Review Article

HER2 Positive and Triple Negative Breast Cancer: A Review

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ABSTRACT:

Background: Cancer is the most common cause of mortality and morbidity seen in all over the world. Breast cancer is the second most prevalent type of non-skin cancer and the fifth most common cause of cancer-related mortality worldwide, accounting for 10.4% of all cancer incidences among women. HER2 is a protein that plays a role in cell growth and differentiation accounts for 15-20% of HER2-Positive breast cancer. Lack of expression of Estrogen & Progesterone Receptor and the absence of human epidermal growth factor receptor 2 (HER2) and accounts for 15% of Triple negative breast cancer of all cases.

Objectives: Improving the prognosis of overall survival and disease-free survival of HER2-Positive and Triple Negative Breast Cancer. Reducing the risk of recurrence through effective adjuvant chemotherapy. Balancing the treatment efficacy with minimal side effects and improving overall quality of life.

Methods: Relevant articles from various journals were analyzed and reviewed.

Conclusion: Advanced targeted therapies have improved the treatment and prognosis of HER2-Positive and Triple Negative Breast Cancer.

Keywords: Breast Cancer, HER2 Positive, TNBC, Chemotherapy, NACT

INTRODUCTION:

The World Health Organization (WHO) defines "breast cancer" as malignancies that arise in the breast tissue, typically from the inner lining of the ducts or the lobules supplying to the milk ducts. Breast cancer is the second most prevalent type of non-skin cancer (after lung cancer) and the fifth most common cause of cancer-related mortality worldwide, accounting for 10.4% of all cancer incidences among women. 5,19,000 fatalities globally from breast cancer in 2004 (7% of all deaths; nearly 1% of all deaths) were attributed to the disease. Women are almost 100 times more likely than men to develop breast cancer, but men typically have worse results because of delayed diagnosis. The glandular tissues and the stromal (supporting) tissues are the two primary tissue types that make up the breast. The lobules, or milk-producing glands, and the ducts, or milk tubes, are located in the glandular tissues, whereas the stromal tissues are the fatty and fibrous connective tissues of the breast. Additionally, lymphatic and immune system tissue that eliminates waste products and cellular fluids makes up the breast [1].

Types of Breast Cancer:

1. **Non-Invasive Breast Cancer** cells that remain inside the ducts and do not spread to the breast's surrounding fatty and connective tissues. The most frequent non-invasive breast cancer kind, accounting for 90% of cases, is ductal carcinoma in situ (DCIS). Less frequently occurring lobular carcinoma in situ (LCIS) is thought to be a sign of an elevated risk of breast cancer.

2. **Invasive Breast cancer** cells that spread to the surrounding fatty and connective tissues of the breast after breaching the duct and lobular wall.

Causes of Breast Cancer:

- Genetic Factors
- Significant Family History
- Hormonal Causes
- Lifestyle and Dietary Cause

Signs and Symptoms:

- A lump in the breast or underarm is the typical sign of breast cancer. Being familiar with the texture, size, cyclical variations and skin condition of your breasts can be achieved by performing monthly breast self-examinations (BSEs).
- Breast cancer is generally indicated by symptoms like breast swelling or lump (mass), swelling in the armpit (lymph nodes), clear or bloody nipple discharge, nipple pain, inverted

(retracted) nipple, scaly or pitted skin on nipple, persistent breast tenderness, and unusual breast pain or discomfort.

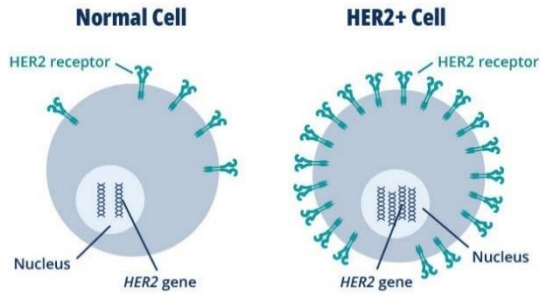
Diagnosis & Management:

Breast cancer is usually diagnosed by biopsy of nodule detected by mammogram or by PET-CT scan. Chemotherapy (Neoadjuvant & Adjuvant), Radiation Therapy, Surgery (Breast Conserving surgery – Lumpectomy, Quadrantectomy & Mastectomy) are the treatment [1].

