The Breast 58 (2021) 170–172

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

# Locoregional therapy in de novo metastatic breast cancer. The unanswered question

## 1. Facts and figures

Breast cancer has now overtaken lung cancer as the world's mostly commonly-diagnosed cancer, according to statistics released by the International Agency for Research on Cancer (IARC) in December 2020. Five to eight percent of newly diagnosed breast cancer cases are metastatic at diagnosis. Intriguingly this number has not changed over the last decade even with the widespread use of more sensitive systemic staging modalities like PET-CT.

Since the first patient was recruited in the Tata memorial trial in 2005 [1] we have seen significant advances in the field of targeted therapies for ER+ and Her-2 positive breast cancer and immunotherapy for triple negative breast cancer (TNBC) leading to improvement in the control of systemic disease. Survival for these patients especially in ER and HER2 positive patients raised to 20–40% at 5 years thus making the topic of locoregional therapy (LRT) of the primary tumour increasingly relevant.

## 2. The available retrospective data

The majority of available data come from retrospective trials analysing studies conducted before the new millennium. The conclusions of all the published meta-analyses including large population based studies and smaller institutional studies point to an overall survival (OS) benefit from primary tumour resection in de novo metastatic breast cancer.

We should not forget however that in many of these studies the recruitment interval was as large as 20 years with the consequent heterogeneity in inclusion criteria and available treatments.

In these studies women offered primary tumour resection were predominantly younger, fitter and with less metastatic burden thus introducing the risk of selection bias.

## 3. The randomized clinical trials (RCTs) data

At the present moment four prospective randomized studies have completed accrual and presented their results [1–4]. Three of these trials have been published in peer-reviewed journals and one trial (the ECOG-ACRIN) presented its preliminary findings at the ASCO 2020 virtual meeting. The first trial, The Tata Memorial from India, included 350 patients randomized to surgery after primary systemic treatment, showed no OS benefit from LRT and was heavily criticized for suboptimal systemic therapy with a limited use of taxanes and omission of anti-HER2 therapy in 92% of patients with HER2 positive disease [1]. The subsequent Turkish study, randomized patients at presentation between surgery of the primary versus no surgery, initially reported no difference in survival at 3 years of follow up, however, with a longer follow-up of 5 years, the median survival was significantly improved for patients receiving local therapy. However in this trial there was an imbalance between the arms with the group proposed for surgery having younger patients, more frequently ER positive and HER2 negative, and with single bone metastases, factors that could have had impact on the result [2]. Moreover the patients in the treatment arm were offered upfront surgery. The Austrian POSYTIVE trial due to poor recruitment, was stopped prematurely after 5 years when only 90 patients of the pre-planned 254, had been enrolled, 45 in each arm and therefore it did not achieve the required statistical power for a reliable analysis [3]. Nevertheless the two groups were balanced and again no advantage for surgery of the primary tumour was observed. The preliminary data of the fourth trial presented at ASCO 2020 demonstrated again no significant difference in OS but reported that the 3-year locoregional recurrence or progression was significantly higher in the systemic therapy alone arm [4]. We eagerly await the full peer-reviewed publication and longer follow up data for this trial.

## 4. Where do we go from here?

In this meta-analysis of 4 RCTs spanning 970 patients, Reinhorm et al. [5] reports that LRT for the primary tumour confers no OS benefit in patients presenting with de novo stage IV breast cancer despite the significant improvement in locoregional control. In contrast with previous meta-analyses [6] the authors have included only RCTs in order to overcome the selection bias introduced in retrospective studies.

