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.

Funding Department of Atomic Energy, Government of India.

Lancet Oncol 2015

Published Online
September 10, 2015
http://dx.doi.org/10.1016/S1470-2045(15)00135-7

See Online/Comment
http://dx.doi.org/10.1016/S1470-2045(15)00221-1

See Online for podcast interview with Rajendra Badwe

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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

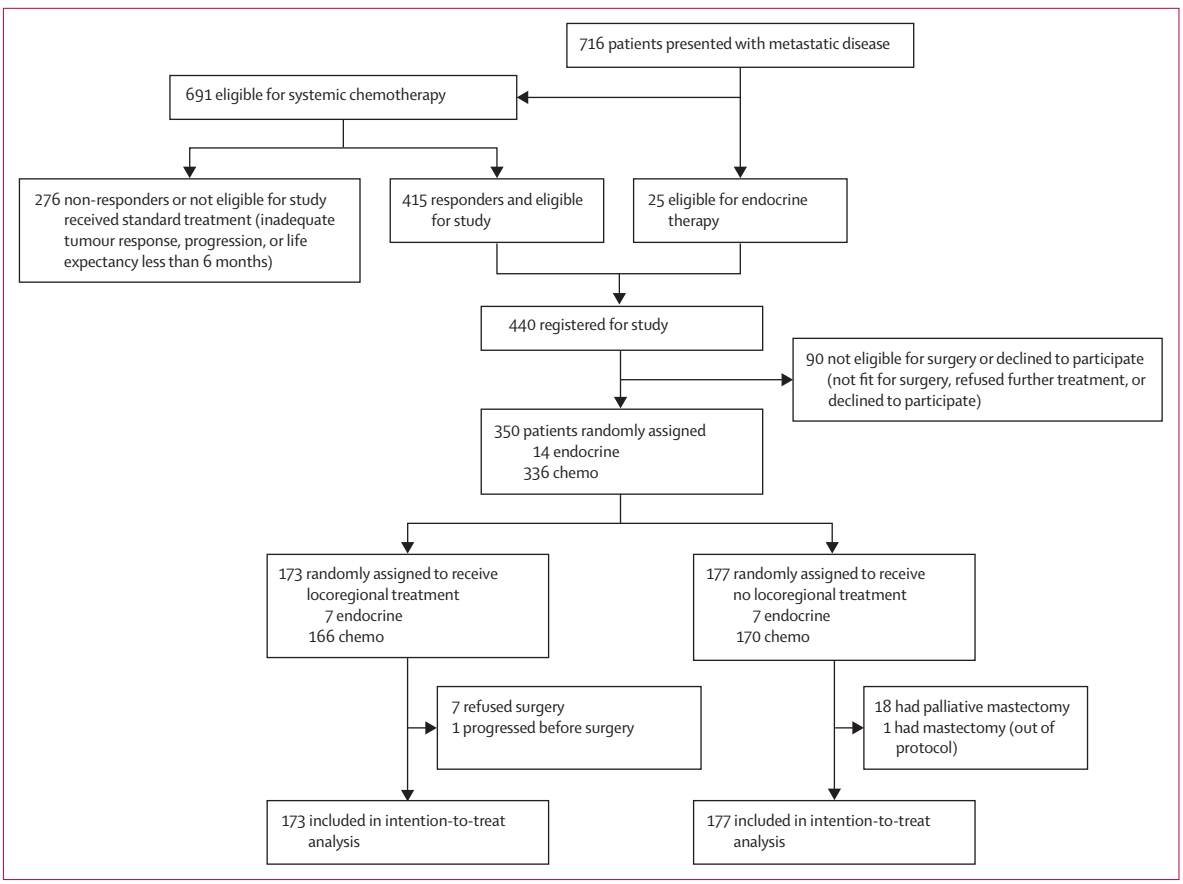

Figure 1: **Trial profile**

an aromatase inhibitor (letrozole 2·5 mg per day or anastrazole 1 mg per day) if they were postmenopausal. Endocrine therapy was continued until disease progression. Patients who presented with unresectable primary tumours and who were eligible for systemic treatment received six cycles of anthracycline-based combination chemotherapy (eg, FEC or FAC: 500 mg/m² fluorouracil plus 500 mg/m² cyclophosphamide plus 90–100 mg/m² epirubicin or 50 mg/m² doxorubicin, given every 3 weeks) or eight cycles of a sequential anthracycline-taxane regimen (eg, 90–100 mg/m² epirubicin or 60 mg/m² doxorubicin plus 600 mg/m² cyclophosphamide every 3 weeks for four cycles followed by 175 mg/m² paclitaxel every 3 weeks for four cycles) or six cycles of concurrent anthracycline-taxane chemotherapy (eg, 75 mg/m² docetaxel plus 50 mg/m² doxorubicin plus 500 mg/m² cyclophosphamide), with assessment of response after three or four cycles and after the last cycle of chemotherapy. Response was measured by physical examination. Response was assessed clinically with WHO criteria where tumour regression of greater than or equal to 50% is considered a response. Response in bone lesions was defined as abrogation of symptoms, sclerosis in an area previously reported as lytic, or disappearance of a previously noted lesion on radionuclide bone scan. Patients who achieved a complete or partial response at the end of planned course of chemotherapy were registered, and if eligible, randomly assigned.

