCA2 gene mutation.[33]

c) Reproductive factors and steroid hormones
Late age at first pregnancy, nulliparity, early menstruation, and late menopause have all been consistently associated with an increased risk of breast cancer. The use of exogenous hormones in the form of oral contraceptives and hormone replacement therapy (HRT) shows a risk of breast cancer of around 25%.[3, 33]

d) Environmental factor
Smoking, food (eg, charred and processed meats, regular alcohol consumption, and environmental carcinogens (eg, exposure to pesticides, radiation) increase the risk of bilateral breast cancer.[3, 33]

e) Obesity
Women with BMI > 30 kg/m2 are a risk factor for contralateral breast cancer

f) Histology of the first lobular tumor [34]

g) Treatment received for first tumor [34]

h) Tumor size and initial stage at diagnosis [34]

i) Receptor status and Her - 2/neu positive patient[34]

Pathophysiology

Breast cancer usually occurs due to the interaction between environmental and genetic factors. The PI3K/AKT pathway and the RAS/MEK/ERK pathway are pathways that protect normal cells from cell suicide. When the genes encoding these protective pathways are mutated, cells become incapable of undergoing apoptosis when they are no longer needed, which can then lead to the development of cancer. This mutation has been shown experimentally to be associated with estrogen exposure. This suggests that abnormalities in growth factor signaling may facilitate malignant cell growth. Over expression of leptinin in breast adipose tissue leads to increased cell proliferation and cancer

The familial tendency to develop breast cancer is called hereditary breast - ovarian cancer syndrome. Several mutations associated with cancer, such as p53, BRCA1 and BRCA2, occur in mechanisms to repair errors in DNA that lead to uncontrolled division, lack of attachment, and metastases to distant organs. Inherited mutations in the BRCA1 or BRCA2 genes can interfere with DNA cross - link repair and DNA double - strand breaking. GATA - 3 directly controls the expression of the estrogen receptor (ER) and other genes related to epithelial differentiation. Loss of GATA - 3 causes inhibition of differentiation and poor prognosis due to increased invasion of cancer cells in the contralateral breast so that bilateral mammary glands and distant metastases can occur.

Diagnosis

a) Anamnesis[7]

Main complaint:

- Lump in the breast
- Growth rate with/without pain
- Nipple discharge, nipple retraction and crusting
- Skin disorders, dimpling, peaud'orange, ulceration, venectation
- Armpit lumps and arm edema

Additional complaints:

- Bone pain (vertebrae, femur)
- Shortness and so on

b) Physical examination[7]

The physical examination begins with assessing the general status (vital signs - a thorough examination of the body) to look for possible metastases and/or secondary medical disorders. Furthermore, an examination was carried out to assess the status of local and regionalists. This examination is carried out systematically, inspection and palpation.

Inspection is carried out with the patient sitting, upper and lower clothing removed and arms positioned at the side, above the head and akimbo. Inspection of both breasts, axillae and around the clavicles to identify signs of primary tumor and possible metastases to lymph nodes.

Figure 2.1: Inspection techniques

Palpation of the breasts is performed with the patient in a supine position, the ipsilateral arm above the head and the back supported by a pillow. Both breasts are palpated systematically and thoroughly either circularly or radially. Axillary palpation is performed in a sitting position with the examiner's arm supporting the patient's arm. Palpation is also done infra and supraclavicular.

