Review

Eur J Breast Health 2023; 19(3): 186-190
DOI: 10.4274/ejbh.galenos.2023.2023-6-2

Treatment Changes in Breast Cancer Management and De-Escalation of Breast Surgery

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ABSTRACT

A better understanding of tumor biology and new drugs have led to significant changes in the management of breast cancer (BC). Radical mastectomy, which had been the treatment for BC for more than a century, was based on the hypothesis that BC is a local-regional disease. In the 1970s, Fisher's studies showed that cancer cells could reach the systemic circulation without passage through the regional lymphatic system. Multidisciplinary treatment of BC, which was now considered a systemic disease, was started and radical mastectomy was replaced by breast-conserving surgery (BCS)+, axillary dissection (AD), systemic chemotherapy, hormonotherapy, and radiotherapy in early-stage BC. Modified radical mastectomy, chemotherapy, and radiotherapy were applied as a treatment for locally advanced BC. However, later clinical studies demonstrated that the breast can be preserved in those who respond well to neo-adjuvant chemotherapy (NAC). In the early 1990s, sentinel lymph node biopsy (SLNB) in early-stage BC (cN0) was performed using blue dye and radioisotope markers. It was shown that AD may be avoided in SLN-negative patients, and SLNB has been a standard intervention in cN0 patients. In this way, the very serious complications of AD, especially lymphedema, were avoided. BC has been shown to be a heterogeneous disease and the tumor may be divided into four different molecular subtypes. Thus, optimal treatment differed from patient to patient (one size fits all was inappropriate), individualized treatments have emerged and over-treatment was avoided. The prolongation of life expectancy and the decrease in recurrence led to an increase in the rate of BCS, an acceptable cosmetic result with oncoplastic surgery, and a better quality of life. The increase in the rate of complete response to NAC with new and targeted agents and especially in human epidermal growth factor receptor-2+ and triple-negative patients with a poor prognosis has led to the use of NAC regardless of cN0. The complete disappearance of the tumor after NAC has been reported by some studies, suggesting that breast surgery may not be needed. However, other studies have shown that vacuum biopsies performed on the tumor bed have a high rate of false negativity. Therefore, it is difficult to suggest that there is no need for lumpectomy, which is cheaper and safer today. The false negativity rate of SLNB is high in patients with cN1 at the time of diagnosis and cN0 after NAC (approximately 13%). In order to reduce this rate to ≤5%, clinical studies have recommended the use of the dual method, marking the positive lymph node before chemotherapy and removing 3–4 nodules with SLN. In summary, a better understanding of tumor biology and new drugs have changed the management of BC and de-escalate the role of surgical treatment.

Keywords: Breast cancer management, surgery, chemotherapy, sentinel lymph node biopsy, molecular subtypes

Cite this article as: Ozmen T, Ozmen V. Treatment Changes in Breast Cancer Management and De-Escalation of Breast Surgery. Eur J Breast Health 2023; 19(3): 186-190

Key Points

- Breast cancer management
- Surgery
- Chemotherapy
- Sentinel lymph node biopsy
- Molecular subtypes

Today, modern breast cancer treatment uses a multimodal approach that combines surgery, radiotherapy, systemic therapy and immunotherapy. The aim is to apply these different treatments according to the demographic, clinical and pathological characteristics of the patients and the tumor and to obtain a good cosmetic outcome while maintaining oncological safety.

We can evaluate the changes in the biology and treatment of breast cancer under three different hypothesis headings. These are: I. Local-

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Received: 06.06.2023
Accepted: 08.06.2023
Available Online Date: 03.07.2023

Regional Disease Hypothesis, II. Systemic Disease Hypothesis, III. Intermediate Hypothesis. These three hypotheses will be reviewed in detail below.

