Is primary surgery for locally advanced/metastatic breast cancer a better choice than chemotherapic treatment?

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INTRODUCTION: *A part of the literature supports the undoubtful advantage of neoadjuvant chemotherapy on the overall survival and for the possibility of surgical conservative treatment in locally advanced tumours after downstaging. Other authors report that primitive tumour's surgical removal at first, improves survival in cases with locally advanced /metastatic disease. The advantages were improvement of patient's health status, removal of a reservoir of neoplastic cell neoangiogenic cytokines and growth factors,and cytoreduction.*
MATERIALS AND METHODS: *Aim of this study is to evaluate the effectiveness on the survival of a primary surgical treatment of the locally advanced tumours comparing two homogeneous groups. In the first group (GROUP 1) 40 patients were enrolled with stage III A, III B,IV tumours and were treated with primary surgery. The second group (GROUP 2) was made up of 40 patients with similar stage treated with neoadjuvant chemotherapy. The surgical treatment had the intention* to *remove the entire primary tumour.*
RESULTS: *After a median follow up of 48,2 months,22,5 % of GROUP 1 died and 30 % of GROUP 2. The average survival of patients in GROUP 1 was 27,1 months while in GROUP 2 there was an average survival of 16,8 months.*
CONCLUSION: *In conclusion surgical treatment plays a key role in the treatment of advanced/metastatic disease and is an independent factor associated with survival.*

KEY WORDS: Advanced breast cancer, Metastatic breast cancer, Neoadjuvant treatment, Primary surgery

Introduction

According to AJCC TNM classification [1] the group of locally advanced tumours is made up by stage IIB, IIIA, IIIB, (including tumours of any T, with extension to the chest wall,ulceration and/or ipsilateral satellite nodules and/or edema (including peau d'orange) of the skin and/or inflammatory carcinoma), IIIC tumours (any T, N3, M0). Inflammatory carcinoma is rare,but is the most aggressive tumour form (5yr survival in 5% of cases) [2]. The first results of the use of a neoadjuvant chemotherapic treatment in the locally advanced breast cancer were published in the 70's by De Lena [3] and Valagussa [4] : there were advantages in disease free survival and overall survival.These data were confirmed by Horton [5] and Buzdar [6]. Actually the multimodal treatment is considered the standard for locally advanced breast cancer [7,8].

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Aim of the Study

A part of the literature support the undoubtful advantage of neoadjuvant chemotherapy on the overall survival and for the possibility of surgical conservative treatment in locally advanced tumours after downstaging. Other authors like Blanchard [9], Rapiti[10], Babiera[11], Gnerlich[12] report that primitive tumour's surgical removal at first in cases with locally advanced disease and/or metastases improves survival. According to their idea, an improvement of patient's health status, the removal of a continuous reservoir of neoplastic cells, neo-angiogenic cytokines and growth factors would represent the advantages given by primary surgery in stage III-IV disease. In addiction cytoreduction contributes to the achievement of the minimal effective concentration for the chemotherapic molecules thanks to the removal of tumour's necrotic areas. Aim of this study is to evaluate the effectiveness on the survival of a primary surgical treatment of the locally advanced tumours comparing two homogeneous groups of study. A group underwent to neoadjuvant chemotherapy while the other one to a surgical removal before adjuvant chemotherapy.