HER 2 Positive Breast Cancer:

HER2 stands for human epidermal growth factor receptor 2, a protein that plays a role in cell growth and differentiation. Normally, HER2 receptors help to control the growth and repair of breast cells.

However, when the HER2 gene mutates, it can lead to an overproduction of the HER2 protein. The receptor tyrosine-protein kinase erbB-2 known as Human Epidermal Growth Factor Receptor 2 (HER 2) is typically involved in the proliferation of breast cells that are called as HER2- Positive Breast Cancer. Approximately 15-20% of breast cancers are HER2-Positive breast cancer [2].

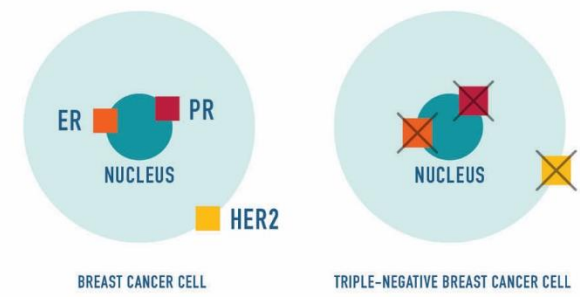


(Fig. 1) HER2 Gene Amplification / protein overexpression

Triple Negative Breast Cancer (TNBC):

TNBC can account for up to 15% of all cases. TNBC is defined by the lack of expression of the estrogen receptor (ER), the progesterone receptor (PR) and the absence of human epidermal growth factor receptor 2 (HER2) overexpression and/or gene amplification.

According to the guidelines of the American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP), ER and PR are considered negative when <1% of tumor cells show nuclear staining via immunohistochemistry. It is more common in younger women and women with a BRCA1 gene mutation. [3]



(Fig. 2) Breast cancer cells typically have some combination of the estrogen receptor (ER), progesterone receptor (PR), and overexpressed HER2. But triple-negative breast cancer (TNBC) cells lack all three of these.

Objectives of HER2-Positive and Triple Negative Breast Cancer:

- Improving the prognosis of overall survival and disease-free survival of HER2-Positive and Triple Negative Breast Cancer.
- Reducing the risk of recurrence through effective adjuvant chemotherapy (post-surgery treatment).
- Balance treatment efficacy with minimizing side effects & improving patients' quality of life[2,3].

Diagnostic Test in HER2- Positive Breast Cancer:

Immunohistochemistry (IHC): Measures the amount of HER2 protein on the surface of cells. Results are scored from 0 to 3+, with 3+ indicating HER2-positivity [4].

❖ Immunohistochemistry (IHC) for HER2 Positive sensitivity testing:

IHC Score	HER 2-test amplification	HER2 status
0	No staining or incomplete and faint/barely perceptible membrane staining n < 10% of tumor cells	Negative
1+	Incomplete and faint/barely perceptible membrane staining in >10% of tumor cells	Low **NO** ⬆
2+	Weak-moderate complete membrane staining in >10% of tumor cells or intense membrane staining n<10% of tumor cells	FISH amplification **YES** ⬇
3+	Complete and intense membrane staining in >10% of tumor cells	Positive

❖ Fluorescence In Situ Hybridization (FISH): Measures the number of copies of the HER2 gene within the cancer cells. It provides a positive or negative result [5].

