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ORIGINAL ARTICLE – BREAST ONCOLOGY

Intervention for Hepatic and Pulmonary Metastases in Breast Cancer Patients: Prospective, Multi-institutional Registry Study–IMET, Protocol MF 14-02

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ABSTRACT

Background. One fourth of early-stage breast cancer cases become metastatic during the follow-up period. Limited metastasis is a metastatic disease condition in which the number of metastatic sites and the extent of the disease both are limited, and the disease is amenable to metastatic intervention. This prospective study aimed to evaluate intervention for limited metastases in the lung, liver, or both.

Methods. The study enrolled luminal A/B and/or human epidermal growth factor receptor 2 (HER2)-neu+ patients with operable lung and/or liver metastases in the follow-up assessment after completion of primary breast cancer treatment and patients with a diagnosis of metastasis after 2014. Demographic, clinical, tumor-specific, and metastasis detection-free interval (MDFI) data were collected. Bone metastasis in addition to lung and liver metastases also was included in the analysis. The patients were divided into two groups according to the method of treatment for metastases: systemic therapy alone (ST) group or intervention (IT) group.

Results. Until June 2020, 200 patients were enrolled in the study. The demographic data were similar between the two groups. The median follow-up time was 77 months (range 55–107 months) in the IT group (n = 119; 59.5%) and 57 months (range 39–84) in the ST-only group (n = 81; 40.5%). The median MDFI was 40 months (range 23–70 months) in the IT group, and 35 months (range 13–61 months) in the ST-only group (p = 0.47). The groups had similar surgeries for the primary tumor and axilla. Most of the patients had liver metastases (49.5%, n = 99), and 42% (n = 84) of the patients had lung metastases. Both lung and liver metastases were found in 8.5% (n = 17) of the patients. The primary tumor was estrogen receptor/progesterone receptor-positive in 75% (n = 150) of the patients, and 32% (n = 64) of the patients

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had HER2-neu+ tumors. Metastatic-site resection was performed for 32% ($n = 64$) of the patients, and 27.5% ($n = 55$) of the patients underwent metastatic ablative interventions. In the Kaplan-Meier survival analysis, the hazard of death (HoD) was 56% lower in the IT group than in the ST-only group (hazard ratio [HR], 0.44; 95% confidence interval [CI] 0.26–0.72; $p = 0.001$). The HoD was lower in the IT group than in the ST-only group for the patients younger than 55 years (HR, 0.32; 95% CI 0.17–0.62; $p = 0.0007$). In the multivariable Cox regression model, HoD was significantly lower for the patients who underwent intervention for metastases and had an MDFI longer than 24 months, but their liver metastases doubled the risk of death compared with lung metastases. **Conclusion.** Metastasis-directed interventions have reduced the risk of death for patients with limited lung/liver metastases who are amenable to interventions after completion of primary cancer treatment. For a select group of patients, such as those with luminal A/B or HER2-neu+ breast cancer who are younger than 55 years with limited metastases to the lung and liver or an MDFI longer than 24 months, surgical or ablative therapy for metastases should be considered and discussed on tumor boards.

Breast cancer (BC), the most common type of cancer for women worldwide, is responsible for one in four of all female cancers.[1] Distant organ metastases are responsible for breast cancer-related deaths. Up to 10% of cases are metastatic at the time of diagnosis (de novo), and approximately 20–30% of women with breast cancer diagnosed at an early stage become metastatic during the follow-up period.[2–4]

Breast cancer most commonly metastasizes to the bones, but bone metastases represent an entity different from other types of metastases in terms of their biologic behavior and occurrence mechanisms. For that reason, specific current treatment strategies have been developed for patients with bone metastases.[5] Lungs and liver are the organs to which breast cancer metastasizes most frequently, excluding bone metastasis.

The conventional treatment methods for stage 4 patients with organ metastases are chemotherapy, hormone therapy, and targeted therapies, as well as their combinations.[6] These treatments have been applied with palliative expectations. However, developments in systemic therapy (ST) are promising. It has been observed that the 5-year survival rates for stage 4 patients receiving ST increases by 1–2% each year.[7] These developments have excited clinicians and accelerated the search for more aggressive treatments, including primary locoregional therapy for metastatic disease.[8, 9] The second reason for this acceleration is that metastatic disease currently is detected at stages with less tumor burden and operative morbidity is decreased in this modern surgery era.[10] The aim is to redirect the intent of the treatment from palliative toward curative.

