

SURGERY ROLE IN ADVANCED BREAST CANCER TREATMENT – UP TO DATE SHORT REVIEW

DAN BRATU¹, ALIN MIHEȚIU², CIPRIAN TĂNĂȘESCU³

^{1,2,3}County Clinical Emergency Hospital, Sibiu, “Lucian Blaga” University of Sibiu

Keywords: surgery, breast cancer, advanced stages

Abstract: Breast cancer is the world's second cancer as frequency occupying the first place among women. In Western Europe and in the US, due to addressability and national screening programs between 5 and 15% of cases addressed to physician in stage IV. At national level, the frequency of breast cancer at this stage is high. At this stage, surgery has a palliative purpose, but more and more studies have shown better survival rates for those who are surgically treated in association with systemic therapy.

INTRODUCTION

Romania ranks second to last in Europe in women who have no breast check in their lifetime, being among the last three in Europe that does not have a national screening program for breast cancer. Although the incidence of this disease in Romania is two times lower than the European average, mortality does not follow the same trend. The incidence of breast cancer in Romania is 12.27% with 9629 diagnosed cases annually and with a mortality of 7.22%. Unfortunately about 80% of all cases are diagnosed in advanced stages (III and IV), in Western Europe the proportion is inverse.^(1,2) Therefore, we can say it is a public health problem for our country.

The role of surgery at this stage is a questionable one, usually considering that this stage is reserved only for systemic treatment, surgery being indicated only for local complications. It brings more and more into discussion the relationship between surgery and prolonging survival rate in patients in this stage.

AIM

Establishing a relationship between stage IV breast cancer, surgical treatment and increasing life expectancy in patients who only benefit from systemic therapy.

MATERIALS AND METHODS

A review of the literature was conducted using the PubMed, Scopus, Scholar, Medline, OVID, and ASCO databases to study the most representative data published over the last 15 years regarding the relationship between advanced breast cancer and surgical treatment

RESULTS AND DISCUSSIONS

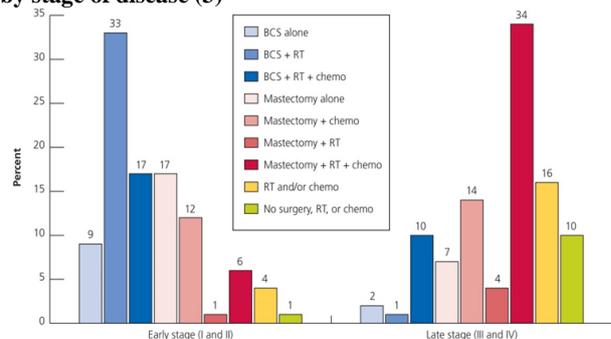
Advanced breast cancer includes stages III and IV. Stage III is locally advanced breast cancer, which means the cancer has spread to lymph nodes and/or other tissue in the breast, but not to further sites in the body. Stage IV is metastatic breast cancer. At this stage, the cancer has spread to other sites of the body, such as the bones, liver, lungs, brain and/or others. The TNM Classification of malignant tumours (TNM) is a globally recognised standard for classifying the extent of spread of cancer. It is a classification system of the anatomical extent of tumour cancers. Stage III in breast cancer is divided in III A, III B, III C.

Stage III A means T0, N2 (metastases in ipsilateral axillary lymph nodes), M0; T1 (tumour ≤ 20 mm in greatest dimension), N2, M0; T3 (tumour > 50 mm in greatest dimension), N1 (micrometastases; or metastases in 1-3 axillary lymph nodes and/or in internal mammary nodes; and/or in clinically negative internal mammary nodes with micrometastases or macrometastases by sentinel lymph node biopsy)/N2, M0. Stage III B means T4 (tumour of any size with direct extension to the chest wall and/or to the skin (ulceration or skin nodules), not including invasion of dermis alone) N1/N2, M0. Stage III C means any T, N3 (metastases in ipsilateral infraclavicular lymph nodes, with or without level I, II axillary node involvement, or in ipsilateral internal mammary lymph nodes), M0. Stage 4 – any T, any N, M1.

Usually, advanced stage breast cancer surgery, especially in stage 4, has a palliative target for local complications such as suppuration or haemorrhage. Recent reviews of databases suggest that approximately 40-60% of the patients with advanced stages are receiving surgical treatment of their primary tumour as a component of therapy, a rate that is higher than what would be for palliative purposes alone.

Increasingly, data suggest the role of surgery in advanced breast cancer, not in getting healing, but in increasing survival rates, breast conservative surgery (BCS) or mastectomy being use more frequently than in the past decades.

Figure no. 1. Female breast cancer treatment patterns (%) by stage of disease (3)



The existence of a favourable profile seems to be a key factor in survival prolongation. Thus, the young age (under

²Corresponding author: Alin Mihețiu, B-dul. Corneliu Coposu, Nr. 2-4, Sibiu, România, E-mail: alin_mihetiu@yahoo.com, Phone: +40751 619292
Article received on 11.01.2019 and accepted for publication on 29.03.2019
ACTA MEDICA TRANSILVANICA March 2019;24(1):56-59

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50 years) of the absence of metastasis or their presence on the bone and soft tissues are factors that in combination with the systemic treatment (chemotherapy, radiotherapy, immunotherapy or hormone therapy) alongside with surgery improves life expectancy.(3,4)

Figures no. 1,2,3,4. Advanced breast cancer



The presence of estrogen and progesterone receptors (E +, P +) in combination with surgery revealed increased life expectancy at 4.13 years compared with non-surgical groups (2.42 years). Patients with negative estrogenic and progesterone receptors, metastases and surgery recorded an average survival of 2.36 years.(5)

Figures no. 5,6,7,8. Advanced breast cancer mastectomy



Other study found that the survival benefit of surgery was present not only in the group of patients with the more favourable hormone receptor-positive status, but also in patients with HER-2/neu-amplified disease when targeted systemic therapy was used.