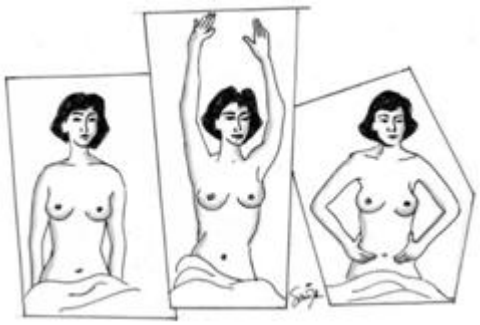

Figure 2.2: Palpation technique

After physical examination, the TNM classification is used to evaluate tumor size, affected lymph nodes and evidence of distant metastases. The TNM system was adapted by The America Joint Committee on Cancer Staging and Resuid Reformatting. These stages based on physiology provide a more accurate prognosis, as follows:

Table 2.2: Classification of TNM ca mammae

TUMOR SIZE (T)	
Thx	No tumors
To	Could not demonstrate the presence of a primary tumor
T1	Tumor with a diameter, less than 2 cm
T2	Tumors with a diameter of more than 2 - 5 cm
T3	Tumor with a diameter of more than 5 cm
T4	Tumors regardless of size have shown expansion
	directly to the chest wall or skin.
REGIONAL LIMPHO NODUS (N)	
Nx	The axillary glands are not palpable.
No	There were no homolateral axillary gland metastases.
N1	Metastases to homolateral axillary glands but still can
	moved.
N2	Metastases to homolateral axillary glands, attached fixed one
	each other or the surrounding tissue
N3	Metastasis to supraclavicular/infraclavicular homolateral nodes
	or an arm odeme
REMOTE METASTASE (M)	
Mo	No distant metastases
M1	Distant metastases still extend beyond the breast

For the purposes of treatment and prognosis, breast cancer is divided into 4 stages, namely:

- Stage I

The size of the tumor is not more than 2 cm and there is no spread to other organs or to the supraclavicular lymph nodes.

- Stage II

The size of the tumor is between 2 - 5 cn and there is no spread to other organs or to the supraclavicular lymph nodes.

- Stage III

The size of the tumor is more than 5 cm and there is no spread to other organs or to the supraclavicular lymph nodes.

- Stage IV

Regardless of the size of the tumor, if there has been spread to the organs of the body or the supraclavicular lymph nodes, it enters stage IV.

c) Mammography of the breast[7, 37]

Mammography is imaging using X - rays of compressed breast tissue to produce a mammogram (picture of the mammography result). To obtain a good interpretation of imaging results, it is necessary to have two mammogram positions with different projections of 45 degrees (craniocaudal and mediolateral oblique). Mammography can be used to screen for breast cancer, diagnose breast cancer, and follow up on treatment. Mammography is performed on women aged over 35 years, but because Indonesians' breasts are denser, the best results for mammography should be done at age > 40 years. Mammography examination should be done on the 7 - 10th day counting from the first day of menstruation; at this time it will reduce the discomfort in women when compressed and will give optimal results.

Primary signs in the form of:

- The increased density of the tumor
- Irregular tumor boundaries due to infiltration into the surrounding tissue or unclear boundaries (comet sign)
- Translucent appearance around the tumor
- Stellate overview.
- Presence of micro-calcifications according to Egan's criteria
- The clinical size of the tumor is larger than radiological.

Secondary sign:

- Skin retraction or skin thickening
- Increased vascularization
- Change in nipple position
- Axillary lymph nodes (+)
- The state of the tumor area and irregular fibroglandular tissue
- Threadlike sub areolar tissue density

d) Breast ultrasound[7, 37]

One of the advantages of ultrasound is in detecting cystic masses. Ultrasound images of lumps that must be suspected of being malignant include:

- Uneven surface
- Taller than wider
- Hyperechoic type
- Heterogeneous internal echo
- Vascularization increased, irregular and into the tumor at an angle of 90 degrees

e) Anatomical pathology examination[7, 37]

Pathological examination of breast cancer includes cytological examination, morphology (histopathology), immunohistochemical examination, in situ hybridization and gene array (only done in research and special cases).

f) Immunohistochemical examination (IHK) [7, 37]

The examination method uses antibodies as probes to detect antigens in tissue sections or other forms of cell preparations. The CPI is the standard for determining breast cancer subtypes. Examination of CPI in breast carcinoma plays a role in helping to predict systemic therapy response and prognosis.