Status	Score	Significance	Reflex HER2 FISH
Positive	3+	Uniform intense membrane staining of >30% tumor cells	No
Equivocal	2+	Complete membrane staining, non-uniform or weak in intensity, in at least 10% of the cells or intense complete membrane staining in 30% or less of tumor cells	Yes
Negative	1+	Weak or incomplete membrane staining in any population of tumor cells	No
Negative	0	No staining	No

Diagnostic Tests in Triple Negative Breast Cancer:

Immunohistochemistry in Triple Negative Breast Cancer (TNBC):

- Estrogen Receptor (ER) Negative: The cancer cells do not have receptors for estrogen.
- Progesterone Receptor (PR) Negative: The cancer cells do not have receptors for progesterone.
- HER2 Negative: The cancer cells do not overexpress the HER2 protein [6].

IHC Markers

- ER and PR: Antibodies against ER and PR are used to detect the presence of these hormone receptors.
- HER2: Anti-HER2 antibodies are used.
- Ki-67: Antibodies against the Ki-67 protein, a marker of proliferation, are used.
- Androgen Receptor (AR): Antibodies against the androgen receptor are use [6].

Grading:

HER2-Positive breast cancer [7]

Grade 1 (Low grade)	Well differentiated cells that look more like normal cells
Grade 2 (Intermediate grade)	Moderately differentiated
Grade 3 (High Grade)	Poorly differentiated cells that look very different from normal cells.

Triple Negative Breast Cancer [8]

Grade 1 (Low grade)	Rare in TNBC
Grade 2 (Intermediate grade)	Less Common
Grade 3 (High Grade)	Most TNBC cases are grade 3, aggressive type

BI-RADS CATEGORY:

The Breast Imaging Reporting and Data System (BI-RADS) is a standardized system used for interpreting and reporting mammography, ultrasound, and MRI results of breast imaging. Developed by the American College of Radiology (ACR), BI-RADS helps radiologists communicate findings consistently and clearly, aiding in management decisions. The BI-RADS system includes categories ranging from 0 to 6 [10].

BI-RADS 0: Incomplete

Additional imaging evaluation and/or prior mammograms for comparison are needed.

BI-RADS 1: Negative

No significant findings.

BI-RADS 2: Benign Finding

Non-cancerous findings such as cysts or fibroadenomas.

BI-RADS 3: Probably Benign

Findings have a high probability (≥ 98%) of being benign.

BI-RADS 4: Suspicious Abnormality

Findings that do not have the classic appearance of cancer but have a reasonable probability (2-95%) of being malignant

Subcategories:

4A: Low suspicion for malignancy (2-10%).

4B: Moderate suspicion for malignancy (10-50%).

4C: High suspicion for malignancy (50-95%).

Management: Tissue diagnosis (e.g., biopsy).

BI-RADS 5: Highly Suggestive of Malignancy

Findings have a high probability (≥ 95%) of being cancer.

BI-RADS 6: Known Biopsy-Proven Malignancy

Lesions already confirmed as cancer through biopsy [10].

STAGING: Staging determines the extent of cancer spread and is based on the TNM system (Tumor size, Node involvement, Metastasis) [9]

Adjuvant Chemotherapy:

