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Minerva Surgery 2021 December;76(6):506-11
DOI: 10.23736/S2724-5691.21.09007-9

ORIGINAL ARTICLE
SURGICAL TREATMENT OF BREAST CANCER

Impact on survival of primary tumor resection in patients with metastatic breast cancer: preliminary results of a retrospective analysis

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ABSTRACT

BACKGROUND: Treatment of *de-novo* metastatic breast cancer is usually centered around systemic therapy, with local therapy (surgery and radiation therapy) largely reserved for palliation in patients with significant symptoms from primary tumor. The efficacy of locoregional treatment like surgery and/or radiotherapy is still controversial and the debate about surgical resection of primary tumor (PT) in de novo metastatic breast cancer (MBC) patients persists.

METHODS: All patients with *de-novo* MBC undergone surgical treatment between January 2015 and January 2020 at the Multidisciplinary Breast Center of the IRCCS A. Gemelli University Polyclinic Foundation in Rome were included in this study. The primary endpoint was overall survival (OS) after PT resection, the secondary endpoint was progression free survival (PFS). The survival analyses were done using Kaplan-Meier method. Patients and tumor characteristics were analyzed in an exploratory modality in order to identify prognostic factor.

RESULTS: Forty-five patients received resection of the primary breast cancer (26 mastectomy and 19 breast conserving surgery). Median age of diagnosis was 53 years old (range 25-75 years old). Median follow-up was 25.67 months. The median OS was not reached with 75% of patients alive over 2 years from PT resection. The median PFS was not reached with 64% of patients alive over 2 years from PT resection. For both PFS and OS only the triple negative (TN) immunophenotype appears to be a prognostically unfavorable factor in multivariate analysis.

CONCLUSIONS: In view of the low number of disease progression events and deaths, although our results are preliminary, surgical treatment of primary breast cancer in metastatic setting seems to be an option after systemic therapies in luminal and HER2 positive breast cancer. Randomized prospective trials for each immunophenotype are necessary in order to confirm this evidence.

(*Cite this article as:* Orlandi A, D'Archi S, Garufi G, Franco A, Carnassale B, Palazzo A, *et al*. Impact on survival of primary tumor resection in patients with metastatic breast cancer: preliminary results of a retrospective analysis. Minerva Surg 2021;76:506-11. DOI: 10.23736/S2724-5691.21.09007-9)

KEY WORDS: Breast neoplasms; Neoplasm metastasis; Margins of excision; Disease-free survival.

De-novo MBC is diagnosed in a small proportion of patients (less than 10%).[1] For these patients, systemic therapy is the standard of care and locoregional surgical treatment is usually performed only with a palliative aim focused on improving quality of life. Although treatment

for these patients is largely centered around systemic therapy, with local therapy largely reserved for palliation, it has been postulated that removal of the primary breast cancer may improve survival.[2] The biological mechanism underlying this process includes the crosstalk among the PT and the metastatic foci, the reversion of tumor-induced immunosuppression by PT removal, the decrease of metastatic potential by eliminating breast cancer stem cells, disrupting the seeding potential of new metastases.[3, 4] But the surgical procedure itself may have negative impacts such as a transient inflammation, turning on the angiogenic switch in the wound healing process, and a temporary immunosuppressive state which, subsequently, might imbalance microenvironment-tumor interactions eventually triggering the metastatic cascade. Moreover, surgical intervention may result in delayed administration of systemic therapy, surgical morbidities, loss of the primary cancer as a marker of disease response, and disruption of cytokines that may restrict the growth of distant metastases.[3-7]

That having said, the role of breast cancer surgery in the context of *de novo* metastatic breast cancer remains controversial. In the last years, several retrospective studies and meta-analysis have reported a survival benefit for metastatic breast patients who underwent locoregional treatment of the PT[8-10] suggesting that, for these patients, PT resection not only limits locoregional progression, but also progression free-survival (PFS) and overall survival (OS).[11-13] Due to the retrospective nature of these studies, reasonable concerns emerged regarding the consistency of the available clinical data.[14, 15] Two randomized clinical trials from Turkey and India evaluated the efficacy of locoregional resection in metastatic breast cancer and reported conflicting results regarding its impact on OS.[16, 17] The ECOG-ACRIN E2108 trial presented at ASCO 2020 had to definitively clarify the role of primary tumor surgery in patients with stage IV breast cancer.[18] In this trial, 390 patients with stage IV breast cancer and intact primary tumor who did not progress after 4-8 months of systemic therapy were randomized to locoregional treatment (surgery and radiotherapy) accompanied by systemic therapy or continued systemic therapy alone. No significant difference between the 3-year overall survival rate (68.4% for locoregional treatment vs 67.9%) and progression-free survival (P=0.40) between the groups was showed. However, the presentation of the data left substantial doubts for the timing chosen for surgical treatment and patient selection (metastatic diffusion, immunophenotype, and response to systemic treatment). International guidelines recommend PT surgery only in a small and selected subset of patients, for example those with oligometastatic disease or low volume metastatic disease, suggesting the need for a prospective clinical trial addressing these specific situations.[18]

