



## Benefits of adjuvant and neoadjuvant chemotherapy on operative outcomes in improving the quality of life

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### Abstract

Breast Cancer that develops from breast tissue is the second leading cause of cancer deaths in women and it is the disease women fear the most. There are various types of chemotherapies which are used in every phase of the survivor system. The current mini-review mainly talks about the benefits, characteristics, alternatives and associates of adjuvant and neo-adjuvant chemotherapy on the treatment phase and recovery phase in improving the quality of life thus giving the insights into learning the trends of chemotherapies practically.

**Keywords:** breast cancer, women, chemotherapy, adjuvant, Neo-adjuvant, quality of life

### Introduction

Cancer is a group of disease in which cells are aggressive (grow and divide without respect to normal limits), invasive (invade and destroy adjacent tissues), and sometimes metastatic (spread to other locations in the body). These three malignant properties of cancers differentiate them from benign tumors, which are self-limited in their growth (local) and do not invade or metastasize (although some benign tumor types are capable of becoming malignant)<sup>[1]</sup>. Breast Cancer begins in the breast tissue and may start in the duct or lobe of the breast. When the "controls" in breast cells are not working properly, they divide continually and a lump or tumor is formed.

Breast cancer is the most common form of cancer among women. The second most common cause of cancer related mortality 1 of 8 (12.2%) women are diagnosed with breast cancer in their lifetime. Incidence rates are highest in North America, Australia and Western Europe; intermediate in South America, the Caribbean and Eastern Europe and lowest in China, Japan and India<sup>[2]</sup>. Over the years there has been decline in breast cancer mortality rates due to early detection by screening and more effective treatment modalities. Risk factors are incident of breast cancer increases with age. More than 80% of breast cancer cases occur in women over 50<sup>[3]</sup>. About 13.7% deaths are reported in women due to breast cancer globally. In India number of breast cancer cases is 1, 15,000 per year and expected to rise to 2,50,000 new cases. In India 60% of breast cancers are detected in advanced stage and about 1 in 3000 pregnant or lactating women are have breast cancer<sup>[4]</sup>.

Approximately 10% of breast cancer is due to inherited genetic predisposition and a woman whose mother or sister has had breast cancer is at relative risk 2 to 3 times compared to other women<sup>[5]</sup>.

In Hereditary breast cancer, BRCA1 or BRCA2 genes are now believed to be responsible for 30% to 50% of

hereditary breast cancer, ovarian cancer or both in families with a history of these cancers and also about 90% of BRCA1 carriers will develop breast cancer in whole lifetime<sup>[6]</sup>. Other defective genes that contribute to breast cancer includes BRCA3 p53 (Li-Fraumeni syndrome) CHEK2 (Variant of Li-fraumeni) PTEN (Cowden syndrome) LKBI/STK11 (Peutz-Jeghers syndrome) ATM (ataxia telangiectasia) respectively. Mutations in these tumour-suppressor genes also predispose affected women to ovarian cancer<sup>[7]</sup>. Certain types of benign breast disease like Hyperplasia increases the risk by 1.5 to 2 fold and Atypical hyperplasia by 4 to 5 fold. Hormonal Factors like levels of estrogen risk: Early age at menarche, Late age at menopause, Nulliparity, Late age at first child-birth, Obesity<sup>[8]</sup>. Environmental Factors like, High fat intake, Excess alcohol consumption, Ionizing radiation also contributes a major factor. Hormone exposure increases the number of potential target cells by stimulating breast growth<sup>[9]</sup>. It also drives cycles of proliferation that can cause DNA damage. It's characteristics of a cancerous lesion include a hard, immovable, single dominant lesion with irregular borders. However, these features cannot reliably distinguish a benign from a malignant tumor<sup>[10]</sup>. Neoadjuvant chemotherapy is delivered before surgery with the goal of shrinking a tumor or stopping the spread of cancer to make surgery less invasive and more effective. Adjuvant chemotherapy is administered after surgery to kill any remaining cancer cells with the goal of reducing the chances of recurrence. The Article overviews the types of chemotherapy used in breast cancer and assessing their benefits and risks by giving insight into the procedures leading to better quality of life.

