



## Original article

## Impact of locoregional treatment on survival in patients presented with metastatic breast carcinoma



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## ABSTRACT

**Objectives:** In this study, we tried to evaluate the efficacy of locoregional treatment (LRT) in patients with metastatic breast carcinoma (MBC).

**Materials and methods:** The medical records of 227 patients with MBC at initial presentation between April 1999 and January 2013 were retrospectively evaluated. The median age at diagnosis was 50 years (range, 27–83 years). Thirty-nine patients (17%) had no LRT. Among patients who had LRT, 2 (1%) had locoregional radiotherapy (RT) alone, 54 (29%) had surgery alone [mastectomy,  $n = 50$ ; breast conserving surgery (BCS),  $n = 4$ ] and 132 (70%) had surgery (mastectomy,  $n = 119$ ; BCS,  $n = 13$ ) followed by locoregional RT.

**Results:** The median follow-up time was 35 months (range, 4–149 months). Five-year OS and PFS rates were 44% and 20%, respectively. In both univariate and multivariate analysis LRT per se did not affect OS and PFS rates. However, the 5-year OS and PFS rates were significantly higher in patients treated with locoregional RT than the ones who were not. The corresponding rates were 56% vs. 24% for OS and 27% vs. 7% for PFS ( $p < 0.001$ ). Median survival was 67 months and 37 months, respectively.

**Conclusion:** Our study showed that patients with MBC who received postoperative locoregional RT may have a survival advantage compared with patients who were only treated by surgery. A phase III trial testing the role of adjuvant locoregional RT may help to distinguish patients who will benefit from adjuvant RT.

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## Introduction

Metastasis at the time of diagnosis has been observed in 3–10% of women with breast carcinoma and it has been traditionally considered to be an incurable disease [1]. Median survival of these patients has been reported to be in the range of 16–24 months though some patients have been reported to have prolonged survival [2,3].

Generally these patients had been treated by systemic treatment either as chemotherapy or hormonal therapy and locoregional treatment (LRT) had been traditionally reserved for patients with symptomatic tumors as with bleeding, ulceration or pain [4].

However, in recent years with the introduction of more effective systemic therapies such as taxane-based chemotherapy, aromatase inhibitors or targeted therapies as trastuzumab or bevacizumab, patients with metastatic disease are observed to live longer and even some live more than a decade [5,6]. Several retrospective studies including Surveillance, Epidemiology, and End Results (SEER) 1988–2003 database analysis showed that local therapy improved survival rates in these patients [6–17]. More recently, two randomized trials were presented in the San Antonio Breast Cancer Symposium, one from India and one from Turkey evaluated the efficacy of local treatment in patients with metastatic breast cancer (MBC) [18,19]. There are also ongoing studies from United States, Austria and Netherlands evaluating the role of local treatment in patients with metastasis at diagnosis [20]. Hopefully the long term results of these phase III trials will highlight which patients will most likely benefit from LRT.

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In our retrospective study, we tried to evaluate the efficacy of LRT in patients with MBC and to find out whether adjuvant locoregional radiotherapy (RT) further improved the survival rates.

## Materials and methods

The medical records of 227 patients with MBC at initial presentation between April 1999 and January 2013 in our institute were retrospectively evaluated. LRT is defined as surgery and/or RT of the primary tumor and regional lymph nodes. This retrospective study was approved by the institutional ethics committee. Follow-up information was obtained from the patient charts, any hospital notes, referring doctors, general directorate of population and citizenship affairs, and as a last resort, from patients and/or next of kin.

Patient, tumor and treatment characteristics used for this analysis included the following: age at diagnosis (<50 years vs. ≥50 years), menopausal status, grade, histological subtype (ductal, lobular, other), T stage (T1–2 vs. T3–4) and N stage (N0 vs. N+), estrogen receptor (ER), progesterone receptor (PR), and HER2/neu status (positive vs. negative vs. unknown), metastatic sites (bone-only vs. others), visceral metastases (yes vs. no), and number (solitary vs. multiple) of metastases, use of hormonal therapy, chemotherapy, RT, type of surgery [mastectomy vs. breast conserving surgery (BCS)], timing of LRT, RT volume [breast/chest wall (CW) ± lymphatic] and response to systemic therapy. All the patient and treatment characteristics are listed in Tables 1 and 2.

Patients were analyzed based on primary treatment: those who had LRT versus who did not, those who received RT versus those who did not, and those who had surgery versus those who did not. Systemic treatment was analyzed as chemotherapy alone, hormonal therapy alone, or both. Response to chemotherapy when used before LRT was also recorded by using the Response Evaluation Criteria in Solid Tumors (RECIST).