In this retrospective study we analyze the clinical outcomes of patients with *de-novo* stage IV breast cancer who underwent locoregional treatment of the PT in order to investigate the subsets of patients who will be most likely to benefit from surgery.

Materials and methods

Patient selection

At the Multidisciplinary Breast Center of the IRCCS A. Gemelli University Polyclinic Foundation in Rome, between January 2015 and January 2020, 47 patients with de novo metastatic breast cancer underwent locoregional treatment. Only patients with *de novo* metastatic breast cancer were included, patients with stage I-III at initial diagnosis and later recurrence, with secondary tumors, with fewer than two months follow up, or in whom correct disease staging was difficult because of irregular systemic work-up studies were excluded. The indication to perform PT surgery was decided in a multidisciplinary meeting, composed by oncologists, surgeons, radiotherapists, radiologists, pathologists, geneticists and psychologists. Indications for surgery included: patient wish, significant tumor pain, refractory tumor bleeding. Factors such as estrogen receptor status (ER), progesterone receptor status (PR), human epidermal growth factor 2 (HER2 status), Ki-67 labelling index were identified by preoperative needle biopsy according to ASCO-CAP guidelines. Molecular subtypes were classified as Luminal A-like (ER and/or PR+, Ki-67 <25% and HER2 negative), luminal

B-like (ER and/or PR+, Ki-67 >25% and HER2 negative), HER2 positive (ER and PR +/-, any Ki-67% and HER2 positive) and triple negative (TN: ER, PR and HER2 negative).

Treatment

Patients included in this study underwent surgical resection and radiotherapy in case of breast conserving surgery. Surgery has been performed as soon as a good response to systemic treatment was demonstrated. All patients were reviewed by a multidisciplinary team before the initiation of the treatments. The most appropriate surgical treatment was decided in a multidisciplinary meeting, considering the overall conditions of the patients, breast volume and extension of the neoplasm. For clinically node-negative patients, sentinel lymph node biopsy (SNB) was performed to assess axillary involvement, axillary dissection (AD) was required for SNB positive patients, patients with positive nodes presenting before surgery and patients with unidentified sentinel lymph node during surgery. Breast conserving surgery was followed by radiotherapy (RT) to the whole breast and/or regional (axillary, supraclavicular, and/or internal mammary) lymph nodes (LNs), and mastectomy was followed by RT to the chest wall in cases with a positive/close margin and/or regional LNs for ≥T3 and ≥N2 disease.

Statistical analysis

Results are expressed as median and range. Statistical analysis was performed using the MedCalc (version 14.0 for Windows). Fisher's Exact test was used for comparison of categorical variables. A P value equal to or less than 0.05 was considered statistically significant. Overall survival and PFS were produced using the Kaplan-Meier method. Patients were considered censored for OS when alive after last registered contact, or without disease progression for the purposes of PFS.

The primary endpoint was progression-free survival (PFS) assessed in terms of the percentage of patients alive from the time of surgery (PT) to date of last follow-up without relapsing breast cancer (locoregional, contralateral, or distant).

The secondary endpoint was overall survival (OS) assessed in terms of the percentage of patients alive from the time of primary surgery (PT) to the date of last follow-up

The study population was dichotomic stratified for patients (age: <65 *versus* >65) and tumor characteristics (grading: G1-2 *versus* G3; Ki-67 expression: <25 *versus* >25; immunophenotype: luminal *versus* other, HER2+ *versus* other, TN *versus* other; metastatic site: bone only *versus* other; and systemic therapy: chemotherapy-based *versus* hormonal-based) in order to explore potential prognostic factor. Univariate analysis will be performed for each factor and those showing a P<0.1 will be analyzed in multivariate by cox proportional-hazards regression.

Results

Patient and tumor characteristics

Between January 2015 and January 2020, 45 patients with de novo metastatic breast cancer underwent LRT. The patients and tumor characteristics are listed in Supplementary Digital Material 1 (Supplementary Table I). Median age at diagnosis was 53 years old (range 25-75 years old).

