



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 POSITIVE 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, Reinhorn 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

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	POSITIVE	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.

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