Due to the important heterogeneity of the reported studies, it is difficult to accept the conclusion without uncertainties. However in the pooled analysis compared to the control group, surgery of the primary was not associated with OS in the ITT population. Multiple sensitivity analysis for OS and leave-one-out sensitivity analysis for

DOI of original article: https://doi.org/10.1016/j.breast.2021.05.003.

https://doi.org/10.1016/j.breast.2021.05.002

**Table 1**
Trials addressing impact of local therapy for the primary tumor in de NOVO metastatic breast cancer.

| COUNTRY | CLINICAL TRIAL ID | CURRENT NAME | ACCRUAL PERIOD | N | Type | INITIAL TREATMENT | RADIOTHERAPY | PRIMARY END POINT | STATUS | RESULT | Publication |
|---|---|---|---|---|---|---|---|---|---|---|---|
| [1] India | NCT00193778 | Tata Memorial | 2005–2012 | 350 | RCT | ST | If indicated | OS | Completed | No benefit PS | Lancet Oncol 2015 |
| [2] Turkey | NCT00557986 | MF07-01 | 2008–2012 | 281 | RCT | Surgery | For BCT only | OS | Completed | Benefit PS | Ann Surg Onc 2018 |
| [3] Austria | NCT01015625 | POSYTIVE | 2010–2019 | 90 | RCT | Surgery | If indicated | OS | Completed | No benefit PS | Ann Surg 2018 |
| [4] US | NCT01242800 | ECOG-ACRIN E2108 | 2011–2025 (15) | 256 | RCT | ST | If indicated | OS | Completed | No benefit PS | Abstract ASCO 2020 |
| [11] Japan | JCOG1017 | PRIM-BC | 2011–2018 | 407 | RCT | ST | Not addressed | OS | Completed | NO REPORT | |
| [9]Turkey | NCT02125630 | BOMET MF 14-01 | 2014–2019 | 506 | RCT | Surgery | Not addressed | OS | Completed | Benefit PS | Abstract St Gallen 2021 |
| [10] US | NCT02364557 | NRG-BR002 | 2014–2022 | 402 | RCT | ST | No information | PFS/OS | Recruiting | NO REPORT | |
| [8] US | NCT00941759 | TBCRC 013 | 2009–2016 | 127 | PR | ST | Not addressed | OS | Completed | No benefit PS | JCO 2016 Supp |

N – number of patients; RCT – Randomized Controlled Trial; PR- Prospective Registry; ST-Systemic Treatment; OS-Overall Survival; PFS-Progression Free Survival; PS – Primary Surgery.

OS have shown similar results. In the subgroup analysis surgery was not associated with an OS improvement in any tumour subtype or bone only versus visceral disease.

De novo stage IV breast cancer displays extensive heterogeneity in relation to its metastatic pattern and differential response of the primary tumour and metastatic sites to systemic therapy. In the absence of well-designed, adequately powered, and carefully conducted RCTs utilizing modern targeted biological agents and immunotherapy, the local management strategy of the primary tumour of every patient with de novo stage IV breast cancer should be determined only after a careful multidisciplinary discussion [7].

Excellent responders to systemic therapy at both the primary and distant disease sites are unlikely to derive a survival benefit from local surgery and this was observed in the prospective registry study TBCRC 013 [8]. However patients whose primary tumour does not respond well to systemic therapy, but with an important response of the metastatic sites, will derive benefit from local surgery in terms not only of optimal local control but also by reducing the burden of therapy resistant residual tumour cells although OS benefit is not proven. The benefit of local therapy in optimising local disease control has been observed in this meta-analysis and in the individual studies included [5]. Furthermore, patients with ER + oligometastatic disease confined to bone are most likely to benefit from LRT of the primary tumour in view of their prolonged survival as shown by the recent results of the BOMET protocol MF14-01 partially presented this year in St Gallen, although again an imbalance between the groups (bone only vs multiple bone metastases) was observed [9].

We eagerly await the results of NRG BR002 to further clarify the role of ablative therapy to all sites of disease in patients with oligometastatic disease [10].

All the randomized trials designed to evaluate the impact of surgery of the primary tumour in de novo metastatic breast cancer have reported some data with the exception of the Japanese trial PRIM-BC, with results expected before 2024 [11].