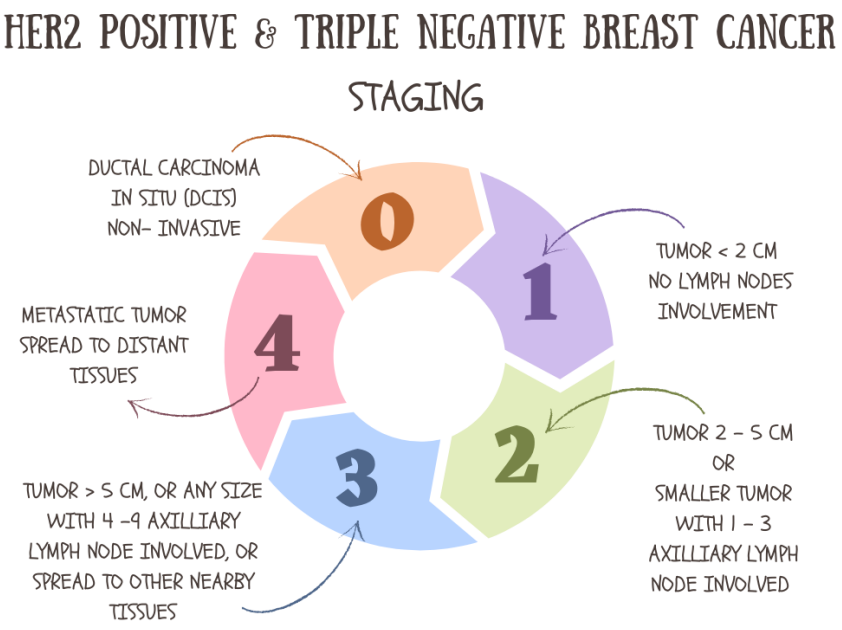
It has been shown that adjuvant chemotherapy is beneficial for survival when used to eradicate occult distant metastases that were already present at the time of surgery [11].

Neoadjuvant Chemotherapy treatment for HER2-Positive Breast Cancer:

❖ **TCH Regimen: (Docetaxel+ Carboplatin+ Trastuzumab)**

"TCH" is a chemotherapy regimen commonly used in the treatment of breast cancer. The acronym stands for,

- **T**: Docetaxel (Taxotere)
- **C**: Carboplatin
- **H**: Trastuzumab (Herceptin)



Management of HER2-Positive and Triple Negative Breast Cancer:

Neoadjuvant Chemotherapy (NACT):

The term neoadjuvant chemotherapy (NACT) is used to describe chemotherapy given before locoregional therapy. Despite the prefix 'neo' from Greek meaning 'new' with the adjective 'adjuvant' from Latin meaning 'assistant', such treatment is not new; it was shown to be effective therapy. The aim of NACT was to achieve prompt tumour shrinkage thus facilitating subsequent radical mastectomy or radiotherapy.

Indications:

The TCH regimen is used for patients with HER2-positive breast cancer. HER2 (human epidermal growth factor receptor 2) is a protein that can promote the growth of cancer cells. In about one of every five breast cancers, the cancer cells have a gene mutation that makes an excess of the HER2 protein.

Administration:

The TCH regimen is typically administered in cycles, with each cycle lasting 21 days. The number of cycles can vary depending on the patient's

specific condition and response to treatment, but a common approach involves six cycles.

Side Effects:

Like all chemotherapy regimens, TCH can cause side effects. These may include:

- Fatigue
- Nausea and vomiting
- Hair loss
- Neutropenia (low white blood cell count)
- Anaemia (low red blood cell count)
- Increased risk of infection
- Peripheral neuropathy (numbness and tingling in the hands and feet)
- Cardiotoxicity (heart-related side effects, particularly with trastuzumab)

Monitoring and Support:

Patients on the TCH regimen require regular monitoring to manage side effects and to assess their response to treatment. This often involves:

- Blood tests to monitor blood cell counts and organ function.
- Heart function tests, especially with the use of trastuzumab.
- Supportive medications to manage side effects, such as anti-nausea drugs and growth factors to boost white blood cell counts.

The other treatment options involved in treating HER2-Positive Breast Cancer are:

❖ AC Regimen (Adriamycin + Cyclophosphamide) – 4 cycles – Each cycle lasts 21 days.
❖ Weekly Paclitaxel – 12 cycles
❖ TC Regimen (Docetaxel + Cyclophosphamide) – 4 cycles – Each cycle lasts 21 days.

Neoadjuvant Chemotherapy for Triple Negative Breast Cancer:

Anthracyclines (Adriamycin) & Taxanes (Paclitaxel) are used in the treatment of Triple Negative Breast Cancer.

