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ORIGINAL ARTICLE – BREAST ONCOLOGY

The Effect of Primary Surgery in Patients with De Novo Stage IV Breast Cancer with Bone Metastasis Only (Protocol BOMET MF 14-01): A Multi-Center, Prospective Registry Study

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ABSTRACT

Background. More evidence shows that primary surgery for de novo metastatic breast cancer (BC) prolongs overall survival (OS) in selected cases. The aim of this study was to evaluate the role of locoregional treatment (LRT) in BC patients with de novo stage IV bone only metastasis (BOM).

Methods. The prospective, multicenter registry study BOMET MF14-01 was initiated in May 2014. Patients with de novo stage IV BOM BC were divided into two groups: those receiving systemic treatment (ST group) and those receiving LRT (LRT group). Patients who received LRT were further divided into two groups: ST after LRT

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(LRT + ST group) and ST before LRT (ST + LRT group).

Results. We included 505 patients in this study; 240 (47.5%) patients in the ST group and 265 (52.5%) in the LRT group. One hundred and thirteen patients (26.3%) died in the 34-month median follow-up, 85 (35.4%) in the ST group and 28 (10.5%) in LRT group. Local progression was observed in 39 (16.2%) of the patients in the ST group and 18 (6.7%) in the LRT group ($p = 0.001$). Hazard of death was 60% lower in the LRT group compared with the ST group (HR 0.40, 95% CI 0.30–0.54, $p < 0.0001$).

Conclusion. In this prospectively maintained registry study, we found that LRT prolonged survival and decreased locoregional recurrence in the median 3-year follow-up. Timing of primary breast surgery either at diagnosis or after ST provided a survival benefit similar to ST alone in de novo stage IV BOM BC patients.

Breast cancer (BC) has a broad biological spectrum ranging from local to metastatic disease.[1] Approximately 10% of newly diagnosed BC cases are seen at the metastatic stage. In more than 20% of these patients, a limited number of organs or systems are involved, a condition known as oligometastatic disease. It is believed that oligometastatic disease is caused by cells with lower malignant potential; this concept constitutes a separate category within the metastatic disease group. Therefore, especially in limited metastatic disease, the objective is complete clinical and pathological remission with more aggressive treatment.[2] Locoregional therapy (LRT) for an intact primary tumor is one of the treatment alternatives for this purpose. Most retrospective series have demonstrated that primary tumor surgery in metastatic disease prevents locoregional progression and increases disease-free survival and overall survival (OS). In these studies, the presence of oligometastatic disease in patients with bone metastases rather than visceral organ metastasis has emerged as a factor that prolongs survival in those undergoing surgery.[3–9] Meta-analyses show that this survival advantage favors LRT and is more pronounced in patients with a smaller metastatic burden and metastasis in only one site, especially those with bone only metastasis (BOM).[10,11] However, these studies have been criticized for selection bias.[12] Randomized controlled trials (RCTs) were planned to investigate the survival benefit found with LRT by eliminating the biases. The long-term results of a multicenter, phase III, randomized controlled MF07-01 study showed that LRT reduced the risk of death by 33% compared with systemic therapy (ST) alone.[13] All these findings suggest that patients with isolated bone metastases should be considered a separate entity. The protocol BOMET MF14-01 was planned to investigate the effects of primary tumor surgery on OS, systemic progression-free survival (SPFS), locoregional progression-free survival (LRFS), and relapse in patients with isolated bone metastases.

PATIENTS AND METHODS

Protocol BOMET MF14-01 is a multi-center prospective registry study; patients with stage IV BC with BOM at presentation who underwent primary breast surgery followed by ST or received ST only after the registration date of May 2014 were included. First analyses were completed considering two groups: those receiving systemic treatment (ST group) and those receiving LRT (LRT group). Patients who received LRT were further divided into two groups: ST after LRT (LRT + ST group) and ST before LRT (ST + LRT group). Treatment options and sequence was determined by treating physicians.

Bone metastases were requested to be preferably verified by bone biopsy. In cases where bone metastases could not be confirmed by biopsy, positron emission tomography–computed tomography (PET/CT) and bone scintigraphy were used for diagnosis. If bone biopsy was not performed in solitary metastasis, these two tests were used to confirm bone metastasis. In multiple bone metastases, one of the two tests was considered sufficient. Only 5.9% of the patients (30/505) had bone biopsies to confirm the metastasis. PET/CT, computed tomography (CT), magnetic resonance imaging, ultrasonography, or chest X-rays confirmed that there was no metastasis other than bone metastasis. The numbers of bone metastases were grouped as solitary (single), oligo (< 4 metastases), and multiple (≥ 4) metastases. To compare ST before and after surgery, we also considered 5 as a cutoff number for metastases. Anti-HER2 therapy was given to all HER2/neu-positive patients, and hormonotherapy was given to all patients with hormone receptor-positive tumors. All treatment modalities and decisions for primary tumors and metastases were left to the discretion of the treating physicians. LRFS, SPFS, and OS were recorded. Patients were followed every 3–6 months until they died or the date the statistical analysis was completed.