At the time of registration, patients underwent standard physical examination and mammography to document the extent of locoregional disease and metastatic tumour assessment with either contrast-enhanced CT scan of the chest and abdomen or PET-CT scan. An isotope bone scan was undertaken in all patients. Histopathological confirmation of oestrogen receptor and progesterone receptor expression, and HER2 amplification was obtained in all patients by use of standard immunohistochemical techniques. Core or incisional biopsy was done in all patients at the time of initial work-up as per institutional protocol and the tissue was paraffin embedded. Immunohistochemistry for HER2 protein expression was done with the 3B5 monoclonal antibody (Immunotech, Marseilles, France, dilution 1:10) and using the standard avidin-biotin complex peroxidase method. HER2 receptor amplification was scored as per ASCO-CAP guidelines, where 1+ was regarded as negative, 3+ as positive, and 2+ as equivocal and requiring FISH testing for confirmation, if the patient could afford targeted treatment. ER and PR monoclonal mouse anti-

	Locoregional treatment group (n=173)	No locoregional treatment group (n=177)
Age (years)		
Median	48	48
Site of metastasis		
Bone	50 (29%)	50 (28%)
Visceral	75 (43%)	77 (44%)
Bone and visceral	48 (28%)	50 (28%)
Number of metastases		
≤3	44 (25%)	45 (26%)
>3	129 (75%)	132 (74%)
Oestrogen receptor or progesterone receptor		
Negative	71 (41%)	71 (40%)
Positive	102 (59%)	106 (60%)
Menopausal status†		
Pre and peri	74 (43%)	88 (50%)
Post	99 (57%)	89 (50%)
HER2 status		
Negative (including 1+)	124 (72%)	108 (61%)
Positive (3+)	45 (26%)	62 (35%)
Not known or equivocal (2+)	4 (2%)	7 (4%)

Data are n (%) unless stated otherwise. †Perimenopausal: history of no menstruation up to one preceding year; postmenopausal: cessation of menstrual cycles for more than 1 year.

