Archives of Surgical Research | Review Article

Early Breast Cancer Management following ESMO Guidelines: An Overview

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IMPORTANCE Breast cancer is the most prevalent cancer among women and rarely in the male population. With the advent of breast screening programs across the globe, early cancer detection is being done and the patients are increasingly being managed through breast conservation. National Comprehensive Cancer Network (NCCN) and the European Society for Medical Oncology (ESMO) have provided guidelines to follow to effectively diagnose and amicably manage the cases of early breast cancer with the aim of reduction in mortality rate and enhancing disease-free survival outcomes. This review provides an overview of the management of early breast cancer in light of ESMO Guidelines and the local perspective.

KEYWORDS Early breast cancer, ESMO guidelines, mammography, mastectomy, breast conservative therapy, radiotherapy

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Review Article

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The data shown by WHO breast cancer is the most prevalent type of cancers among women, with the incidence of 25% of all female cancers in the world. According to International Agency for Research on Cancer, 2016, breast cancer is the fifth leading cause of death from cancer[1]. Incidence of breast cancer in women of early age (less than 40 years) is rather very uncommon in developed countries, it is gathered that 1 in 68 women can have breast cancer before the age of 40 years and 1 in 220 women will have breast cancer before the age of 30[2,3]. The incidence of early breast cancer in women less than age 50 years has been increased 0.2% per year since the mid-1990s[3], for women less than 40 years age there is very limited data that shows this trend[4,5]. In an analysis based on a surveillance, patients with less than 30 years age or between 30-39 years face more aggressive breast cancer and have less breast cancer specific survival than patients from age group of 40-59 years[6]. In 2018, there was around 2.1 million newly diagnosed breast cancer cases of females worldwide, approximating for one in four cancer cases among women[7].

Risk factors of early breast cancer are: positive family history causing genetic predisposition, hormone replacement therapy, and exposure to estrogens, higher breast density, low parity, ionizing radiation and history of atypical hyperplasia. Consumption of alcohol, obesity and western style food can also be the influencing factors to increased incidence of breast cancer[7].

Due to improved treatment standards and early detection of the breast cancer the mortality rate has decreased significantly especially in younger age groups, in most Western countries[8,9]. On the contrary, the prevalence of early breast cancer is rising due to improvements in treatment results and raised incidence. However, breast cancer remains one of the leading causes of cancer related deaths in women beside lung cancer, which has high mortality in women, in some countries.

Breast cancer in males is very rare, around 1% incidence rate. The important risk factors of it in males include positive family history, radiation exposure, hormonal imbalance disorders especially gynecomastia and cirrhosis and genetic predisposition[10].

METHODS

This systemic review is written according to PRISMA guidelines on early breast cancer management.

Search Strategy and Data Extraction:

All the literature was reviewed narratively for analysis. PubMed, ERIC, and Google Scholar from 1996-2021 were used as search engines for comprehensive study. Search terms were "early breast cancer" AND "ESMO guidelines for breast cancer" OR "Asian adaptations for ESMO guidelines" AND "breast cancer management". Review of all search papers were conducted according to the selected search strategy. In addition, the reference search papers were also included for comprehensive literature review.

Selection Criteria and Quality Assessment:

450 articles were identified and their Abstracts were reviewed using the computer literature search of PubMed and Google scholars. 25 articles were excluded for duplication, remaining 425 articles were viewed and 58 articles related to the topic were included in this literature review. 9 full-text articles were assessed for eligibility and 37 articles were excluded on the basis of exclusion criteria. All papers from 2005 to 2021 were included. Exclusion criteria included duplicate articles, poster presentations, articles not related to the topic, articles on advanced breast cancer management, guidelines other than ESMO.

Data Extraction and Detailed Analysis:

Detailed analysis of each paper was done. Information about, name of the author, year of publication, country of origin, methods of study and themes are described in Table 1.