Statistical Analysis

Continuous variables with normal distribution and categorical variable differences between the LRT and ST groups were analyzed using *t*-tests and chi-square tests, respectively. Violations of normal distribution were tested using the Shapiro-Wilk test, and the Kruskal-Wallis test was used for variables without normal distribution. Survival rates for the LRT and ST groups were estimated using

Kaplan-Meier log-rank tests. Univariate and multivariate Cox models with baseline, clinical, tumor, and metastasis characteristics were run to estimate hazard ratio (HR) and 95% confidence interval (CI) for survival. The proportional hazards assumption was tested to analyze OS and survival of each group. For all comparisons and analyses, the proportional hazards assumption was met ($P > 0.20$). *P*-values of less than 0.05 were considered statistically significant. Statistical analyses were conducted with R version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria, https://www.r-project.org) software packages.

RESULTS

We included 505 patients in the study; 240 (48%) patients formed the ST group, and 265 (52%) patients formed the LRT group. Eighty-five (32%) patients in the LRT group had received ST prior to primary breast surgery (ST + LRT group) and 180 (68%) patients underwent breast surgery prior to ST (LRT + ST group). The median time between starting ST and LRT was 194 days. Patients in the LRT group were significantly younger than those in the ST group (54.0 ± 13.8 vs 51.1 ± 12.9, $p = 0.02$) (Table 1). The difference in tumor size distribution between the groups was statistically significant; the LRT group (17%, $n = 45$) had more T3 tumors compared with the ST group (8%, $n = 20$) ($p = 0.0006$). Eighty-six percent (86%, $n = 206$) of those in the ST group and 84% ($n = 224$) in the LRT group had estrogen receptor (ER)/progesterone receptor (PR)-positive tumors. Twenty-eight percent ($n = 68$) of patients in the ST group and 29% ($n = 79$) in the LRT group had HER2/neu (+) tumors. Biological subtypes were similar between the groups ($P > 0.05$). Thirty-two percent (32%, $n = 76$) in the ST group had solitary bone metastasis vs 52% ($n = 138$) in the LRT group ($p = 0.0001$). Patients with oligometastases constituted 53% ($n = 128$) of patients in the ST group and 76% ($n = 201$) of those in the LRT group ($p = 0.0001$). Patients with more than five metastases were also evaluated to investigate the effect of increasing metastasis number on survival. Twenty-seven percent (27%, $n = 64$) in the ST group and 15% ($n = 41$) in the LRT group had more than five metastases ($p = 0.002$) (Table 1).

No patients received dual blockade as anti-HER2 therapy or received CDK4/6 inhibitors as hormonotherapy. Radiation therapy (RT) to the primary tumor bed after breast surgery was applied to 68% ($n = 180$) of the patients in the LRT group, whereas palliative RT was given to 9% ($n = 21$) of the patients in the ST group after locoregional recurrence (Table 2). One hundred and eighty-three patients (69%) in the LRT group had undergone mastectomy and 82 patients (31%) had breast conserving surgery.

TABLE 1. Demographic and tumor characteristics of patients

		ST n:240 (%)	LRT n:265 (%)	*P*
Age (mean, years ± SD)		54.0±13.8	51.1±12.9	0.02
BMI (kg/m^2, mean ± SD)		28.3±4.5	27.8±4.5	0.21
Median follow-up (months)		33 (25–41)	34.9(24–45)	0.66
Tumor size	T1	28 (12)	48 (18)	0.0006
	T2	192 (80)	172 (65)	
	T3	20 (8)	45 (17)	
Grade	I	38 (16)	27 (10)	0.02
	II	95 (40)	135 (51)	
	III	107 (45)	103 (39)	
Histology	IDC	195 (81)	218 (82)	0.94
	ILC	20 (8)	20 (8)	
	Other	25 (10)	27 (10)	
ER/PR (+)		206 (86)	224 (85)	0.67
HER2/neu (+)		68 (28)	76 (29)	0.93
Triple negative		20 (8)	16 (6)	0.32
Bone metastasis number	Solitary	76 (32)	138 (52)	<0.0001
	Oligometastases (< 4 metastases)	128 (53)	201 (76)	<0.0001
	Multiple (≥ 4 metastases)	111 (46)	64 (24)	0.003
	> 5 metastases	64 (27)	41 (15)	0.002

BMI body mass index, *ER* estrogen receptor, *PR* progesterone receptor, *ILC* invasive lobular carcinoma, *IDC* invasive ductal carcinoma, *ST* systemic treatment, *LRT* locoregional treatment (ST+LRT and LRT+ST as LRT group)