Although interventions for metastatic lesions are at low recommendation levels in guidelines,[6] it should be acknowledged that this topic is a promising field of research. It has been stated that with an "adjuvant intervention/surgery," the resistant clones will be removed and the systemic spread due to cancer heterogeneity will be reduced by a reduction of the tumor burden. The number of interventions performed for metastatic breast cancer has dramatically increased during the past 2 decades. Several case series on resection of lung and liver metastases in oligometastatic breast cancer have been reported, and most of the data are from small series of patients collected over many years.[11, 12]

For single or oligometastatic disease, local treatment is thought to increase survival, and for potentially curable metastatic patients, different interventional treatment methods can be applied.[11, 13] This prospective, multi-center registry study aimed to investigate the importance of interventions for operable lung and/or liver metastasis for breast cancer survival.

METHODS

This study was a multicentric, prospective registry study. Ethics committee approval was obtained. All the patients were women, and 29 centers participated in the study. The study enrolled luminal A/B and/or human epidermal growth factor receptor 2 (HER2)-neu+ patients with operable lung and/or liver metastasis in the follow-up evaluation after completion of primary breast cancer treatment and patients with metastases diagnosed between October 2014 and June 2020.

Limited metastasis is defined as a single resectable metastasis or fewer than five total metastases within surgical resection limits that can be resected with R0 resection of the lung and/or liver metastases. Although this was not a randomized controlled trial, all breast cancer subtypes with resectable lung and/or liver metastases were prospectively collected. The attending clinicians and tumor boards at the centers decided whether the metastases should be treated with ST only or with intervention.

The statistical analysis did not include patients with triple-negative metastatic breast tumors because of their shorter overall survival. Due to the survival difference between metachronous and de novo stage 4 breast cancer, the latter group of patients was excluded from this analysis.

The patients were divided into two groups according to the treatment method used for metastases: the ST-only group and the intervention (IT) group. Demographics, clinical and tumor-specific data (patients' age, menopause status, tumor type and stage, receptor status [estrogen {ER}, progesterone {PR}, HER2-neu] of the primary tumor, and tumor load in the lung and/or liver metastases) and metastasis detection-free interval (MDFI) data were collected. Bone metastasis in addition to lung and liver metastases also was included in the analysis. The study also recorded treatment-related and follow-up data, intervention method (surgical resection, radiofrequency [RF] ablation, transcatheter arterial radioembolization [TARE], stereotactic radiosurgery, radiation therapy), median follow-up time, incidence of tumor recurrence, time to recurrence, and overall survival (OS).

Overall survival was calculated from the date of breast cancer diagnosis until death or last follow-up visit. Lung and/or liver metastases were defined as metachronous if the interval between resection of the primary tumor and the first diagnosis of metastases was longer than 3 months. Progression-free interval was defined as the duration from diagnosis of metastasis to detection of disease progression. Metastasis detection-free interval (MDFI) was defined as the period between the date of primary breast cancer surgery and the first distant metastasis. Post-distance recurrence survival (PDRS) was defined as the time between the date of the distant metastasis diagnosis and the last follow-up visit or death.

Because numerous different chemotherapy regimens (before and after the intervention) were administered to this cohort of patients during their life span, chemotherapy regimens in both the ST-alone and IT groups were not included in this study. However, all ER+/PR+ patients received hormone therapy (premenopausal tamoxifen and postmenopausal aromatase enzyme inhibitors), and all the HER-2neu+ patients received targeted therapy in addition to chemotherapy.

After the primary breast cancer surgery, all the patients were followed up every 3 months for the first 2 or 3 years, then every 6 months for up to 5 years. The physical exam of the patient determined the diagnostic tool used for metastatic diagnosis. The patients with metastatic breast cancer in the current study had positron emission tomography (PET)-computed tomography (CT) scans 3 months after the metastatic-site intervention, then 3- to 6-month PET-CT follow-up evaluations. Additional scans such as bone scans, brain magnetic resonance imaging (MRI) scans, and other tests were administered if necessary.

Statistical Analysis

Student *t* tests were used to compare continuous variables with normal distribution between the IT and ST-only groups. Violations of normal distribution were tested using the Shapiro–Wilk test, and the Wilcoxon rank-sum test was used for variables without normal distribution. Chi-square tests were used to compare the distribution of categorical variables. Survival rates for the IT and ST-only groups were estimated using Kaplan–Meier log-rank tests. Uni- and multivariable Cox models with clinical, tumor, and metastasis characteristics were run to estimate the hazard ratio (HR) and 95% confidence interval (CI) for survival rate estimates. All p values lower than 0.05 were considered statistically significant. The statistical analyses were performed with R version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria; https://www.r-project.org) software packages.