❖ **Anthracycline(e.g., Doxorubicin/Adriamycin)**

❖ **Doxorubicin (Adriamycin)** is a type of anthracycline that works by intercalating DNA, inhibiting topoisomerase II, and generating free radicals, leading to DNA damage and cell death.

Regimen involving Doxorubicin:

- Often used in combination with cyclophosphamide (AC regimen).
- Administered intravenously.

Side Effects:

- Cardiotoxicity (potential heart damage), requiring monitoring of heart function.
- Myelosuppression (decreased bone marrow activity leading to lower blood cell counts).
- Nausea and vomiting.
- Hair loss.
- Risk of secondary cancers (though rare).

❖**Taxanes (e.g., Paclitaxel/Taxol)**

Paclitaxel (Taxol) is a type of taxane that stabilizes microtubules and prevents their disassembly, thereby inhibiting cell division and leading to cell death.

Regimen involving Paclitaxel:

- Often used after the administration of anthracyclines (sequential therapy) or in combination (concurrent therapy).
- Administered intravenously, typically weekly or every three weeks.

Side Effects:

- Peripheral neuropathy (numbness and tingling in the hands and feet)
- Myelosuppression
- Allergic reactions (premedication with steroids and antihistamines is common)
- Hair loss
- Fatigue

Monitoring parameters: Cardiac monitoring, neuropathy, blood tests and supportive care[12].

Surgery: Surgery is the primary breast cancer treatment. Breast cancer surgeries include:

➢ **Mastectomy: A mastectomy is a surgical procedure** to remove one or both breasts, partially or completely. It's often used to treat breast cancer or reduce the risk of developing breast cancer.

Types of Mastectomies:

1. Total (Simple) Mastectomy
2. Modified Radical Mastectomy
3. Radical Mastectomy
4. Skin-Sparing Mastectomy

5. Nipple-Sparing Mastectomy

Potential Complications:

- Infection.
- Bleeding or hematoma formation.
- Seroma (fluid buildup under the skin).
- Lymphedema (swelling due to lymph node removal).
- Pain or changes in sensation in the chest or arm.
- Complications related to reconstruction if performed [13].

➢ **Lumpectomy:** A lumpectomy, also known as breast-conserving surgery, is a surgical procedure to remove a breast tumour (lump) and a small margin of surrounding healthy tissue. It's often used to treat early-stage breast cancer, aiming to conserve as much of the breast as possible.

Indications for Lumpectomy:

1. **Early-Stage Breast Cancer**
2. **Ductal Carcinoma In-Situ (DCIS)**

Potential Complications:

- Infection.
- Bleeding or hematoma formation.
- Seroma (fluid buildup under the skin).
- Changes in breast shape or appearance.
- Pain or tenderness in the breast or underarm area.
- Lymphedema (if lymph nodes are removed) [14].

➢ **Breast Reconstruction:** Breast reconstruction is a surgical procedure to restore the shape of the breast after a mastectomy or lumpectomy. The goal is to create a breast that is similar in shape, size, and appearance to the natural breast [15].

Adjuvant Chemotherapy for HER2-Positive and Triple Negative Breast Cancer:

AC-T Regimen:

The AC-T regimen is a combination chemotherapy treatment often used in the management of certain types of cancer, particularly breast cancer. This regimen includes the following drugs:

1. **Adriamycin (Doxorubicin)**
2. **Cyclophosphamide**
3. **Taxanes (Paclitaxel or Docetaxel)**

Side Effects:

Common side effects of the AC-T regimen can include:

- Nausea and vomiting
- Hair loss
- Fatigue
- Increased risk of infections (due to lowered white blood cell counts)
- Mouth sores
- Neuropathy (nerve damage causing numbness and tingling, more common with Taxanes)

Monitoring and Supportive Care:

Patients undergoing the AC-T regimen typically require close monitoring, including regular blood tests to check blood counts, liver and kidney function, and cardiac function (due to the potential cardiotoxicity of Adriamycin). Supportive care measures, such as anti-nausea medications and growth factors to boost white blood cell counts, are often used to help manage side effects [12].

