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ORIGINAL ARTICLE – BREAST ONCOLOGY

Randomized Trial Comparing Resection of Primary Tumor with No Surgery in Stage IV Breast Cancer at Presentation: Protocol MF07-01

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ABSTRACT

Background. The MF07-01 trial is a multicenter, phase III, randomized, controlled study comparing locoregional treatment (LRT) followed by systemic therapy (ST) with ST alone for treatment-naïve stage IV breast cancer (BC) patients.

Methods. At initial diagnosis, patients were randomized 1:1 to either the LRT or ST group. All the patients were given ST either immediately after randomization or after surgical resection of the intact primary tumor.

Results. The trial enrolled 274 patients: 138 in the LRT group and 136 in the ST group. Hazard of death was 34% lower in the LRT group than in the ST group (hazard ratio [HR], 0.66; 95% confidence interval [CI], 0.49–0.88; $p = 0.005$). Unplanned subgroup analyses showed that the risk of death was statistically lower in the LRT group than in the ST group with respect to estrogen receptor (ER)/progesterone receptor (PR)(+) (HR 0.64; 95% CI 0.46–0.91; $p = 0.01$), human epidermal growth factor 2 (HER2)/neu(–) (HR 0.64; 95% CI 0.45–0.91; $p = 0.01$), patients younger than 55 years (HR 0.57; 95% CI 0.38–0.86; $p = 0.007$), and patients with solitary bone-only metastases (HR 0.47; 95% CI 0.23–0.98; $p = 0.04$).

Conclusion. In the current trial, improvement in 36-month survival was not observed with upfront surgery for stage IV breast cancer patients. However, a longer follow-up study (median, 40 months) showed statistically significant improvement in median survival. When locoregional treatment in de novo stage IV BC is discussed with the patient as an option, practitioners must consider age, performance status, comorbidities, tumor type, and metastatic disease burden.

The incidence of synchronous distant metastatic disease in breast cancer (BC) patients with a new diagnosis is up to 10%.[1–3] In this patient population, systemic therapy (ST) is the current standard of care. Fortunately, advances in adjuvant therapies and better understanding of tumor biology appear to have improved patient survival from stage IV BC.[4–6]

Primary tumor resection in the setting of stage IV BC and its impact on survival remain controversial. Primary tumor extirpation has been shown to improve survival in other settings.[7–10] Possible explanations for this survival advantage include augmented immunomodulation through decreased tumor burden, decreased metastatic potential via elimination of BC stem cells and removal of the "seed source" of new metastases, increased chemotherapeutic efficacy, and decreased likelihood of the development of potentially resistant cell lines.[11,12]

Retrospective studies and meta-analyses suggest that primary tumor resection for appropriately selected de novo stage IV BC patients not only limits locoregional progression, but also prolongs disease-free and overall survival (OS).[1–3,13–26] These studies typically had selection biases due to their retrospective nature, possibly explaining enhanced survival of those patients undergoing resection of their primary tumor in the setting of metastatic disease.[14] Patients offered surgery tend to be younger and healthier, express a more favorable tumor histology, and present with a lower locoregional disease burden with metastases in more surgically favorable locations than those patients not offered surgery. Further limitations of these trials such as lack of detailed treatment information and timing of surgery were evident. Conversely, some studies suggest that upfront surgery can adversely affect survival for stage IV BC patients, especially patients with increased metastatic tumor burden.[27–29]

The MF07-01 trial was a phase III, multicentric, randomized, controlled clinical study comparing locoregional treatment (LRT) with primary ST for de novo stage IV BC patients. The primary aim of the study was to assess the efficacy of LRT for OS, and the secondary end points included rates of locoregional progression/relapse (LPR) and 30 day-mortality.