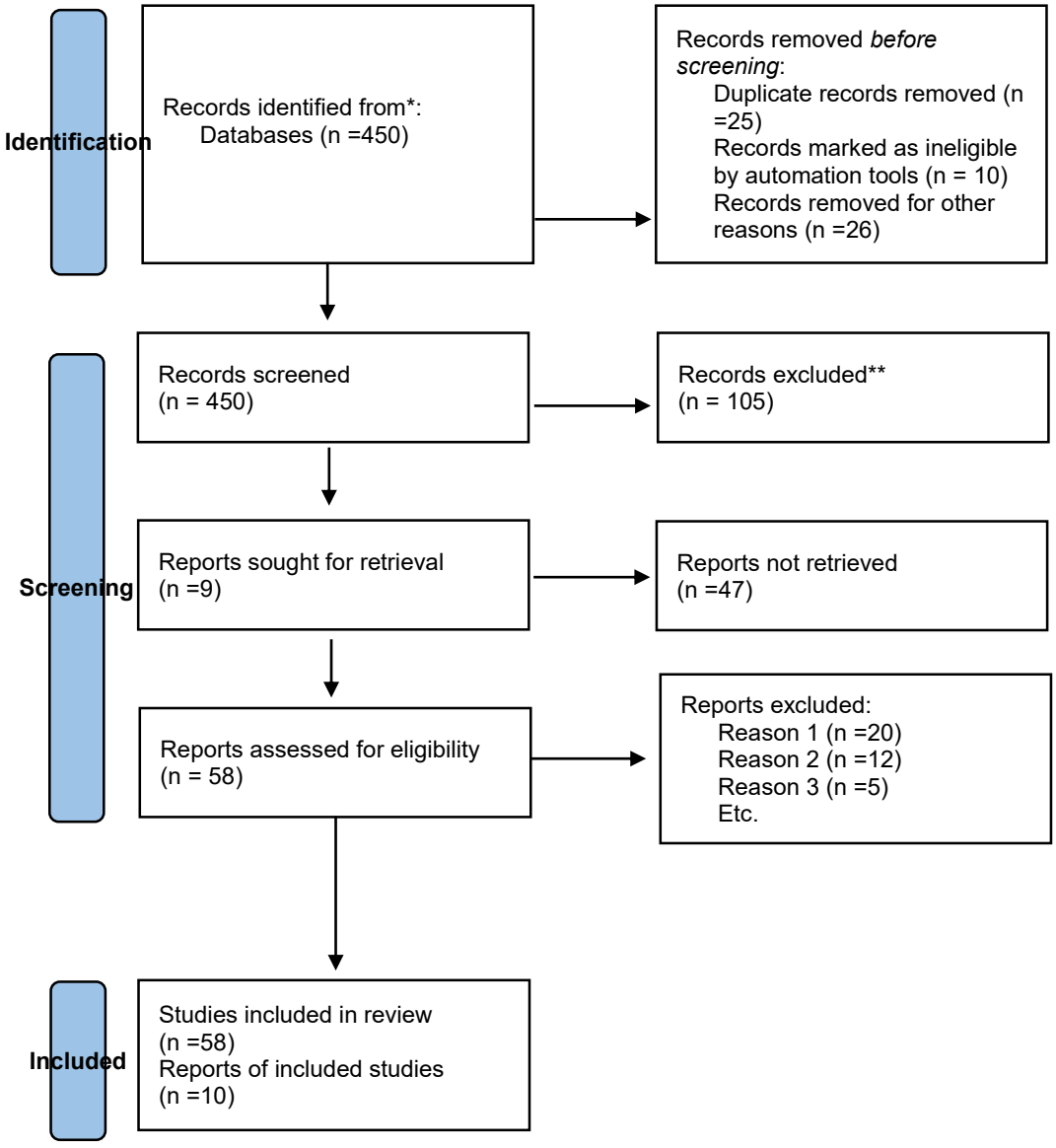

Figure 1: PRISMA Flowchart- Article selection process through computer literature search and analysis:

Year	Author	Country	Research method	Theme identified
2005	A. Goldhirsch et al.	Switzerland	Meeting highlights of primary therapy for breast cancer	Primary Therapy of Early Breast Cancer and their implications for patient care
2008	Sohee Park et al.	Korea	Systemic literature review	Breast cancer aetiology in Asia
2012	W. van de Water	Netherland	Data was obtained Netherlands Cancer Registry database between 2005 and 2008, for women with breast cancer.	Patients' adherence to breast cancer treatment
2012	Susan. harris et al.	Canada	Literature review via different data base search	Breast cancer rehabilitation need.
2011	Balman˜ a et al.	Spain	Literature review	BRACA mutation and screening in patient with breast cancer
2015	Senkus et al	Poland	Guidelines were developed in accordance with the ESMO standard operating procedures.	Early breast cancer staging and different ways for treatment.
2019	Cardoso et al.	Portugal	Literature reviews ESMO-MCBS was used to calculate scores for new indications approved by the EMA since 1 January 2016	Screening and treatment recommendations for early breast cancer
2020	Rudy Leon De Wild e et. Al	India	Literature review comparing different guidelines for invasive breast cancer	Restricted comparison of latest guidelines for different breast cancer guidelines
2020	Y.H Park	Korea	Operating guidelines for Asian women with early breast cancer	Pan Asian adaptations for early breast cancer management, ESMO-KSMO initiative
2021	Morgan et al.	United Kingdom	prospective, longitudinal, multicentre observational cohort study	Impact of omission of breast cancer surgery in older women with oestrogen receptor-positive early breast cancer on quality-of-life outcomes