Table 1: **Baseline characteristics of the intention-to-treat population**

	Locoregional treatment group	No locoregional treatment group
Upfront randomly assigned and received pre-randomisation endocrine treatment	7/173 (4%)	7/177 (4%)
Aromatase inhibitor	5/7 (71%)	4/7 (57%)
Tamoxifen	2/7 (29%)	3/7 (43%)
Received pre-randomisation chemotherapy	166/173 (96%)	170/177 (96%)
CAF/CEF	159/166 (96%)	161/170 (95%)
Anthracycline plus taxane	6 /166 (4%)	9/170 (5%)
Paclitaxel plus carboplatin	1/166 (1%)	0/170 (0%)
HER2-targeted treatment in HER2 3+ patients	1/ 45 (2%)	0/62 (0%)
Eligible for post- randomization endocrine treatment	102/173 (59%)	106/177 (60%)
Aromatase inhibitor	51/102 (50%)	46/106 (43%)
Tamoxifen	50/102 (49%)	60/106 (57%)
Not received	1/102 (1%)	0/106 (0%)
Premenopausal or perimenopausal women with hormone responsive tumours	49/74 (66%)	58/88 (66%)
Ovarian suppression		
Surgical (bilateral salpingoophorectomy)	38/49 (78%)	21/58 (36%)
Medical	0/49 (0%)	1/58 (2%)
Radiation	0/49 (0%)	17/58 (29%)
Not done	11/49 (22%)	19/58 (33%)

Data are n (%).

Table 2: **Systemic treatment before progression**

human estrogen receptor used was DAKO, Carpinteria, CA, USA (Clone 1D5; dilution 1:50), and the monoclonal mouse anti-human progesterone receptor was DAKO, Carpinteria, CA, USA (Clone PgR 636; dilution 1:50).

We assessed menopausal status at the time of presentation (before systemic chemotherapy) and defined a patient as premenopausal if she gave a history of a regular menstrual cycle. Those who gave a history of no menstruation for up to 1 year before presentation were defined as perimenopausal and those who gave a history of no menstruation for more than 1 year were defined as postmenopausal.

Locoregional treatment consisted of a standard surgical procedure that was either mastectomy or breast conserving surgery accompanied by full axillary lymph node dissection. In patients with persistent or residual supra-clavicular lymph nodes, we did a supra-clavicular fossa dissection to achieve complete surgical clearance. Surgical margins were managed according to standard guidelines applicable in non-metastatic breast cancer.[26] In premenopausal patients who continued to have menstrual cycles after chemotherapy and who had oestrogen or progesterone receptor-positive tumours, bilateral oophorectomy was done at the time of surgical removal of the primary tumour. Patients with oestrogen or progesterone receptor positive tumours received standard endocrine therapy after locoregional treatment, which was 20 mg per day tamoxifen for premenopausal patients and an aromatase inhibitor (2·5 mg letrozole per day or 1 mg anastrazole per day) or tamoxifen for post-menopausal patients, until disease progression.

Surgery was followed by standard postoperative adjuvant radiation treatment to the chest wall or remaining breast as per standard institutional practice for non-metastatic patients. In cases of modified radical mastectomy conventional external beam radiotherapy was delivered to the chest wall with or without the supraclavicular fossa at a dose of 45 Gy, 20 fractions over 4 weeks. For patients with breast-conserving surgery, the dose differed depending on clinical stage. Women presenting with operable breast cancer who underwent breast conserving surgery received whole breast radiotherapy at a dose of 45 Gy, 25 fractions over 5 weeks with a tumour bed boost of 15 Gy, six fractions over 1 week. For those with locally advanced cancers, after breast-conserving surgery, the whole breast radiotherapy dose was 50 Gy, 25 fractions over 5 weeks with with a tumour bed boost of 15 Gy, six fractions over 1 week. All patients who underwent breast-conserving surgery received postoperative radiation. In those patients who underwent mastectomy, those with a pre-chemotherapy tumour size of more than 5 cm or skin or chest wall involvement or axillary lymph node-positive disease received postoperative radiation.

Patients in the no locoregional treatment group were kept under observation after the last cycle of planned chemotherapy. If they were premenopausal, continued to have menstrual cycles after chemotherapy, and had

oestrogen or progesterone-receptor positive tumours, they underwent bilateral oophorectomy and received standard endocrine treatment as described until disease progression.