I. Local Regional Disease Hypothesis (Halstedian Hypothesis)

The Halstedian paradigm, the first hypothesis of breast cancer (BC) biology, guided BC treatment for nearly a century (1). Halsted thought that cancer in the breast first invaded local tissues and lymph nodes and then spread to distant organs. He defined radical mastectomy (RM) as the removal of the skin of the breast, pectoral muscles, lymphatic ducts and ipsilateral lymph nodes. In the article containing 50 patients, he showed that he reduced the local recurrence rate to 6%, in contrast to his colleagues in the same period (1). Although RM provided a high rate of local control, there was no evidence that it provided better survival. In addition, this intervention had significant morbidities, such as arm edema, loss of arm function, loss of body image and psychological morbidities. Following his work on lymphatic anatomy, Gray reported in 1939 that the deep fascia on the pectoral major muscle lacked lymphatic ducts (2). As a result of the serious thoracic deformity and other complications of RM and Gray's research, Patey and Dyson (3) defined modified radical mastectomy (MRM) including preservation of the pectoralis major muscle. By comparing 118 patients with RM and MRM, they showed that MRM was as effective as RM in the treatment of BC and had less morbidity (3). They also showed that partial mastectomy and axillary dissection may be performed in small tumors, but the risk of local recurrence may be high, so axillary radiotherapy can be added to simple mastectomy, but radiotherapy may be more harmful than axillary dissection. After these studies, MRM became the first-choice surgical procedure (4).

II. Systemic Disease Hypothesis (Fisherian Hypothesis)

The lack of an increase in survival despite the adoption of a radical surgical intervention led scientists to conduct new research into the biology of BC. Bernard Fisher revealed that BC may be a systemic disease at the beginning of his experimental and clinical studies (5). He reported that cancer cells entering the bloodstream during the formation of the tumor migrated to distant organs and metastasized systemically. According to Fisher, hematogenous spread in particular did not necessarily involve lymph nodes. Thus regional lymph nodes may not have been the first monitors of distant metastases but were a potential focus for dissemination of the disease depending on the tumor-patient relationship (6). Experimental studies have shown that tumor cells can pass trans-nodally into the systemic circulation. His results invalidated the notion that lymph nodes are passive filters, showing that cancer cells can go directly to the lymph ducts as well as pass directly into the bloodstream through lymphatic-venous collaterals. The systemic disease hypothesis showed that BC treatment should be multidisciplinary, and chemotherapy and radiotherapy should be added to surgical treatment and this concept has been widely accepted.

Long-term results of combined chemotherapy [cyclophosphamide, methotrexate, and 5-Fluorouracil (CMF)], which was published by Bonadonna (7, 8) in 1973 for the systemic treatment of BC, showed that CMF given once a month and for 12 cycles after RM increased survival and disease-free survival in lymph node positive patients.

Endocrine therapy (ET) for BC is one of the first applications of individualized treatment for cancer. At the end of the 19th century, Sir George Thomas Beatson first discovered the positive effect of bilateral oophorectomy on the development of BC lesions in women with advanced disease, and ET was born (9). Research into antihormonal agents has shown that only patients with the expression of hormone receptors benefit from treatment with the selective estrogen receptor modulator, tamoxifen (9). This knowledge has led to the development of third-generation aromatase inhibitors (AI) such as anastrozole, letrozole and exemestane, to reduce estrogen levels in hormone-receptor-positive post-menopausal BC patients (10). ET (ovarian suppression, tamoxifen and AI) has been shown in clinical studies to increase survival and reduce recurrences in hormone receptor positive pre-menopausal patients (10-13).

Long-term results from the NSABP B-04 study compared simple mastectomy and RM interventions in patients with clinically negative axillae and showed that they had similar overall survival results (14). In the Milan study and in the NSABP-06 studies, patients who underwent total mastectomy and patients who received partial mastectomy + axillary lymph node dissection (ALND) and radiotherapy did not show comparable survival rates (15, 16). Thus, in early-stage BC, breast-conserving surgery (BCS) and radiotherapy have become a standard surgical intervention.