Table 1: Various early breast cancer guidelines documents and their overview.

SCREENING OF BREAST CANCER ACCORDING TO ESMO GUIDELINES

For the detection of breast cancers at pre-clinical stage, population-based mammography screening needs to be introduced on national and regional level[10]. The ESMO guidelines recommend indicators and parameters that should be monitored during any screening process to ensure its quality and to reach an accurate diagnosis [11]. ECIBC (European Commission Initiative on Breast Cancer) has strongly recommended mammography screening for women aging from 50-69 years and conditional recommendations for women under this age group[11]. Effectiveness of mammography in women of 40-49 years of age is shown limited especially in age group 40-44 years but the greatest mortality reduction has been seen in the women of 50-69 years old age group[12]. IARC (International Agency for Research on Cancer) also concluded that in its breast cancer screening report in 2015[13]. There is no consensus about the effectivity of mammography on the reduction of mortality in breast cancer cases. Breast cancer mortality reduction of 20% was viewed in women of 50-70 years age group in a UK review of mammography screening trials[14]. Generalized awareness among population and mammography screening together with improved treatment contribute in overall reduction of the breast cancer. There is also controversy regarding the use of ultrasound (US) for breast cancer as a supplementary screening method.

For women with positive family history of breast cancer, with or without BRCA mutations, the recommendation is to get annual mammography with magnetic resonance imaging (MRI) as opposed to only mammography, to detect the disease at a more favorable stage. However, there is no proof showing the mortality reduction[15]. There is controversy on the use of US.

Recommendations:

• For the age group 50-69 years, annual or every 2 years mammography is recommended, it can also be done for women of age groups 40-49 and 70-74 but the evidence for benefit is less well established

• Annual MRI and annual mammography are recommendations for women with strong familial history of breast cancer, with or without BRCA mutations.

DIAGNOSIS AND PATHOLOGY

The diagnosis of breast cancer is based on history, clinical examination, imaging and further confirmed by pathological assessment after taking the biopsy. Clinical examination consists of bimanual palpation of breasts and regional lymph nodes and assessment of the distant metastasis for instance in bones, liver and lungs. A neurological examination is only done when the symptoms are present.

Imaging techniques include mammography, ultrasound and MRI. Mammography and ultrasound are always done bilaterally and regional lymph nodes are always assessed along them[16]. An MRI is not a routinely done modality but is considered only in certain circumstances which are following:

- Positive family history with positive BRCA mutations
- Lobular carcinomas
- Dense breast tissue
- Suspicion of multicentricity
- Large discrepancies between imaging and clinical examination
- Before administering neoadjuvant systemic therapy
- Inconclusive findings of conventional imaging
- In cases of breast implants

It is important to inquire the complete medical history, personal history, family history regarding any kind of carcinomas including breast or ovarian, menopausal status (if unconfirmed then measure serum estradiol and FSH levels) and complete physical examination.

After imaging, pretreatment disease evaluation consists of pathological screening of the primary tumor and histology of the lymph nodes if suspicion of their involvement is present.

Core needle biopsy should be done either by ultrasound or stereotactic guidance for the pathological diagnosis, it should be done before starting any kind of treatment. It is recommended that at least 2-3 core biopsies are collected, in case of multicentric tumors all lesions should be sampled. A marker in the form of surgical clip or carbon must be left into the tumour site at the time of biopsy, to make sure the resection of the correct site and to enable pathological assessment of the surgical specimen. The pathological report should include the histological type of the tumor, its grade, estrogen receptor (ER) status, and for invasive cancer immunohistochemistry (IHC) evaluation of PgR and HER2 expression.