RESULTS

The study enrolled 200 women: 119 (59.5%) in the IT group and 81 (40.5%) in the ST-only group. The mean age of all the patients was 51.0 ± 12.2 years (range 23–88 years). Of the 200 women, 104 (52%) were postmenopausal.

Segmental mastectomy was the primary breast cancer surgery for 68 women (34%), and 51 women (25.5%) had sentinel lymph node biopsies. The metastasis cases included 73 women (36.5%) with isolated lung metastases, 65 women (32.5%) with isolated liver metastases, 11 women (5.5%) with both lung and bone metastases, 34 women (17%) with both liver and bone metastases, and 17 women (8.5%) with multiple metastases (lung, liver, and bone).

The metastases were confirmed by biopsy for 86 women (72.3%) in the IT group and 51 women (62.9%) in the ST-only group ($p = 0.16$). Most of the patients had ER/PR-positive primary tumors ($n = 150$, 75%), and 64 patients (32%) had HER2-neu+ primary breast cancer. The patient and tumor characteristics in the two groups were similar, as shown in Table 1.

The metastasis-site receptors were compared with the initial tumor receptors. Although 7.9% (10/127) of the patients with ER+ primary tumors became negative in metastases, all received hormone therapy because the primary tumor was positive. Furthermore, one patient whose primary tumor was ER− and 7 patients whose primary tumor was PR− had metastatic sites that were respectively ER+ and PR+, and hormone therapy was initiated for these patients. In addition, the metastatic-site biopsy showed that 30.8% (12/ 39) of the HER2-neu+ primary

TABLE 1 Patient and tumor characteristics in the two groups

	IT (n = 119) n (%)	ST (n = 81) n (%)	p value
Mean age (years)	50.4 ± 11.4	51.9 ± 13.4	0.39
Menopause	58 (49)	46 (57)	0.26
ER+/PR+	85 (71)	65 (80)	0.16
HER2-neu+	37 (31)	27 (33)	0.74
Breast surgery			
Mastectomy	76 (64)	55 (68)	0.61
Segmental mastectomy	42 (36)	26 (32)	
Axillary surgery			0.73
SLNB	31 (27)	20 (25)	
ALND	83 (73)	60 (75)	
Primary tumor histopathology			0.63
IDC	112 (95)	73 (91)	
ILC	2 (2)	3 (4)	
Mixture (IDC + ILC)	2 (2)	3 (4)	
Metaplastic	0 (0)	0 (0)	
Others	2 (2)	1 (1)	
Lymph node status			0.10
NX	12 (10)	2 (2)	
N0	29 (24)	22 (27)	
N1	40 (34)	27 (33)	
N2	26 (22)	14 (17)	
N3	12 (10)	16 (20)	
Biopsy to metastasis	86 (72)	51 (63)	0.16
Metastasis site			0.01
Lung only	47 (39)	26 (32)	
Liver only	46 (39)	19 (23)	
Lung + liver + bone	5 (4)	12 (15)	
Lung + bone	5 (4)	6 (7)	
Liver + bone	16 (13)	18 (22)	
Intervention type			
Lung metastasectomy	39 (32.8)	–	
Liver metastasectomy	25 (21)	–	
Liver RF	17 (14.3)	–	
Lung radiosurgery	14 (11.7)	–	
Liver radiosurgery	17 (14.3)	–	
Liver TARE	7 (5.9)	–	

IT intervention, *ST* systemic therapy alone, *ER* estrogen receptor, *PR* progesterone receptor, *HER2* human epidermal growth factor receptor 2, *SLNB* sentinel lymph node biopsy, *ALNB* axillary lymph node biopsy, *IDC* invasive ductal carcinoma, *ILC* ınvasive lobular carcinoma, *RF* radiofrequency, *TARE* transcatheter arterial radioembolization

tumors became negative, whereas 11.8% (12/102) of the HER2-neu− tumors became positive, and the HER2+ patients received targeted therapy.

In the IT group, 39 patients (32.8%) underwent lung metastasectomy, and 14 patients (11.7%) were treated with lung radiosurgery. Liver metastasectomy was performed for 25 patients (21%), and other interventions for liver metastases (RF, radiosurgery, TARE) were performed for 41 patients (34.5%) (Table 1).

