Primary Surgery with Systemic Therapy in Patients with de Novo Stage IV Breast Cancer: 10-year Follow-up; Protocol MF07-01 Randomized Clinical Trial

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BACKGROUND: The aim of this randomized clinical trial was to evaluate the overall survival (OS) data of patients diagnosed with de novo stage IV breast cancer (BC) who received locoregional treatment (LRT) over a 10-year follow-up.

STUDY DESIGN: The MF07-01 is a 1:1 multicenter, randomized clinical trial comparing the LRT with systemic therapy (ST), where ST was given to all patients either immediately after randomization or after surgical resection of the intact primary tumor.

RESULTS: A total of 278 patients were randomized and 265 patients were in the final analysis. At 10-year follow-up, survivals were 19% (95% CI 13%−28%) and 5% (95% CI 2%−12%) in the LRT group and ST group, respectively. Median survival was 46 months for the LRT group and 35 months for the ST group, and hazard of death was 29% lower in the LRT group compared with the ST group (hazard ratio [HR] 0.71; 95% CI 0.59−0.86; $p = 0.0003$).

CONCLUSIONS: Patients with a diagnosis of de novo stage IV BC who underwent LRT followed by ST had a 14% higher chance of OS by the end of the 10-year follow-up compared with the patients who received only ST. The longer study follow-up revealed that LRT should be presented to patients when discussing treatment options. (J Am Coll Surg 2021;233:742−752. © 2021 by the American College of Surgeons. Published by Elsevier Inc. All rights reserved.)

Although the incidence of synchronous distant metastatic disease in newly diagnosed breast cancer (BC) patients has been relatively constant over the last decades,[1-3] advances in adjuvant therapies and a better understanding of tumor biology appear to have improved patient overall survival (OS).[4-6] Systemic therapy (ST) was considered the first

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Abbreviations and Acronyms

BC = breast cancer
ER = estrogen receptor
HR = hazard ratio
LRP = locoregional progression
LRT = locoregional treatment
OS = overall survival
PR = progesterone receptor
QoL = quality of life
ST = systemic therapy
TN = triple negative

and only choice for care in this patient population in most of the institutes until more data showed that locoregional treatment (LRT) provided better OS and locoregional control of the disease.[7-19] In the last 2 decades, evidence of an OS benefit with primary surgery in de novo BC patients has been substantially increasing in the literature.

In 2002, Khan and colleagues,[7] using cases from the National Cancer Data Base (NCDB) of the American College of Surgeons, showed an OS benefit from local therapy in the stage IV setting. Retrospective studies and meta-analyses published between 2002 and 2013 suggest that primary tumor resection in appropriately selected de novo stage IV BC patients not only limits locoregional progression, but also prolongs disease-free survival and OS.[7-19] These studies typically had selection biases, and retrospective studies ended suggesting the need for prospective studies. In 2015, Badwe and coauthors[20] presented the first randomized clinical trial (RCT) to compare the effect of LRT vs no treatment on outcomes in women with metastatic breast cancer at initial presentation, suggesting that LRT is not associated with improved OS in de novo metastatic BC patients. Our group initiated the MF07-01 study in 2007 as a phase III, multicenter clinical RCT. The MF07-01 study comparing LRT with primary ST in de novo stage IV BC patients found a statistically significant improvement in OS with primary surgery at the median 40-month (range 1,131 mos) follow-up.[21] Recently, Khan and colleagues[22] presented the results of the multicenter, phase 3, ECOG-ACRIN 2108 study at the plenary session of the American Society of Clinical Oncology (ASCO) 2020 virtual meeting. They found no statistical difference in terms of 3-year OS (68.4% vs 67.9%) (hazard ratio [HR] 1.09; 90% confidence interval [CI] 0.80−1.49; p = 0.63). In addition, no progression-free survival benefit was observed between the ST and early LRT groups (p = 0.40).[22] The objective of this study was to evaluate the importance of LRT in patients diagnosed with de novo stage IV BC on the OS over a 10-year follow-up.

METHODS

Between November 2007 and December 2012, 312 patients were recruited for the MF07-01 trial. Thirty-four patients did not meet inclusion criteria, 13 withdrew from the study during follow-up, and 265 patients were evaluated in the final analysis (LRT group, n = 134; ST group, n = 131) (Fig. 1). Patient and tumor characteristics, treatment, and metastatic site distribution are presented in Table 1.

The MF07-01 trial study protocol was published in 2009.[23] Participating centers obtained local ethics committee approval before entering the study. Randomization of subjects was done centrally by data center computer through the Internet. Study design and accrual methods, along with survival data for patients with a median 40-month (range 1 to 131 months), follow-up were also presented in detail in our previous publication.[21] However, we want to express once again that the MF07-01 trial design is different than most of the published or presented prospective series. In this trial, eligible patients were randomly assigned to 1 of 2 study arms: LRT with subsequent ST, or primary ST. Patients in the LRT group received ST after primary tumor resection, whereas the ST group patients began receiving ST immediately after randomization.

One of the pitfalls of the MF07-01 randomized study is that LRT group patients had higher rates of estrogen receptor (ER)/progesterone receptor (PR) positivity (86% vs 73%, p = 0.01) and lower rates of triple negative

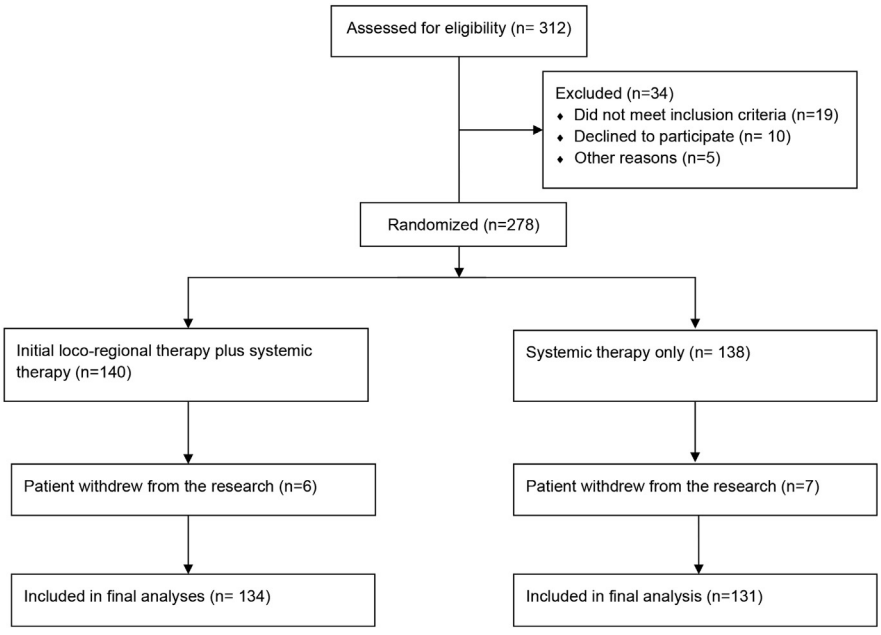

Figure 1. Consolidated Standards of Reporting Trials flow diagram.