In high-risk groups, genetic counselling and testing for BRCA1 and BRCA2 should be done, high risk groups would be;

- Patients with positive family history of ovarian, pancreatic and/or metastatic prostate cancer
- Breast cancer got diagnosed before 50 years of age
- Triple negative breast cancer (TNBC) diagnosed before the age of 60
- Personal history of ovarian cancer
- Male gender[17,18]

Recommendations:

- Bilateral mammogram and US of breasts and axillae should be done in all cases. MRI is recommended in certain cases following the standard imaging.
- Pathological diagnosis is based on the histology of the primary tumor and cytology of the axillary lymph nodes, if their involvement is suspected
- Histological type of the tumor, its grade, IHC evaluation of ER, PgR, HER2 and some form of proliferation markers e.g. Ki67 for invasive cancer should be present in pathological report
- TIL (Tumour-infiltrating lymphocyte) scoring is important and can be used to add information in patient's prognosis but the treatment should not be affected by it
- Genetic counselling and BRCA1 and BRCA2 germline mutations testing should be offered to high-risk group of patients

STAGING OF THE BREAST CANCER:

Breast cancer should be staged according to the eighth edition of the American Joint Committee on Cancer (AJCC) TNM (tumour, node, metastasis) staging system[19]. Asymptomatic distant metastasis is rare in case of breast cancer so most patients do not benefit from very extensive laboratory tests including tumor markers[20] and radiological staging. Recommended minimum blood work before surgery and systemic neoadjuvant therapy is complete blood count (CBC), liver function test (LFT), renal function test (RFT), alkaline phosphatase (ALP) and calcium (Ca2) levels. US, CT or MRI scan of abdomen, CT scan of chest and a bone scan are recommended for the patients of:

- Clinically suspected axillary lymph node involvement
- More than 5cm tumors
- Clinical suspicion of metastases
- Aggressive biology

In case of early breast cancer, the most important prognostic factors are expression of HER2, proliferation markers e.g. Ki67 and ER/PgR, the number of positive lymph nodes, histology of the tumor, its grade, size and presence of vascular invasion.

Clinical parameters like age, stage of the tumor, expression of HER2, PgR, and ER and histological grade have also been integrated into scoring systems for the sake of relatively accurate probability of recurrence and mortality from breast cancer. Examples of these scoring systems are NPI (Nottingham Prognostic Index), the PREDICT score and the computer program Adjuvant, which is currently unavailable[21–23].

The only validated predictive factors are ER/PgR and HER2 qualifying patients for endocrine therapy (ET) and ani HER2 therapy, respectively. Higher ER expression is usually associated with decreased absolute benefit of chemotherapy (ChT).

Recommendations:

• Staging of the breast cancer should be according to TNM staging system of AJCC.
• Extensive laboratory testing which includes tumour markers and radiological staging is not a necessity for all patients.
• Minimum blood tests including CBC, LFTs, RFTs, ALP and Ca2 levels are recommended before surgery.
• CT of chest, abdomen and bone scan is recommended only for higher-risk group patients (high tumour burden, aggressive biology, signs, symptoms or laboratory values suggesting the presence of metastases)
• Fluorodeoxyglucose (FDG) positron emission tomography (PET)-CT scanning may be useful when conventional methods are inconclusive
• Pathological assessment of the post-operative surgical specimens is recommended to be made according to the TNM system
• Gene expression profiles may be used to complement pathological assessment and may help in decision making of adjuvant chemotherapy

TREATMENT:

1. General Rules:

Specialized units/care centers: Specialized institutions or departments that treat breast cancer patients in high volume approx. 150 new patients every year result in improved outcomes. These centers should be certified by accredited body. European Parliament and European Commission recommend the treatment of breast cancer patients in specialized units [24].

Recommendations:

• Breast cancer treatment should be in specialized centers where multidisciplinary teams should be present consisting of medical oncologists, radiation oncologists, breast surgeons, breast radiologists, breast pathologists and breast nurses and staff [24,25]
• Breast center should be able to refer patients to plastic surgeons, psychologists, physiotherapists and geneticists, upon requirement
• Breast nurse should be available to act as patient's navigator in specialized centers [24,25]

Patient's counselling and full disclosure: Upon hearing the diagnosis of breast cancer, patient finds herself/himself in gush of feelings which needs to be processed and rationally needs a plan to further move with the treatment. It generates different kinds of reaction in patients and this needs to be tailored according to each person's reaction. Patients need space to process the information about their diagnosis, so they can cope psychologically with the treatment plan.