After completion of the study intervention, patients were followed up for survival and assessed for locoregional and distant progression. Patients were assessed once every 3 months; a detailed history was taken and a physical examination was done by one of the clinical investigators. Radiological assessment for metastatic progression (CT or PET-CT scan with or without radioisotope bone scan) was triggered by any clinical or symptomatic evidence of disease progression. Data from animal studies suggests that surgical intervention for metastatic breast cancer could be detrimental, with an increase in distant disease in the surgery group.[4] Thus, as a safety measure, a single assessment, as described above, that was not triggered by symptoms was done at about 12 weeks from randomisation.

At the time of disease progression, patients received further treatment according to standard institutional practice, which was usually further appropriate systemic therapy that could include further lines of chemotherapy or endocrine treatment, if applicable. HER2-targeted therapy was allowed and encouraged in patients with HER2 receptor-positive tumours, if financially feasible. Additionally, salvage surgery was offered in the no treatment group for pain, fungation, or bleeding. Patients suitable for surgical salvage were those whose tumours were amenable to surgical resection (with either primary closure or flap) with no likely gross residual disease after surgery. In symptomatic patients in whom surgical salvage was not feasible, palliative radiation was an option. After the accrual of the first 100 patients in the study, subsequent patients underwent health-related quality-of-life assessments during follow-up visits using validated instruments (EORTC QLQ C-30 and BR-23).

	Locoregional treatment group	No locoregional treatment group
Patients with disease progression	142/173 (82%)	128/177 (72%)
Lines of systemic chemotherapy* (taxane based, platinum based, capecitabine, and others), range (mean)	1–3 (1·3)	1–4 (1·6)
Patients with HER2 3+ tumours	35/173 (20%)	55/177 (31%)
HER2 targeted therapy received	0/35 (0%)	8/55 (15%)
Lines of endocrine therapy* (tamoxifen, aromastase inhibitors, and progestins), range (mean)	1–4 (1·17)	1–3 (1·36)
Premenopausal patients with hormone sensitive tumours	12/173 (69%)	7/177 (4%)
Ovarian suppression	3/12 (25%)	5/7 (71%)

Data are n (%) unless otherwise stated. *Post-progression hormone receptor-negative patients received several lines of chemotherapy. Hormone receptor-positive patients received the next line of hormone therapy depending on what was offered as first line. Those that escaped hormone suppression (ie, were refractory or hormone therapy resistant) or had a progression-free survival of less than 6 months after the last treatment received systemic chemotherapy similar to their hormone receptor-negative counterparts.

Table 3: **Systemic therapy in patients with progression of disease**

	Locoregional treatment group (n=173)	No locoregional treatment (n=177)
Surgery		
Modified radical mastectomy	125 (72%)	1 (1%)
Breast-conserving surgery	40 (23%)	NA
No surgery	8 (5%)	176 (99%)
Palliative surgery upon progression	1 (1%)	18 (10%)
Radiotherapy		
Chest wall and breast with supraclavicular fossa	119 (69%)	NA
Chest wall alone	19 (11%)	NA
No radiotherapy	8 (5%)	NA
Not known	27 (16%)	..

NA=not done.

Table 4: **Details of locoregional treatment**

Outcomes

The primary endpoint was overall survival, defined as the time from randomisation to death from any cause. Secondary endpoints were locoregional progression-free survival, distant progression-free survival, and health-related quality of life. An analysis of health-related quality of life in this trial has been done in a subset of patients and will be analysed and reported separately.[27] For the purpose of classifying the site of progression, ipsilateral chest wall, breast, axilla, and supraclavicular regions were deemed to be within the locoregional field, whereas other sites were regarded as distant. We defined locoregional progression-free survival as the time interval from randomisation to the date of first clinically or radiologically documented locoregional progression, defined as more than a 25% increase in the size of pre-existing lesions or the appearance of new lesions in the locoregional field. We defined distant progression-free survival as the time interval from randomisation to the date of first clinically or radiologically documented distant progression, defined as the appearance of new distant metastatic lesions or a symptomatic increase in existing distant metastatic lesions. Patients who had locoregional progression or distant progression as their first event were censored at this point of time for distant progression-free survival or locoregional progression-free survival, respectively.