Pertuzumab +Trastuzumab + Docetaxel:

The combination of Pertuzumab, Trastuzumab, and Docetaxel is a commonly used regimen for the treatment of HER2-positive breast cancer.

Indications:

This regimen is typically used for:

- Neoadjuvant treatment (before surgery) in HER2-positive, locally advanced, inflammatory, or early-stage breast cancer.
- Adjuvant treatment (after surgery) in HER2-positive breast cancer.
- First-line treatment for HER2-positive metastatic breast cancer.

Common Side Effects:

- **Pertuzumab and Trastuzumab**
  - Diarrhoea
  - Infusion-related reactions (fever, chills, rash)
  - Cardiotoxicity (heart problems, including decreased heart function)

- **Docetaxel**:
  - Neutropenia (low white blood cell counts)
  - Fatigue
  - Hair loss
  - Neuropathy (nerve damage causing numbness and tingling)

- Nail changes

Monitoring and Supportive Care:

Patients receiving this regimen require regular monitoring, including:

- Cardiac function tests (e.g., echocardiograms or MUGA scans) due to the potential cardiotoxicity of pertuzumab and trastuzumab.
- Blood tests to monitor for neutropenia and other side effects.
- Supportive medications to manage side effects, such as anti-nausea drugs, growth factors to boost white blood cell counts, and medications to manage diarrhoea [12].

Importance of Neoadjuvant Therapy in HER2-Positive Breast Cancer

1. **Tumour Shrinkage:** Neoadjuvant therapy can significantly shrink tumours, making them operable and allowing for less extensive surgery, potentially conserving more breast tissue.
2. **Assessment of Treatment Response:** It provides an opportunity to assess the tumour's response to therapy.
3. **Early Systemic Treatment:** Administering systemic therapy early can target micro metastatic disease, potentially improving long-term outcomes.
4. **Personalized Treatment**: The response to neoadjuvant therapy can help tailor postoperative (adjuvant) treatment.

Importance of Neoadjuvant Therapy in Triple-Negative Breast Cancer (TNBC)

1. **Tumour Reduction:** Similar to HER2-positive cancers, neoadjuvant therapy can reduce tumour size, making surgery easier and potentially less invasive.
2. **Prognostic Information:** The response to neoadjuvant chemotherapy in TNBC can be a strong predictor of long-term outcomes.
3. **Early Intervention:** TNBC is an aggressive subtype, and early systemic treatment can help control the disease and address micro metastatic spread.

Drawbacks and Limitations of Neoadjuvant Chemotherapy in HER2-Positive and Triple Negative Breast Cancer:

- Toxicity and Side effects
- Delayed surgery leads to the progression of disease
- Clinical and molecular subtypes
- Cost efficacy [16]

Future Directions:

Clinical trials and ongoing research are key to enhancing the prognosis for patients with TNBC and HER2-positive status. Priorities for treating HER2-positive breast cancer include creating new targeted therapies and comprehending resistance mechanisms. Finding new targets for therapy for TNBC, enhancing specific treatment plans, and perfecting immunotherapy techniques [17].

Conclusion:

HER2-positive and triple-negative breast cancer (TNBC) are two aggressive subtypes of breast cancer that present unique challenges and opportunities in treatment and management. Neoadjuvant therapy has dramatically improved the prognosis for HER2 Positive & TNBC Patients by enhancing survival rate and reducing recurrence. Neoadjuvant therapy, which includes HER2-Targeted agents combined with chemotherapy, has been particularly effective in shrinking tumours pre-operatively and improving surgical outcomes. Recent advancements in immunotherapy provides hope for improved treatment options.

REFERENCES:

1. Sharma GN, Dave R, Sanadya J, Sharma P, Sharma K. Various types and management of breast cancer: an overview. Journal of advanced pharmaceutical technology & research. 2010 Apr 1;1(2):109-26.