Patients and Methods

The patients selected in this study were treated at "San Giuseppe Moscati" hospital in Avellino in the period between 2003 and 2007.The patients were divided in two homogeneous groups. In the first group (GROUP 1) 40 patients were enrolled with stage IIIA, IIIB, IV tumours. In the second group (GROUP 2) were selected 40 patient with similar stage of the first group,treated with neoadjuvant chemotherapy. The patients who died during the follow up for causes unrelated with the pathology and those who were surgically untreatable for comorbidities were excluded from the study. The time of survival was calculated evaluating the span between time of diagnosis and staging and death/last follow up control in 2012. The surgical treatment had the intention to remove the entire primary tumour. The features of the 80 patients were summarized in Table I. 5 patients (6,25%) presented a stage IIIA disease, 15 (18.75%) had a stage IIIB disease, 60 (75%) showed a IV stage disease. In 3.75% [3] of patients in stage IIIA, in 8,75% [7] of patients in stage IIIB, and in 11.25% 9 of patients in stage IV were removed the axillary lymphnodes (Fig. 2). An average number of 16.9 lymphnodes for patient was removed and the metastatic lymphnodes were on average 4.15 for patient. The median age of diagnosis was 60.4 years. The surgical treatment was radical or radical modified or simple mastectomy in 77 % of cases ; the remaining part (23%) of patients underwent to tissue sparing resections or enlarged quadrantectomy. 95% of patients was Caucasic, 80,4% was in postmenopausal age. Considering tumour's features 46.25% of tumours had a diameter between 2 and 5 cm , 78.75% was ER+, 47.5% was PR+. The histology showed a strong predominance of Invasive Ductal Carcinoma (92. 2%) while the remaining 7.8 % reported Invasive Lobular Carcinoma (Fig. 1). In patients without primary surgical treatment, the histological diagnosis was made using core biopsy and excisional biopsy. The most common metastatic site was the bone tissue (55%), followed by lungs (12.5%) and liver (11.25%). Only 1,25 % of patients was irradiated on the breast or the thoracic wall after the surgical treatment. 28.75% of patients received adjuvant chemotherapy,38.75 % adjuvant hormonotherapy, 27.5% received both therapies.

Results

After a median follow up of 48.2 months ,22.5 % [9] of Group 1 patients (treated with primary surgery) died versus 30 % [12] of Group 2 patients (treated with neoadjuvant therapy) (p=0.0001). The average survival of patients treated with primary surgery (Group1) was 27.1 months while Group 2 patients had an average survival

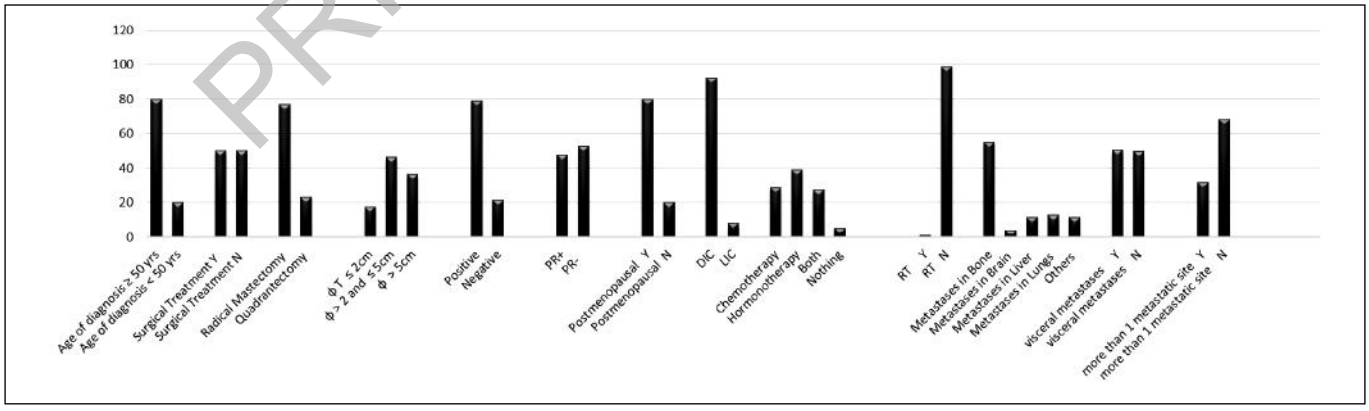

Fig. 1: Feaures of the patients.