Statistical analysis

The trial was designed with overall survival as the primary efficacy endpoint with a planned sample of 350 patients. The trial had 80% power to detect a hazard ratio of 0·75 for death from any cause with locoregional treatment compared with no locoregional treatment, with a two-sided alpha of 0·05. We hypothesised that overall survival with no locoregional treatment would be 18 months in the study population and would increase to 24 months with locoregional treatment.

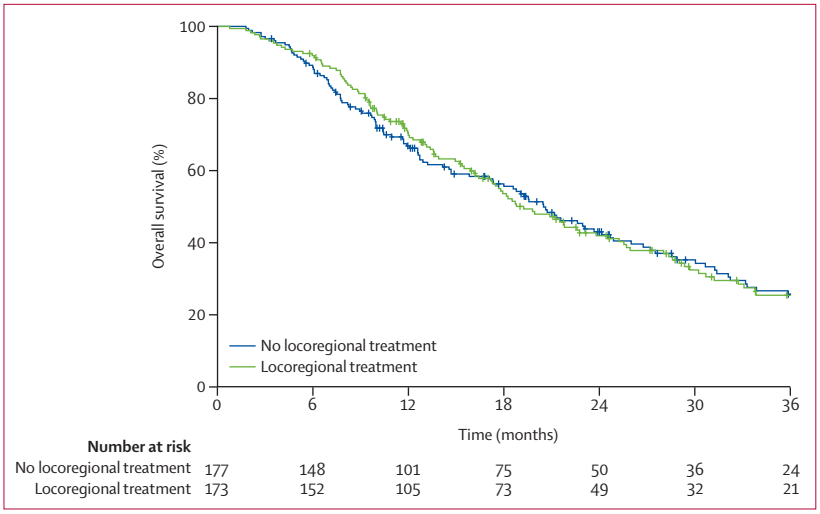

Figure 2: **Kaplan-Meier plot of overall survival**

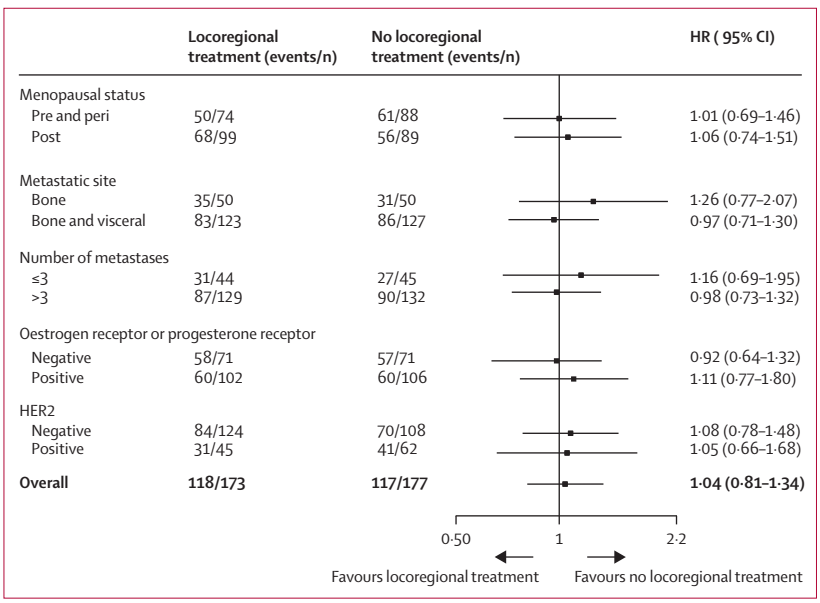

Figure 3: **Forest plot of overall survival subgroup analyses, unadjusted hazard ratios**

The primary endpoint was assessed in the intention-to-treat population and tested by means of two-sided log-rank tests. We used Kaplan-Meier methods to estimate medians for the primary and secondary endpoints, 2-year survival, and corresponding 95% CI. Analysis of overall survival was done in pre-specified subgroups defined by stratification factors. Additionally, two post-hoc analyses were done to assess results in subgroups defined by HER2 receptor status (non-amplified *vs* amplified) and menopausal status (pre-menopausal or perimenopausal *vs* post-menopausal). We also used a multivariate Cox proportional-hazards model, with the stratification factors, as well as HER2 status and menopausal status as covariates, to estimate hazard ratios and 95% CI for the primary efficacy end point.