METHODS

The protocol for this study has been previously published.[30] Participating centers obtained local ethics committee approval before entering the study. To evaluate metastases, thoracoabdominal computerized tomography (CT), whole-body bone scintigraphy, and/or magnetic resonance imaging (MRI) and fluorodeoxyglucose (FDG) whole-body positron emission tomography (PET)/CT were performed initially and at follow-up visits per institutional protocol. In the setting of solitary bone metastasis, two distinct imaging methods (whole-body bone scintigraphy and FDG-PET/CT) were performed to confirm diagnoses. Based on lower analyzable bone tissue yield, lesion access difficulty, and complications, biopsy was not planned for patients with bone lesions. The decision to perform a biopsy of each metastatic site was left to each investigator.

At the time of study inclusion, eligible patients were randomly assigned to one of two study arms: LRT with subsequent ST or primary ST. The patients in the LRT group received ST after primary tumor resection, whereas the patients in the ST group began receiving ST immediately after randomization (Fig. 1). The LRT consisted of complete resection (no tumor on margins) of the primary tumor (either as mastectomy or breast-conserving surgery [BCS]). For clinically node-negative patients, sentinel lymph node (SLN) biopsy was allowed to assess axillary involvement. Axillary clearance was not required for SLN-negative patients. However, standard levels 1 and 2 axillary clearance was required for SLN-positive patients, patients with positive lymph node or nodes presenting before surgery, and patients with unidentified SLN during surgery. All the patients who underwent BCS received radiotherapy (RT) to the whole breast as indicated in early-stage BC unless the patient died earlier. Breast RT was planned to be administered within 3–6 months after surgery. Decisions to administer RT to the breast, regional lymph basins, thoracic wall, and metastatic site were made by each