The treatment approach of our institute in MBC was to give upfront chemotherapy in these patients and when there was complete or near complete response, LRT was offered. More than half of our patients on the other hand were treated with LRT first and systemic treatment thereafter. The reason for this schedule was that these patients were staged with only abdominal ultrasonography (USG) and chest x-ray, and found out with metastases after surgery when positron emission tomography (PET)/computed tomography (CT) or bone scintigraphy was performed. Postoperative locoregional RT was typically applied to patients when BCS was performed and in patients with lymph node metastasis, tumor ≥5 cm or T4 disease at initial presentation or close or positive surgical margins when modified radical mastectomy (MRM) was applied. RT was applied with tangential fields to the whole breast or CW with or without lymphatic RT. The median dose to the whole breast or CW was 50 Gy. In case of BCS, a tumor bed boost dose of 10 Gy was also applied. Again a total dose of 50 Gy was applied to regional lymphatics when indicated. Patients with residual bone metastases after chemotherapy also received a course of external beam RT to the residual metastatic sites.

## Statistics

Overall Survival (OS) was defined as the time between the date of diagnosis and the date of death or the last follow-up. Progression free Survival (PFS) was defined as the time between the date of diagnosis and the date of any failure. Survival analysis was carried out using the Kaplan–Meier method and comparisons were made using the log-rank test. The Chi-square test was used to compare patient, tumor and treatment-related characteristics according to treatment groups. Multivariate Cox regression analysis was performed using following prognostic variables for their impact on OS:

**Table 1**  
Clinicopathologic characteristics in the entire cohort and comparisons between patients with and without locoregional treatment.

Characteristic	Entire cohort (n = 227)	LRT (n = 188)	No LRT (n = 39)	p <sup>a</sup>
Age (y)				0.22
Median (range)	50 (27–83)	50 (27–83)	52 (29–79)	
<50	109 (48)	94 (50)	15 (39)	
≥50	118 (52)	94 (50)	24 (62)	
Menopausal status				0.07
Premenopausal	100 (44)	81 (43)	19 (49)	
Postmenopausal	104 (46)	84 (45)	20 (51)	
Perimenopausal	23 (10)	23 (12)		
Histology				0.086
IDC	161 (71)	140 (74)	21 (54)	
ILC	18 (8)	13 (7)	5 (13)	
Other	46 (20)	35 (19)	11 (28)	
Unknown	2 (1)		2 (5)	
T stage				0.004
T1–2	117 (52)	105 (56)	12 (31)	
T3–4	110 (48)	83 (44)	27 (69)	
N stage				0.944
N0	24 (11)	20 (11)	4 (10)	
N+	203 (89)	168 (89)	35 (90)	
Grade				<0.001
I	10 (4)	8 (4)	2 (5)	
II	95 (42)	79 (42)	16 (41)	
III	88 (39)	81 (43)	7 (18)	
Unknown	34 (15)	20 (11)	14 (36)	
Estrogen receptor status				0.707
Positive	153 (67)	125 (67)	28 (72)	
Negative	70 (31)	59 (31)	11 (28)	
Unknown	4 (2)	4 (2)		
Progesterone receptor status				0.910
Positive	152 (67)	125 (67)	27 (69)	
Negative	70 (31)	58 (31)	12 (31)	
Unknown	5 (2)	5 (2)		
Her2/neu status				0.528
Positive	73 (32)	62 (33)	11 (28)	
Negative	146 (64)	119 (63)	27 (69)	
Unknown	8 (4)	7 (4)	1 (3)	
Triple negative tumor				0.929
Yes	18 (8)	15 (8)	3 (8)	
No	200 (88)	165 (88)	35 (89)	
Unknown	9 (4)	8 (4)	1 (3)	
Site(s) of metastases				0.211
Bone-only	92 (41)	80 (43)	12 (31)	
Others	135 (59)	108 (57)	27 (69)	
Visceral metastases				0.08
No	117 (52)	102 (54)	15 (39)	
Yes	110 (48)	86 (46)	24 (61)	
Number of metastases				0.003
1	43 (19)	42 (22)	1 (3)	
≥2	184 (81)	146 (78)	38 (97)	

Abbreviations: LRT = locoregional treatment; IDC = invasive ductal carcinoma; ILC = invasive lobular carcinoma.

Data presented as number (%) unless otherwise specified.

<sup>a</sup> Test statistics applied to known values only.

Age at diagnosis, tumor grade, T and N stage, type of surgery, ER and PR status, number of metastases, presence of visceral metastases, bone only versus other metastases, presence of surgery, and use of RT. All statistical analysis was conducted using SPSS version 18.0 (Chicago, Illinois, USA). All analysis used the conventional  $p < 0.05$  level of significance.

## Results

### Patient, tumor, and treatment characteristics

The median follow-up time was 35 months (range, 4–149 months). The characteristics of the patients and tumors for all 227

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