TABLE 2 Treatments to primary breast tumor and intervention to metastatic sites

	ST (n:240) %	All LRT* (n:265) %	*P*
Bisphosphonates	210 (88)	201 (76)	0.001
Hormonotherapy	204 (85)	224 (85)	0.88
Chemotherapy	234 (97)	251 (95)	0.11
Intervention for metastasis (surgery and/or RT)	148 (61.6)	146 (55)	0.25
RT for primary tumor	21 (9) (palliative RT)	180 (68)	

RT radiation therapy, *ST* systemic treatment, **All LRT* locoregional treatment (ST+LRT and LRT+ST as LRT group)

One hundred and five patients (39.6%) in the LRT group underwent sentinel lymph node biopsy and 208 (78.4%) patients underwent axillary lymph node dissection. Eighty percent of patients (n = 68) had mastectomy in the subgroup of patients who received ST before surgery, and this was 63% (n = 114) in the patient subgroup who underwent LRT at presentation followed by ST. The comparison of the ST group with the surgery subgroups when ST was given before and after primary breast surgery is shown in Table 3.

After a median follow-up of 33 (range 25–41) months in the ST group and 34.9 (range 24–45) months in the LRT group, local progression was observed in 39 (16.2%) of the patients in the ST group and 18 (6.7%) in the LRT group

TABLE 3. Comparison of the ST group with the surgery subgroups where ST was given before and after primary bresat surgey

		ST n:240 (%)	LRT+ST n:180 (%)	ST+LRT n:85 (%)	*p*
Age (mean, years ± SD)		54.0±13.8[a]	52.1±12.3[a]	49.1±14.0[b]	0.01
BMI (Kg/m^2 mean ± SD)		28.3±4.5	27.7±4.7	28.0±4.1	0.41
Median follow-up (months)		33 (25–41)	35 (25–44)	34(23–47)	0.91
Tumor size	T1	28(12)	36 (20)	12 (14)	0.001
	T2	192 (80)	118 (66)	54 (64)	
	T3	20 (8)	26 (14)	19 (22)	
Grade	I	38 (16)	20 (11)	7 (8)	0.08
	II	95 (40)	89 (49)	46 (54)	
	III	107 (45)	71 (39)	32 (38)	
Histology	IDC	195 (81)	148 (82)	70 (82)	0.88
	ILC	20 (8)	12 (7)	8 (9)	
	Other	25 (10)	20 (11)	7 (8)	
ER/PR (+)		206 (86)	152 (84)	72 (85)	0.85
HER2/neu(+)		68 (28)	58 (32)	18 (21)	0.18
Triple negative		20 (9)	12 (7)	4 (5)	0.51
Bisphosphonates		210 (88)	140 (78)	61 (72)	0.002
Hormonotherapy		204 (85)	152 (84)	72 (85)	0.98
Chemotherapy		234 (97)	168 (93)	83 (98)	0.07
Intervention for metastasis (surgery/RT)		148 (61.6)	93 (51.6)	53 (62.3)	0.24
RT for primary tumor		21 (9)	108 (60)	72 (85)	< 0.0001
Surgery type	BCS	0	65 (36)	17 (20)	< 0.0001
	Mastectomy	0	114 (63)	68 (80)	
Bone metastasis number	Solitary	76 (32)	107 (59)	31 (36)	< 0.0001
	Oligometastasis	53 (22)	35 (19)	28 (33)	
	Multiple	111 (46)	38 (21)	26 (31)	
	> 5 Metastases	64 (27)	24 (13)	17 (20)	

BMI body mass index, *IDC* invasive ductal cancer, *ILC* invasive lobular cancer, *ER* estrogen receptor, *PR* progesterone receptor, *ST* systemic treatment, *BCS* breast conserving surgery, *RT* radiation therapy, *LRT* locoregional treatment