(TN) tumors (7% vs 18%, p = 0.01) compared with patients in the ST group.

Statistical analysis

Kaplan-Meier survival curves were used, and the survival curves for treatment arms were compared using log-rank tests. Univariate and multivariable Cox models, adjusted for clinical, tumor, and metastasis characteristics, were used to estimate hazard ratio and 95% CI for survival. For all Cox models, the proportional hazards assumption was tested using the scaled Schoenfeld residuals (p values > 0.20). Values of $p < 0.05$ were considered statistically significant. Statistical analyses were conducted with R version 3.6.1 (R Foundation for Statistical Computing) software packages.

RESULTS

At the 10-year follow-up, hazard of death was 29% lower in the LRT group compared with the ST group (HR 0.71; 95% CI 0.59−0.86; p = 0.0003) (Fig. 2). It is important to note that OS was similar for the LRT and ST groups (60%, 95% CI 51−68 and 51%, 95% CI 42−59, respectively, p = 0.10) at 3-year follow-up. However, by the 5-year follow-up, 42% of patients had survived in the LRT group and only 24% (95% CI 32.5−50.4 and 95% CI 17−33, respectively, p = 0.005) had survived in the ST group.[21] By the end of the 10-year follow-up, 19% of patients had survived in the LRT group and 5% had survived in the ST group (p = 0.0003).

Figure 3 shows a forest plot analysis of OS subgroup analyses with HRs. At 10-year follow-up, OS was statistically higher in the LRT group than in the ST group with respect to ER/PR (+) (HR 0.71; 95% CI 0.58−0.88; p = 0.002) (eFig. 1), HER2/neu (-) (HR 0.72; 95% CI 0.58−0.90; p = 0.004) (eFig. 2), patients < 55 years old (HR 0.67; 95% CI 0.53−0.87; p = 0.002) (eFig. 3), and patients with solitary bone-only metastases (HR 0.55; 95% CI 0.36−0.86; p = 0.009) (eFig. 4). These data are very similar with respect to our previous publication of 5-year follow-up analysis. However, at the 10-year follow-up, we found that OS was also statistically significant higher in the LRT group than in the ST group in HER2/neu (+) patients (HR 0.69; 95% CI 0.85−0.98; p = 0.04) (eFig. 5), and slightly better in patients ≥55 years old (HR 0.75; 95% CI 0.57−0.99; p = 0.045) (eFig. 6).

In patients with TN subtype, at 10-year follow-up, 9 of 10 (90%) patients had died, with a median survival of 17.5 months in the LRT group, and 21 of 23 (91%) patients died, with a median survival of 18 months in the ST group (HR 0.88; 95% CI 0.51-1.54; p = 0.66) (eFig. 7). A similar OS was found for ER/PR (-) patients at 10-year follow-up. Median survivals were 17 and 19 months for the LRT and ST groups, respectively (HR 1.03; 95% CI 0.69−1.55; p = 0.88). Only 1 patient was alive in each group (eFig. 8).

Median survival was 6.5 months longer in the LRT group compared with the ST group in bone only

Table 1. Demographic, Clinical, Treatment, and Tumor Characteristics Comparisons Between the Locoregional Treatment and Systemic Therapy Groups

Characteristic	LRT (n = 134)	ST (n = 131)	p Value
Age, y mean ± SD	51.9 ± 12.7	51.7 ± 13.5	0.93
BMI, kg/m^2, mean ± SD	27.4 ± 5.1	27.9 ± 5.1	0.43
Follow-up, mo, mean ± SD	55.6 ± 38.9	41.1 ± 31.1	0.001
Follow-up, median (IQR)	46 (23,56)	35 (18,41)	0.01
Tumor size, cm, n (%)			0.24
T1	12 (9)	11 (8)	
T2	68 (51)	55 (42)	
T3	30 (22)	28 (21)	
T4	24 (18)	37 (28)	
Histologic grade*, n (%)			0.18
Grade I	6 (4)	9 (9)	
Grade II	54 (40)	31 (31)	
Grade III	74 (55)	60 (60)	
Tumor type, n (%)			0.38
Invasive ductal	105 (78)	110 (85)	
Invasive lobular	15 (11)	11 (8)	
Mixed tumor type	10 (7)	5 (4)	
Others	4 (4)	5 (3)	
ER/PR(+)†, n (%)	115 (86)	95 (73)	0.01
Her 2/neu(+)†, n (%)	40 (30)	37 (28)	0.80
Triple negative, n (%)	10 (7)	23 (18)	0.01
Treatment, n (%)			
BCS + axillary evaluation	35 (26)	–	NA
M + axillary evaluation	99 (74)	–	NA
SLNB‡	21 (16)	–	NA
ALND	134 (100)	–	NA
Positive LN	120 (90)	–	NA
Intervention to metastasis	34 (25)	42 (32)	0.23
Anthracycline-based CT	124 (93)	115 (88)	0.26
Bisphosphonates	28 (28)	18 (20)	0.20
Metastasis site, n (%)			
All bone	100 (75)	88 (67)	0.18
No bone	34 (25)	43 (33)	
Solitary/multiple metastasis, n (%)			0.82
Solitary bone	31 (23)	20 (15)	
Multiple bone	37 (28)	34 (26)	
Solitary pulmonary or liver	13 (10)	15 (11)	
Multiple pulmonary or liver	13 (10)	14 (11)	

Distribution of categorical values between the 2 groups is tested with chi-square tests.
*Missing data; 31 patients in the ST group.
†Patients with ER/PR (+) tumor received hormonal therapy, and patients with Her2/neu (+) received trastuzumab.
‡SLNB (+) patients underwent ALND.
ALND, axillary lymph node dissection; BCS, breast-conserving surgery; CT, chemotherapy; ER, estrogen receptor; Her2, Her2/neu; IQR, interquartile range; LN, lymph node; LRT, locoregional treatment; M, mastectomy; NA, not applicable; PR, progesterone receptor; SLNB, sentinel lymph node biopsy; ST, systemic therapy.

