



Controversies in Oncology: Surgery of the primary tumour in patients presenting with de novo metastatic breast cancer: to do or not to do?

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To cite: Poggio F, Lambertini M, de Azambuja E. Controversies in Oncology: Surgery of the primary tumour in patients presenting with de novo metastatic breast cancer: to do or not to do? *ESMO Open* 2018;3:e000324. doi:10.1136/esmoopen-2018-000324

Received 9 January 2018
Accepted 10 January 2018

Approximately 5%–10% of patients with newly diagnosed breast cancer present with distant metastasis (ie, de novo metastatic disease).¹ The appropriate clinical management of patients with de novo metastatic breast cancer is still very controversial; specifically, the need for radical locoregional treatment and its consequent benefit in this setting remains still highly debatable.

In 2012, a meta-analysis of 15 retrospective study including about 30 000 patients investigated the role of radical locoregional treatment of the primary tumour in patients with de novo metastatic breast cancer. The surgical resection of the primary breast tumour was independently associated with a statistically significant improvement in overall survival (OS; HR 0.69, 95% CI 0.63 to 0.77, $P < 0.00001$).² Nevertheless, the reliability of the evidence deriving exclusively from retrospective studies can be limited due to several potential biases including the fact that patients who underwent surgery were often characterised by having a more limited metastatic dissemination, no (or limited) visceral involvement, younger age, better performance status and were selected for having had prior response to systemic therapy.

Recently, three prospective randomised studies investigated the role of surgery of the primary tumour in patients with de novo metastatic breast cancer.^{3–5} However, conflicting results were reported. In the Indian trial, patients with de novo metastatic breast cancer were randomised to receive or not a radical locoregional surgical treatment in the absence of tumour progression after prior exposure to 6 months of an anthracycline/taxane-based chemotherapy. Patients were stratified according to site/number of distant metastases and hormonal receptor status. Surgery of the primary breast tumour did not improve OS (19.2 vs 20.5

months; $P = 0.79$). On the contrary, distant progression free survival (PFS) of patients receiving radical locoregional treatment was significantly worse as compared with that of patients who did not undergo surgery (11.3 vs 19.8 months; $P = 0.012$). Notably, the majority of the patients included in this study presented with symptomatic disease, and among those with human epidermal growth factor receptor 2 (HER2)-positive disease (about 30%), only one patient received trastuzumab in addition to chemotherapy before randomisation.³ The Turkish MF07-01 trial randomised patients with de novo metastatic breast cancer to undergo or not to surgery of the primary tumour before starting systemic therapy. Endocrine therapy and trastuzumab were given to patients if indicated. The 3-year OS was similar in patients who received or not surgery of the primary breast tumour; however, at a median follow-up of 5 years, the use of surgery significantly prolonged median OS by about 9 months (46 vs 37 months; $P = 0.005$). In an unplanned subset analysis, patients with more indolent characteristics (such as hormonal receptor-positive/HER2-negative tumours, bone-only metastases, age younger than 55 years) derived the most important survival benefit when receiving initial surgery. In interpreting the results of this study, it should be noted that there was an imbalance in favour of the surgery arm with respect to number and location of metastases. Moreover, patients were randomised before starting any systemic treatment and they were not selected for being the respondents to the administered first-line treatment.⁴ Lastly, the Austrian Breast & Colorectal Cancer Study Group (ABCSCG)-28/Posytive trial investigated whether immediate resection of the primary breast tumour followed by standard systemic therapy improves median survival compared with no surgical resection among 90 patients

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Table 1 Randomised phase III trials assessed the impact of locoregional surgical treatment

Study name (NCT/UMIN)	Initial therapy	Study design	Status
SUBMIT (NCT01392586)	Surgery	Upfront surgery followed by systemic therapy versus systemic therapy	Terminated (due to low accrual rate)
ECOG 2108(NCT01242800)	Systemic therapy	Delayed local therapy (only if local progression) versus primary tumour resection and locoregional radiotherapy	Accrual completed
JCOG1017 (UMIN000005586)	Systemic therapy	Systemic therapy alone versus primary tumour resection plus systemic therapy	Nearly completed

with de novo metastatic breast cancer; the trial had to be stopped prematurely due to insufficient recruitment. Both arms were well balanced regarding first-line treatment (endocrine therapy vs chemotherapy); however, no additional information about the type of therapies were reported. The preliminary results, presented in abstract form at the 2017 ASCO Annual meeting, reported no significant benefit in OS in the patients who received immediate surgery of the primary breast tumour (34.6 vs 54.8 months; $P=0.267$), at a median follow-up of 37.5 months.⁵