The median follow-up time was 77 months (range 55–107 months) in the IT group and 57 months (range 39–84 months) in the ST-only group (p = 0.002). The times from primary tumor surgery to metastasis in the two groups were similar. The median MDFI was 40 months (range 23–70 months) in the IT group and 35 months (range 13–61 months) in the ST-only group (p = 0.47). Disease progression occurred for 20 patients (17%) in the IT group and 13 patients (16%) in the ST-only group.

During the follow-up period, 29 patients (24.4%) in the IT group and 32 patients (39.5%) in the ST-only group died. The OS was significantly longer for the IT group (90%; 95% CI 85–96) than for the ST-only group (70%; 95% CI 60–82%) during the 5-year follow-up period (p = 0.002).

The hazard of death (HoD) ratio was 56% lower in the IT group than in the ST-only group (HR, 0.44; 95% CI 0.26–0.72; p = 0.001) during a median follow-up period of 70 months (range 45–101 months). The HoD was lower in the IT group than in the ST-only group for the patients younger than 55 years (HR, 0.32; 95% CI 0.17–0.62; p = 0.0007), those with ER+ and/or PR+ tumors (HR, 0.51; 95% CI 0.29–0.88; p = 0.02), and those with HER2-neu+ tumors (HR, 0.25; 95% CI 0.09–0.69; p = 0.008) (Fig. 1a–d). No significant difference in OS was detected between the HR+ HER2-neu+ group and the HR– HER2-neu+ group (p = 0.14). Moreover, during a total of 80 months of post-distance follow-up evaluation, HoD was 61% lower in the IT group than in the ST-only group (HR, 0.39; 95% CI 0.23–0.64; p = 0.001; Fig. 2).

The median overall survival rate was 62 months for the patients whose metastases developed less than 2 years after diagnosis and 137 months for the patients whose metastases developed more than 2 years later ($p < 0.001$). In the multivariable Cox regression model, HoD was significantly lower for the patients who underwent intervention for metastases and who had an MDFI longer than 24 months. Having liver metastases doubled the HoD compared with the HoD for the patients who had lung metastases (Table 2).

DISCUSSION

Until the beginning of the 21st century, the number of studies on liver and lung interventions for metastatic BC were limited. Retrospective single-center case series with a