metastasis patients, but this difference was not significant (HR 0.8; 95% CI 0.61–1.04; p = 0.1) (eFig. 9). In the solitary bone metastasis subgroup, median survival was 14 months longer in the LRT group compared with the ST group (HR 0.55; 95% CI 0.36–0.86; p = 0.009) (Fig. 3). However, the difference was only 3 months in

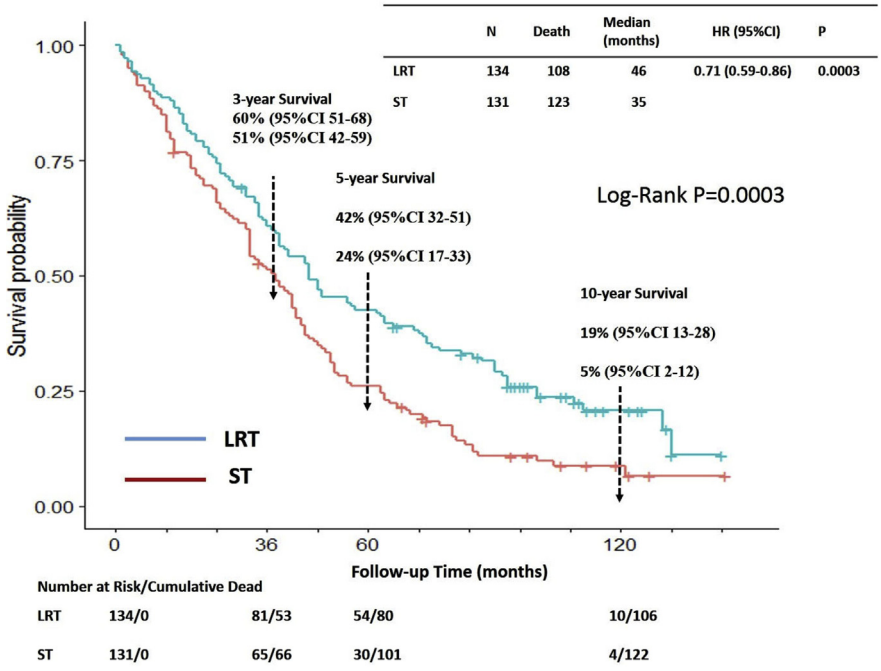

Figure 2. Comparison of overall survival between the locoregional treatment (LRT) and systemic therapy (ST) groups. HR, hazard ratio.

the multiple bone metastasis group and was not significant (p = 0.59) (Fig. 3).

At the 10-year follow-up, solitary pulmonary/liver metastases and multiple pulmonary/liver metastases patients had no survival benefit from LRT (HR 0.69; 95% CI 0.37−1.29 and HR 1.14; 95% CI 0.63−2.08, respectively) (Fig. 3). Locoregional progression (LRP) was found higher in the ST group: it was 1% (n = 2) in

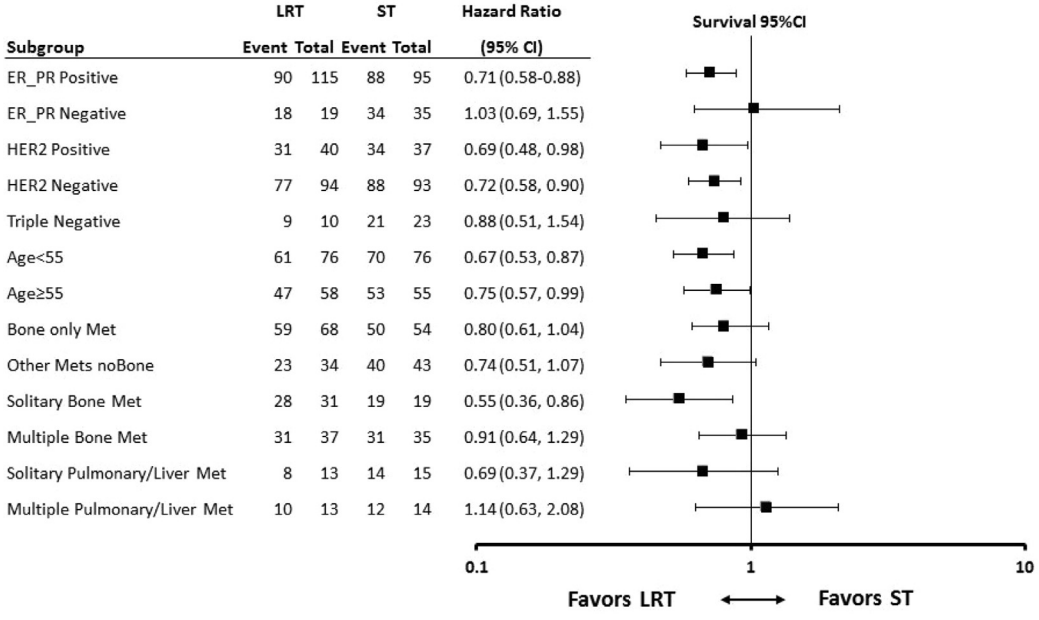

Figure 3. Forest plot of overall survival subgroup analyses with un-adjusted hazard ratio estimates. ER, estrogen receptor; Met, metastasis; PR, progesterone receptor.

Table 2. Univariate and Multivariable Cox Model Analysis of Overall Survival for Clinically İmportant Parameters

Parameter	HR	95% CI	p Value	HR*$_{adj}$	95% CI	p Value
LRT	0.71	0.59−0.86	0.0003	0.79	0.65−0.96	0.02
Age < 55	0.78	0.60−1.02	0.07	0.97	0.71−1.33	0.87
T2 tumor	1.43	1.00−2.05	0.05	1.23	0.85−1.79	0.26
ER/PR (+)	0.57	0.46−0.71	<0.0001	0.61	0.46−0.82	0.001
Triple-negative	1.53	1.16−-2.00	0.002	0.98	0.69−1.40	0.93
Bisphosphonate usage†	0.59	0.41−0.86	0.005	0.61	0.42−0.89	0.01
≥2 organ metastases	1.48	1.12−1.97	0.006	1.54	1.15−2.05	0.003

*Adjusted HR results from multivariable Cox models constructed with only significant univariate model variables.
†Considering patients with bone-only metastasis
ER, estrogen receptor; HR, hazard ratio; LRT, loco regional treatment; PR, progesterone receptor

the LRT group and 14% (n = 18) in the ST group (p = 0.001) at 10 years. Nine patients (50%) received loco-regional radiation therapy and 3 (17%) patients underwent loco-regional surgery in the ST group after locoregional progression.