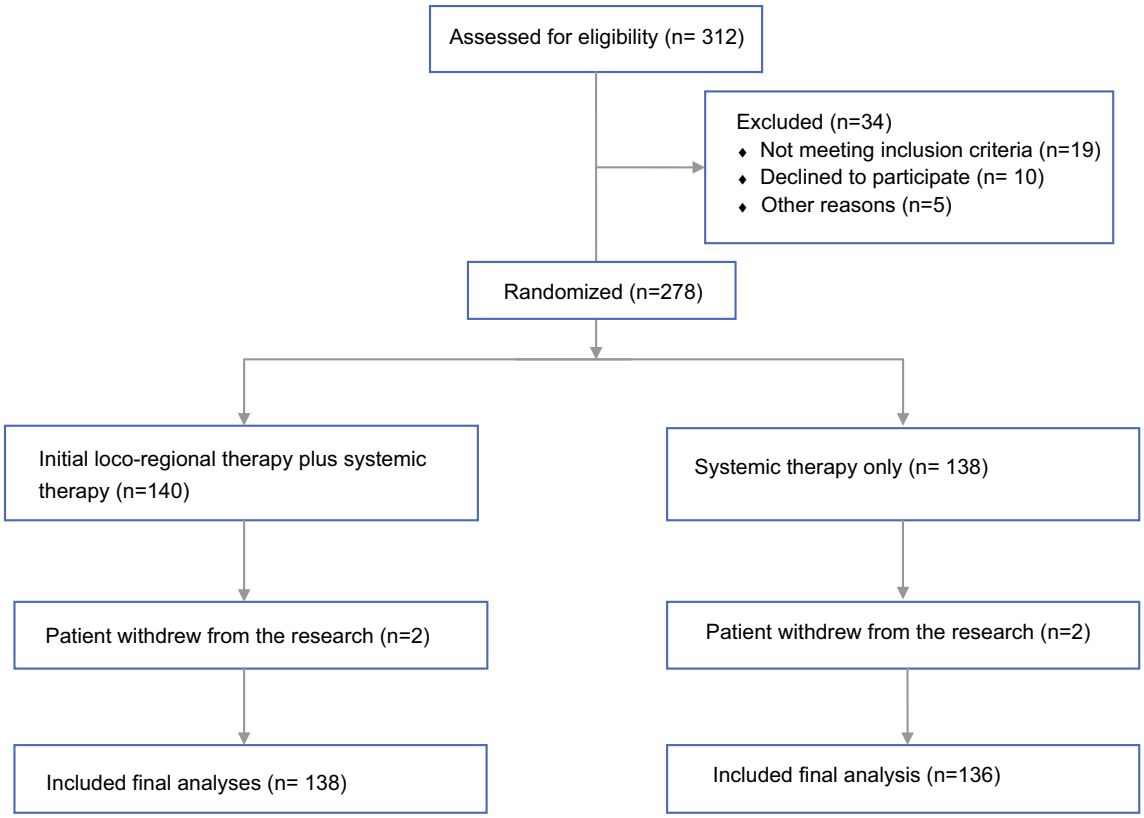

FIG. 1 Consort flow diagram

institution per their treatment protocols. The time from surgery to initiation of systemic therapy was recorded. Patients were followed up to 30 days after surgery and then every 3 months until death was observed.

The study defined LPR as clinically or radiologically documented size progression of the primary tumor, ulceration, bleeding, or fungation, or as findings of new locoregional lesions.

Statistical Analysis

Sample size calculation was based on retrospective studies comparing stage IV BC patients who underwent surgical resection with those who did not. The assumptive OS difference at 36 months between the two study groups was determined to be 18% (35% in the LRT group vs. 17% in the ST group). A 10% dropout rate, including patients lost to follow-up evaluation, was assumed. A one-sided log-rank test with a 95% confidence interval (CI) (alpha, 0.05) and 90% power (1-beta, 0.9) sample size calculation showed that 271 patients needed to be randomized. Because we hypothesized that the survival rate would be greater in the LRT group than in the ST group, we used a one-sided log-rank test for power calculations, with 136 patients assigned to each study arm. The primary end point was OS, and modified intention-to-treat analyses of survival included all deaths.

Stratification factors such as patient age, tumor size, histology grade/type, receptor status, and triple-negative status could be important for de novo stage IV BC patients. However, the specific stratification factors that would be most important in these patients for planning a priori recruitment and randomization based on specific stratification factors were unclear. Also, numerable stratification factors were prohibitive to recruitment of sufficient patients for each group within the prespecified recruitment period. During the recruitment period, estrogen receptor (ER)/progesterone receptor (PR) status data collection was not required. Hence, ER/PR status was unknown at randomization. As such, no stratification was planned. Rather, we adapted a statistical alternative to stratified randomization, adjusting analysis of treatment effectiveness for covariates using multivariate analysis (post-stratification).[31]

Continuous and categorical variable differences between the LRT and ST groups were analyzed using the *t* test and Chi square test, respectively. The log-rank test was used to estimate OS, and Kaplan–Meier survival curves were used to estimate 3- and 5-year survival rates for the LRT and ST groups. We used multivariate Cox models with baseline and clinical characteristics including age, tumor size,

grade, ER/PR status, human epidermal growth factor 2 (HER2)/neu, triple-negative, bone-only metastasis, locoregional progression, intervention to metastasis, chemotherapy, and use of bisphosphonates in the model to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the OS.

Statistical analyses were conducted with SAS/STAT version 9.3 (SAS Institute, Inc., Cary, NC, USA), SPSS v22.0 (released 2013; IBM Corp, Armonk, NY, USA), IBM SPSS Statistics for Windows, version 22.0.

RESULTS

Between November 2007 and December 2012, the study recruited 312 patients. Of these patients, 34 did not meet the inclusion criteria, and 4 withdrew from the study. Therefore, 274 patients were randomized into the LRT ($n = 138$) or ST ($n = 136$) group (Fig. 1). The patient cohorts were similar with respect to age, BMI, and HER2/neu-positivity ($p > 0.05$) (Table 1). The patients in the LRT group had higher rates of ER/PR positivity (85.5% vs. 71.8%; $p < 0.05$) and lower rates of triple-negative tumors (7.3% vs. 17.4%; $p < 0.05$) than the patients in the ST group. Most of the LRT group patients ($n = 102$, 74%) had undergone mastectomy and axillary lymph node dissection.

Most patients had bone-only metastasis or bone metastasis with other metastases. The incidence of solitary bone metastases was similar between the cohorts (66.7% in the LRT group vs. 60% in the ST group; $p > 0.05$).