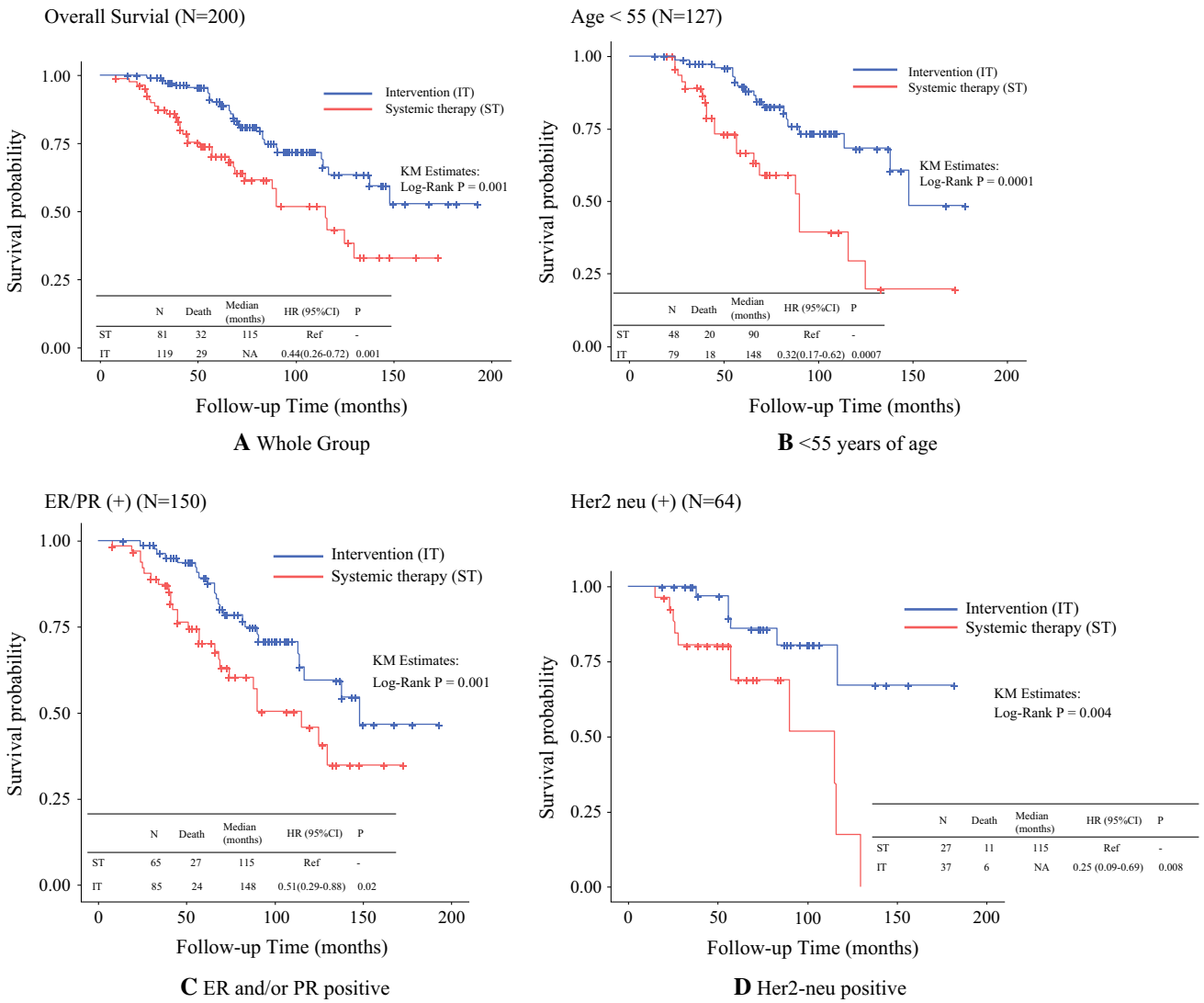

FIG. 1 Overall survival graphs of **A** the whole group, **B** the patients younger than 55 years, **C** the patients with ER+ and/or PR+ tumors, and **D** the HER2-neu+ patients. *ER* estrogen receptor, *PR* progesterone receptor, *HER2* human epidermal growth factor receptor 2

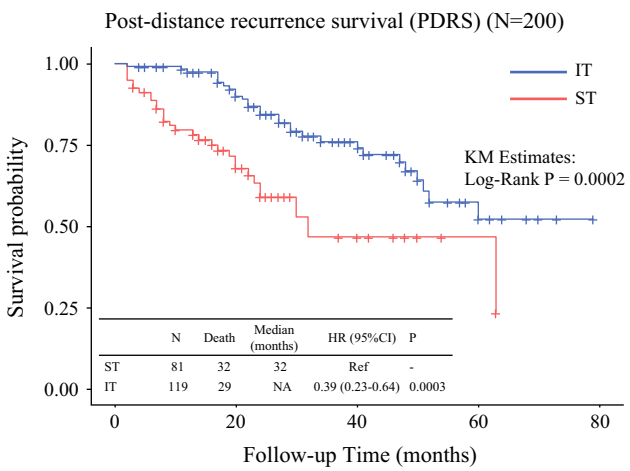

FIG. 2. Post-distance recurrence survival (n = 200).

limited number of patients have been published during the last 2 decades. Recently, prospective randomized studies with a closer focus on radiation therapy as an intervention for metastatic sites have been initiated.[14] We believe that while we are waiting for the results from randomized controlled trials, our prospectively collected data will serve as an additional source to inform clinicians making decisions regarding interventions for metastasis.

The current results of our study show that surgical resection or ablative interventions may contribute to the survival of breast cancer patients with a limited number and operable metachronous hepatic/pulmonary metastases. It is understood that especially patients younger than 55 years with luminal A/B or HER2-neu+ breast cancer or an MDFI longer than 24 months can benefit more from metastases interventions.

TABLE 2 Uni- and multivariable Cox models for overall survival

Parameter	HR (95% CI)	*p* value	HR_{adj} (95% CI)	p_{adj}
Metastasis intervention	0.44 (0.26–0.72)	0.001	0.39 (0.23–0.67)	0.0007
MDFI > 24 months	0.20 (0.10–0.37)	< 0.0001	0.17 (0.09–0.34)	< 0.0001
Age < 55 years	0.92 (0.55–1.56)	0.77	–	–
Pre-menopause	1.09 (0.64–1.77)	0.80	–	–
ER+/PR+	1.46 (0.74–2.88)	0.28	–	–
HER2-neu+	0.94 (0.54–1.65)	0.84	–	–
Primary breast surgery				
Segmental mastectomy	Reference	–		
Mastectomy	0.98 (0.58–1.65)	0.94	–	–
Metastasis site				
Lung	Reference	–	Ref	–
Liver	1.98 (1.03–3.83)	0.04	2.07 (1.05–4.06)	0.03
Lung + bone	1.11 (0.26–4.83)	0.89	1.16 (0.27–5.10)	0.84
Liver + bone	2.14 (1.08–4.22)	0.03	2.26 (1.12–4.57)	0.02
Multiple	1.01 (0.40–2.55)	0.98	0.80 (0.31–2.07)	0.64
Lymph node status				
N0	Reference	–		
N1	0.63 (0.31–1.28)	0.21	–	–
N2	1.11 (0.54–2.33)	0.76	–	–
N3	1.59 (0.76–3.32)	0.22	–	–