### Adjuvant Chemotherapy

Adjuvant therapy is treatment given in addition to your breast surgery. It's used to kill any cancer cells that may be left in your breast or the rest of your body with the goal of

reducing the chances of recurrence [11]. Adjuvant chemotherapy has become an important component of breast cancer management in the last 30 years. Robust evidence for its use has been generated in successive reviews of individual patient data by the Early Breast Cancer Trialists Cooperative Group [12]. Chemotherapy after surgery may be omitted in some group of patients with Low grade tumors with strong estrogen and progesterone receptor positivity, without lympho-vascular space invasion which are  $\leq 2$ cm and node negative in post-menopausal women [13].

### Optimal Adjuvant chemotherapy

Anthracycline based chemotherapy is the backbone of adjuvant chemotherapy [14]. In node negative early breast cancer patients 6 cycles of anthracycline based chemotherapy should be used. In those with positive lymph nodes or locally advanced breast cancer, anthracycline and taxane based chemotherapy given sequentially is preferred [15]. If taxane based chemotherapy is not feasible or contraindicated, 6 cycles of anthracycline based chemotherapy is an acceptable alternative.

CMF chemotherapy may be considered as an acceptable alternative when anthracycline based chemotherapy is not possible due to feasibility issues or contraindications. Ovarian ablation (surgical or radiation) may be considered in certain patients, in hormone receptor positive patients.

### Adjuvant Hormonal Therapy

Adjuvant hormonal therapy significantly improves survival in both pre and post- menopausal women expressing hormone receptors. It should be given to all patients expressing any degree of estrogen and or progesterone receptor positivity. The optimal duration of hormone therapy is 5 years.

Pre-menopausal women should receive tamoxifen for 5 years and in addition of ovarian suppression to tamoxifen till now not proven to be of additional benefit [16]. In Post-menopausal women aromatase inhibitors is preferred either for 5 years or as switch therapy with 2-3 years of Tamoxifen [17]. Tamoxifen for 5 years in post-menopausal women is an acceptable alternative to aromatase inhibitors [18].

### Adjuvant Targeted Therapy

Adjuvant targeted therapy is currently recommended with trastuzumab in patients with HER2 positive disease either after completion of chemotherapy or starting with the taxane component of the chemotherapy regimen. This is based on the proven benefits of adjuvant trastuzumab in disease-free and overall survival. American Society of Clinical Oncology and the College of American Pathologists (ASCO/CAP) guidelines suggest the criteria of  $>30\%$  intense and complete staining (IHC) or FISH amplification  $>2.2$  for HER2 positivity [19].

The present standard is to give trastuzumab for 1 year and there is also some evidence for the benefit of shorter duration (9-12 weeks) of adjuvant trastuzumab therapy and this is an acceptable alternative in view of its wider financial feasibility [20]. When not feasible, the use of chemotherapy (preferable anthracycline based) without trastuzumab is an acceptable alternative in patients with HER 2 over expressing tumours [21]. Patients should be routinely screened for cardiac contraindications to trastuzumab before

starting this therapy and the cardiac function should be routinely monitored every 3-4months using echocardiography or MUGA scan during this treatment

### Neoadjuvant Chemotherapy

Neoadjuvant chemotherapy is given with the primary aim of making inoperable tumors operable in locally advanced breast cancer. LABC patients have higher rate of relapse and poor survival. Neoadjuvant chemotherapy (NACT) is one of the standard therapy options for the management of LABC. The optimal number of chemotherapy cycles is usually 3 to 6 cycles of neoadjuvant chemotherapy [22].

Anthracycline and taxane based chemotherapy is preferred [23]. Sandwich therapy (chemotherapy followed by surgery followed by more chemotherapy) is widely practiced and is appropriate. Anthracycline based chemotherapy alone may also be used when taxane based chemotherapy not possible or contraindicated. In HER2 positive patients' trastuzumab may be added to chemotherapy in the neoadjuvant setting, if feasible [24]. Despite randomized evidence indicating its cardiac safety in the neoadjuvant setting, concomitant use of anthracyclines and trastuzumab is not widely practiced. Taxanes (paclitaxel or docetaxel) are the preferred concomitant partner for trastuzumab. Neoadjuvant hormone therapy may be considered in post-menopausal women with strong hormone receptor positivity [25]. Aromatase inhibitors are preferred over tamoxifen in this setting [26]. The optimal duration of treatment is not well defined but may vary from 4-8 months or until after best response [27].