In a multivariable Cox proportional model with significant baseline and clinical characteristics, survival was independently associated with LRT (HR 0.79; 95% CI 0.65−0.96; p = 0.02), ER/PR (+) (HR 0.61; 95% CI 0.46-0.82; p = 0.001), bisphosphonate use (HR= 0.61; 95% CI 0.42−0.89; p = 0.01), and more than 2 organ metastases at initial presentation (HR 1.54; 95% CI 1.15−2.05; p = 0.003) (Table 2).

DISCUSSION

Although conclusions about OS benefits with surgery in de novo metastatic BC in the literature have been conflicting, National Comprehensive Cancer Network guidelines and metanalysis recommends LRT in selected patients.[24] Recently published, the largest meta-analysis and NCDB results showed that LRT resulted in a 31.8% to 36.2% reduction in mortality, and especially, surgery followed by radiation therapy had the highest 3-year OS, of 69.4%, in addition to ST.[25,26] The MF07-01 trial is the first randomized study to show a statistically significant improvement in median OS with primary surgery; this benefit was found to be more significant as the follow-up period increases. In the first analysis after the 3-year follow-up, OS was similar for the LRT and ST groups. In 2018, we published the 5-year follow-up MF07-01 study data and showed that 41.6% and 24.4% of patients were alive in the LRT and ST groups, respectively (p = 0.005). In this analysis, OS was 19% (95% CI 13%−28%) and 5% (95% CI 2%−12%) in the LRT group and ST group, respectively, at 10-year follow-up. A similar 10-year survival benefit was seen in a study that reviewed 24,015 cases from the NCDB, where 5- and 10-year OS were 41.1% and 14.4%, respectively, in the surgery before ST group, compared with 27.5% and 8.5%, respectively, in the ST alone group (p < 0.001).[27]

In one of the earlier RCTs, an Indian study, LRT did not show an OS benefit compared with no LRT. However, 26% of LRT patients and 35% of 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.[20] Khan and colleagues[22] presented the results of the multicenter, phase 3, ECOG-ACRIN 2108 study at the plenary session of the ASCO 2020 virtual meeting. They assigned 256 eligible patients to ST based on patient and tumor characteristics. Those who did not progress during 4 to 8 months of treatment were then assigned to continue ST alone (n = 131) or ST plus LRT ± radiation (n = 125). They found no statistical difference between 2 groups in terms of 3-year OS (68.4% vs 67.9%) (HR 1.09, 90% CI 0.80−1.49; p = 0.63). In addition, no progression-free survival benefit was observed between the ST and early LRT groups (p = 0.40). However, LRP or progression was significantly higher in the ST arm alone (25.6% vs 10.2%; p = 0.003). They concluded that based on the available data, patients with de novo metastatic BC should not be offered LRT for primary tumor with the expectation of OS benefit.[22] This study presentation is criticized for its failure to obtain negative surgical margins in 20% of patients in the LRT group. Another criticism of this study is its significant portion of patients with high tumor burden; 44% of patients had fascia and skin invasion with nodules and 48% had T4 and/or N2/3 disease. We will get answers to questions about this RCT when the manuscript is published.[28]

Regarding our analysis and previous studies, ER status, young age, and tumor burden are important risk factors in

determining good candidates for initial surgery. At 5-year and 10-year follow-up, we found a significant OS benefit with primary surgery in patients with ER/PR (+), HER2/neu (-), patients with solitary bone metastasis, and younger patients < 55 years old. Co and colleagues[29] evaluated de novo metastatic BC patients between 2007 and 2016, from a prospectively maintained database. They found that 5-year OS in the surgical group was significantly better than that in the nonsurgical group (43.9% vs 33.9%; p = 0.026). Multivariable analysis found that positive ER status was the only positive prognostic factor in the analysis (HR 0.42, 95% CI 0.25−0.68; p = 0.001).[29]

One of the important findings from 10-year follow-up data that differs from our previous publication was the benefit of LRT in HER2/neu (+) patients. A median 8-month OS benefit was found between the LRT and ST groups (HR 0.69, 95% CI 0.85−0.98; p = 0.04). Mudgway and associates[30] evaluated the impact of primary tumor resection on OS in HER2/neu (+) stage IV BC patients by using the NCDB. They found that surgery was associated with improved OS (HR 0.56, 95% CI 0.40−0.77), and in the subgroup analysis of LRT of the primary site for metastatic HER2/neu (+) BC, it was found to be associated with improved OS in selected patients.[30]

In the MF07-01 study, most patients with TN subtype and ER/PR (-) died during follow-up. Median OS for TN patients was 17.5 and 18 months for the LRT and ST groups, respectively (HR 0.88, 95% CI 0.51−1.54; p = 0.66). In ER/PR (-) patients, the median OS was 17 and 19 months in the LRT and ST groups, respectively (HR1.03, 95% CI 0.69−1.55; p = 0.88). OS was similar in these TN and ER/PR (-) patients. Pons-Tostivint and coworkers[31] conducted a multicenter retrospective study of 4,276 women diagnosed with de novo metastatic BC, selected from the French Epidemiological Strategy and Medical Economics database between 2008 and 2014. LRT was associated with a significantly better OS in de novo metastatic BC patients, including patients with visceral involvement at diagnosis. However, LRT did not affect OS in TN patients.[31] In a previous retrospective study, Neuman and associates[32] stated that the OS benefit with primary breast surgery in stage IV BC was limited to patients with ER/PR (+) or HER-2/neu (+) tumors, but patients with TN disease did not experience any differential improvement in OS.[32]