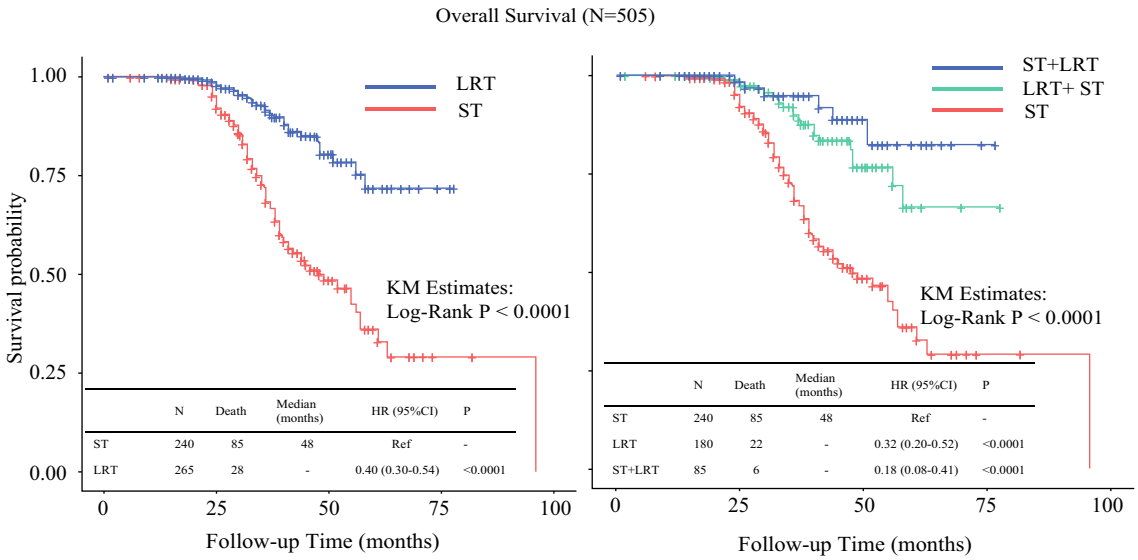

FIG. 1. Combined (ST + LRT and LRT + ST as a surgery group) survival analysis. *ST* systemic treatment, *LRT* locoregional treatment

($p = 0.001$). There were 85 deaths (35.4%) in the ST group and 28 deaths (10.5%) in the LRT group. Five-year OS was 72% in the LRT group and 33% in the ST group (HR 0.40, 95% CI 0.30–0.54, $p < 0.0001$) (Fig. 1). The 5-year LRFS rates were 78% in the LRT group and 52% in the ST group (HR 0.51, 95% CI 0.34–0.75, $p = 0.0008$)]. The 5-year SPFS was 43% in the LRT group and 20% in the ST group (HR 0.57, CI: 0.46–0.71, $p < 0.0001$).

Subgroup analysis according to age and biological tumor characteristics showed that while surgical intervention contributed to survival in hormone receptor (+) and HER2/neu (−) patients (HR 0.45, 95% CI 0.32–0.67, $p < 0.0001$) and in HER2/neu (+) patients (HR 0.27, 95% CI 0.14–0.55, $p = 0.0002$), survival contribution in the LRT group was not shown in triple negative (TN) patients ($p = 0.08$) (Fig. 2).

In a multivariate Cox proportional model with significant baseline and clinical characteristics, LRT (HR 0.41, 95% CI 0.30–0.57, $p < 0.0001$), T3 tumor (HR 3.85, 95% CI 1.30–11.45, $p = 0.02$), and multiple metastases (HR 1.53, 95% CI 1.02–2.29; $p = 0.04$) were independently associated with survival. Patients with multiple metastases were also grouped according to the number of metastatic lesions. In the survival analysis performed according to these groupings, it was observed that survival decreased as the number of metastatic lesions increased. The contribution of surgical treatment to survival was seen in all metastasis groups. In patients with solitary metastases, the 5-year OS was 45% in the ST group and 75% in the LRT group ($p = 0.0005$). OS was 42% and 72%, respectively, in patients with oligometastases ($p = 002$). In patients with multiple metastases, the 5-year OS was 31% in the ST group and 69% in the LRT group ($p = 0.0001$). In patients with more than five metastases, these rates were 14% and 49%, respectively ($p = 0.005$) (Fig. 3).

DISCUSSION

Although BC is a tumor with good prognosis compared with other solid organ cancers, in cases with distant metastasis, 5-year survival decreases to below 30%.[14] Therefore, distant metastasis is the most important factor that shortens survival. The rate of metastatic disease at the time of diagnosis (de novo metastasis) is 6–10%, even in the USA. This ratio is much higher in developing countries.[15] Metastatic disease occurs as BOM in more than half of patients with de novo metastasis in BC. Metastatic disease defines a heterogeneous group of diseases. Tumor characteristics such as stage, tumor biology, genotypic characteristics, metastatic site, size, and number of metastases determine the clinical course and prognosis of metastatic disease in addition to patient characteristics like age, race, and reproductive characteristics. BOM is required to be treated as a separate entity within the metastatic disease due to its longer survival and biological characteristics differing from that of the primary tumor. It has been shown that hormone receptor (+), HER2/neu (−), low-grade tumors, and elderly patients are prone to de novo bone metastasis.[16] In our series, the rate of hormone receptor (+) patients was 85%, and the rate of low-grade patients was 58%. Regarding the treatment options, the LRT group had more younger patients than the ST group (51.1 ± 12.9 vs 54.0 ± 13.8, respectively, $p = 0.02$), and the LRT group had more T3 tumors (17% vs 8%, respectively, $p = 0.0006$). It was also observed that a statistically

