



# The Role of Primary Surgery in *De Novo* Metastatic Breast Carcinoma

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## ABSTRACT

Approximately 6-10% of all breast carcinoma is metastatic at diagnosis, termed *de novo* metastatic breast carcinoma (dnMBC). Systemic therapy remains the first line of treatment in dnMBC, but there is growing evidence that adjuvant locoregional treatment (LRT) of the primary tumor increases progression-free and overall survival (OS). Although selection bias may exist, real-world data from nearly half a million patients show that patients are undergoing primary tumor removal because of the survival benefit. The main question for the advocates for LRT in this patient population is not whether primary surgery is beneficial in dnMBC patients, but rather who is a good candidate for it. Oligometastatic disease (OMD) is a distinct subset of dnMBC that affects a limited number of organs. A better OS can be achieved with LRT in breast cancer patients, especially in those with OMD, bone only, or favorable subtypes. Though there is currently no consensus among breast care specialists on how to treat dnMBC patients, primary surgery for dnMBC should be taken into consideration for a subset of patients following an extensive multidisciplinary discussion.

**Keywords:** Locoregional treatment; metastatic breast carcinoma; oligometastatic disease; survival; systemic therapy

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## Key Points

- There are currently no specific guidelines for the treatment of *de novo* metastatic breast cancer (dnMBC) patients.
- Locoregional treatment in stage IV breast cancer may have a potential role in a subgroup of patients with dnMBC.
- Patient age, metastatic burden, and molecular subtypes are important parameters for patient selection.
- With more aggressive treatment, complete clinical and pathological remission can be achieved, especially in oligometastatic patients.
- Primary surgery for dnMBC should be considered for a subset of patients following a thorough multidisciplinary discussion.

## Introduction

The incidence of new-onset primary breast carcinoma (BC) with synchronous metastases at diagnosis is commonly known as *de novo* metastatic breast carcinoma (dnMBC). The incidence of dnMBC is approximately 6-10% (1, 2). With improved imaging modalities, the number of patients diagnosed with dnMBC has increased. As the mechanisms of tumor biology are better understood and with the advent of new systemic treatment (ST) agents, survival has increased in patients with dnMBC. Although the first choice of therapy in patients with stage IV breast cancer (BC) is still ST, there is currently data that suggests that some subgroups of patients with dnMBC may benefit from primary locoregional treatment (LRT). Surgical removal

of a primary tumor may improve survival by reducing tumor burden, decreasing immunomodulatory effects, removing the risk of new-onset metastatic illnesses, and reducing the likelihood of resistance (3, 4).

In 2002, Khan et al. (5) conducted a retrospective study indicating that primary surgery may have a role in the treatment of dnMBC. This study generated much interest and numerous retrospective studies and meta-analyses were then published (6-17). Many of these trials indicate that LRT is beneficial against local progression and improves disease-free survival (DFS) and overall survival (OS). However, these trials had inherent patient selection bias because of their retrospective design, rendering the data unreliable. Patients were younger, had less metastatic burden, and usually had favorable molecular subtypes in

the LRT arms. Meta-analysis also showed that LRT improved survival (18-21). Consequently, randomized studies were designed to verify this hypothesis.

### Prospective Randomized Clinical Trials

At the time of writing, the results of four prospective studies with differing methodologies have been published. However, it is important to review and discuss the available data in order to identify subgroups of dnMBC patients that could benefit the most from LRT of the primary tumor (22).

In 2015, Badwe et al. (23) published an Indian study with a total of 350 patients who had ST first and patients who did not progress were later randomly assigned to LRT or continued ST. The findings of this study demonstrated that LRT is ineffective in terms of OS [19.2 months for the LRT group vs 20.5 months in the ST group; hazard ratio (HR) 1.04, 95% confidence interval (CI) 0.81-1.34;  $p = 0.79$ ]. Furthermore, the site of metastasis (bone, visceral organ, and visceral organ with bone) did not correlate with OS. Individuals in the LRT group had significantly improved locoregional progression-free survival, but distant metastases were associated with poorer results (median 11.3 and 19.8 months for LRT and ST, respectively). The most controversial part of the study was that 26% of LRT patients and 35% of ST patients who were HER2-positive did not receive anti-HER2 medication.