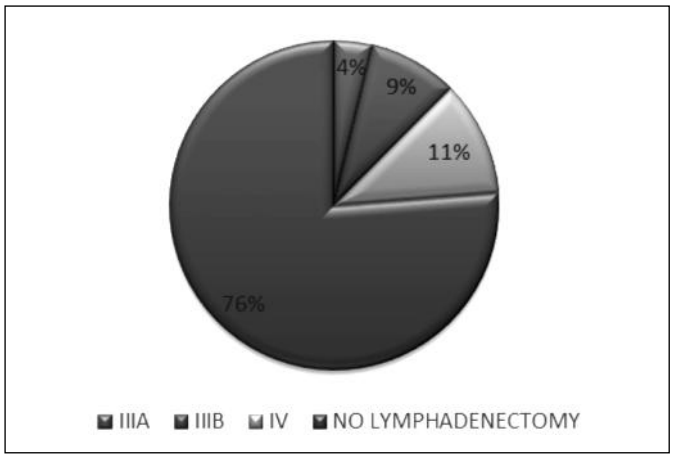

Fig. 2: Patient who tunderwent to lymphadenectomy.

of 16, 8 months (Fig. 4). This result was statistically and clinically significant (p=0, 0001). Group 1 patients with age >50 years were more (85%) than Group 2 (72,5%) (Fig. 3). Patients of Group I over 50 years of age had a median survival of 26,2 months while in Group 2 had a median survival of 30,2 months. Group I patients younger than 50 years reported an average survival of 24.8 months in group 1 and 28,2 months in Group 2. The age of patients was not statistically significant for the survival (p=0.18). In Group 1 33% [7] of deceased patients had a tumour >2 cm of diameter and 23. 8% [5] had a tumour ≤ 2 cm. In Group 2 33% [7] of deceased patients had a tumour > 2cm of diameter and 9, 5 % [2] had a tumour ≤ 2 cm. Patients of Group 1 with tumour ≤ 2 cm had an average survival of 29, 6 months, while for patients of Group 2 with the same tumour's diameter the average survival was 25.8 months (Fig. 5). Patients who didn't receive surgical treatment were more probably ER- and PR- and had a higher incidence of bone metastases. These differences were not statistically significant. The differences between the two group in percentages of visceral and multiple metastases were statistically significant. The average survival for patients with ER+ and/or ER was 42.4 months in Group 1 and 34,2 months in Group 2. Analysing all the variables, we obtained that patients' survival was significantly higher in Group 1 (treated primitively with surgery) (p=0.0001),if tumour was ER+ and/or PR+. The time of survival of ER- pati.nts was 28,2 months in Group 1 vs. 20,6 months in Group 2 (p=0,009). The average survival of patients with visceral metastases was 12.7 months in Group 1 vs. 8,8 months in Group 2. We found no significant difference between the two groups in time of survival for patients with bone metastases (Group 1 =31,5 months; Group 2 = 27.8 months, p=0.225), while survival in patients with more metastatic sites was 7.8 months in Group 1 vs. 12.7 months in Group 2.

Discussion

The opinions about the surgical treatment of advanced and/or metastatic breast cancer are controversial [13]. The Halstedian theories considered that breast cancer spread for contiguity, so radical mastectomy avoided local and metastatic spreading. This thesis was supported by the general conviction that local control played a key-role on patients' survival [14]. Fisher et al. suggested that breast cancer spread chaotically by haematogenous and lymphatic route, so local control didn't influence the development of metastases and survival [15]. Studies about radio-therapy showed that residual pathology or recurrent local disease could be source of metastases, so an aggressive local control may prevent the metastatic spreading improving survival [16-18]. Considering the metastatic disease, some Authors had evidenced that the aggressive surgical treatment of the isolated brain, liver,