2. Montemurro F, Di Cosimo S, Arpino G. Human epidermal growth factor receptor 2 (HER2)-positive and hormone receptor-positive breast cancer: new insights into molecular interactions and clinical implications. Annals of Oncology. 2013 Nov 1;24(11):2715-24.

3. van den Ende, N. S., Nguyen, A. H., Jager, A., Kok, M., Debets, R., & van Deurzen, C. H. M. (2023). Triple-negative breast cancer and predictive markers of response to neoadjuvant chemotherapy: A systematic review. International Journal of Molecular Sciences, 24(3), 2969.

4. Ivanova M, Porta FM, D'Ercole M, Pescia C, Sajjadi E, Cursano G, De Camilli E, Pala O,

Mazzarol G, Venetis K, Guerini-Rocco E. Standardized pathology report for HER2 testing in compliance with 2023 ASCO/CAP updates and 2023 ESMO consensus statements on HER2-low breast cancer. Virchows Archiv. 2024 Jan;484(1):3-14.

5. Gutierrez C, Schiff R. HER2: biology, detection, and clinical implications. Archives of pathology & laboratory medicine. 2011 Jan 1;135(1):55-62.

6. Yadav BS, Chanana P, Jhamb S. Biomarkers in triple negative breast cancer: A review. World journal of clinical oncology. 2015 Dec 12;6(6):252.

7. What is a breast cancer's grade? [Internet]. Cancer.org. [cited 2024 Jul 20]. Available from: https://www.cancer.org/cancer/types/breast-cancer/understanding-a-breast-cancer-diagnosis/breast-cancer-grades.html

8. Geyer FC, Pareja F, Weigelt B, Rakha E, Ellis IO, Schnitt SJ, Reis-Filho JS. The spectrum of triple-negative breast disease: high-and low-grade lesions. The American journal of pathology. 2017 Oct 1;187(10):2139-51.

9. Stages of breast cancer [Internet]. Cancer.org. [cited 2024 Jul 20]. Available from: https://www.cancer.org/cancer/types/breast-cancer/understanding-a-breast-cancer-diagnosis/stages-of-breast-cancer.html

10. Magny SJ, Shikhman R, Keppke AL. Breast imaging reporting and data system. InStatPearls [Internet] 2022 Aug 29. StatPearls publishing.

11. Charfare H, Limongelli S, Purushotham AD. Neoadjuvant chemotherapy in breast cancer. Journal of British Surgery. 2005 Jan;92(1):14-23.

12. Chu E. Physicians' Cancer Chemotherapy Drug Manual 2017. Jones & Bartlett Learning; 2016 Dec 16.

13. Hopkinsmedicine.org. [cited 2024 Jul 20]. Available from: https://www.hopkinsmedicine.org/health/conditions-and-diseases/breast-

14. Lumpectomy [Internet]. Mayoclinic.org. 2022 [cited 2024 Jul 20]. Available from: https://www.mayoclinic.org/tests-procedures/lumpectomy/about/pac-20394650

15. Breast reconstruction with flap surgery [Internet]. Mayoclinic.org. 2022 [cited 2024 Jul 20]. Available from: https://www.mayoclinic.org/tests-procedures/breast-reconstruction-flap/about/pac-20384937

16. Korde LA, Somerfield MR, Carey LA, Crews JR, Denduluri N, Hwang ES, Khan SA, Loibl S, Morris EA, Perez A, Regan MM. Neoadjuvant chemotherapy, endocrine therapy, and targeted therapy for breast cancer: ASCO guideline. Journal of Clinical Oncology. 2021 May 1;39(13):1485-505.

17. Wang J, Xu B. Targeted therapeutic options and future perspectives for HER2-positive breast cancer. Signal transduction and targeted therapy. 2019 Sep 13;4(1):34.