Both irradiation rates and surgical intervention to metastatic sites were similar in the LRT and ST groups ($p = 0.07$). In the LRT group, ST was started 27.1 ± 9.9 days after surgery. Chemotherapy regimens and use of bisphosphonates did not differ between the two groups ($p > 0.05$).

The 30-day mortality rate was similar in the LRT (1.4%) and ST (1.5%) groups. The median follow-up period among the survivors was 54.5 months (range 45–70 months) for the LRT group and 55 months (range 45–74 months) for the ST group ($p = 0.85$). During the 40-month follow-up period, 76 (55%) of the 138 patients in the LRT group and 101 (74%) of the 136 patients in the ST group died. The hazard of death was 34% lower in the LRT group than in the ST group (HR 0.66; 95% CI 0.49–0.88; $p = 0.005$; Fig. 2). At 3 years, the survival was similar for the LRT (60%; 95% CI 51–68%) and ST (51%; 95% CI 42–59%) groups ($p = 0.10$). However, by the fifth year of the follow-up period, 41.6% (95% CI 32.5–50.4%) of the patients were alive in the LRT group and only 24.4% (95% CI 16.9–32.6%) were alive in the ST group ($p = 0.005$) (Fig. 2).

Unplanned subgroup analyses (Fig. 3) showed that OS was statistically longer in the LRT group than in the ST group with respect to ER/PR(+) (HR 0.63; 95% CI 0.44–0.89; $p = 0.008$) (Fig. S4), HER2/neu(–) (HR 0.64; 95% CI 0.45–0.91; $p = 0.01$), patients younger than 55 years (HR 0.57; 95% CI 0.38–0.86; $p = 0.007$) (Fig. S5), and patients with solitary bone-only metastases (HR 0.47; 95% CI 0.23–0.98; $p = 0.04$) (Fig. S6). Median survival was 14 months longer in the LRT group than in the ST group with respect to bone-only metastasis (HR 0.67; 95% CI 0.43–1.07; $p = 0.09$). In the solitary bone metastasis subgroup, the 5-year survival rate was 51.7% (95% CI 31.2–68.9%) in the LRT group and 29.2% (95% CI 11.4–49.6%) in the ST group, with a 9.5-month median longer survival (HR 0.47; 95% CI 0.23–0.98; $p = 0.04$).

Because most patients (68%) died within the median 40-month follow-up period, we analyzed 3-year survival for the patients with multiple pulmonary/liver metastases (31%; 95% CI 9–55% in the LRT group vs. 67%; 95% CI 38–85% in the ST group) ($p = 0.05$) (Fig. S7).

The rate of LPR was higher in the ST group: 1% ($n = 2$) in the LRT group and 11% ($n = 15$) in the ST group ($p = 0.001$). In the ST group, eight patients underwent palliative surgery, and two patients received RT for locoregional progression. For 38% of the patients, post-mastectomy radiation therapy (PMRT) was performed. The median survival period after PMRT was 41 months (95% CI 37.2–44.2 months) and 35 months for those without PMRT (95% CI 23.2–46.73 months; $p = 0.36$).

In a multivariate Cox proportional model with a significant baseline and clinical characteristics, survival was independently associated with age younger than 55 years (HR 0.69; 95% CI 0.51–0.93; $p = 0.01$) and use of bisphosphonates (HR 0.56; 95% CI 0.38–0.82; $p = 0.003$). The association of T4 tumor stage with OS was marginal (HR 1.49; 95% CI 1.00–2.19; $p = 0.05$), but ER/PR(+) (HR 0.64; 95% CI 0.39–1.04; $p = 0.07$), triple-negativity (HR 1.35; 95% CI 0.77–2.39; $p = 0.29$), and bone-only metastasis at initial presentation (HR 0.78; 95% CI 0.56–1.07; $p = 0.12$) were not associated with OS (Table 2).