Recommendations:

• Information on diagnosis and treatment should be provided repeatedly both verbally and in writing in easy and comprehensive language
• Reliable websites and sources of information are recommended
• All management decisions should actively involve the patient

Early breast cancer treatment is very complex and involve multiple modalities including surgery, radiotherapy, systemic anticancer therapies e.g. ChT, ET etc. Special attention should be paid to the very young or elderly patients. Younger patients should not be overtreated and older patients should not be undertreated. In younger demographic, possible fertility issues should be discussed and fertility-preservation techniques guidance should be provided [26–30].

Recommendations:

• Choice of treatment should be based on the size and location of primary tumour, number of lesions, extent of lymph node involvement and as well as the menopausal status, age, health status and treatment preference of the patient
• Age with other factors should be considered but should not be the sole determinant for withholding or recommending a treatment
• Premenopausal younger patients fertility-preservation techniques should be discussed before starting any systemic treatment

2. Local Treatment:

Surgery: Surgeons and patients both are more invested in breast conservation techniques for surgical point of view for more than 30years. Presently, in western Europe, 60-80% of cases of new breast cancers are amenable to breast conservation. For the subtypes which are highly sensitive to chemotherapy such as triple-negative and HER2 positive, a neoadjuvant approach should be preferred.
Mastectomy is still carried out in some patients due to:

• tumor size as compared to breast size
• multicentricity of tumor
• failed to get negative surgical margins even after multiple resections
• prior radiation exposure to the chest wall or breast
• oncoplastic breast conservation is not suitable
• patient's choice[31]

Breast Conserving Surgery (BCS): For breast cancer, BCS is considered the primary surgical choice. Achieving acceptable cosmesis is now emphasized and breast surgeons are trained to decrease the local impact of tumor excision on cosmetics by using tissue displacement techniques. Contrary to BCS techniques, there are rising number of breast cancer patients who are opting for bilateral mastectomy[32]. There is data showing that patients with early breast cancer who opt for BCS have better survival as compared to the ones having mastectomy [33–36].
According to the recommendations of the CAP (College of American Pathologists), status of the margin of the lesion should always be reported. In case of positive margin, the exact anatomic location of the positive margin should be specified. In case of negative margins, the distance of invasive cancer should be reported [37–39].
Tumor bed is marked with clips as a standard procedure to facilitate the accurate radiation boost, if indicated.
Recommendations:
• BCS maintain better cosmetic outcomes hence it's the preferred treatment modality in early breast cancer patients.
• It is essential to carefully assess the margins of the resection site. At the ink margin, no tumor is required and for in situ carcinoma more than 2mm resection is preferred

Mastectomy: There are three major types of mastectomy; simple mastectomy, skin sparing mastectomy (SSM) and nipple sparing mastectomy (NSM). NSM improves cosmetic outcomes for therapeutic and prophylactic surgeries also from an oncologist point of view it is considered to be safe in some patients[40,41]. In most women, the prospect of losing a breast is relatively easy when they get to know the option of immediate recnstruction[25]. Inflammatory breast cancer is the only reason to advice against the immediate reconstruction. After post-operative radiotherapy (RT), implant-based reconstruction may result in unfavorable aesthetic[42,43]. Temporary expander before RT may help post mastectomy radiotherapy (PMRT). There are multiple surgical options for breast reconstruction, among the autologous tissue flap repair, silicone gel implants are being used which are considered to be safe and have fewer problems regarding capsular rupture. Patient should be counselled regarding the risk of anaplastic large cell lymphoma in case of breast implant based reconstruction surgery. For the autologous repair, flaps can be taken from latissimus dorsi, transverse rectus abdominis or deep inferior epigastric perforator among others.
Recommendations:
• All females going through mastectomy should be informed and offered breast reconstruction.
• Except for the patients going through inflammatory carcinoma, immediate breast reconstruction should be proposed to all.
• For the optimal reconstruction, patient related factors and preferences should be taken into account

Axillary Management: In primary breast cancer, one of the strongest predictors for long term prognosis is axillary lymph node status. Axillary lymph node dissection (ALND) results in lymphedema[44,45]. Axillary clearance along wit RT to axilla increases lymphedema upto 40%. Whereas sentinel lymph node biopsy (SLNB) causes less shoulder stiffness which in turns allow less hospital stay.

