Locoregional treatment versus no treatment of the primary tumour in metastatic breast cancer: an open-label randomised controlled trial

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Summary

Background The role of locoregional treatment in women with metastatic breast cancer at first presentation is unclear. Preclinical evidence suggests that such treatment might help the growth of metastatic disease, whereas many retrospective analyses in clinical cohorts have suggested a favourable effect of locoregional treatment in these patients. We aimed to compare the effect of locoregional treatment with no treatment on outcome in women with metastatic breast cancer at initial presentation.

Methods In this open-label, randomised controlled trial, we recruited previously untreated patients (≤65 years of age with an estimated remaining life expectancy of at least 1 year) presenting with de-novo metastatic breast cancer from Tata Memorial Centre, Mumbai, India. Patients were randomly assigned (1:1) to receive locoregional treatment directed at their primary breast tumour and axillary lymph nodes, or no locoregional treatment, by a computer-generated block randomisation sequence (block size of four). Randomisation was stratified by site of distant metastases, number of metastatic lesions, and hormone receptor status. Patients with resectable primary tumour in the breast that could be treated with endocrine therapy were randomly assigned upfront, whereas those with an unresectable primary tumour were planned for chemotherapy before randomisation. Of the patients who had chemotherapy before randomisation, we randomly assigned patients who had an objective tumour response after six to eight cycles of chemotherapy. The primary endpoint was overall survival analysed by intention to treat. This study is registered with ClinicalTrials.gov, NCT00193778.

Findings Between Feb 7, 2005, and Jan 18, 2013, of the 716 women presenting with de-novo metastatic breast cancer, we randomly assigned 350 patients: 173 to locoregional treatment and 177 to no locoregional treatment. At data cut-off of Nov 1, 2013, median follow-up was 23 months (IQR 12·2–38·7) with 235 deaths (locoregional treatment n=118, no locoregional treatment n=117). Median overall survival was 19·2 months (95% CI 15·98–22·46) in the locoregional treatment group and 20·5 months (16·96–23·98) in the no-locoregional treatment group (HR 1·04, 95% CI 0·81–1·34; p=0·79), and the corresponding 2-year overall survival was 41·9% (95% CI 33·9–49·7) in the locoregional treatment group and 43·0% (35·2–50·8) in the no locoregional treatment group. The only adverse event noted was wound infection related to surgery in one patient in the locoregional treatment group.

Interpretation There is no evidence to suggest that locoregional treatment of the primary tumour affects overall survival in patients with metastatic breast cancer at initial presentation who have responded to front-line chemotherapy, and this procedure should not be part of routine practice.

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Introduction

Metastatic breast cancer is deemed an incurable disease with the main goals of treatment being prolongation of survival and palliation of symptoms. About 3–8% of patients with newly diagnosed disease have distant metastases at initial presentation.[1] The mainstay of treatment is systemic therapy, which includes chemotherapy, endocrine therapy, and targeted drugs. Traditionally, locoregional treatment (surgery or radiation) has been used only for control of fungation and bleeding.

Data from experiments in animal models of different cancers have suggested that surgical removal of the primary tumour could potentially increase metastatic spread.[2–5] By contrast, removal of the primary tumour was shown to improve survival in patients with metastatic renal cell carcinoma.[6,7] Removal of the primary tumour could potentially improve the outcome in breast cancer by removing drug resistant clones of cancer cells. Our trial was motivated by several retrospective analyses[8–20] that reported an overall survival benefit of locoregional treatment in patients with metastatic breast cancer. However, these studies are disparate in terms of patient numbers, indications for surgery, timing of surgery, and type of surgical intervention. Therefore, their results were probably affected by selection bias and a limited ability to control for potential confounding factors. Other retrospective analyses that have attempted to control for these biases have not shown any survival advantage after locoregional treatment.[21–25] A recent meta-analysis of