DISCUSSION

Almost half of de novo stage IV BC patients undergo breast surgery because it has been found to improve local control and prolong survival in retrospective studies.[2,13] Our investigation is the first randomized study to show statistically significant improvement in median survival with surgery at the 5-year follow-up evaluation. We designed this study protocol based on literature published before 2007, assuming a 3-year OS of 35% in the LRT group and 17% in the ST group. However, with ongoing

TABLE 1 Patient, tumor characteristics, treatment, and metastatic site distribution

	LRT (n = 138) n (%)	ST (n = 136) n (%)	p value
Mean age (years)	51.8 ± 12.6	51.5 ± 13.6	0.87
Mean BMI (kg/m^2)	27.6 ± 5.2	27.8 ± 6.0	0.70
Mean follow-up (months)	40.5 ± 22.0	35.8 ± 21.7	0.08
Median follow-up (25, 75%)	41.0 (24, 54)	37 (18, 49)	0.10
Tumor size (%)			0.23
T1	12 (8.7)	11 (8.1)	
T2	72 (52.2)	58 (42.7)	
T3	30 (21.7)	30 (22.1)	
T4	24 (17.4)	37 (27.2)	
Histologic grade (%)			0.16
1	6 (4.4)	10 (9.6)	
2	55 (39.9)	33 (31.7)	
3	77 (55.8)	61 (58.9)	
Tumor type (%)			0.26
Invasive ductal	110 (79.7)	115 (84.6)	
Invasive lobular	15 (10.9)	13 (9.6)	
Mixed tumor type	13 (9.4)	8 (5.8)	
ER/PR(+) (%)[a]	118 (85.5)	97 (71.8)	0.01
HER2/neu(+) (%)[b]	42 (30.4)	42 (31.1)	0.90
Triple-negative (%)	10 (7.3)	23 (17.4)	0.01
Treatment (%)			
BCS + axillary evaluation	36 (26)	–	NA
M + axillary evaluation	102 (74)	–	NA
SLNB[c]	23 (17)	–	NA
ALND	128 (92.8)	–	NA
Positive LN	123 (89.1)	–	NA
Intervention to metastasis	35 (25)	48 (35)	0.07
Anthracycline-based CT	127 (92.0)	120 (89)	0.38
Bisphosphonates	37 (26.8)	32 (23.5)	0.53
Metastasis site (%)			0.17
Bone only	71 (51)	55 (40)	
Bone + others	33 (24)	37 (27)	
Others (no bone)	34 (25)	44 (32)	
Solitary/multiple metastasis (%)			0.71
Solitary bone	33 (34)	20 (24)	
Multiple bone	38 (39)	35 (41)	
Solitary pulmonary or liver	13 (13)	15 (18)	
Multiple pulmonary or liver	13 (13)	15 (18)	

LRT locoregional treatment, *ST* systemic therapy, *BMI* body mass index, *ER* estrogen receptor, *PR* progesterone receptor, *HER2* HER2/neu, *BCS* breast-conserving surgery, *NA* not applicable, *M* mastectomy, *SLNB* sentinel lymph node biopsy, *ALND* axillary lymph node dissection, *LN* lymph node, *CT* chemotherapy

[a]Patients with ER/PR(+) tumor received hormonal therapy

[b]Patients with HER2/neu(+) received trastuzumab

[c]SLNB(+) patients underwent ALND

improvements in treatment, including availability of targeted therapy, 3-year survival exceeded 50% for our patients.

Despite retrospective studies on survival benefits for patients receiving postsurgery chemotherapy, the only published randomized study on de novo stage IV BC tested