The standard immunohistochemical examination for breast cancer is:

- Hormonal receptors namely estrogen receptor (ER) and progesterone receptor (PR)
- HER2
- Ki - 67

ER and PR examinations are performed on material from paraffin blocks (core biopsy and excision specimens), and can also be from cytology smears or cell blocks. Examination should be carried out on specimens fixed with 10% Neutral Buffer Formalin (NBF). The result is positive if > 1% of the cell nuclei are stained (either with weak, medium or strong intensity). HER2 (c - erbB - 2, HER2/neu) status testing is currently recommended for invasive breast carcinoma (DCIS was not evaluated for HER2). HER2 examination must be performed on a paraffin block of tissue fixed with 10% NBF and cannot be performed from a cytology smear. The results stated positive HER2 on HER2 +3, while HER2 +2 required further examination in the form of in situ hybridization.

Chaudry's criterion is also used to diagnose bilateral breast cancer to distinguish whether this is a new primary tumor or a contralateral metastasis.

Table 2.3: Chaundry's criteria in diagnosing bilateral breast cancer6

Chaudry's criteria	Case
Presence of in situ components (absolute criteria)	found - match
Different histological types, with a greater degree of differentiation (relative criteria)	found - match
No local/regional/distant metastases from the first cancer (relative criteria)	In accordance

Management

Therapy for breast cancer must be preceded by a complete and accurate diagnosis (including staging). Diagnosis and therapy of breast cancer must be carried out with a humanist and comprehensive approach.

Therapy for breast cancer is largely determined by the extent of disease or stage and the expression of biomolecular - signaling. In addition to having the expected therapeutic effect, breast cancer therapy also has several adverse effects, so before giving therapy the pros and cons must be considered and must be communicated to the patient and family. Apart from that, factors of age, comorbidities, evidence - based, cost - effective, and when to stop the systemic treatment series, including end of life issues, must be considered.

1) Surgery[8, 38, 39]

Surgery is the earliest known therapy for the treatment of breast cancer. Types of surgery on ca mammae:

- **Modified radical mastectomy (Modified Radical Mastectomy)**

MRM is the surgical removal of breast tumors and the entire breast including the nipple - areola complex, accompanied by en bloc level I to II axillary lymph node dissection. Indications: Stage I, II, IIIA and IIIB breast cancer. If needed in stage IIIb, it can be done after neoadjuvant therapy for tumor reduction.

- **Classic Radical Mastectomy (Classic Radical Mastectomy)**

Radical mastectomy is the en bloc removal of the breast, nipple - areola complex, pectoralis major and minor muscles, and level I, II, III axillary lymph nodes. This type of action was the first surgery Halsted recognized for breast cancer, but with increasing biological knowledge and smaller tumors being found, more minimal operations have developed. Indications: (1) stage IIIb breast cancer that is still operable; (2) tumor with infiltration of the pectoratlis major mucosa.

- **Mastectomy with oncoplasty technique**

Surgical reconstruction can be considered at a capable institution or surgeon who is competent in breast reconstruction without abandoning the principles of oncological surgery. Reconstruction can be performed using autologous tissue such as the latissimus dorsi (LD) flap or transverse rectus abdominis myocutaneous (TRAM) flap; or with a prosthesis such as silicone. Reconstruction can be done in one stage or two stages, for example by using the previous tissue expander.

- **Simple mastectomy**

A simple mastectomy is removal of the entire breast and the nipple - areolar complex, without dissection of the axillary lymph nodes.

Indication:

- Large phyllodes tumor
- Advanced breast malignancy with the goal of palliative tumor removal
- Paget's disease without tumor mass
- DCIS

- **Subcutaneous Mastectomy (Nipple - skin - sparing mastectomy)**

Subcutaneous mastectomy is the removal of all breast tissue, with preservation of the skin and the nipple - areola complex, with or without axillary lymph node dissection. Indications: prophylactic mastectomy, oncoplasty procedures.