HR hazard ratio, *CI* confidence interval, HR_{adj} HR adjusted for variables significant in univariate models, p_{adj} *p* Values adjusted for variables significant in univariate models, *MDFI* metastasis detection-free interval, *ER* estrogen receptor, *PR* progesterone receptor, *HER2* human epidermal growth factor receptor 2

Unlike colorectal cancers, breast cancer metastasizes to the liver through the systemic circulation, not via the splanchnic flow. The rate of isolated liver metastases is 10%. Breast cancer cells are present in the systemic circulation a long time before they reach the liver.[15] However, half of the patients who experience metastases will have liver metastases.[16]

Recently, the 5-year survival rates for patients with liver metastases have increased slightly to above 20%, but these rates are not satisfactory.[17] Resistance to ST and deletion of receptor positivity in metastatic sites are the greatest obstacles to improving results.[4] In the Institute of Marine and Environmental Technology (IMET) study, 7.9% of ER+, 29.6% of PR+, and 30.8% HER2-neu+ tumors became negative in their respective receptors in metastases. Three case-matched analyses have increased interest in the subject.[4, 18, 19] In these studies, patients who had resection were matched with those who did not and analyzed in terms of age, time from diagnosis to metastasis, stage of primary tumor, receptor status, and histologic features.

Although the results from the aforementioned studies are conflicting, the study from Memorial Sloan Kettering Cancer Center suggested that interventions for liver metastases did not contribute to OS. However, patients had a longer recurrence-free survival, so they incidentally received less chemotherapy. In this study, local ablative methods were included in interventions applied to the liver.[18]

A French study showed that the risk of death was three times higher for patients who did not undergo liver resection and were treated with chemotherapy alone.[19] However, this study did not include patients who underwent intervention with local ablative methods, patients who progressed under chemotherapy, patients with more than four lesions, or patients whose liver function would remain less than 30% after resection.

A case series by Ruiz et al.[4] also from France, showed a 72% reduction in the risk of death with liver resection (HR, 0.28; 95%, CI 0.15–0.52; $p < 0.001$). The average survival rate for patients with breast cancer liver metastases treated with chemotherapy was 31 months, whereas this period stretched to 81 months when liver resection was added to the treatment. This study also excluded patients with multi-organ metastases and patients with disease progression under chemotherapy.

In our study, we observed that interventions for liver and/or lung metastases provide an OS advantage over the ST-only treatment ($p = 0.001$). The subgroup analysis showed no significant survival difference between the ST and IT groups for the patients with liver metastases

($p = 0.08$), but the IT group had a significant survival advantage over the ST-only group ($p = 0.001$) for the patients with lung metastases.

The American National Cancer Database had 9244 patients with breasts cancer liver metastases, and 28.5% of these patients had isolated liver metastases. The median OS was 46.4 months for the patients with isolated metastases who received chemotherapy and 15.6 months for those who did not. This period increased to 69.7 months when liver resection was added to chemotherapy. The mean survival was 27.9 months for the patients with multi-organ metastases who received chemotherapy and 8.8 months for those who did not ($p < 0.001$). Therefore, the findings showed that adding liver resection to treatment did not contribute to survival for these multi-organ metastatic patients.[20]

In our study, the rate of OS for the patients with single organ-only metastases (lung only or liver only) was similar to that for the other subgroups (liver + bone, lung + bone, and multiple metastases) (HR, 1.18; 95% CI 0.70–1.97; $p = 0.53$), and intervention for metastases showed improved survival for the patients with operable liver and/or lung metastases ($p = 0.001$). However, it is known that liver resection may contribute to survival for patients with limited extrahepatic metastases (e.g., bone and perihepatic lymph nodes) because liver metastases play a more decisive role in mortality than lung or bone metastases.[21] In our study, we also observed that liver metastases doubled the HoD (HR, 2.07; 95% CI 1.05–4.06; $p = 0.03$) compared with lung metastases.