The OS benefit offered by surgery for de novo stage IV BC varies by metastatic tumor burden. The incidence of solitary bone metastases was similar between cohorts (23% in the LRT group and 15% in the ST group, p > 0.05) in the MF07-01 study. Solitary bone metastasis patients' median OS was 14 months longer in the LRT group compared with the ST group (HR 0.55, 95% CI 0.36−0.86; p = 0.009). Hazard of death was 45% less in the solitary bone metastasis group in the LRT group compared with the ST group. Based on retrospective studies and the prospectively maintained database by Co and colleagues,[29] the presence of visceral metastasis (HR 1.67, 95% CI 1.03−2.72; p = 0.038) was a significant adverse prognostic factor through multivariable analysis.[11,28,33] This finding was similar in the MF07-01 trial showing that upfront LRT had a significantly worse prognosis in patients with liver/pulmonary metastases. Although a limited number of patients were included in this analysis, only 20% of patients (n = 11) had survived at the 10-year follow-up in pulmonary/liver metastasis. However, in solitary pulmonary/liver metastatic patients, the scenario may be different. Ten-year follow-up data from the MF07-01 trial showed that 38% of patients (n = 5) in the LRT group and 7% (n = 1) in the ST group with solitary liver/pulmonary metastases had survived at 10-year follow-up. Two patients in the LRT group had liver metastasis interventions. The prognosis of patients with solitary solid organ metastasis may differ from that of patients with multiple metastases. Wang and associates[34] conducted a retrospective cohort study with de novo stage IV BC patients diagnosed between 2010 and 2015 based on the SEER database, aiming to determine the OS benefit of primary surgery on the basis of metastatic pattern. The weighted 3-year OS for the surgery group was 54.5%, compared to 47.7% (p < 0.001) for the nonsurgery group. The magnitude of difference in OS with surgery was significantly correlated with metastatic patterns (p < 0.05). Significant survival improvements in the surgery group compared with the nonsurgery group were observed in patients with bone-only metastasis (adjusted HR 0.83, p < 0.05) or multiple metastases with bone involved (adjusted HR 0.76, p < 0.05), whereas an OS inferiority of surgery was found for patients with multiple visceral organ-only metastases (adjusted HR 2.08, p < 0.05).[34] By the end of the 10-year analysis of the MF07-01 study, the percentage of surviving patients in all bone (solitary bone, multiple bone, bone with visceral organ metastasis) group was 44% (n = 15); in the no bone metastasis group (visceral organ only metastasis), it was 15% for the LRT group, whereas in the ST group, the percentages of surviving patients

were 32% (n = 11) and 9% (n = 3) for all bone and no bone metastasis groups, respectively.

Meta-analyses showed that the OS advantage of LRT is more pronounced in patients with less metastatic burden and metastasis in only 1 site, especially those with bone only metastasis.[18,19] In our analysis at the 10-year follow-up, the multivariable Cox proportional model showed that the hazard of death was higher in patients with more than 2 organ metastases at initial presentation (HR 1.54, p = 0.003). Multivariable logistic regression models also indicated that 2 or more organ metastases (OR 0.44, p = 0.01) were associated with adverse prognostic factors with OS beyond 5 years.

At the 10-year follow-up, we found that the rate of LRP was 14 times higher in the ST group (14% in the ST vs 1% in the LRT group) and concluded that LRT controls LRP in de novo stage IV BC patients, in whom long OS is expected. The results of the studies showing an OS benefit from LRT in patients with de novo metastatic BC presents the question of whether the advantage of surgery causes a worse quality of life (QoL) in those patients. One of the secondary endpoints of the MF07-01 study was QoL measurements. The MF07-01Q study aimed to evaluate QoL in patients who had LRT in order to learn whether prolonged OS after LRT is accompanied by a decline in QoL. The MF07-01Q study demonstrated that LRT has no detrimental effect on QoL compared with ST only in patients who lived longer than 3 years. However, we found that the toxic effects of continued ST may cause lower physical QoL scores when compared with those of the general population and stage I-III BC patients.[35] Khan and coworkers[22] also presented health-related QoL measurements from their study at ASCO 2020. Although there was no significant difference in health-related QoL measurements between both groups at 6 and 30 months, it was worse in the early LRT arm at the 18-month evaluation.[22] Si and colleagues[36] evaluated the effect of local resection on controlling local symptoms and improving QoL in de novo stage IV BC patients. They defined a new term, "local progress/recurrence of symptoms" (LPRS) to refer to the local problems caused by tumor progression/recurrence. They found that primary surgery could reduce the occurrence of LPRS, and patients without LPRS had longer OS (45 months vs 2.9 months, p = 0.001). QoL in patients with de novo stage IV BC can be improved by reducing the incidence of local symptoms through primary tumor surgery.[36]

CONCLUSIONS

Patients' OS in the setting of de novo metastatic BC is better today than it was a decade ago, and 10-year follow-up of the MF07-01 study suggests that primary surgery plays a role, especially in some of the patient groups. While waiting for the JCOG 1017 trial results, results from studies with methodologies similar to those of the MF07-01 study should be considered for future treatment of de novo stage IV BC patients, and the possibility of LRT to prolong the OS and for loco-regional control should be discussed by the tumor board. Younger age, tumor molecular type, less metastatic disease burden (especially bone only and solitary bone), and performance status and comorbidities are important factors in favor of surgery in such patients.

Author Contributions

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Analysis and interpretation of data: Soran, Ozbas, Sezgin
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APPENDIX

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Invited Commentary

Surgical Extirpation of the Primary Tumor in Stage IV Breast Cancer: The Debate Continues