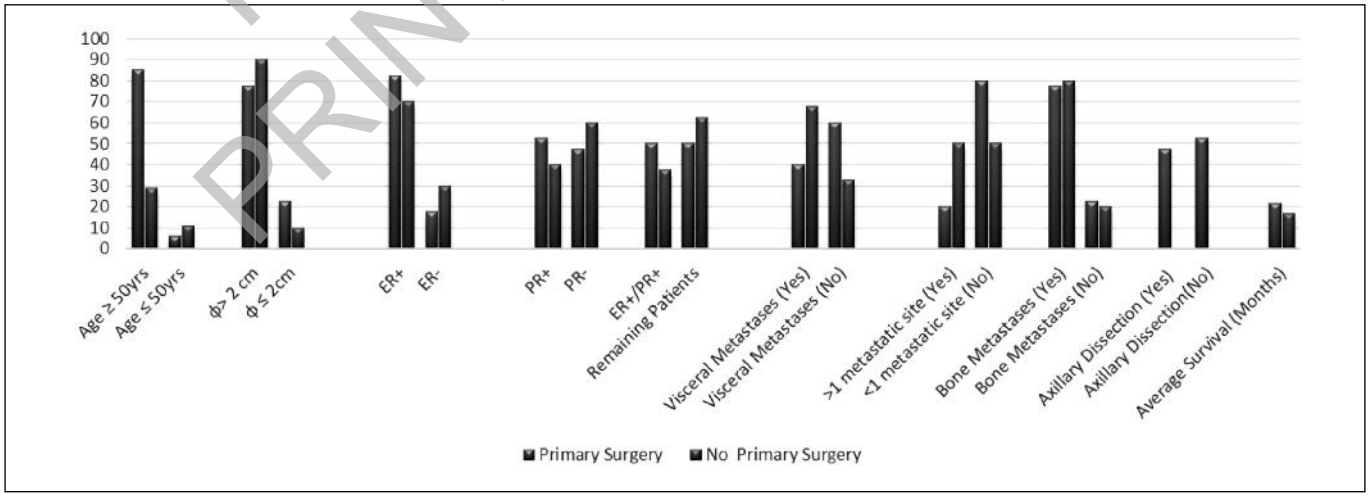

Fig. 3: Feature if the two groups.

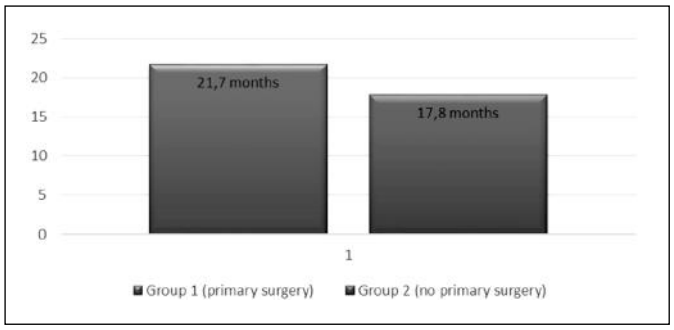

Fig. 4: Comparison between the time of survival of the two groups.

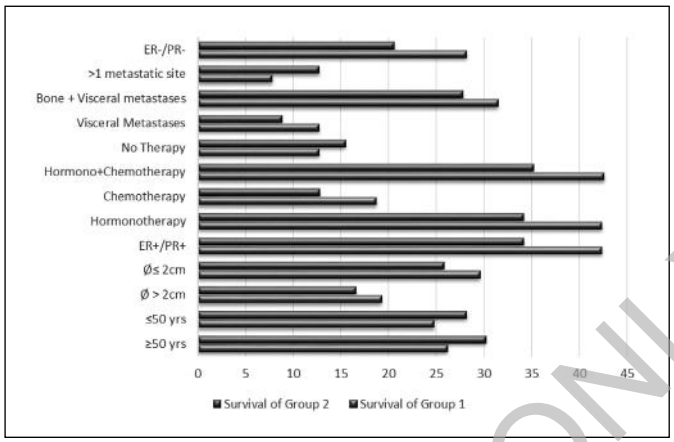

Fig. 5: Influence of the survival of the variables.