In a meta-analysis of 43 articles, liver resection increased OS (mean 5-year survival, 37%) for the patients who had breast cancer, with low mortality (0.7%) and morbidity (20%) rates.[22] The mean time between breast surgery and diagnosis of liver metastases is reported to be 35 months. A fundamental conceptual problem arose in this meta-analysis: the patients with de novo metastases were included in these studies, and de novo metastases were treated with chemotherapy alone, whereas no intervention was applied to the primary site. Considering the survival effect of primary locoregional therapy on metastatic patients, it is questionable to include de novo stage 4 breast cancer in an analysis. In our study, we included only metachronous metastatic patients, and all the patients had surgery for primary breast cancer.

The MDFI between diagnosis and metastasis is an important prognostic factor,[23] and in the IMET study, it was 40 months (range 23–70 months) in the IT group and 35 months (range 13–61 months) in the ST-only group ($p = 0.47$). The HoD was significantly lower in the IT group than in the ST group for the patients who had an MDFI longer than 24 months than for the patients who had a shorter MDFI. However, a multivariable Cox analysis that included the MDFI in the model showed that intervention was independent from MDFI and that enhanced survival still was evident.

A study reported from the MD Anderson Cancer Center investigated prognostic factors for breast cancer metastases to the liver. In this study, the 5-year survival rate was 56% for the patients treated with chemotherapy and liver resection, whereas it was 40% for the patients treated with chemotherapy alone. The mean survival period for the group treated with chemotherapy plus liver resection was 81 months for the HER2-neu+ tumors, 75 months for the luminal B tumors, 53 months for the luminal A tumors, and 17 months for the triple negative (TN) tumors. These figures were 30, 48, 30, and 15 months, respectively, for the patients treated with chemotherapy alone.[24]

Although the shortest survival is seen with TN tumors, we did not include the TN group in our study. The HER2-neu+ level appears to be an important prognostic factor for prolonged survival due to the availability of anti-HER2 treatments.[25] In addition to tumor biology, MDFI length, the stage of the primary tumor at the time of diagnosis, and complete surgical resection are other factors affecting survival.[26]

The median survival rate is 42 months for patients who experience metastases less than 2 years after diagnosis and 57.5 months for patients who experience metastases more than 2 years later.[27] A short MDFI is a parameter that reflects the aggressive biology of the disease.

In our study, the median OS was 62 months for the patients who experienced metastases less than 2 years after diagnosis and 137 months for the patients who experienced metastases more than 2 years later ($p < 0.001$). We also found that the HoD was lower in the IT group than in the ST only-group for the patients younger than 55 years and for those with ER+ and/or PR+ and HER2-neu+ tumors. In Kaplan–Meier survival analysis, the HoD ratio was 56% lower in the IT group than in the ST-only group (HR, 044; 95% CI 0.26–0.72; $p = 0.001$).

Lung metastases are more common than liver metastases. The rate of metastatic breast cancer with isolated lung or pleural metastases is between 15 and 20%. The median survival with ST is 18–22 months.[28] Most lung metastases are not suitable for resection. For that reason, fewer studies on this subject have been published, and patient series are more limited. In a study by Meimarakis et al.[29] 66 (81.5%) of 81 patients with lung metastases had the opportunity to have R0 resection performed. The mean survival time for the R0 patients was 103 months, decreasing to 23.6 months with R1 resections and to 20.2 months with R2 resections. Additional mediastinal and hilar lymph node dissection did not contribute to the

survival. The presence of hormone receptors and solitary metastases appeared to be additional factors that increased survival.

Other studies have reported isolated breast cancer lung metastasis, MDFI, number of metastases, and complete resection status as additional prognostic factors.[30] A meta-analysis of 1937 patients from 16 studies showed a 46% 5 year survival rate after lung metastasectomy. An MDFI shorter than 3 years, incomplete resection, multiple metastases, and HR− have emerged as unfavorable prognostic factors.[31]

One of the largest and most recent series on this topic has been reported from Japan. For 258 patients who underwent lung resection, of whom 215 had solitary metastases, the 5-year OS was 64.9%, and the 10-year OS was 50.4%.[32] These are the longest reported OS periods.

Prognostic factors reported to be unfavorable are an MDFI shorter than 36 months, large tumor size, and lymph node metastasis. In our study, the 5-year survival rate was 90% for the IT group and 70% for the ST-only group. The HoD ratio was 56% lower in the IT group than in the ST-only group, and the HoD was significantly lower when the MDFI was longer than 24 months. We looked at PDRS and found that IT had a 29% higher 3-year survival rate (76%; 95% CI 68–86%) than the ST-only group (47%; 95% CI 34–64%).