Panel: Research in context

Evidence before the study

To identify other studies of locoregional treatment of the primary tumour in patients with metastatic breast cancer we did a detailed search, with no time restriction, in PubMed and congress abstracts of the American Society of Clinical Oncology, European Society of Medical Oncology, and San Antonio Breast Cancer Symposium. We used the search terms "locoregional", "surgery", "metastatic", and "breast", and restricted our search to English language reports and publications. Our search identified several non-randomised, non-controlled, mainly retrospective studies, and few meta-analyses of these studies. There was no randomised controlled trial published in a peer-reviewed journal and only one randomised trial presented at a conference. The retrospective data suggested an overall survival benefit for patients treated with surgery, with or without radiation, for the primary breast tumour. However, these studies had several biases. The randomised trial presented as an abstract did not show superiority of surgical treatment of the primary tumour compared with no surgical treatment in these patients.

Added value of the study

For patients with de-novo metastatic breast cancer, our study is the first conclusive evidence that locoregional treatment of the primary tumour provides no meaningful survival benefit.

Implications of the available evidence

The results of this randomised trial suggest that locoregional treatment should not be a part of standard treatment for the subset of women presenting with de-novo metastatic breast cancer who respond to first-line systemic therapy. Our results refute the currently available retrospective evidence of a survival benefit for patients presenting with metastatic breast cancer who are given locoregional treatment for the primary tumour in the presence of distant metastasis.

these studies suggested a significantly improved overall survival with surgical resection of the primary tumour.[17] However, for the above mentioned reasons, this cannot be deemed definitive, practice-changing evidence.

To address this uncertainty, we did a randomised controlled trial comparing overall survival after locoregional treatment versus no locoregional treatment in patients with metastatic breast cancer at first presentation.

Methods

Study design and participants

In this open-label, randomised controlled trial in patients with untreated metastatic breast cancer at initial presentation, we recruited patients from Tata Memorial Centre, Mumbai. At the time of registration, eligible patients had histopathologically confirmed metastatic breast cancer, had not received any previous cancer-directed treatment, were 65 years or younger, and had an estimated life expectancy of at least 1 year. Patients with measurable and non-measureable disease were included. Other eligibility criteria were fitness to receive anthracycline chemotherapy, defined by adequate cardiac and liver functions. Major exclusion criteria at the time of registration were any previous cancer treatment, a single focus of metastatic disease amenable to treatment with curative intent, multiple liver metastases with grossly deranged liver function test, and involvement of more than two visceral organs, because of shorter life expectancy.

We registered patients with resectable hormone-sensitive primary breast tumours upfront, whereas those with unresectable primary tumours received chemotherapy first and patients with a complete or partial response were registered for the study.

Registered patients were eligible for randomisation if they had an estimated life expectancy of at least 6 months (at time of randomisation) and were fit to undergo general anaesthesia for major surgery. The major exclusion criterion at the time of randomisation was local or distant progression or stable disease (defined by WHO criteria as less than 50% decrease in tumour volume) in response to the preceding chemotherapy or ulceration, fungation, or bleeding at the local site that mandated palliative locoregional treatment.

The study was done in accordance with the Declaration of Helsinki and the ethical principles of the Good Clinical Practice framework of the International Conference on Harmonisation and was approved by the Institutional Review Board of Tata Memorial Centre. Patients provided written informed consent before being randomly assigned.

Randomisation and masking

Eligible patients were randomly assigned (1:1) to receive locoregional treatment directed at their primary breast tumour and axillary lymph nodes, or no locoregional treatment, with a computer-generated randomisation sequence and a telephone call to the central research office. RH generated the random sequence. We used a block randomisation method with a block size of four. The stratification factors were site of distant metastases (visceral *vs* bone *vs* both), number of metastatic lesions (2–3 *vs* >3), and hormone receptor status (oestrogen or progesterone receptor positive or both *vs* both negative). The study was periodically monitored for compliance with the protocol and patient safety by the institutional data monitoring and safety subcommittee.

Procedures

Patients eligible for upfront randomisation followed by endocrine therapy received tamoxifen 20 mg per day if they were premenopaual and tamoxifen 20 mg per day or