and lung metastases could improve the long-term survival[19]. In the current studies the surgical treatment of breast cancer in stage III A, IIIB and IV was associated to an improvement of survival after examining important variables as age, ethnic group, expression of ER and PR, number of metastatic sites and visceral metastases [20,21]. In the previous studies factors influencing positively survival were negative margins, metastases only in bones, systemic treatment, while negative factors were positive margins, hyperexpression of HER2/neu, visceral metastases. Actually, the results about the expression of hormonal receptors on tumour's surface could extend the knowledge of tumour's features and biological behaviour. A limitation of our study is the unavailability of resection margins' status in some cases; this was apparently significant (there is an advantage of surgical treatment only with negative margins [22]. However 77% of Group 1 patients underwent to mastectomy; so considering the average tumour's diameter (3.5cm), we could support the idea that all the margins of the entire group were negative and not conditioning the overall survival of patients. The role of surgery in the treatment of locally advanced breast cancer is controversial. A part of literature advocates neodjuvant therapy as an appropriate treatment of metastatic /locally advanced breast cancer while another part supports the idea of a primary surgical treatment. Studies in animal model showed that breast cancer could induce immunosuppression and a poor response to chemotherapy [23,24]. In the murine model the removal of the primary tumour lead to a restoration of the immune response also in the case of metastatic disease [25]. The surgical treatment of advanced disease could be reserved only to selected groups of women whose life quality is worsened by a bulky, painful, infiltrating mass [26,27]. Cachexia and malnutrition, resulting in reduced immunocompetence and tolerance to chemotherapy, are often contributing factors in the failure of medical therapy. In the latter case, the resection of the primary tumour, rather than achieving curative purposes can promote the improvement of the general state of the patient, thereby making she able to tolerate the toxicity of chemotherapy [28,29]. The response to chemotherapy is also improved by surgical cytoreduction because the removal of a mass containing necrotic and devascularized areas could facilitate a faster achievement of drugs' minimum effective concentration in the tumoral site [30]. Khan and Ruiterkamp, showing that the removal of the primary tumour not only helps to improve the general conditions significantly increases survival, have opened up new horizons and more interesting to the surgical treatment of advanced disease [31,32]. In a retrospective study of 16,023 patients based on data from the American College Surgeons referred to the period between 1990 and 1993, Khan showed that women treated with surgical resection of the primary tumour locally advanced have a better survival rate at 3 years if the resection margins are free of cancer than women not treated surgically (35% vs. 26%). Rapiti in a work based on the analysis of data from the cancer registry in Geneva, showed a reduction in mortality of 40% after R0 resection of the tumour [33].

Conclusion

Surgical treatment plays a key role in the treatment of advanced metastatic/disease and is and independent factor associated with survival (HR=0,710, P=0,006). Moreover ER and PR status and the number of metastases were factors influencing prognosis. Patients with ER/PR+ were more represented in Group 1 than in Group 2. Therefore the positivity of ER/PR had influenced greatly the survival. The presence of multiple metastases was associated to a poorer survival in both groups of the study.

Riassunto

Una parte della letteratura supporta l'indubbio vantaggio della terapia neoadiuvante sulla sopravvivenza com-

plessiva e per la possibilità di un trattamento chirurgico conservativo nei tumori localmente avanzati. Altri autori ritengono che la rimozione di un tumore primitivo in casi con malattia localmente avanzata o metastatica possa migliorare la sopravvivenza. I vantaggi risiedono in un miglioramento dello stato di salute del paziente, nella rimozione di un reservoir di cellule neoplastiche,citochine neoangiogeniche e fattori di crescita ,nella citoriduzione. Scopo di questo studio è valutare l'efficacia sulla sopravvivenza di un trattamento chirurgico primario per tumori localmente avanzati comparando due gruppi di studio omogenei. Nel primo gruppo (Gruppo 1) sono stati selezionati 40 pazienti con stadio III A, IIIB, IV e sono stati trattati con chirurgia primaria. Il gruppo 2 è costituito da pazienti con il medesimo stadio di malattia trattati con terapia neoadiuvante. Il trattamento chirurgico era sempre rivolto alla completa rimozione del tumore primario. Dopo un follow up mediano di 48,2 mesi era morto il 22,5% dei pazienti del gruppo 1 e il 30% di quelli del gruppo 2. La sopravvivenza media dei pazienti del gruppo 1 era di 27,1 mesi mentre nel gruppo 2 vi era una sopravvivenza media di 16,8 mesi. In conclusione il trattamento chirurgico riveste un ruolo importante nel trattamento della malattia avanzata/metastatica e è un fattore indipendente associato con la sopravvivenza.

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