Taking into consideration all the information already available if primary tumour ablation is considered in de novo metastatic breast cancer, the local surgical approach for treating the intact primary tumour should be preferably conservative, when feasible, aiming to remove the tumour with clear resection margins. In the absence of a conclusively proven OS benefit, more radical surgical approaches such as mastectomy should be discouraged. Although the role of radiotherapy after surgery of the primary has not been systematically evaluated in the analysed randomized trials, meta-analysis of existent retrospective studies suggested that, in addition to local surgery, radiation therapy further improves local control and may elicit a systemic immune response against the tumour and therefore it should be considered an integral part of LRT [6].

## 5. Conclusion

The progress in addressing this unresolved issue has been slow. We are all aware of the difficulty in conducting these trials and the heterogeneity inherent to the definition of de novo metastatic breast cancer (Table 1). We anticipate that with the results yet to be published, a pooled analysis of patient data, from all the randomized trials will help us to obtain a more definite response to our still unanswered question.

## Declaration of competing interest

Both authors declare no conflict of interest.

## References

[1] 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(13):1380–8.
[2] Soran A, Ozmen V, Ozbas S, Karanlik H, Muslumanoglu M, Igci A, et al. Randomized trial comparing resection of primary tumor with No surgery in stage IV breast cancer at presentation: protocol MF07-01. Ann Surg Oncol 2018;25(11):3141–9.
[3] Fitzal F, Bjelic-Radisic V, Knauer M, Steger G, Hubalek M, Balic M, et al. Impact of breast surgery in primary metastasized breast cancer: outcomes of the prospective randomized phase III ABCSG-28 POSYTIVE trial. Ann Surg 2019;269(6):1163–9.
[4] Khan SA, Zhao F, Solin LJ, Goldstein LJ, Cella D, Basik M, et al. 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;38(18_suppl). LBA2-LBA.
[5] Reinhorn DJ, Mutai R, Yerushalmi R, Moore A, Amir E, Goldvaser H. Locoregional therapy in de novo metastatic breast cancer: systemic review and meta-analysis. Breast 2021;58:173–81.
[6] Gera R, Chehade H, Wazir U, Tayeh S, Kasem A, Mokbel K. Locoregional therapy of the primary tumour in de novo stage IV breast cancer in 216 066 patients: a meta-analysis. Sci Rep 2020;10(1):2952.
[7] 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(12):1623–49.
[8] King TA, Lyman J, Gonen M, Reyes S, Hwang E-SS, Rugo HS, et al. A prospective analysis of surgery and survival in stage IV breast cancer (TBCRC 013). J Clin Oncol 2016;34(15_suppl):1006.
[9] Soran A, Dogan L, Ozbas S, Isık A, Trablus D, Demirci U, et al. The effect of primary surgery in patients with stage IV breast cancer with bone metastasis only (protocol bomet MF14-01); a multi-center, registry study. Breast 2021;56:S68.
[10] Chmura SJ, Winter KA, Al-Hallaq HA, Borges VF, Jaskowiak NT, Matuszak M, et al. NRG-BR002: a phase IIR/III trial of standard of care therapy with or without stereotactic body radiotherapy (SBRT) and/or surgical ablation for newly oligometastatic breast cancer (NCT02364557). J Clin Oncol 2019;37(15_suppl):TPS1117 [TPS].
[11] Shien T, Mizutani T, Tanaka K, Kinoshita T, Hara F, Fujisawa T, et al. A randomized controlled trial comparing primary tumor resection plus systemic therapy with systemic therapy alone in metastatic breast cancer (JCOG1017 PRIM-BC). J Clin Oncol 2017;35(15_suppl):TPS588 [TPS].

Maria-Joao Cardoso[a,*], Kefah Mokbel[b]
[a] *Breast Unit Champalimaud Clinical Center, Champalimaud Foundation, And Nova Medical School, Lisbon, Portugal*

[b] *The London Breast Institute, Princess Grace Hospital, London, W1U 5NY, UK*

[*] Corresponding author.
*E-mail address:* maria.joao.cardoso@fundacaochampalimaud.ptr (M.-J. Cardoso).

22 April 2021
Available online 7 May 2021