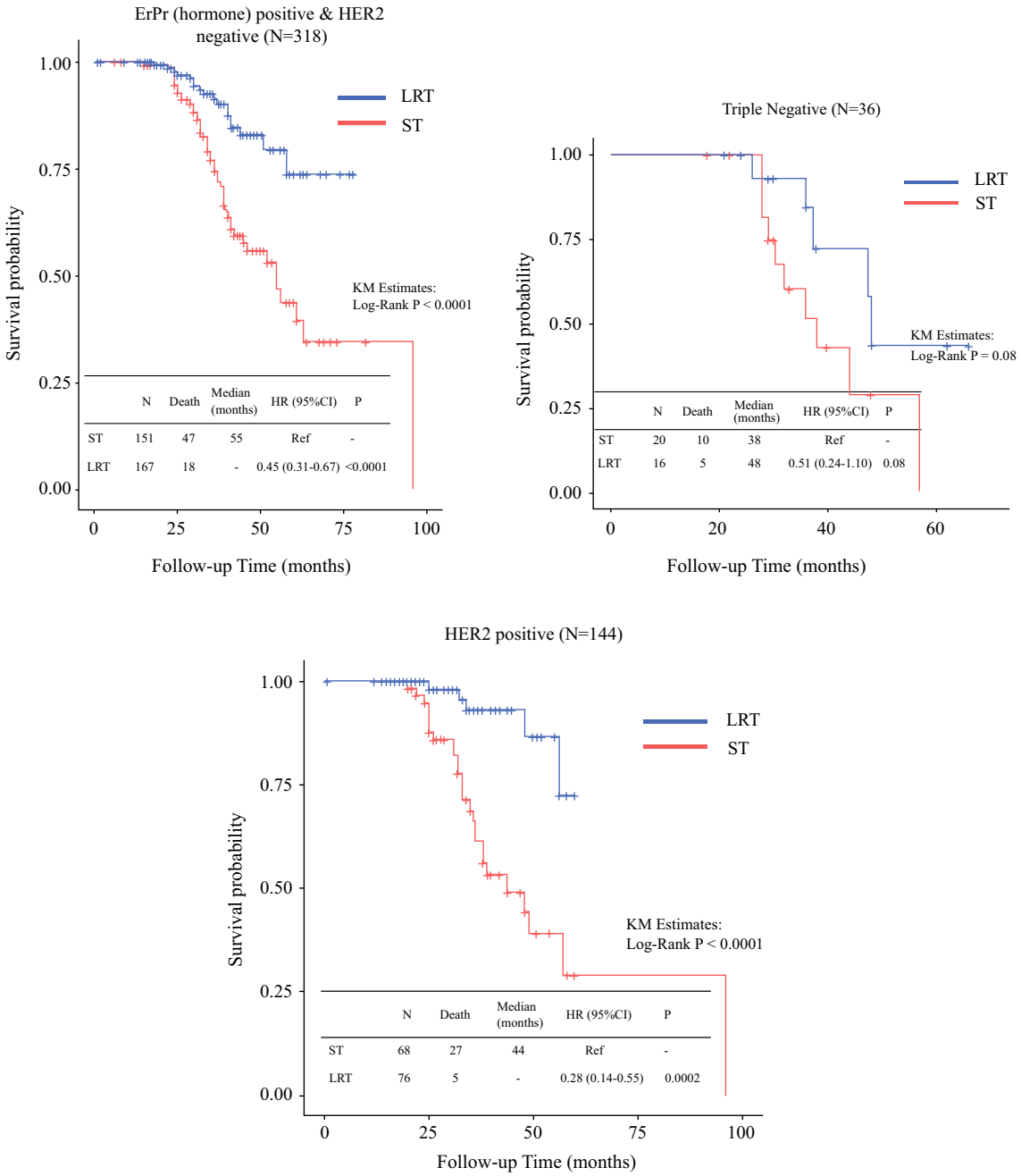

FIG. 2. Combined (ST + LRT and LRT + ST as a surgery group) survival analysis of ER/PR (+), HER2/neu (−), triple negative, and HER2/neu (+) patients. *ST* systemic treatment, *LRT* locoregional treatment

significant higher number of younger patients and patients with T3 tumors in the LRT group had received ST before surgery (Table 3). This observation shows that clinicians tended to choose LRT, but their treatment tended to start with ST before performing LRT more in younger patients and in those with bigger tumor size; it may be speculated that clinicians were considering not only overall survival, but also local control in de novo stage IV BOM BC. In addition to this speculation, due to the similarity with non-metastatic BC, it seems that clinicians should consider evaluating tumor response before LRT.