Recommendations:
• In early and clinically node negative breast cancer, SLNB is considered the standard for axillary staging on the contrary to full lymph node clearance
• In case of positive SLNB, micro metastases or 1-2 positive sentinel lymph nodes, is to be treated with post-operative axillary RT instead of further axillary resection
• Irrespective the kind of breast surgery performed, radiation therapy to the axilla is recommended treatment with positive SLNB

Surgery for Intra-Epithelial Neoplasia: Intra-epithelial neoplasia or ductal carcinoma in situ (DCIS) is treated either by total mastectomy or BCS, main aim is to get clear resection margins. 2mm margin is considered adequate in case of DCIS with WBRT (whole breast radiotherapy) as the line of treatment [38], as it is associated with decreased recurrence and cosmetically improved results. SLNB is not required in case of DCIS as risk of a positive sentinel lymph node with pure DCIS is 7%–9% and most of the metastases found are micro metastases [46,47]. SLNB is only recommended in cases where risk of invasion is present.
Lobular carcinoma in situ (LCIS) unlike DCIS considered as a risk for future development of invasive cancer in both breasts and no active treatment is required.

Recommendations:
• Recommended treatment of DCIS is BCS followed by WBRT or total mastectomy
• a 2-mm margin is adequate in DCIS with WBRT after BCS
• SLNB is not a routine recommendation for DCIS apart from patients requiring mastectomy for large tumors

Management of occult breast cancer: Occult breast cancer is a tumor in absence of any primary tumor in the breast but present as a lymph node metastases. It consists of less than 0.5% of all breast cancer cases[48]. In order to exclude another primary tumour site PET-CT and MRI breast is done. Its treatment is by axillary lymph node dissection (ALND) however in case of low axillary disease burden axillary RT can be an option.

Recommendations:
• ALND and WBRT are recommended treatment options for occult breast cancer

Risk Reducing Mastectomy: BRCA1 mutation carriers have 65-90% risk of developing breast cancer with 10-year

risk of contralateral development of breast cancer is 25-31% [49].

Recommendations:
• Bilateral prophylactic mastectomy and reconstruction surgery is considered a risk reducing surgery in BRCA1and BRCA2 carriers
• Patients opting for bilateral mastectomy who fall in non-high risk group should be counselled for breast conservation as BCS has high survival outcomes

Radiotherapy:

Recommendations:
• After BCS post-operative radiotherapy is strongly recommended[50]
• In high risk of recurrence patients, boost RT is recommended to reduce the risk of relapse [51,52]
• For patients with a low risk for local recurrence, accelerated partial-breast irradiation (APBI) is recommended treatment option
• For patients having positive resection margins, involved axillary lymph nodes and T3–T4 tumours, post mastectomy radiotherapy (PMRT) is recommended[53]
• In patients with positive lymph nodes, comprehensive nodal radiotherapy is recommended line of treatment[54]
• Axillary RT is not recommended after ALND on the operation site of axilla[53]
• For routine postoperative RT for breast cancer 15–16 fractions of 3 Gy/fraction are recommended [55–57]
• DCIS diagnosed females who are treated with BCS, WBRT is recommended for them [58–60]
• Radiation therapy can be omitted in patients with low risk of DCIS, PMRT is not recommended in DCIS

3. Systemic (neo) adjuvant therapy:

General recommendations: Neoadjuvant therapy should be administered within 12 weeks post-operatively to obtain maximum benefit.

Recommendations:
• Adjuvant systemic therapy should preferably start within 3 to 6 weeks after surgery and neoadjuvant systemic therapy should begin after diagnosis and staging is completed within 2-4 weeks
• The use of chemotherapy (ChT) in luminal B-like HER2-negative patients depends on the individual risk of recurrence, the presumed response to endocrine therapy (ET) and the patient's preference.
• B-like HER2-positive light tumors should be treated with ChT, ET and anti-HER2. In some low-risk patients (T1abN0), the combination of anti-HER2 therapy and ET alone may be used, with the possible exception of selected very low risk cases, such as T1aN0 tumors
• If ChT and RT are to be used, ChT should generally precede RT. RT can be delivered safely during anti-HER2, ET and ChT treatment without anthracycline, taxane.
• Anti-HER2 treatment can be systematically combined with non-anthracycline-based ChT, ET and RT
• Patients with TNBC should receive ChT.
• ChT should not be used at the same time as ET, with the exception of gonadotropin releasing analogues (GnRH) used for ovarian protection [61]
• Tamoxifen for 5-10 years is standard of care for premenopausal women and if they become postmenopausal within the first 5 years of tamoxifen, a switch to letrozole should be considered, depending on the expected risk of late recurrence.
• Ovarian function suppression (OFS) during ChT offers some protection of ovarian function and does not negatively impact oncologic results and should be used with other methods of fertility preservation. OFS to ET should be strongly considered in patients requiring ChT who recover their periods within the first 2 years.