Seven patients had luminal A-like tumor (15.6%), 13 of them had luminal B-like type (28.9%), 14 patients were affected by a HER2+ tumor (31.1%) and 11 of them by TN (24.4%). At the definitive histological examination of breast primary tumor 10 patients (22.2%) presented a pathological complete response (pCR) while 17 were luminal A-like (37.8%), eight luminal B-like (17.8%), three HER2+ (6.7%), seven TN (15.5%). Ki-67 status at preoperative needle biopsy was ≥25 in 35 patients (77.8%), <25 in 10 patients (22.2%) while its value at the definitive histological evaluation was ≥25 in 17 patients (37,8%), <25% in 18 patients (40%) and not evaluable in 10 patients for pCR.

Most of patients had T4 diseases (40%) and N1 disease (68.8%), multicentric tumors were identified in 6,4% patients, only 2.1% patients had bilateral disease.

Bones were the most common site of distant metastasis (22 patients; 48.9%) followed by liver metastasis (15 patients; 33.3%), lung metastasis

(seven patients; 15.5%), distant lymph nodes (three patients; 6.7%). 35 patients (77.8%) were affected by a single site metastatic cancer while 10 patients (22.2%) had multiple site metastatic cancer.

All patients received systemic treatment: 22 patients (48.9%) paclitaxel-based chemotherapy, 14 patients (31.1%) trastuzumab + paclitaxel +/- pertuzumab and nine patient hormonal-based therapy (20%). Surgery was performed when a good systemic disease control was achived (median 11 months, range 8-43).

The locoregional treatment consisted of complete resection (no tumor on inked margin) of the primary tumor. 18 patients (40%) underwent breast conserving surgery, and 27 patients (60%) underwent mastectomy. Six patients underwent only SNB (13.3%) and 39 underwent AD (86.8%).

Surgery was followed by radiotherapy (RT) in 21 patients (46.6%); all the patients who underwent breast conserving surgery received RT to the whole breast and/or regional (axillary, supraclavicular, and/or internal mammary) LNs, and patients who underwent mastectomy received RT to the chest wall in cases with a positive/close margin and/or regional LNs for ≥T3 and ≥N2 disease.

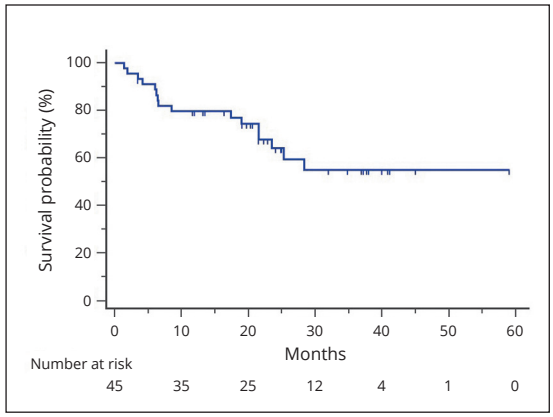

Figure 1.—Progression-free survival in all the population.

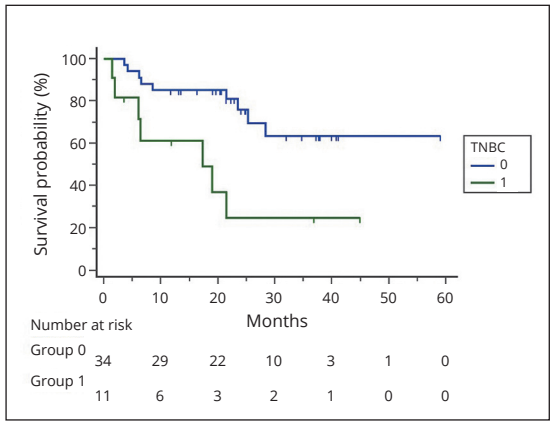

Figure 2.—Progression-free survival in TNBC *versus* other subtypes.

Oncological outcomes

The median follow-up duration was 25.67 months (range 3.50-58.15).

In all population median PFS was not reached, at the time of this first analysis 64.4% of patients did not show disease progression (Figure 1).