We used SPSS (version 18.0) statistical software for statistical analysis.

This study is registered with ClinicalTrials.gov, NCT00193778.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had access to the data and the corresponding author had final responsibility to submit for publication.

Results

From Feb 7, 2005, to Jan 18, 2013, 716 patients presented at Tata Memorial Centre with de-novo metastatic disease, of whom 25 were candidates for first-line endocrine treatment and 14 (56%) of 25 were eligible to be randomly assigned to the treatment groups. The remaining 691 women received chemotherapy as their first-line treatment, of whom 415 (60%) had a complete or partial response. Of the 415 responders, 336 (81%) were eligible to be randomly assigned. Of the 350 randomly assigned patients, 173 patients were assigned to locoregional treatment and 177 were assigned to no locoregional treatment (figure 1). Baseline demographic and disease characteristics were well balanced between groups (table 1). Median duration of follow-up was 23 months (IQR 12·2–38·7) at data cutoff on Nov 1, 2013.

Table 2 shows details of chemotherapy and endocrine therapy received by patients before randomisation and after randomisation but before progression. Systemic therapies given to patients after progression are shown in table 3. Table 4 shows details of the surgical intervention and radiation treatment given to patients in both groups. Eight (5%) of 173 patients in the locoregional treatment group did not undergo locoregional treatment. 18 (10%) of 177 patients in the no locoregional treatment group underwent surgical removal of the primary tumour for palliation of symptoms upon progression a median 4·1 months (IQR 3–15) after randomisation (table 3). One patient in the locoregional treatment group had an adverse event related to surgery (wound infection, grade 3); no other adverse events were noted.

At the time of data cutoff, we recorded 235 deaths (118 in the locoregional treatment group and 117 in the no locoregional treatment group). Locoregional treatment did not result in a significant improvement in overall survival compared with no locoregional treatment (median survival 19·2 months [95% CI 15·98–22·46] *vs* 20·5 months [16·96–23·98]; HR 1·04, 95% CI 0·81–1·34; p=0·79; figure 2). 2-year overall survival was 41·9% (95% CI 33·9–49·7) in the locoregional treatment group and 43·0% (95% CI 35·2–50·8) in the no locoregional treatment group (figure 2). Ten (6%) of 177 women in the no locoregional treatment group, and five (3%) of 173 in

the locoregional treatment group, died of local recurrence and locally uncontrolled disease, despite several lines of systemic chemotherapy. There was no difference in overall survival between the two groups after adjusting for the stratification factors, menopausal status, and HER2 status (locoregional treatment *vs* no-locoregional treatment, adjusted HR 1·05, 95% CI 0·81–1·36; p=0·73). The findings from subgroup analyses of overall survival were consistent with the overall result (figure 3).

In a multivariate Cox proportional hazards model with stratification factors only, overall survival was independently associated with expression of the oestrogen or progesterone receptor (HR 0·37, 95% CI 0·28–0·48; p<0·0001) and fewer distant metastatic sites at initial presentation (0·61, 0·45–0·83; p=0·0020). The site of metastasis at initial presentation was not associated with overall survival (bone *vs* visceral with or without bone; HR 0·96, 95% CI 0·71–1·29; p=0·79).