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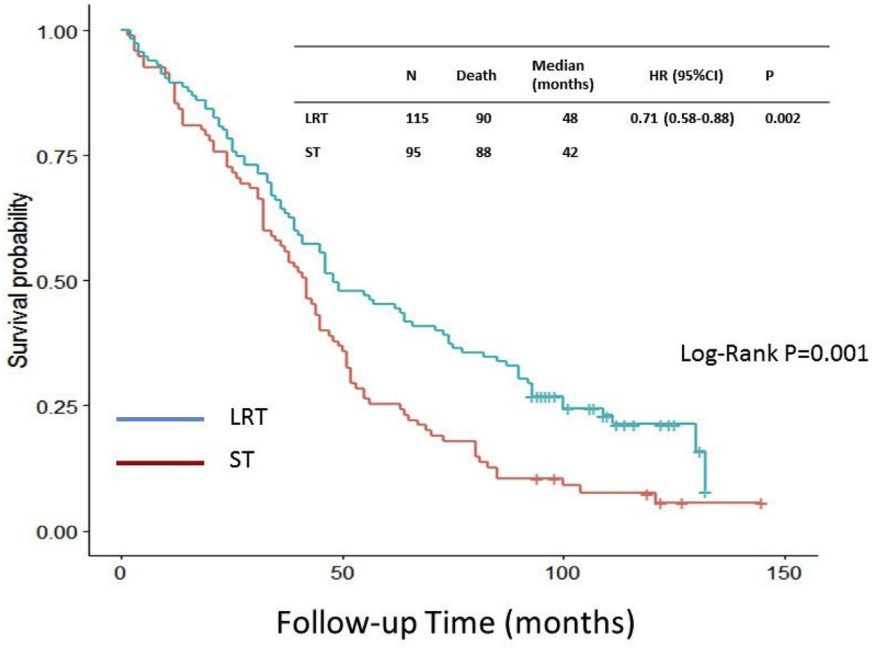
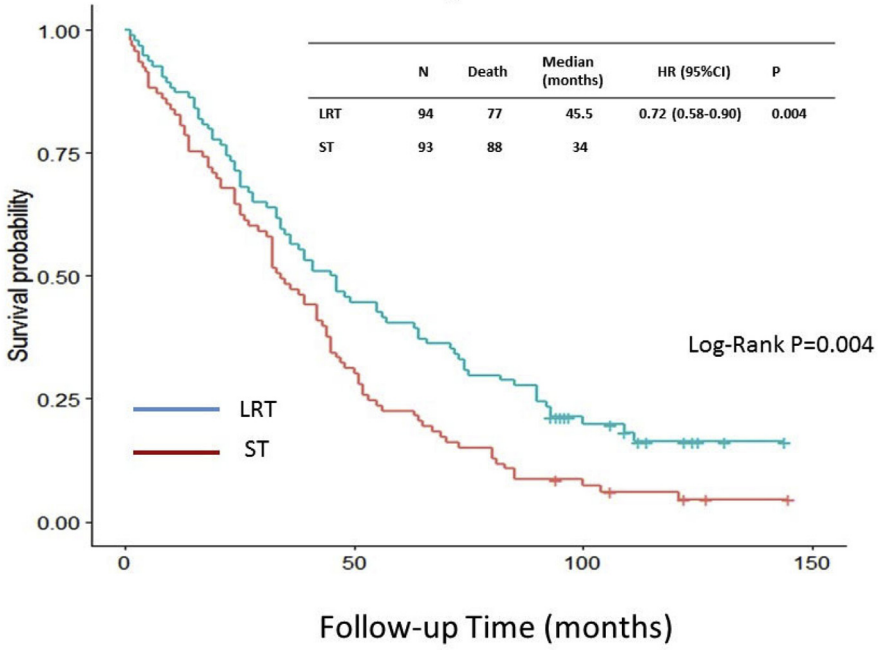
In 2019, approximately 6% of the estimated 268,600 women in the US with newly diagnosed breast cancer had metastatic disease at the time of diagnosis.[1] Historically, systemic therapy has been the primary treatment option for patients with metastatic disease. Surgical removal of the primary tumor and/or lymph nodes was not believed to contribute to improved outcomes or survival. However, multiple retrospective studies were then published demonstrating improved survival with removal of the primary tumor.[2,3] The main criticism of those retrospective analyses was the potential for selection bias. In other words, those patients with more favorable outcomes were preferentially selected to undergo operations. As a result, there was great interest in prospective randomized data that could guide decision making in patients with de novo metastatic breast cancer. In addition, as systemic therapy continues to evolve and targeted therapies are developed, the life expectancy of patients with metastatic disease continues to lengthen. The potential benefits of surgical therapy in patients with optimal systemic options were hypothesized to occur secondary to extirpation of the source of the malignancy.[4]

The study by Soran and colleagues[5] represents one of the few prospective randomized studies comparing local treatment with systemic therapy in patients with metastatic breast cancer. Patients were randomized to receive either locoregional therapy (LRT) with subsequent systemic therapy or primary systemic therapy (ST) alone. The 3-year overall survival rate was similar between the 2 groups (60%; 95% CI, 51% to 68% for LRT and 51%; 95% CI, 42% to 59% for ST; $p = 0.10$). However, at 5-year follow-up, 42% of patients were alive in the LRT group and only 24% were alive in the ST group ($p = 0.005$). Finally, 10-year overall survival rate remained significantly higher in the LRT arm (19%) compared with the ST arm (5%) ($p = 0.0003$). Overall survival varied in subgroup analysis at the 5-year follow-up and 10-year follow-up, whereby overall survival was significantly higher in the LRT group compared with the ST group in patients with estrogen receptor/progesterone receptor-positive disease ($p = 0.002$) and HER2-negative disease ($p = 0.004$), in patients younger than 55 years of age at diagnosis ($p = 0.002$), and in patients with bone-only metastasis ($p = 0.009$). Interestingly, at the 10-year follow-up, patients in the LRT group with HER2-positive disease also had increased survival compared with the ST group ($p = 0.04$) and in patients older than 55 years at diagnosis ($p = 0.045$).

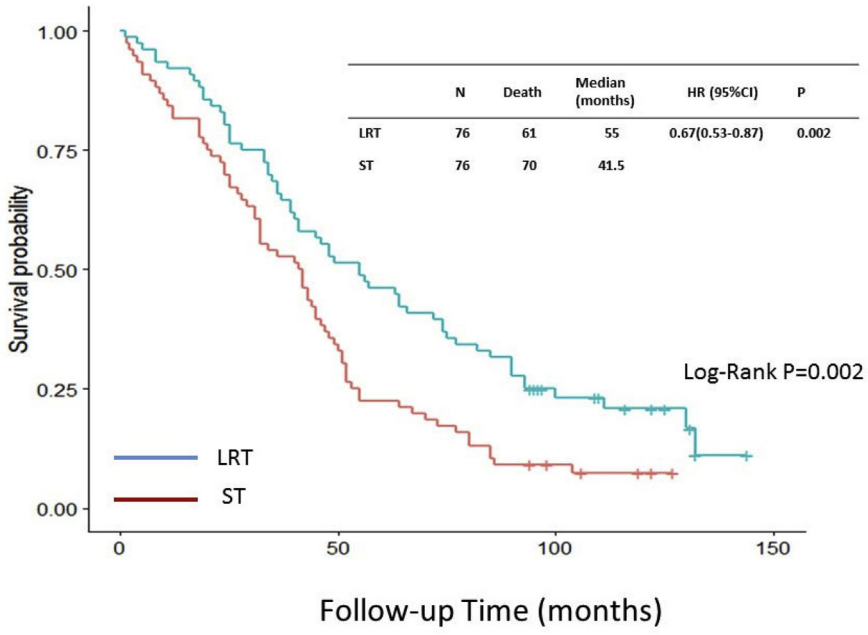
We would argue that the original concerns about selection bias in the published retrospective studies might also be present in the current randomized trial. Specifically, there was a significantly higher number of hormone receptor-positive patients in the LRT arm (86% vs 73% in the ST arm, $p = 0.01$) and a significantly higher number of triple-negative patients in the ST arm (18% vs 7% in the LRT arm; $p = 0.01$). Overall survival for patients with de novo metastatic breast cancer has improved in the past decade since this trial initiated enrollment, primarily in the hormone receptor-positive patients and in those