In the series of Wang et al., the highest OS after LRT was in patients with BOM. While there was no difference in survival in favor of LRT in patients without bone metastasis, a survival difference in favor of LRT was observed in patients with bone metastasis, although it was accompanied by visceral metastasis. Among patients with multiple organ metastases, the longest survival was

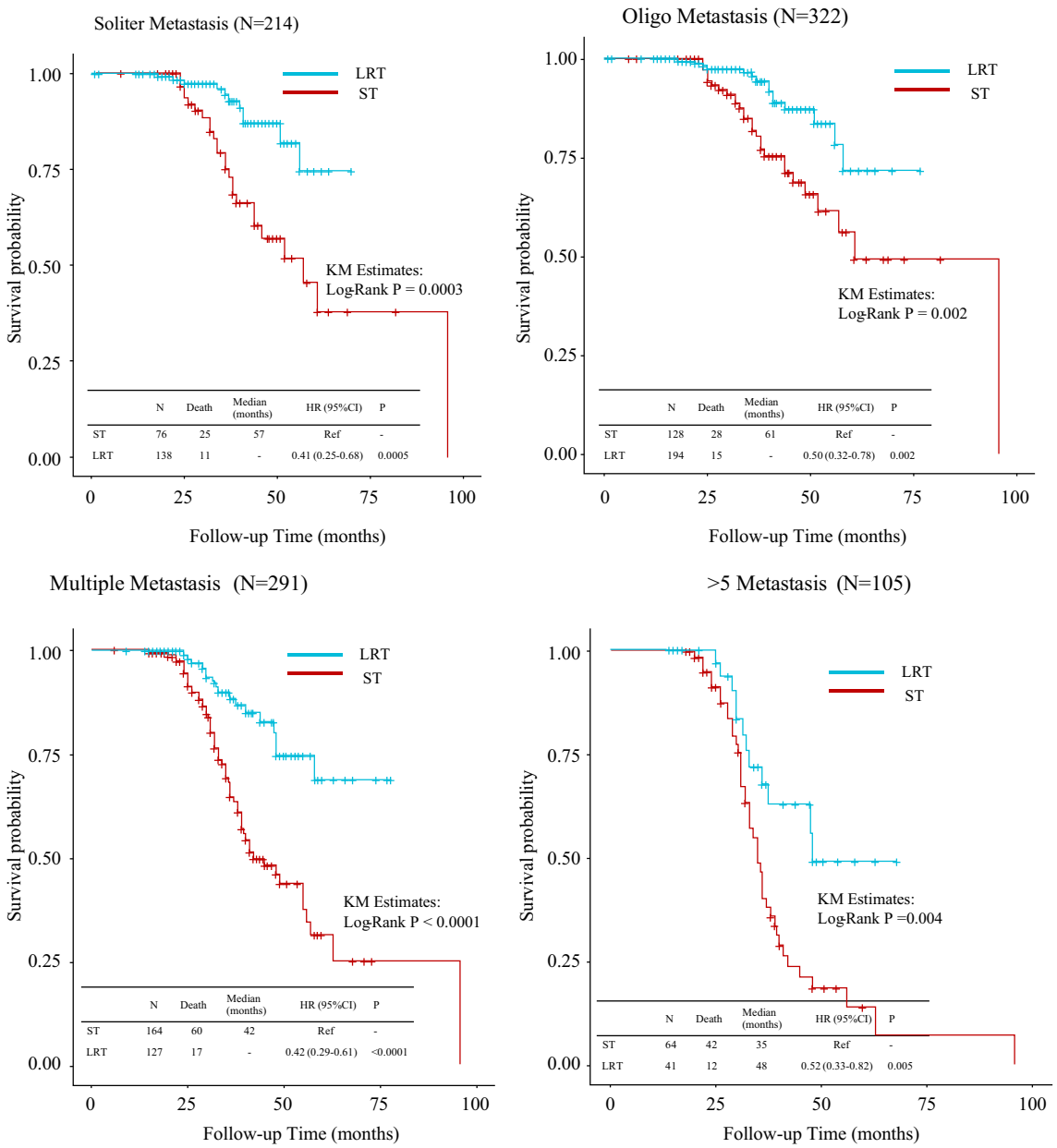

FIG. 3. Combined (ST+LRT and LRT+ST as a surgery group) survival analysis of patients based on the number of bone metastases

obtained in patients who first developed bone metastases.[17] In our series, there were no patients with visceral metastasis. Five-year OS was statistically significantly greater in the LRT group compared with the ST group (72% in the LRT group and 33% in the ST group, HR 0.40, 95% CI 0.30–0.54, $p < 0.0001$) (Fig. 1). Two important RCTs investigating the survival benefit of primary LRT in de novo stage IV metastatic BC have been published. In a study from India, in contrast to the results of our series, the survival contribution of LRT in patients responding to first-line CT regardless of the site and number of metastases could not be shown.[18] In the MF-07-01 study, LRT was shown to provide a longer survival time than ST alone. Similar to the BOMET study, it was determined that the survival contribution of LRT was higher in patients with BOM. While it was observed that LRT reduced the risk of death in patients with BOM by 33% (HR 0.67, 95% CI 0.43–1.07, $p = 0.09$) in the MF07-01 RCT, and this rate was 60% (HR 0.40, 95% CI 0.30–0.54, $p < 0.0001$) in the current BOMET study. In subgroup analysis of the MF07-01 study, the risk of death was lower in patients with solitary bone metastases; median survival was 14 months longer in the LRT group among patients with solitary bone metastases.[13] In the BOMET study, a similar OS advantage was seen in all metastasis groups; 5-year OS was 75%, 72%, and 69% for patients with solitary, oligometastases,