- **Breast - Conserving Therapy (BCT)**

Classical definition of BCT includes breast conserving surgery (BCS) and radiotherapy (whole breast and tumor sit). BCS is surgery for breast tumors by maintaining the shape (cosmetic) of the breast, with or without reconstruction. The procedure performed is lumpectomy or quadrantectomy accompanied by level 1 and level 2 axillary lymph node dissection.

The primary goal of BCT is oncological tumor eradication while maintaining breast shape and sensory function. In general, BCT is a safe surgical option in early - stage breast cancer patients with certain conditions. The addition of radiotherapy to BCS is said to give better results.

Indication:

- Stage I and II breast cancer
- Stage III breast cancer with partial response after neoadjuvant therapy

Contraindications:

- Multicentric breast cancer, especially multicentric in more than 1 quadrant of the breast.
- Breast cancer with pregnancy

- Vascular and collagen disease (relative)
- Tumor in the central quadrant (relative)

Condition:
- Affordable mammography, frozen section, and radiotherapy facilities.
- Adequate proportion between tumor size and breast size.
- Patient choice and an in - depth discussion has been carried out.
- Performed by surgeons who are competent and have an experienced team (oncology consultant surgical specialists).

- **Bilateral Salfino Ovariectomy (SOB)**

Bilateral salfongo ovariectomy is the removal of both ovaries with/without removal of the Fallopian tubes either openly or laparoscopically. This procedure may be performed by a specialist in general surgery or a Specialist Consultant Surgical Oncologist, provided that there is no primary lesion in the uterine organs. Indications: premenopausal stage IV breast carcinoma with positive hormone receptors.

- **Metastasectomy**

Metastasectomy is the removal of metastatic tumors in breast cancer. This action is still controversial among experts, but it is said that metastasectomy has a longer life expectancy if certain indications and conditions are met. This action is performed on breast cancer with skin, lung, liver, and contralateral breast metastases. In brain metastases, metastatectomy has clinical benefits that are still controversial.

Indication:
- Single metastatic tumor in one organ
- There are symptoms and signs due to pressure on the surrounding organs

Condition:
- General condition is quite good (good performance status = WHO score >3)
- Estimated survival more than 6 months
- Disease - free period >36 months

1) Systemic therapy[8, 38]

Chemotherapy given can be in the form of a single drug or in the form of a combination of several combinations of chemotherapy drugs. Chemotherapy is given gradually, usually as many as 6 - 8 cycles in order to get the expected effect with acceptable side effects.

2) Hormonal therapy[8, 38]

Hormonal therapy is given in cases with positive hormones. Hormonal therapy can be given at stages I to IV. In cases of cancer with luminal A (ER+, PR+, Her2 -) the main adjuvant therapy option is hormonal instead of chemotherapy. Chemotherapy is no better than hormonal therapy. The choice of tamoxifen therapy should take precedence over giving aromatase inhibitors, especially in postmenopausal patients and Her2 - . The duration of hormonal adjuvant administration is 5 - 10 years.

3) Target therapy[8, 38]

Administration of anti - Her2 only in cases with a positive Her2 CPI examination. The first choice of anti - Her2 is herceptin, preferably in cases with an early stage and a good prognosis (for one year: every 3 weeks).

4) Radiotherapy8, 38

Radiotherapy is an important modality in the management of breast cancer. Radiotherapy in the management of breast cancer can be given as adjuvant and palliative curative therapy.

Prognosis

The mBBC type has a lower survival rate than sBBC, although overall survival does not differ. Patients with mBBC must be followed closely to detect early relapse and maximize quality of life.

Conclusion

Bilateral breast cancer is a rare malignancy that requires comprehensive understanding for effective diagnosis and management. This review provides an overview of the disease, including its classification, risk factors, pathophysiology, diagnosis, management, and prognosis. Further research is needed to enhance understanding of the disease and improve patient care.

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