The median time interval from randomisation to first metastatic radiological assessment was 3·4 months (IQR 3·2–5·1) in the locoregional treatment group and 3·2 months (3·0–4·9) in the no locoregional treatment group. Locoregional treatment resulted in a significant improvement in locoregional progression-free survival compared with that in the no locoregional treatment group (median not attained *vs* 18·2 months [95% CI 15·1–21·3]; HR 0·16, 95% CI 0·10–0·26; p<0·0001; figure 4A). By contrast, locoregional treatment resulted in a significant detriment in distant progression-free survival compared with that in the no locoregional treatment group (median 11·3 months [95% CI 7·7–14·84] *vs* 19·8 months [10·26–29·0]; HR 1·42, 95% CI 1·08–1·85; p=0·012; figure 4B).

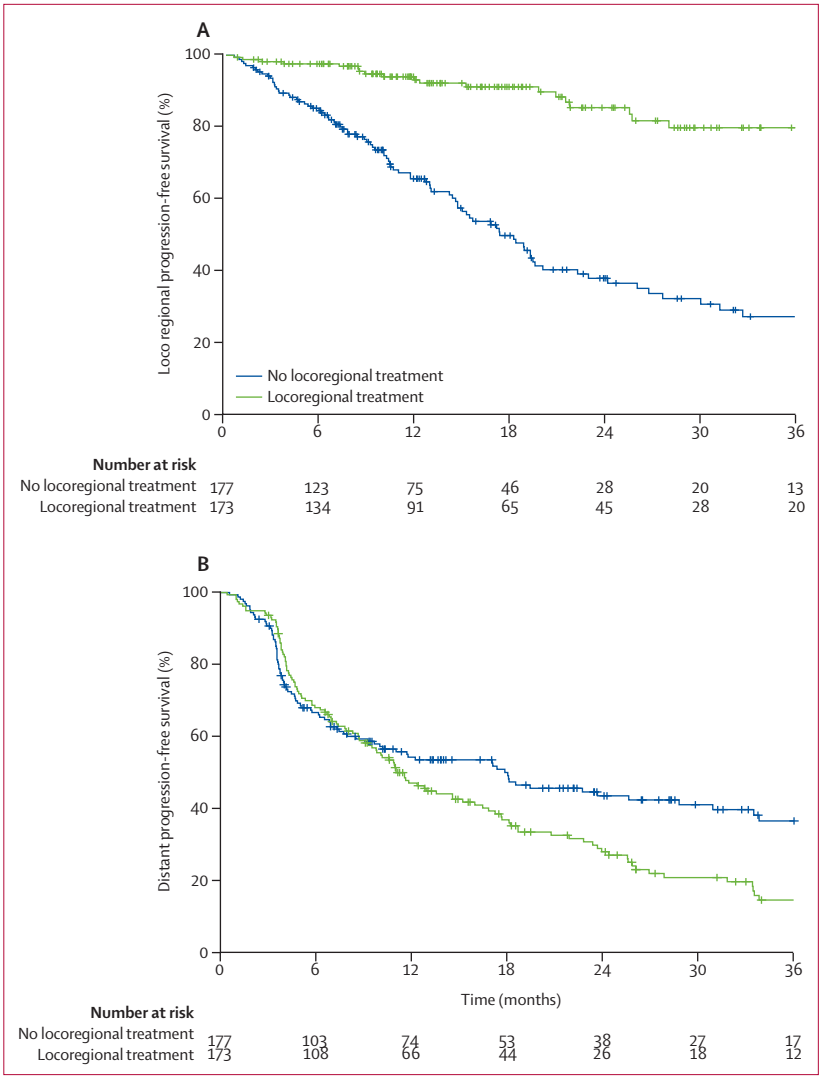

Figure 4: **Kaplan-Meier plot of locoregional progression-free survival (A) and distant progression-free survival (B)**

Discussion

To our knowledge, this is the first randomised controlled trial that has reported the comparison of the effect of locoregional treatment versus no locoregional treatment of a primary breast tumour in patients with metastatic disease at their initial presentation who have responded to first-line chemotherapy. We noted no benefit of locoregional treatment in this patient population in terms of overall survival. Furthermore there was no evidence that any patient subgroup defined by menopausal status, metastatic disease burden, oestrogen or progesterone receptor status, or HER2 receptor status derived any survival benefit from this procedure. Additionally, our data suggest that surgical treatment of the primary tumour in women with metastatic breast cancer cannot be justified on the grounds of achieving palliation and symptom control because only 18 (10%) of 177 women in the no locoregional treatment group required palliative surgery during follow-up.