### Standard Treatment Protocol

#### Mastectomy with Axillary clearance in breast cancer

Modified radical mastectomy (MRM) with axillary clearance is an appropriate surgical option for all stages of operable breast cancer and those who become operable after neo-adjuvant treatment. A modified radical mastectomy involves removal of the entire involved breast using an elliptical skin incision, including the skin overlying the tumor and the nipple-areola complex with the underlying pectoralis fascia, sparing both the pectoralis muscles, along with the removal of at least levels I and II axillary lymph nodes. Level III axillary lymph nodes should always be excised in large tumors, node positive axilla and locally advanced breast cancers post neo-adjuvant chemotherapy.

#### Use of breast conservation therapy (BCT)

Breast conserving surgery should be considered for all eligible patients in developing countries. There is overwhelming evidence for the equivalent safety and efficacy of BCT compared to mastectomy in appropriately selected patients [28]. Tumors in developing parts of the world are most often not screen detected, larger, and there is variable availability of expertise for undertaking breast conservation [29]. Such patients should be referred from secondary to tertiary centers with available expertise and infrastructure for breast conservation. Communication of the axillary dissection with the breast cavity should be avoided as far as possible. Separate incisions prevent transfer of seroma fluid between the lumpectomy and axillary areas and improve the cosmetic outcome.

#### Defining adequacy of margins in primary breast surgery

Margins after BCT should be technically free. Guidelines have variously defined an adequate margin in breast

conservation from 1mm to 10 mm or more<sup>[30]</sup>. Interestingly, the rate of finding IDC in the revised specimens has been in the range of only 30-40%.<sup>[31]</sup>. Although there are conflicting reports, it is evident that obtaining a clean negative margin is desirable.

### **Surgery after neoadjuvant chemotherapy (NACT)**

The standard surgery for patients with LABC is MRM after NACT<sup>[32]</sup>. In selected patients, BCT can be considered. The initial location and extent of tumor should be marked using techniques like biopsy scar, clips, tattoos etc. in patients being planned for NACT. This facilitates ease of subsequent surgery and has a bearing on local control. It should be noted that breast conservation is a valid option in selected cases of large or locally advanced breast cancer who achieve excellent response after NACT. Expert judgment should be applied during the use of this procedure in patients with large and locally advanced breast cancer.

### **Full axillary dissection as a routine standard of care**

A full axillary clearance that includes level III lymph nodes should be undertaken as a standard procedure in breast cancer surgery. There is relative abundance of large, non-screen detected cancers and locally advanced breast cancers in these regions with high possibility of axillary nodal involvement<sup>[33]</sup>. However, it needs to be noted that extensive axillary procedures could lead to increased incidence of adverse effects like shoulder stiffness and arm edema<sup>[34]</sup>.

### **Sentinel lymph node procedure and other axillary sampling in breast cancer patients**

Sentinel lymph node biopsy (SLNB) could be considered in carefully selected patients with early breast cancer in clinically negative axilla in centers that have this expertise. SLNB is not routinely recommended in lieu of formal axillary dissection view of higher degree of nodal positivity in this country. However, centers who have standardized this procedure in their institutions with documented results and less than 5-10% false negative rates, may consider this option in highly selected patients with early breast cancer. Anatomically defined sampling of lower level axillary lymph node should also be considered an alternative form of reduced axillary surgery in centers with this expertise and with the same caveats as for SLNB<sup>[35]</sup>.

### **Depot hydroxyl-progesterone prior to surgery for primary breast cancer**

The adoption of pre-operative injection depot hydroxyl-progesterone as a standard of care in patients with operable breast cancer is not recommended. There is a recent large Randomised trial and other reports suggesting a benefit in node positive tumours but replication of these findings in other studies is needed for routine care recommendation<sup>[36]</sup>

### **Conclusion**

Betterment of every patient's quality of life after a disease break is as essential and necessary as being alive. Breast cancer is the most common invasive cancer in women and the second leading cause of cancer death. The current review article delivers the overview of the benefits in adjuvant and neoadjuvant chemotherapy which are advisable after surgery and before surgery respectively. As

we can see that both the chemotherapies go hand in hand, deeply reducing the risks of reoccurrence and complications thus makes the cancer survivors stronger by improving their quality of life.

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NIL

### **Conflict of Interest**

The authors declare no conflict of Interest

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