The occurrence of serious complications, especially lymphedema, in patients with ALND suggested that axillary dissection may be avoided in cN0 patients. In 1992, Morton performed a radioisotope and in 1994 Giuliano performed the sentinel lymph node biopsy (SLNB) using blue dye (17, 18). In clinical studies, it has been shown that other lymph nodes are also negative in patients diagnosed with early-stage BC (cN0) and SLN negative and axillary dissection is not required in these patients (19).

III. Intermediate Hypothesis

The 20-year follow-up results of the NSABP-B04 study suggested that the disease was local-regional as 36.8% of the patients survived without any systemic treatment (14). However, the presence of distant metastases in 24.5% of the patients and the occurrence of a very significant proportion of these within the first five years showed that BC is prone to spread systemically in some patients. These results show that BC is a heterogeneous cancer, varying between individual patients, that is, it tends to remain local-regional in some patients and systemic in others and this is known as the Intermediate Hypothesis.

The fact that BC remains as a local-regional disease in some patients and that it has a systemic spread while on a smaller scale in some patients suggests that there is an intermediate hypothesis that includes both earlier hypotheses in BC. Indeed, BC is heterogeneous and individual, and not every patient should be given RM, as in the Halsted hypothesis, or multidisciplinary treatment (one size fits all) should not be applied to every patient, as in the Fisher hypothesis. In some patients, even large BC tumors localized in the breast for a long time do not always metastasize systemically, while in other patients it can metastasize even when the tumor is very small.

We know that the biological behavior of BC and the response to treatments vary. In 2000, Perou et al. (20) published molecular portraits of human breast tumors in a paper published in Nature. Using complementary DNA microsequences representing 8,102 human genes, variations in gene expression patterns in 65 breast tumor samples from 42 different individuals were characterized. They showed that tumors can be divided into molecular subtypes such as Luminal A, Luminal B, human epidermal growth factor receptor-2 (HER-2) (+), Basal and Normal Basal Like, which are distinguished by

common differences in gene expression patterns. Today, the molecular subtypes of BC are generally evaluated into four groups: Luminal A; Luminal B; HER-2 (+); and triple-negative. The main purpose here is to apply personalized treatment according to the molecular structure of the cancer and to avoid over-treatment and its complications and economic losses.

New therapeutic drugs have also resulted in significant changes in the surgical treatment of BC, as they prolong life expectancy by reducing recurrence. In particular, there have been significant increases in the rate of BCS and preventive surgery has been performed in appropriate multifocal and multicentric cancers (21, 22). A good cosmetic appearance may be achieved by filling the cavity formed after lumpectomy with the surrounding breast tissue (volume displacement) or muscle tissue (volume displacement). During surgical intervention, the other breast is also operated to provide a symmetrical appearance. In patients who are pathological gene carriers, reconstruction is added to the opposite breast by prophylactic mastectomy.

The increased complete response to chemotherapy with modern drugs added to neoadjuvant chemotherapy (NAC) makes NAC a standard approach in patients with operable early-stage BC. NAC is the first choice, especially in those with HER-2 positive and triple negative molecular subtypes with poor prognosis. The objectives are to destroy the tumor cells that cannot be demonstrated by systemic screening by early initiation of systemic therapy, to assess the response to chemotherapy in vivo, to increase the rate of BCS by shrinking the tumor and to avoid axillary dissection by providing a negative axilla that was positive before treatment.

In patients who are thought to have a clinical and pathological complete response in the breast after NAC, some studies have been conducted only according to the results of vacuum biopsy including surgical intervention to the breast and treatment with radiotherapy (23, 24). In the MD Anderson study, the tumorous area was excised in patients who underwent clinically complete response and vacuum biopsy and false negative results were obtained in 5% of the patients (23). In other studies, false negativity rates ranged from 19% to 49% (24). In an ongoing prospective clinical study, triple-negative and HER-2 positive patients with negative vacuum biopsy after NAC were also given axillary radiotherapy and local recurrence was not observed during the 26.4-month follow-up period (25). However, the number of patients in the study was 31 and the follow-up period was short which should be considered limitations of this study and when considering the reported results. However, today there is no conclusive evidence to dispense with surgical treatment in patients with a full clinical response to NAC, and it is necessary to wait for the long-term results of high quality prospective clinical trials to decide. Breast surgery today is an easier and more economical procedure and should continue.