In patient with age >65 years old PFS was 21.5 months (95% CI 20,082 to 44,576) and not reached in patient with age <65 (HR: 1.9 95% CI 0.64 to 5.6; P=0.19). The medians of PFS stratified for grading (G1 *versus* G2-3) were not reached (HR: 0.95; 95% CI: 0.35 to 2.5; P=0.46). The medians of PFS stratified for Ki-67 (<25 *versus* >25) were not reached (HR: 0.68; 95% CI: 0.24 to 1.9; P=0.49). The medians of PFS stratified for immunophenotype (Luminal versus other) were not reached (HR: 0.99; 95% CI: 0.37 to 2.67; P=0.99). PFS stratified for immunophenotype (HER2 versus other) was not reached for HER2+ and 28.32 months for other (HR: 0.28; 95% CI: 0.1 to 0.81, P=0.07). PFS stratified for immunophenotype (TN *versus* other) was 17.33 months for TN and not reached for other subtypes, this result was statistically significant (HR: 3.76; 95% CI: 1.02 to 13.8, P=0.004) (Figure 2). PFS stratified for metastatic sites (bone only versus other) was not reached for bone only and 28.32 months for other (HR: 0.98; 95% CI: 0.3 to 2.64; P=0.97). PFS stratified for systemic therapy (chemotherapy-based versus hormonal-based) were not reached (HR: 1.28; 95% CI: 0.43 to 3.73; P=0.66). The multivariate analysis confirmed TN as the only negative prognostic factor (P=0.02).

In all population median OS was not reached, at the time of this first analysis 75.5% of patients was alive (Figure 3). In all subgroup median OS was not reached therefore not statistical analysis was performed.

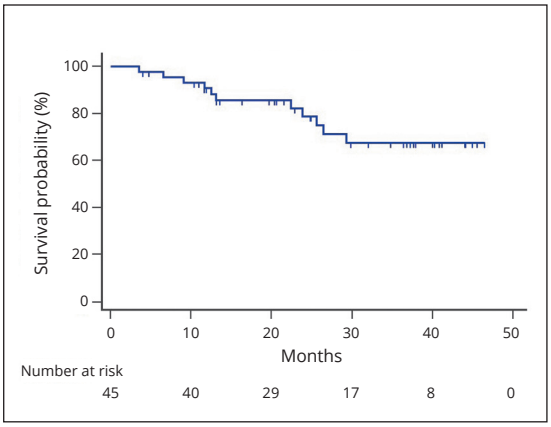

Figure 3.—Overall survival in all population.

Discussion

Management of *de-novo* metastatic breast cancer is controversial in literature. Traditionally it was believed that once a cancer metastasis there is no need for resection of primary tumor, but several studies suggest primary tumor surgical treatment in order to improve patient's survival. According to these theories[2, 3] the removal of the primary tumor reduces the tumor burden increasing the response to systemic therapy. The 5th ESO–ESMO International Consensus Guidelines for Advanced Breast Cancer suggest that the removal of the primary tumor in patients with *de-novo* stage IV breast cancer has not been associated with prolongation of survival, with the possible exception of the subset of patients with bone-only disease.[19] However, it can be considered in selected patients, particularly to improve quality of live (QoL), always taking into account the patient's preferences.

The main limitation of our study, besides the retrospective nature and the absence of a comparator arm with systemic therapy alone, is the limited median follow-up. Both the median PFS and the median OS in the whole population have not yet been reached, so it will be important to acquire a larger number of events in order to have conclusive data.

However, the low number of events, both for PFS and OS with a median follow-up of more than two years, underline that primary surgery in metastatic setting appears to be a feasible treatment and that it may be useful for adequately selected patients. In addition to this consideration, other data already mature in our study allow us to make some inferences that can guide in clinical practice within the recommendations of the guidelines.

Our study underlines the importance of adequately selecting patients with metastatic breast cancer to be referred for primary cancer surgery. The selection that emerges as the main one is that through the immunophenotype. Indeed, important differences in outcome between patients with Luminal-like, HER2+ and TN are already highlighted from the data showed. In terms of PFS, a reduced survival of TN patients is confirmed compared to the other subtypes even in case of resection of the primary tumor. While there is an important advantage in PFS in the HER2+ subtype. Not having a comparison arm with systemic treatment alone, it is not possible to attribute this advantage to surgery on the primary tumor, vice versa it could be intrinsically secondary to the subtype and to the availability and effectiveness of systemic treatments. In the light of the data presented, doubts may emerge about the usefulness of proposing surgical treatment on primary cancer in a TN population, but it appears an option not to be neglected in a HER2+ population. These results are comparable to the most favorable data reported by previous studies.

Therefore, pending new data deriving from prospective and randomized studies, our data confirm that a multidisciplinary approach, as demonstrated for other cancer,[20] including locoregional treatments on primary breast cancer in metastatic setting, should be considered for selected patients.

Conclusions

Primary surgical treatment in metastatic breast cancer could be an important option together with systemic therapies in certain subset of patients, but randomized prospective trials are still necessary in order to confirm this evidence.