and multiple metastases, respectively, in the LRT group; these rates were 45%, 42%, and 31%, respectively, in the ST group (all $p < 0.05$). In patients with more than five metastases, these rates were 49% in the LRT group and 14% in the ST group ($p = 0.005$) (Fig. 3). The Eastern Cooperative Oncology Group [ECOG] 2108 and the Japan Clinical Oncology Group 1017 are RCTs evaluating the effect of LRT in de novo stage IV BC. Khan et al. presented the results of a multicenter, phase III ECOG 2108 study earlier than expected at the American Society of Clinical Oncology 2020 meeting. In this study, patients with de novo stage IV metastatic BC were given ST and patients whose distant metastases remained stable or regressed were divided into ST and LRT groups. There was no difference in OS between the two groups at 3 years (68.4% vs 67.9%) (HR 1.09, 90% CI: 0.80–1.49, $p = 0.63$). However, the 3-year locoregional recurrence/progression rate of the LRT group was lower than that of the ST group (10.2% vs 25.6%; HR 0.37, 95% CI 0.19–0.73). This study was criticized for its failure to obtain negative surgical margins in 20% of patients in the LRT group, which was an important limitation.[19]

In the BOMET study, at 34 months the median follow-up hazard of death was 68% less in the LRT + ST group and 82% less in the ST + LRT group compared with the ST only group ($p = 0.0001$). Our study group supports the hypothesis that metastatic tumor load and tumor biology are the factors contributing the most to survival, and LRT should be expected to contribute to survival by decreasing the tumor burden, especially in hormone receptor (+) patients. The primary tumor is the main source for new metastases and eliminating the main source at presentation may lead to better ST effects. There is also a time window during which ST stabilizes or regresses the primary tumor, and eliminating the source of tumor seeding with LRT may prolong survival. LRT also may eliminate the risk of tumor resistance to ST. The formation of more aggressive phenotypes can be prevented by decreasing tumor-promoting activity regulated by cancer stem cells.[20] When data for the last 5 years was evaluated, it was seen that the survival contribution of primary LRT and ST continues to increase. Careful patient selection for surgical treatment and the contribution of modern chemotherapeutic agents[21] play a significant role in the increase in survival. Today, in the modern era of BC treatment, ST has become standard for the locally advanced stage. Anthracycline- and taxane-based agents and anti-HER2 treatment in HER2/neu (+) patients are the basis of ST. In the BOMET study, 85% ($n = 224$) of patients were ER/PR (+) and received hormonotherapy, and 95% ($n = 251$) received CT in the LRT group. In the ER/PR (+) and HER2/neu (−) subgroup of patients in the BOMET study, the death rate in the median 3-year follow-up was 11% ($n = 18$) in the LRT group; hazard of death was 76% less in the ST + LRT group and it was 62% less in the LRT + ST group; these rates were significantly lower than those in the ST only group ($p = 0.003$ and $p = 0.002$, respectively). In the BOMET study, survival contribution was independent of the time of ST implementation in the LRT group.

Three RCTs and 30 high-quality observational studies with 67,986 patients were included in a meta-analysis by Xiao et al. in 2018.[22] It was seen that 16% of patients in the surgical group of RCTs and 15% of patients in the ST group were patients with BOM. According to the results of this meta-analysis, OS and distant progression-free survival advantages were in favor of LRT. LRT resulted in the longest survival benefit in patients with BOM (HR 0.61, 95% CI 0.37–1.00, $p = 0.05$) and hormone receptor (+) patients (HR 0.65, 95% CI 0.61–0.7, $p = 0.01$). The survival advantage in BOM and hormone receptor (+) patients is more pronounced in the BOMET and MF07-01 studies. In the current BOMET study analyses, LRT resulted in a survival advantage in hormone receptor (+)/HER2/neu (−) patients (HR 0.45, 95% CI 0.31–0.67, $p < 0.0001$). Similar OS benefit was seen in the HER2/neu (+) patients when comparing the LRT group with the ST group (HR 0.27, 95% CI 0.27–0.55, $p = 0.0002$). Although prolonged survival in metastatic disease is considered the success of new targeted agents, LRT has been shown to reduce the risk of death by 44%, even in HER2/neu (+) patients undergoing dual blockade.[23] While the BOMET study showed a survival advantage in HER2/neu (+) patients in favor of primary LRT, this was not the case for TN patients (HR 0.55, 95% CI 0.24–1.10, $p = 0.08$). Similar results have been reported in the series of Pons-Tonstivit et al. and in the MF07-01 RCT.[13,24]