Chemotherapy:

• ChT is recommended in triple-negative, HER2-positive breast cancers and in high-risk HER2-negative luminal-like tumors and ER-negative tumors [62,63].
• ChT should be given in 4-8 cycles for 12-24 weeks. For low-risk patients, 4 cycles can be administered
• The sequential anthracycline / taxane regimen is the norm for the majority of patients.
• Four cycles of doxorubicin and cyclophosphamide (AC) are considered to have an effectiveness equal to 6 cycles of CMF. But should only be used if taxanes are contraindicated [64,65].
• For patients with cardiac complications, treatment regimens without anthracycline can be used.
• Non-anthracycline, taxane-based regimens (4 cycles of docetaxel and cyclophosphamide (TC)) may be used.
• read as an alternative to 4 cycles of anthracycline-based ChT but are less effective[66]
• 5 FU should not be included in anthracycline-based regimens as it increases the toxicity profile.
• Platinum compounds should not be used routinely in the adjuvant setting.
• The use of dose-dense regimens [supported by granulocyte colony stimulating factor (G-CSF)] should be considered, especially in highly proliferative tumors [67,68].

Anti-HER2 therapy:

• Trastuzumab combined with ChT is recommended in patients with positive HER2

Recommendations:
• The (neo) adjuvant trastuzumab is very effective and should be given to all patients with early HER2-positive breast cancer who have no contraindications to its use, with the possible exception of certain cases. at very low risk, such as T1aN0 tumors.
• One year of (neo) adjuvant trastuzumab remains the norm for the vast majority of HER2-positive patients. In low-risk patients who receive anthracycline / taxane-based ChT, the reduction in the duration of trastuzumab to 6 months can be discussed.

• Trastuzumab should generally not be given at the same time as anthracycline-based ChT; it can be safely combined with non-anthracycline-based ChTs (i.e. taxanes).
• Regular cardiac monitoring is mandatory before initiation and during treatment with trastuzumab.
• Double blocking with trastuzumab / lapatinib did not improve long-term results and therefore cannot be recommended.
• Double blocking with trastuzumab / pertuzumab may be considered in high-risk patients, defined as N-positive or ER-negative, for a period of 1 year, starting before or after surgery.
• If available, adjuvant trastuzumab should be replaced by adjuvant T-DM1 in the event of residual invasive disease after the end of neoadjuvant ChT associated with anti-HER2 therapy.
• Prolonged anti-HER2 treatment with neratinib may be considered in certain high-risk patients, with prophylaxis and management of diarrhea, not previously treated with double blocking.

Primary systemic therapy Or PST (neoadjuvant):

When mastectomy is necessary in locally advanced and large cancers, particularly due to the size of the tumor, PST is recommended to decrease the extent of surgery required. The timing of treatment (pre versus postoperative) has no effect on long-term results, apart from a possible small increase in locoregional recurrence in the PST group, but without impact on survival [69,70]

In selected patients with luminal tumors of type A and without indication of ChT, who are not candidates for optimal surgery, preoperative TE consisting of OFS plus an aromatase inhibitor may be considered[71]. ET is not routinely recommended in premenopausal patients.
• PST should be used to reduce the extent of surgery in locally advanced and operable cancers, especially when mastectomy is necessary due to the size of the tumor.
• In triple negative and BRCA positive patients, the platinum compound can be used.
• If PST is used, all ChT should be delivered preoperatively.
• In case of high-risk triple negative, 6 to 8 cycles of capecitabine postoperatively should be administered.
• In postmenopausal patients with ER-positive / HER2-negative cancer requiring preoperative PST TE (4-8 months or until maximal response) should be considered and continued postoperatively.

Bisphosphonates for early breast cancer:

• Prophylactic use of bisphosphonates in postmenopausal women or those undergoing SOF leads to prolonged breast cancer-specific survival [72–74].
• Bisphosphonates also decrease the risk of skeletal complications in treatment-related bone loss [75,76].

Treatment of male breast cancer:

Breast cancers in male patients are invasive ductal carcinomas of the luminal type. The indications and treatment regimens for ChT and anti-HER2 should follow the same recommendations as those for breast cancer in women.