The results from available randomised trials did not report a clear survival benefit for patients with de novo metastatic breast cancer that received a radical locoregional treatment. However, considering the possible patient's selection bias and the use of older and less active systemic therapies, a proper generalisation of these results into the current clinical setting is not possible to be done. Nevertheless, on the other end, subgroup analyses from these trials together with the positive and consistent findings from several retrospective studies may suggest that a subset of patients with de novo metastatic breast cancer might benefit from a radical locoregional treatment of the primary tumour. This may be even more important in the last years considering the important advances in the systemic treatment approaches currently available for patients with metastatic disease, particularly for those with luminal and HER2-positive disease. In fact, the new effective targeted agents (ie, cyclin-dependent kinase (CDK) 4/6 and the mammalian target of rapamycin (mTOR) inhibitors for luminal and the newer anti-HER2 agents pertuzumab and T-DM1 for HER2-positive metastatic breast cancer) has significantly increased both the response rates/tumour shrinkage and the survival outcomes of these patients.^{6,7} Indeed, this subset of patients with metastatic breast cancer can obtain particularly prolonged long-term clinical remission, reaching median survival exceeding now 5 years.⁸ Hence, these patients may be the best candidates for more aggressive and potential curative approaches, including the use of a radical locoregional treatment of the primary tumour. This has been shown by a recent Italian multicentre retrospective study comparing the clinical outcomes of patients with HER2-positive metastatic breast cancer with de novo or recurrent disease who underwent first-line trastuzumab-based therapy. An

exploratory analysis assessed that surgery of the primary tumour in the cohort of patients presenting with de novo metastatic disease was associated with a significant increased PFS (19.3 vs 9.3 months; $P<0.001$) and a doubling in median OS (95.9 vs 46.1 months; $P=0.029$). Of note, among patients with de novo metastatic disease, those who received surgery had better baseline characteristics as compared with those who did not in terms of lower number of metastatic sites, less visceral involvement and less frequently symptomatic disease.⁹ Another study evaluated the impact of initial breast surgery on the long-term prognosis of patients with de novo metastatic breast cancer treated with targeted agents (ie, trastuzumab and bevacizumab) within two prospective studies: any major benefit of surgery was reported in the total population, corroborating the potential benefit from surgical locoregional treatment in patients without any visceral dissemination (median OS: 45.7 vs 27.2 months; $P=0.026$).¹⁰ These results further confirm that a selected group of patients presenting with de novo metastatic disease (ie, with good prognostic features and with available effective systemic therapies) may be the ones benefitting the most from a radical locoregional surgical approach.

Based on the controversial available evidence on this regard, according to the third ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer, breast surgery in patients with de novo metastatic disease should be discussed on a case-by-case basis, always taking into account the patient's preferences.¹¹ Results from different randomised trials on this topic are awaited to help physicians in better identifying who are the best candidates for a radical locoregional treatment (table 1).

In conclusion, surgical treatment of the primary tumour in patients with de novo metastatic breast cancer may not be of benefit for the majority of them. However, a radical locoregional treatment can offer symptomatic local control and it may also contribute to prolong the survival of a selected group of patients. Specifically, we believe that breast surgery of the primary tumour may be considered as a therapeutic option in patients with de novo metastatic breast cancer having a good performance status, oligometastatic disease, no (or limited) visceral involvement, luminal or HER2-positive biology, after initial response to first-line systemic therapies.

Correction notice This article has been corrected since it first published. 'Controversies in Oncology:' has been added to the article title.

Acknowledgements ML acknowledges the support from the European Society for Medical Oncology (ESMO) for a translational research fellowship at Institut Jules Bordet.

Contributors All authors have contributed equally to the structure and content of this article.

Funding This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Provenance and peer review Commissioned; internally peer reviewed.

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