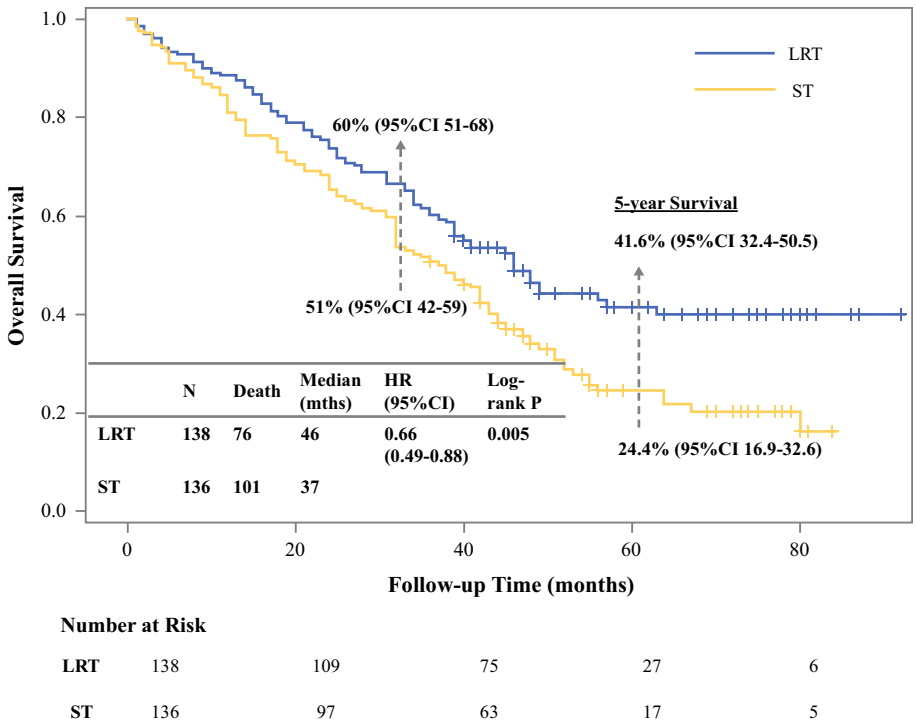

FIG. 2 Comparison of overall survival between the locoregional treatment (LRT) and systematic therapy (ST) groups. The proportional hazards assumption that the ratio of hazards is a constant that does not depend on time is tested for overall and each-group survival analyses. For all comparisons and analyses, the proportional hazards assumption was met ($p > 0.30$)