A recent large-scale evaluation of data showed that primary LRT had been applied to an increasing number of de novo stage IV patients.[14] Primary LRT reduces the risk of cancer-related death by up to 40% in patients with metastasis to single organs other than the brain. This survival advantage increased up to 60% in the BOMET study; the death rate was 25% less in the LRT group compared with the ST group (10.5 % and 35.4%, respectively), and the 5-year OS was 40% higher in the LRT group (72% and 33%, respectively, $p < 0.0001$). Although the BOMET study doesn't include metastases other than bone metastasis at presentation, other studies show that primary LRT may contribute to survival in patients with isolated liver and lung metastasis, but the highest survival contribution was seen in patients with BOM.[25] In studies to date, grading of metastatic burden in patients with multiple metastases has not been considered much. In the study of Co et al., the relationship between the survival contribution of primary LRT and the number of metastases was not shown.[26] However, it should be kept in mind that patients

with visceral metastases were included in this study. In the BOMET study, it was observed that survival decreased as the metastatic load increased and primary LRT contributed to survival in all metastasis groups. The 5-year OS was 75%, 72%, and 69% in patients who underwent LRT with solitary metastasis, oligometastases, and multiple metastases, respectively, but these rates were 45%, 42%, and 31%, respectively, in the ST group ($p < 0.05$). Five-year OS rates were 76% in solitary and 70% in oligometastatic patients in the ST + LRT group, while it was 74% and 76% in the LRT + ST group, respectively. There was no OS benefit for starting with ST in solitary and oligometastatic disease. However, we found a statistically significant difference in the 5-year OS rate in patients with multiple bone metastases, especially with more than five metastases; these were 83% and 67% in the ST + LRT group. In contrast, 5-year OS rates were 55% for those with multiple metastases and 31% in patients with more than five bone metastases in the LRT + ST group. Starting with ST followed by LRT in patients with a higher metastatic disease burden seems to be a more rational approach.

Locoregional progression was 6.7% ($n = 18$) and 16.2% ($n = 39$) in the BOMET study. It was also seen that SPFS was significantly higher in the LRT group (43% vs 20%) in the BOMET study and the 5-year hazard of systemic progression was 43% less in the LRT group ($p < 0.0001$). LRT effectively prevents local progression and controls symptoms in de novo stage IV BC patients. In a study by Si et al., LPFS was 42 and 21 months in patients who underwent and did not undergo LRT, respectively.[27] In the MF07-01 trial, locoregional progression/relapse rates were found to be 1% in the LRT group and 11% in ST group in the median follow up of 55 months.[13] Therefore, LRT should be considered in de novo stage IV BOM BC patients who are expected to live longer, to control the primary disease progression.

Primary LRT studies in metastatic disease have shown that de novo stage IV metastatic disease represents a heterogeneous and complex group of diseases. Tumor biology also seems to determine the site of metastasis. It is reasonable to start with ST in patients with TN tumors and patients with a higher metastatic disease burden. However, it is also reasonable to accept that there is a subgroup of patients who will benefit from LRT, and including LRT in the treatment protocol may contribute to survival. Decreasing the number of tumor cells in the metastatic site by systemic therapy and the elimination of a primary tumor that might be a potential source of new metastasis seems to be the optimal treatment scheme. In summary, ST and primary LRT should be regarded as synergistic treatment modalities that enhance each other's effectiveness.

Several retrospective studies have been conducted to find appropriate ST in BOM, but studies that have evaluated LRT in BOM have been limited;[14,17,22] herein, we investigated the survival benefit of primary breast surgery besides systemic and endocrine therapies. Unlike previous studies evaluating LRT in stage IV disease, a higher number of patients with de novo BOM BC enrolled in our prospective registry study. Although there is a need to assess the effect of BC local therapy on bone-only metastases in a randomized trial, this prospective multi-center patient registry provides a better method for collecting uniform data to evaluate the importance of LRT than retrospective studies, especially those from a single institute. In addition, the BOMET study results may also serve as scientific evidence when initiating randomized studies on this topic.

CONCLUSION

In conclusion, the BOMET MF14-01 trial showed that LRT prolonged OS and SPFS and decreased locoregional recurrence in a median 3-year follow-up. Timing of primary breast surgery either at diagnosis or after ST provided a similar survival benefit compared with ST alone in de novo stage IV BOM BC patients. Although no firm conclusion can be drawn from this observational study without a randomized study, it presents important additional data showing that primary breast surgery should be in the treatment scheme when consulting patients diagnosed with de novo stage IV BOM BC.

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