References

1. Sant M, Allemani C, Berrino F, Coleman MP, Aareleid T, Chaplain G, *et al.*; European Concerted Action on Survival

and Care of Cancer Patients (EUROCARE) Working Group. Breast carcinoma survival in Europe and the United States. Cancer 2004;100:715–22.

2. Smith I. Goals of treatment for patients with metastatic breast cancer. Semin Oncol 2006;33(Suppl 2):S2–5.

3. Danna EA, Sinha P, Gilbert M, Clements VK, Pulaski BA, Ostrand-Rosenberg S. Surgical removal of primary tumor reverses tumor-induced immunosuppression despite the presence of metastatic disease. Cancer Res 2004;64:2205–11.

4. Norton L, Massagué J. Is cancer a disease of self-seeding? Nat Med 2006;12:875–8.

5. Tohme S, Simmons RL, Tsung A. Surgery for Cancer: A Trigger for Metastases. Cancer Res 2017;77:1548–52.

6. Demicheli R, Retsky MW, Hrushesky WJ, Baum M, Gukas ID. The effects of surgery on tumor growth: a century of investigations. Ann Oncol 2008;19:1821–8.

7. Chiarella P, Bruzzo J, Meiss RP, Ruggiero RA. Concomitant tumor resistance. Cancer Lett 2012;324:133–41.

8. Giordano SH, Buzdar AU, Smith TL, Kau SW, Yang Y, Hortobagyi GN. Is breast cancer survival improving? Cancer 2004;100:44–52.

9. Gennari A, Conte P, Rosso R, Orlandini C, Bruzzi P. Survival of metastatic breast carcinoma patients over a 20-year period: a retrospective analysis based on individual patient data from six consecutive studies. Cancer 2005;104:1742–50.

10. Sundquist M, Brudin L, Tejler G. Improved survival in metastatic breast cancer 1985-2016. Breast 2017;31:46–50.

11. Carmichael AR, Anderson ED, Chetty U, Dixon JM. Does local surgery have a role in the management of stage IV breast cancer? Eur J Surg Oncol 2003;29:17–9.

12. Gnerlich J, Jeffe DB, Deshpande AD, Beers C, Zander C, Margenthaler JA. Surgical removal of the primary tumor increases overall survival in patients with metastatic breast cancer: analysis of the 1988-2003 SEER data. Ann Surg Oncol 2007;14:2187–94.

13. Blanchard DK, Bhatia P, Hilsenbeck SG, Elledge RM. Does surgical management of stage IV breast cancer affect outcome? Breast Cancer Res Treat 2006;2006(Suppl 1):18.

14. Khan SA. Surgery for the intact primary and stage IV breast cancer…lacking "robust evidence". Ann Surg Oncol 2013;20:2803–5.

15. Khan SA. Primary tumor resection in stage IV breast cancer: consistent benefit, or consistent bias? Ann Surg Oncol 2007;14:3285–7.

16. Soran A, Ozbas S, Kelsey SF, Gulluoglu BM. Randomized trial comparing locoregional resection of primary tumor with no surgery in stage IV breast cancer at the presentation (Protocol MF07-01): a study of Turkish Federation of the National Societies for Breast Diseases. Breast J 2009;15:399–403.

17. Badwe R, Hawaldar R, Nair N, Kaushik R, Parmar V, Siddique S, *et al.* Locoregional treatment versus no treatment of the primary tumour in metastatic breast cancer: an open-label randomised controlled trial. Lancet Oncol 2015;16:1380–8.

18. Khan SA. A randomized phase III trial of systemic therapy plus early local therapy versus systemic therapy alone in women with de novo stage IV breast cancer: A trial of the ECOG-ACRIN Research Group (E2108). J Clin Oncol 2020;18(Suppl):LBA2.

19. Cardoso F, Paluch-Shimon S, Senkus E, Curigliano G, Aapro MS, André F, *et al.* 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Ann Oncol 2020;31:1623–49.

20. Basso M, Corallo S, Calegari MA, Zurlo IV, Ardito F, Vellone M, *et al.* The impact of multidisciplinary team management on outcome of hepatic resection in liver-limited colorectal metastases. Sci Rep 2020;10:10871.

Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Authors' contributions.—All authors read and approved the final version of the manuscript.

History.—Article first published online: August 2, 2021. - Manuscript accepted: July 27, 2021. - Manuscript received: June 3, 2021.

Supplementary data.—For supplementary materials, please see the HTML version of this article at www.minervamedica.it