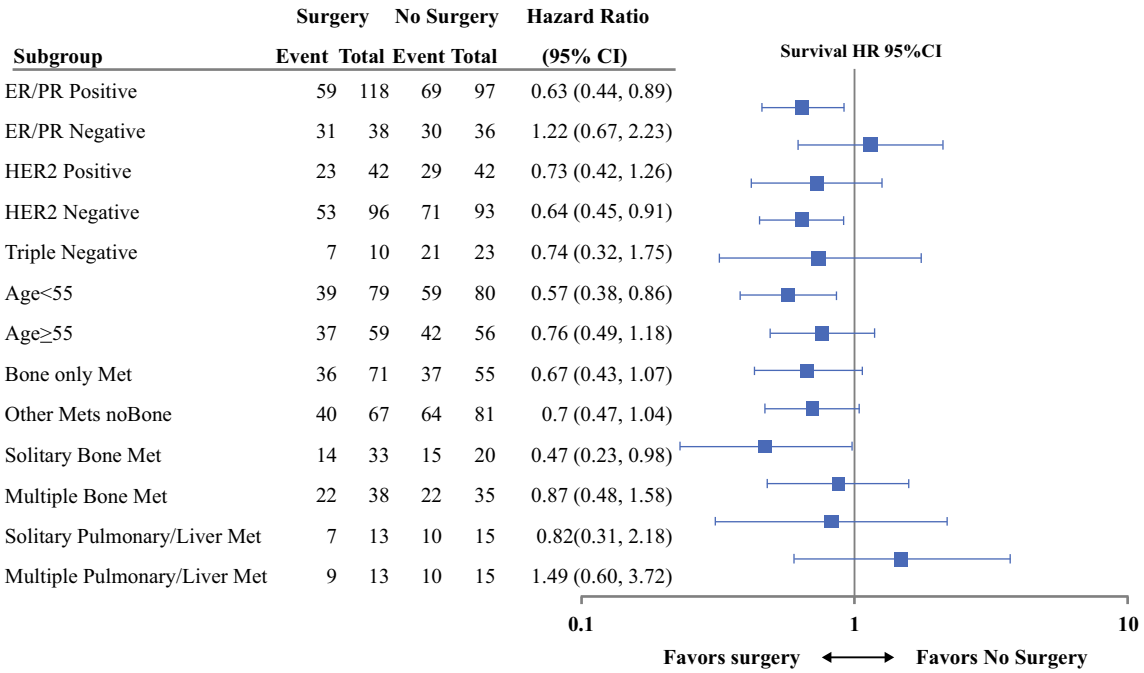

FIG. 3 Forest plot of overall survival subgroup analyses with hazard ratios. *ER* estrogen receptor, *PR* progesterone receptor, *Met* metastasis, *HR* hazard ratio

whether surgery prolongs the survival of patients who had chemotherapy before randomization.[32] In the Indian study, LRT did not have an OS benefit compared with no LRT. Although 26% of the LRT group patients and 35% of the no-LRT patients had tumors positive for HER2/neu, none of those patients received targeted therapy in the LRT group, and 15% received such therapy in the no-LRT group. A similarly designed registry study was presented previously, showing that most patients responded to ST, with no non-responders undergoing surgery.[33] Despite a very limited number of patients in that study, a survival benefit with surgery was not shown for responders. The

TABLE 2 Uni- and multivariate Cox model analysis of clinically important parameters for overall survival

Parameter	HR	95% CI	*p* value	HR^{a}_{adj}	95% CI	*p* value
Age < 55 years	0.75	0.55–1.00	0.05	0.68	0.50–0.92	0.01
T2[b]	0.57	0.42–0.77	0.0003	0.74	0.51–1.06	0.10
T4[b]	1.87	1.35–2.58	0.0002	1.49	1.00–2.19	0.05
ER/PR(+)	0.43	0.31–0.61	< 0.0001	0.64	0.39–1.04	0.07
Triple-negative	2.34	1.56–3.51	< 0.0001	1.35	0.77–2.39	0.29
Bone-only metastasis	0.65	0.48–0.88	0.005	0.78	0.56–1.07	0.12
Bisphosphonates	0.48	0.33–0.71	0.0002	0.56	0.38–0.82	0.003

HR hazard ratio, *CI* confidence interval, *ER* estrogen receptor, *PR* progesterone receptor

[a]Adjusted HR results from multivariate Cox Models with all significant baseline and clinical characteristics included in the model

[b]Clinical tumor size

authors concluded that HER2 status and patient age were strong prognostic factors influencing survival.[33] In the current study, at 3 years, the survival exceeded 50%, comparable with the registry study's 3-year survival rate of 70%. The OS was 20 months in the Indian study, which may be attributed to the absence of targeted therapy.[32,33]

An unplanned subgroup analyses showed that patients with ER/PR(+) or HER2/neu(−), patients with solitary bone metastasis, and patients younger than 55 years had a significant survival benefit with initial surgery. The meta-analyses showed that younger patients with bone-limited metastasis and ER(+) primary tumors lived longer with LRT.[24,25] In the ER/PR(+) subgroup analyses, by the end of the 5-year follow-up period, the median survival periods were 49 months in the LRT group and 42 months in the ST group, indicating a significantly reduced risk of death for the LRT group ($p = 0.008$). Although only a limited number of ER/PR(+) and HER2/neu(+) patients underwent LRT, they had 3.5 months longer median survival than the ST patients (HR, 0.48; 95% CI, 0.23–0.96; $p = 0.04$) (Fig. S8). Of the patients with triple-negative BC, 85% died with a median survival of 17.5 months in the LRT group and 18 months in the ST group (HR 0.74; 95% CI 0.32–1.75; $p = 0.49$) (Fig. S9). Similar findings were observed in a previous retrospective study, and the authors stated that the survival benefit with primary breast surgery in stage IV breast cancer was limited to patients with ER/PR-positive or HER-2/neu-positive tumors. Patients with triple-negative disease did not experience any differential improvement in survival.[34]

It is important to note that the patients in the current study were randomized based solely on biopsy results without prior knowledge of ER/PR or HER2/neu status. As mentioned previously, several stratification factors were equally important for metastatic patients, and for this reason, we conducted this randomized study without stratification. In our study, ER status was not equally distributed. This may raise concerns regarding absolute conclusions about this patient subgroup based on LRT prolonging survival. Regarding our analysis and previous studies, ER status can be considered with other significant factors such as age and tumor burden in the determination of good candidates for initial surgery.