One previous randomised trial[28] in which resection of the primary tumour in patients with metastatic breast cancer was compared with no locoregional treatment reported no overall survival benefit of locoregional treatment at the interim analysis. The results of this trial support the main conclusion of our study regarding the lack of a survival benefit of this procedure in this patient population.

About 60% of our patients had a clinical response to chemotherapy and were deemed eligible for randomisation, which is similar to the response to chemotherapy reported in other unselected cohorts of patients with stage IV breast cancer.[29] Pre-randomisation systemic treatment and post-progression chemotherapy and endocrine treatments were similar in both groups, thus these factors are unlikely to have affected the overall survival results. The overall survival recorded in both groups was lower than figures reported from developed countries. This discrepancy could be due to

later diagnosis in the natural course of de-novo metastatic disease in the Indian patient population. In this context, it is important to note that there is significantly reduced overall survival in symptomatic versus asymptomatic patients with metastatic breast cancer[20,30] and most of our patients had symptomatic disease.[20,30] Moreover 107 (31%) of 350 patients had HER2 receptor-positive disease, but most of these (98 [92%]) patients did not receive HER2-targeted treatment because of financial constraints. Additionally, only some patients received taxane-based chemotherapy, thus an association of these factors and overall survival was not assessed. However, because of randomised treatment allocation, these factors are unlikely to have affected the outcome of this study.

An interesting finding in our study was the significant detriment in distant progression-free survival in women who received locoregional treatment compared with those who did not. This finding is consistent with the results of preclinical studies,[2–5] which showed growth of a metastatic tumour subsequent to the removal of the primary tumour. The mechanisms by which this might happen are unclear, but might include fresh surgical dissemination with increased adhesion of circulating tumour cells to the vascular endothelium of target organs,[31] surgery-induced immunosuppression,[32] surgery-induced angiogenic switch, or the inflammatory cascade. It remains a matter of interest whether a similar growth advantage might also be conferred to micrometastatic disease in early breast cancer and whether events at the time of surgery can be modulated to gain long-term survival advantage.[33] Based on our data, it could be argued that censoring patients who had local progression first in the analysis of distant progression could lead to excess numbers of distant progression in patients who had received locoregional treatment. However, all patients who had local progression were assessed for distant metastatic disease and patients who had both local and distant progression were analysed for both local and distant progression-free survival. The detriment in distant progression-free survival is offset by an improvement in local control and is consistent with the non-significant difference in overall survival at 2 years.

One limitation of our study is that most patients were randomly assigned after receiving and responding to chemotherapy as their first treatment. Therefore, the applicability of these results to patients who receive endocrine therapy or chemotherapy plus HER2-targeted therapy as their first-line treatment is unknown, although there is no reason to believe that there is an interaction between these treatments and the effect of locoregional treatment of the primary tumour.

In conclusion, there is no evidence to suggest that locoregional treatment of the primary tumour confers an overall survival advantage in patients with de-novo metastatic breast cancer and this procedure should not be routinely done.

Contributors

RB conceived the idea, designed, and was the lead investigator, and analysed the data. RB and SG wrote the initial draft of the report. All authors contributed to subsequent revisions and approved the final draft for submission. RH assisted in the design, conduct including random allocation, maintained the database, and analysis of the study. RB, VP, NN, RK, AB, and SG treated patients and acquired the data. SS assisted in the conduct and maintained the database. SG assisted in the study analysis and critically reviewed the manuscript. IM critically reviewed the report. The report was reviewed by all authors who vouch for the completeness and accuracy of the data.

Declaration of interests

We declare no competing interests.

Acknowledgments

This study was funded by the Department of Atomic Energy, Government of India, through a research grant for infrastructure and human resources for clinical research.

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