Although survival analyses focus on OS, when a clinician consults a metastatic breast cancer patient, the advantage of PDRS with IT should be discussed. Notwithstanding, we require quality-of-life data for this cohort of patients, especially in this modern era of advanced technology interventions for the lungs and liver, with acceptable morbidity when weighed against survival gains. A summary of major series examining intervention in hepatic and lung metastases is shown in Table 3.

Other treatment methods targeting metastasis (metastasis-directed therapy) are ablative treatments. Ablative treatments aim to remove or completely destroy the metastatic tissue. Theoretically, it is not possible to remove all tissue with these methods. They are used mostly in cases of oligometastatic disease. Stereotactic body radiotherapy, stereotactic ablative radiotherapy, and hypofractioned image-guided radiotherapy are methods frequently used and researched as ablative methods.[33] Additionally, thermal ablation with RF, chemo-radioembolization, and cryotherapy can be used as local ablative interventions. These methods are safe and have low complication rates. They are preferred mostly for isolated metastases and for patients with lesions smaller than 3 cm for whom surgical intervention cannot be performed. Although the results are not as good as those with surgical

TABLE 3 Summary of major series examining intervention in hepatic and lung metastases

	Study period	No. of patients	Median follow-up	Site of metastasis	Intervention	Survival
Ruiz et al.[4]	2003–2013	ST: 523 IT: 139	80 months	Hepatic	Resection + ST versus ST	Median survival IT: 81 months ST: 31 months
Sadot et al.[18]	1991–2014	ST: 98 IT: 69	73 months	Hepatic	Surgery/ablation + ST versus ST	No significant difference in OS
Mariani et al.[19]	1988–2007	ST: 51 IT: 51	36 months	Hepatic	Resection + ST versus ST	3-Year OS in IT: 80% ST: 50% ($p < 0.0001$)
Chun et al.[24]	1997–2016	ST: 763 IT: 136		Hepatic	Resection + ST versus ST	5-Year OS in IT: 56% ST: 40% ($p = 0.01$)
Meimarakis et al.[29]	1982–2007	81	27.2 months	Pulmonary	Pulmonary resection	Median OS Resection: 103 months No resection: 20 months
Friedel et al.[30]	1960–1994	467	15 years	Pulmonary	Pulmonary resection	Median survival: 35 months
Endoh et al.[32]	1982–2017	253	65 months	Pulmonary	Pulmonary resection	10-Year OS: 50.4%

ST systemic treatment, *IT* intervention, *OS* overall survival

interventions in terms of OS, similar results have been reported with surgical interventions in terms of local palliation and symptom relief.[23, 34, 35]

In our study, we performed radiosurgery for lung metastases in 14 patients (11.7%), radiosurgery for liver metastases in 17 patients (14.3%), RF for liver metastases in 17 patients (14.3%), and TARE for liver metastases in 7 patients (5.9%). Due to the low patient numbers in many of the groups, we did not perform subgroup analyses of different interventional methods. It will be more valuable to study the effect of different local intervention methods on OS and local recurrence after including more cases. Although we could not analyze the subgroups in this study by separating surgery and other interventional methods, intervention for lung and/or liver metastases was shown to reduce the risk of death by 56%. The 5-year survival rate was 90% in the IT group and 70% in the ST only group. This study showed that a subset of patients, including those with Luminal A/B or Her 2 neu (+), younger than 55 years, oligometastasis to the lung or liver, and MDFI longer than 24 months, interventions to metastasis had longer OS compared to patients who only received ST.

This study had some strengths and weaknesses. The strengths were that it was a multicentric study, data were collected prospectively, and the number of patients in the intervention group was high. The weaknesses were that many different interventional methods were used (surgery and ablative methods), some subgroups lacked a sufficient number patients for a subgroup analysis, selection bias may have contributed significantly to the survival differences between the groups, and no quality-of-life survey was conducted before and after the metastatic site interventions.

In conclusion, the IMET study did not have a prospective randomized design, and bias between the groups was may have occurred, but it did provide important scientific data on the subject due to its multicenter prospective registry design, homogeneous groups, and significant patient numbers. Mestastatic-site interventions were associated with improved outcomes. Ultimately, randomized studies will determine whether intervention at lung and liver metastatic sites should be performed. In the meantime, such interventions can be considered for selected patients.

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