We chose the threshold age of 55 years based on the average menopause age in the literature.[35] The patients younger than 55 years who underwent LRT had 14 months longer median OS than the ST patients. The tumors in younger and premenopausal patients are well described in the literature as behaving more aggressively than in older patients.[36,37] Retrospective studies have shown the benefit of LRT for younger de novo stage IV BC patients.[16,22,23,38]

In our study, the LRT patients with HER2/neu(−) tumors lived 12 months longer than the patients with no LRT (Fig. S10). The patients in the registry study with HER2/neu(−) tumors and those younger than 50 years had a 40-month median survival versus the patients with HER2/neu(+), who had a 71-month median survival.[33] A very limited number of patients in our study had ER/PR(−) and HER2/neu(+) tumors, and the median survival period was 11.5 months shorter in the LRT group than in the ST group (HR 2.21; 95% CI 0.91–5.37; $p = 0.08$) (Fig. S11). We may speculate that primary tumor surgery eliminates aggressive clones in HER2/neu(−) tumors, although evidence to prove this is insufficient. Although targeted therapy prolongs survival for metastatic cancer patients, whether primary surgery prolongs OS for HER2/neu(−) patients should be investigated in future studies.

The median survival was almost 10 months longer in the LRT group than in the ST group with solitary bone-only metastasis. At 5 years, 51.7% of the LRT patients and 29.2% of the ST patients were still alive. Our study may be criticized for the diagnosis of solitary bone metastasis without histologic confirmation. Acquiring metastatic-site tissue is not a routine clinical practice in most centers. However a guideline recommends biopsy of metastatic sites at the first recurrence to determine tumor ER/PR and

HER2 status.[39] The statement on this issue is based on cases in which false-negative ER/PR and HER2/neu occurred in the primary tumor. Treatment may change based on positive metastatic-site biopsy results. Conversely, prospective trials have shown bone biopsy samples to be 98–100% concordant with imaging studies.[40,41] To decrease false-negatives on imaging in solitary bone metastasis, two imaging methods were performed to confirm the diagnoses in our study. Several retrospective studies have shown that FDG-PET/CT sensitivity for detection of bone metastases was 83–100% with bone scans.[42–44] In addition to a very high concordance of scans and bone lesion biopsy, histopathologic diagnoses in this subgroup should be equally distributed due to patient randomization. Potential overdiagnosis for a very small number of patients would not affect the outcome.

Our subgroup analysis showed that the patients with multiple liver/pulmonary metastases had a significantly worse prognosis with initial surgery. At 5 years, most of the patients in this subgroup had died. Although a limited number of patients were included in this analysis, 31% of the LRT patients survived at 3 years compared with 67% of the patients without surgery. Our results confirm those from retrospective studies showing that elective upfront surgery appears to play no role in this patient population.[17,38]

In our study, the rate of LPR was 11 times higher in the ST group. In the Indian study, 10% of the patients underwent palliative surgery, and LRT resulted in a significant improvement in LRP-free survival compared with the results for the no-surgery patients.[32] In the registry study, palliative surgery was performed for 18% of the patients who did not respond to ST.[33] Therefore, randomized studies in addition to meta-analyses and retrospective studies have led us to conclude that LRT controls LPR in de novo BC stage IV patients for whom long survival is expected.

In conclusion, patient survival in the setting of metastatic BC is better currently than it was a decade ago, and the current study suggests that surgery plays a role. When LRT in de novo stage IV BC is discussed with the patient as an option, practitioners must consider younger age, performance status, comorbidities, tumor type, and less metastatic disease burden.

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