Recommendations:

• The standard adjuvant ET for male breast cancer patients is tamoxifen. But if contraindicated, IA in combination with a luteinizing hormone releasing hormone (LHRH) agonist may be considered.
• AI alone should not be used as an adjuvant TE in men with breast cancer.

Adjuvant systemic therapy for DCIS:

In ER-positive DCIS, tamoxifen decreases the risk of non-invasive and invasive recurrence and reduce second primary (contralateral) breast cancer in conservatively treated patients. The same is true for patients who have undergone a mastectomy.

PERSONALIZED MEDICINE:

Most significant advancement in modern oncology is shift towards deep molecular analysis. The history of metastatic diseases is revolutionized by detection of gene mutations, amplification and fusions. The door to personalized medicine is opened due to focus on molecular alterations of tumor[77]. Providing best treatment is the most crucial task of personalized medicine. Use of endocrine therapy in luminal breast cancer coins it the pioneer of personalized medicine in oncology [77,78].

Systemic therapy through personalized approach requires identification of targets. Biomarkers including estrogen receptors, progesterone receptors and HER2 play a significant role as predictive factors in preparing patients for personalized treatment. Estrogen and progesterone receptors are used in selecting patients for endocrine treatment, while HER2 is used for antiHER2 therapy selection[78]. Ki67 maybe used in determination of prognosis due to its accessibility and effectiveness[79]. Breast cancer has four different molecular subtypes each one exhibiting distinct phenotypic presentations[80]. These phenotypic presentations are also used for definition of subpopulations and treatment individualization[78].

Tumor size, grade and nodal metastasis are not sufficient for treatment in early diagnosed cases. Hence, personalized medicine entails the use of molecular biomarkers [81]. Evaluation of uPA and PAI1 demonstrate tumor invasiveness and prognosis in both node negative and node positive cases [82]. Oncotype DX is a multigene signature test used to predict recurrence and benefit of adjuvant chemotherapy. MammaPrint test is also used to predict recurrence [81]. MammaPrint, Oncotype Dx, Prosigna, EndoPredict, and Breast Cancer Index are molecular signature tests for ER-positive breast cancer cases used in decision making of adjuvant chemotherapy especially in challenging cases including B-like/HER2-negative and node-negative/node 1-3 positive breast cancer [83].

FOLLOW-UP AND LONG-TERM IMPLICATIONS:

Follow-up of breast cancer patients is required to evaluate local recurrence, contralateral breast cancer and therapy related complications. Furthermore, it is required for patient motivation and psychological support. Node positive cases have higher annual recurrence than node negative cancers. In addition, estrogen negative cases have higher recurrence in first year than estrogen positive cases. However, its recurrence after 5-8 years becomes lesser than estrogen positive cases [84]. Risk of recurrence peaks in second year but in 5-20 years remains 2%-5%. In estrogen and progesterone receptor positive cases relapse can occur after 20 years [85].

Follow-up should constitute detailed history, physical examination, routine mammography, breast ultrasound and MRI in young patients with dense breast tissue or familial cases. There is no indication for laboratory tests, imaging tests or tumor marker evaluation in asymptomatic patients. However, in cases of endocrine therapy routine blood tests are indicated to rule out therapy related cardiovascular complications. Gynaecological examination in required in patients taking tamoxifen [86].

Lifestyle modification has a positive impact on prognosis. Regular exercise and nutritional counselling play a significant role in providing functional and psychological benefits [87]. Rehabilitation services play a vital role in decreasing negative impact of physical, psychological and social factors of breast cancer treatment. Physiotherapy should be directed towards prevention and treatment of lymphoedema and postural defect correction. Upon completion of chemotherapy, radiotherapy and antiHER2 therapy pregnancy maybe considered. There is no indication to avoid blood pressure monitoring or venesection following axillary clearance [78].

Psychological support is required following the end of adjuvant chemotherapy and radiotherapy due to increased incidence of depression and fatigue. In long-term survivorship social factors including work, family and sexuality are required to be addressed in follow-up.

Recommendations:

• Recommended follow-up visits include:
1. 3-4 months in first 2 years
2. 6-8 months from 3-5 years
3. Annual visit afterwards

• Annual imaging tests including bilateral and contralateral mammography, ultrasound and breast MRI.
• Laboratory tests, imaging tests and tumor markers are not indicated in asymptomatic patients.
• Lifestyle modification has a positive impact on prognosis
• Access to rehabilitation services
• Psychological support to address social factors associated with long term survivorship.

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