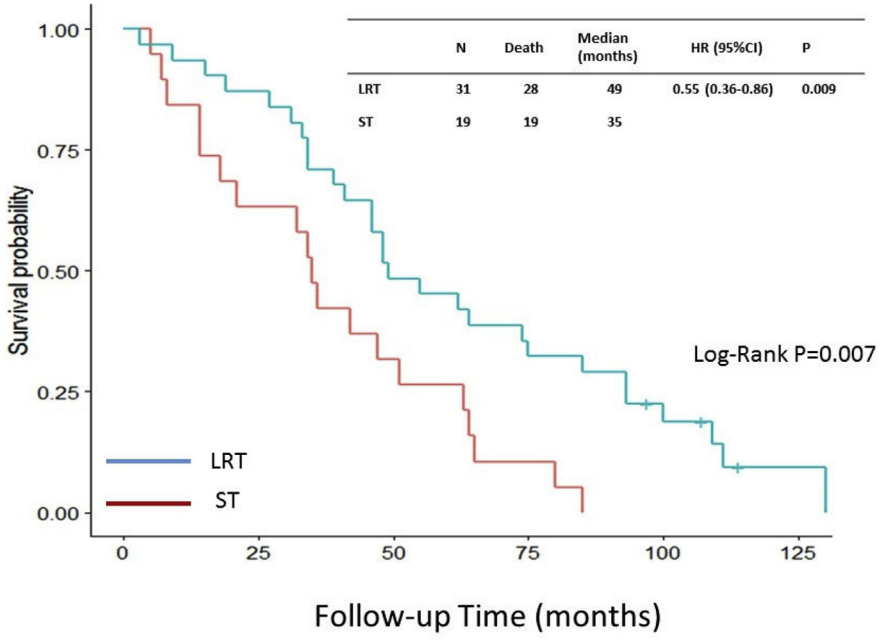
eFigure 1. Comparison of overall survival between the locoregional treatment (LRT) and systemic therapy (ST) groups among patients who are estrogen receptor/ progesterone receptor positive. HR, hazard ratio.



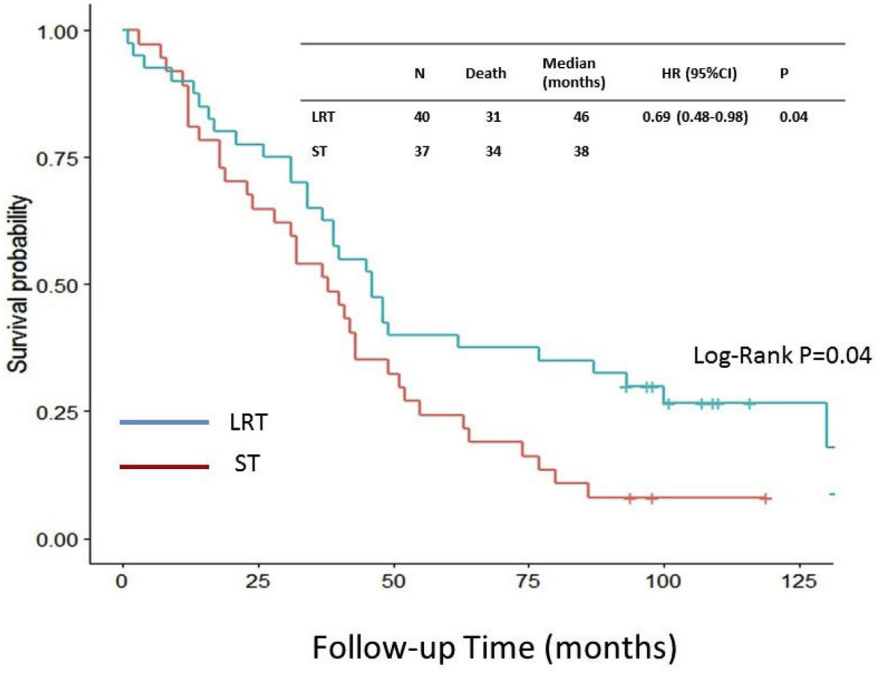
eFigure 2. Comparison of overall survival between the locoregional treatment (LRT) and systemic therapy (ST) groups among patients who are HER2 negative. HR, hazard ratio.



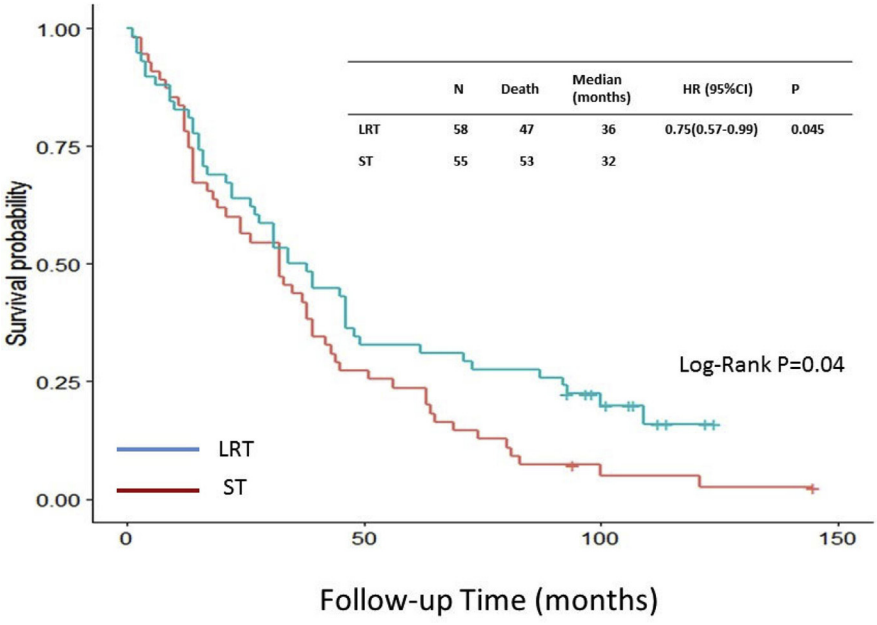
eFigure 3. Comparison of overall survival between the locoregional treatment (LRT) and systemic therapy (ST) groups among patients who are younger than age 55. HR, hazard ratio.