ALND, as mentioned earlier, may have very serious complications, especially lymphedema. ALND is avoided even in patients with limited axilla positivity in sentinel lymph nodes (26, 27).

In the ACOSOG Z0011 study, among women with T1 or T2 invasive primary BC, no palpable axillary lymph node, and 1 or 2 sentinel lymph nodes containing metastases, 10-year overall survival for patients treated with sentinel lymph node dissection alone was non-inferior to overall survival for those treated with ALND (26). These findings do not support routine use of ALND in this patient population based on 10-year outcomes. The AMAROS trial evaluated ALND versus axillary radiotherapy (ART) in patients with cT1-2, node-negative BC and a positive sentinel node (SN) biopsy (27). Ten-year analysis of this study confirms a low axillary local-recurrence rate after both ART and ALND with no difference in overall survival, disease free survival, and loco-regional control. Considering less arm morbidity, ART is preferred over ALND for patients with SN-positive cT1–2 BC.

Modern NAC regimens provide pathologic complete response (pCR) in a significant proportion of patients with node-positive BC (27-31). Axillary pCR response rates vary according to the molecular subtype of the tumor and the stage of the disease, and are 50-70% in HER-2 positive patients, 40–47% in triple negative patients and 15–21% in estrogen positive patients. SLNB is considered an important intervention to determine axillary pCR after NAC and to avoid ALND. However, the rate of false negativity after SLNB is around 13%, which necessitated some research to reduce this rate (32). In these studies, dual method, removal of three or more SLNs, immunohistochemical method, clip of positive lymph nodes, magnetic seed, radio isotope labeling and radar localization techniques were used and the false negativity rate was reduced to around 5% (32-35). Targeted axillary dissection was first descibed by the MD Anderson Cancer Center. In this technique, an iodine–125 seed was placed in the clipped node under ultrasound guidance 1 to 5 days before surgery, mapping agents, including radioisotope (technetium–99m sulfur colloid) and/or blue dye, were injected before or at the time of surgery. During surgery, a gamma probe on the iodine-125 setting was used to identify the seed-containing node, and the technetium-99m setting was used to identify SLNs. All nodes containing blue dye, radioactivity, or which were palpable were removed and labeled as SLNs (36, 37).

Conclusion

BC is the most common cancer in the world and the most common cause of death in women, and with screening, early diagnosis and effective modern treatments, it is possible to live a healthy life while preserving body integrity. Research has resulted in a combination of the hypotheses of BC, as a local and regional or systemic disease, requiring different treatment for each patient, but individual treatment according to the clinical and pathological molecular characteristics of the individual tumors. New treatment agents reduce not only systemic spread but also local regional recurrence in BC. Thus, radical surgery in BC has been replaced by surgical interventions that protect the breast and axilla as far as possible.

Significant changes have been seen in the treatment of BC as a result of a better understanding of the biology of the disease, the treatment of which has been guided only by surgeons for a very long time. Multicenter studies and meta-analyses involving breast surgeons have played an important role in this change. However, with the current understanding of BC, we can say that even in cases where complete breast and axillary response is thought to be obtained after NAC, it is too early to give up BC surgery, which is easy to apply and cost-effective. To achieve this, more effective chemotherapetic agents and more sensitive radiological methods are needed.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: T.O., V.O.; Concept: T.O., V.O.; Design: T.O., V.O.; Data Collection and/ or Processing: T.O., V.O.; Analysis and/or Interpretation: T.O., V.O.; Literature Search: T.O., V.O.; Writing: T.O., V.O.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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