Patients with triple-negative disease did not experience any differential improvement in survival.(6,7,8,9) Besides the hormonal profile, the young age, the absence of metastases or their presence only in bones and soft tissues are elements that associated with a surgical therapy have shown better outcomes in terms of survival.

Perez Fidalgo et al perform a study that results in an average survival rate of 40.4 months in women receiving surgical treatment compared to 24.3 months in the non-surgical group. The results are obtained taking into account patients with metastatic disease.(10)

On the other hand, it seems that metastatic breast cancer associated with surgery has better prognosis if therapy is instituted within 3 months of diagnosis.

On a meta-analysis that included 28,693 advanced breast cancer patients, a superior survival of those who undergo surgery for primary tumour removal was demonstrated.(11)

Other studies on a smaller number of patients but performed over a longer period of time showed that there is no relationship between surgical treatment and survival at this stage. Keeping in reserve that the long duration of the study (21 years) may modify the results, taking into account that multimodal therapy in breast cancer has changed significantly over the last decade and its mandatory association with surgical stretching may improve outcomes.(12)

The mechanism by which the suppression of primary tumour in advanced, even metastatic cancer acts in the sense of diminishing the oncogenic process is incompletely elucidated. There are several hypotheses that suggest that removal of the primary tumour helps controlling the disease and prevents its distant spread.

Initially, removal of the primary tumour was contraindicated, believing that this would cause neoplastic proliferation in the secondary determinations. The mechanisms that explained this relationship were multiple, many of them being widely accepted at some point.

Thus, there is a balance between angiogenic molecules (enhancers versus inhibitors) in the primary tumour creating a secretion of angiogenesis mediators that cause local proliferation, but by secretion of angiogenesis inhibitors, metastasis would be prevented from exacerbating proliferation.

This process is altered in the primary tumour removal with release of angiogenesis enhancers and proliferation of secondary disseminations.(13)

Systemic post-operative inflammation and surgical immunosuppression were factors considered potentiators of neoplastic proliferation.(14)

Recent studies support the feedback relationship between the primary and secondary tumours, the primary tumour acting as the source of metastasis and the metastases acting through a cytokine-mediated mechanism in accelerating the primary tumour angiogenesis.

In the context of the approach to immune modular antineoplastic therapy, the question arises as to how much the primary tumour influences the patient's immune status. The efficacy of immunotherapy depends on many factors, one of which is the immunocompetence of the host.

Studies in mice have shown that subjects with metastases and severe immunosuppression have a favourable immune response after removing the primary tumour.

Thus, a T cell and B cell lymphocyte suppression is demonstrated in the presence of a large tumour burden with primary tumour in place, with increased immune response after removal. It is right that the first phase has been shown to suppress transient immune response, sometimes with proliferation metastatic (non-tropical) studies but dynamic studies on in vivo subjects using bioluminescence technology demonstrate a superior immune response following tumour excision.(15,16,17,18)

Under these conditions, for maximal efficacy, immunotherapy should be administered only after tumour burden is reduced, either by surgery or by other conventional therapies.

With the exception of a few studies that do not find improvement in survival after removal of primary mammary tumour, the vast majority of recent literature notes an increase in survival after surgical treatment.

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Figure no. 9. Primary tumour removal in advanced breast cancer studies (17)

Studies	Number of patients	Outcome
Khan, Stewart, Morrow ¹⁹	16,203 (57.2% had surgery)	3-year survival improved from 26% to 35%
Carmichael et al. ²⁰	20 had surgery	Median survival 23 months
Blumenschein et al. ²¹	45 had surgery	44 months survival was 53%
Babiera et al. ²²	224 (82 had surgery)	Improved disease-free survival, trend toward improved overall survival
Rapiti ²³	300 (127 had surgery)	40% reduced risk of death
Gnerlich et al. ²⁴	9,734 (47% had surgery)	Median survival improved from 21 months to 36 months
Fields et al. ²⁵	409 (187 had surgery)	Median survival improved from 15.4 months to 31.9 months
Rao et al. ²⁶	295 (142 had surgery)	Median survival improved from 16.8 months to 27.1 months
Bafford et al. ²⁷	147 (61 had surgery)	Improved survival confounded by stage migration
Neuman et al. ²⁸	186 (69 had surgery)	Improved survival in estrogen-receptor-positive patients only
Le Scodan et al. ²⁹	581 (320 had locoregional XRT, 78% XRT only, 13% surgery only, 9% both)	3-year survival improved from 26.7% to 43.4%
Petrelli, Barni ³⁰	Meta-analysis of studies	Improved survival independent of confounding factors, directly proportional to exposure to systemic and radiotherapy, inversely correlated with estrogen-receptor status

Although incompletely elucidated by the mechanism, dependence on hormonal profile, metastasis location and age of patients, it seems that surgery finds its indication in improving survival in patients with such a disease.

CONCLUSIONS

Although there is controversy on this subject, more and more studies and research tend to recommend ablation of primary tumour in advanced breast cancer, both for immune response in immunotherapy and also for a better survival in conventional oncology therapy.

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