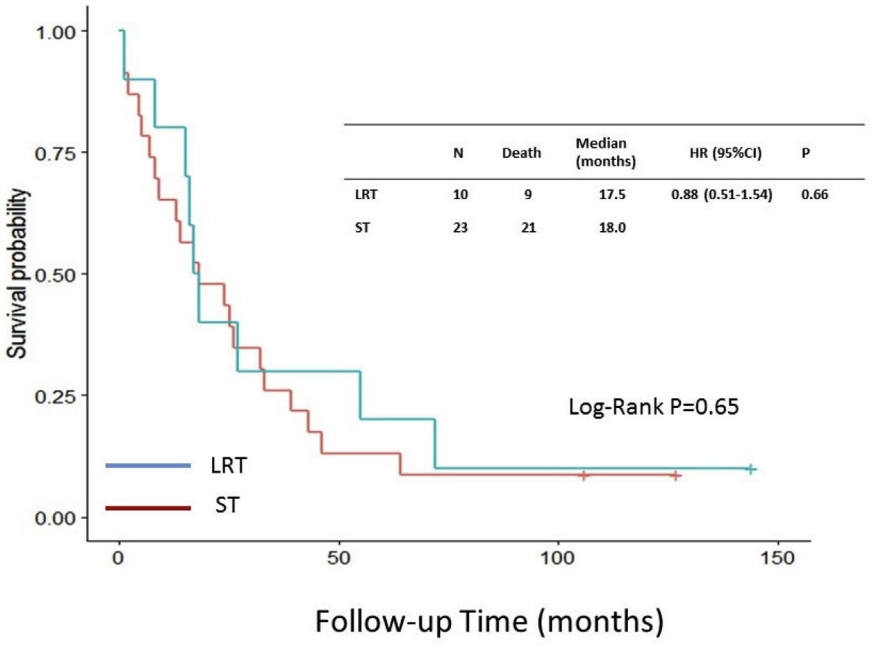
eFigure 4. Comparison of overall survival between the locoregional treatment (LRT) and systemic therapy (ST) groups stratified by solitary bone metastasis status. HR, hazard ratio.



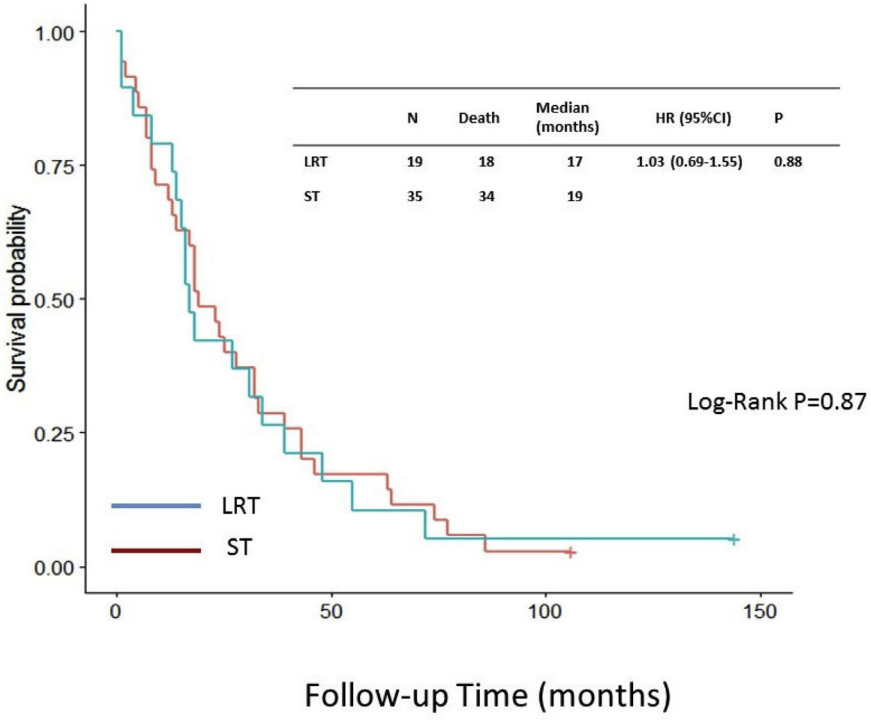
eFigure 5. Comparison of overall survival between the locoregional treatment (LRT) and systemic therapy (ST) groups among patients who are HER2 positive. HR, hazard ratio.



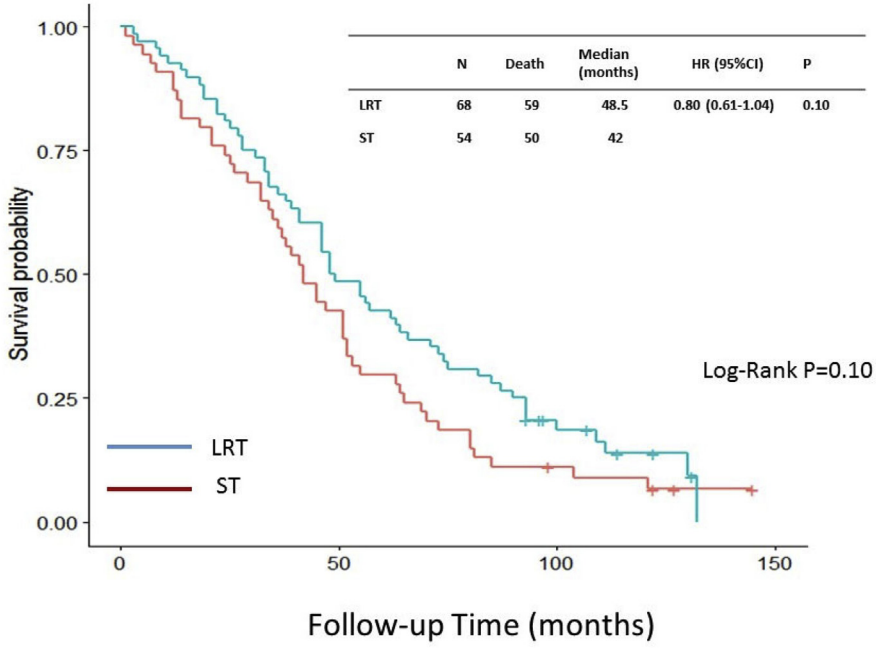
eFigure 6. Comparison of overall survival between the locoregional treatment (LRT) and systemic therapy (ST) groups among patients who are of age 55 and older. HR, hazard ratio.



eFigure 7. Comparison of overall survival between the locoregional treatment (LRT) and systemic therapy (ST) groups among patients who are triple negative. HR, hazard ratio.



eFigure 8. Comparison of overall survival between the locoregional treatment (LRT) and systemic therapy (ST) groups among patients who are ER/PR negative. HR, hazard ratio.



eFigure 9. Comparison of overall survival between the locoregional treatment (LRT) and systemic therapy (ST) groups among patients who have bone only metastasis. HR, hazard ratio.