The MF07-01 protocol, supported by the Turkish Federation of Breast Disease Societies, was the second study, published in 2018 (24). Patients were randomised to either upfront surgery followed by ST or ST alone. The early results of this trial were first presented at the San Antonio Breast Symposium in 2015 with a median 3-year follow up and there was no statistically significant difference between groups in terms of OS. However, at a median of 40 months of follow-up, the LRT group ( $n = 138$ ) had a 34% reduced death risk (HoD), significantly lower than the ST group ( $n = 136$ ) (HR 0.66, 95% CI 0.49 to 0.88,  $p = 0.005$ ). The LRT and ST groups had respective OS rates of 41.6% and 24.4%. In the subgroup analysis, estrogen receptor (ER) positive (HR 0.64, 95% CI 0.46-0.91,  $p = 0.01$ ), HER2 receptor negative (HR 0.64, 95% CI 0.45- 0.91,  $p = 0.01$ ), patients under 55 years of age (HR 0.57, 95% CI 0.38-0.86,  $p = 0.007$ ) and patients with solitary bone metastases (HR 0.47, 95% CI 0.23-0.98,  $p = 0.04$ ) had lower risk of death in the LRT group. In 2021, 10-year follow-up of this study was published (25). The median OS for the LRT group ( $n = 134$ ) was 46 months compared to 35 months for the ST group ( $n = 131$ ). The LRT group had a 29% decreased mortality rate (HR 0.71, 95% CI 0.59 to 0.86,  $p = 0.00003$ ). The OS rates for the LRT and ST groups at 10-years of follow-up were 19% (95% CI 13-28) and 5% (95% CI 2-12), respectively. Using the most recent follow-up information and additional classification criteria, HER2-positive patients in the LRT group had a higher OS rate. The ST group had a 14-fold higher locoregional progression than the LRT group at 10-year follow-up (14% in the ST group versus 1% in the LRT group).

The third prospective trial published in 2019 was the ABCSG-28 POSITIVE study by Fitzal et al. (26). The methodology and design were comparable to the MF07-01 study. Although a sample size of around 254 was intended, only 95 patients were enrolled. This study was stopped early due to poor recruitment that possibly decreased the statistical power. The LRT and ST groups showed comparable OS rates (HR 0.69, 95% CI 0.36-1.33,  $p = 0.27$ ) and time to distant metastases

(HR 0.60, 95% CI 0.34-1.04,  $p = 0.07$ ). Similar rates of locoregional progression were found in both groups (HR 0.933, 0.375-2.322,  $p = 0.882$ ), while the LRT group had significantly fewer cases (17.8% vs. 8.9%,  $p = 0.2148$ ). Surgical margin positivity was observed in 21% of the LRT group. Of note, cT3 and cN2 tumors were more prevalent in the LRT arm (22.2% vs. 6.7% and 15.6% vs. 4.4%, respectively).

The most recent study on this topic was the E2108 trial by Khan et al. (27) published in 2022 after the data was initially presented at ASCO in 2020. The protocol of this study was similar to the Indian study. The initial endpoint was based on OS, while the secondary endpoints were locoregional recurrence and quality of life (QoL). A total of 256 patients with dnMBC who didn't progress after 4-8 months of ST were then randomized to LRT plus ST ( $n = 125$ ) or ST only groups ( $n = 131$ ). Three-year OS rates were similar between groups (68.4% vs. 67.9%; HR, 1.11; 90% CI, 0.82-1.52;  $p = 0.57$ ). No progression-free survival difference was observed between the groups. However, locoregional progression was reduced in the LRT group ( $p < 0.001$ ). It was found that hormone receptor (HR) and HER2 status had no statistically significant influence on overall survival with LRT. Of the patients randomly assigned to the LRT group, 14.4% did not receive primary breast surgery and 7.2% had no axillary surgery at all. Furthermore, 8.4% of patients had positive margins in the final histopathological examination. In addition, adjuvant RT, which is inevitable after breast conserving surgery (BCS), was not performed in 12.9% of the patients. Alternatively, 18.8% (5 of 22) had mastectomies or BCS in the ST group. Sentinel lymph node biopsy/axillary lymph node dissection were performed together in 77% of the patients (17 of 22) who were randomly assigned to the ST group, and RT was also completed in 45% of patients (10 of 22) who underwent surgery. There were no palliative axillary procedures performed in the non-operative arm of the published comparable randomized studies. The curative intent of surgery and RT in the ST arm may statistically mask the cumulative effect of LRT on OS. The E2108 study included only 16% of oligometastatic patients, the vast majority of whom had multiple organ metastasis (84%). As such, the study does not reflect the data from the group that was most expected to respond to LRT.

It is important to note that LRT does not contribute to improved OS, even in the MF07-01 study at 3-year follow-up. However, the long-term results of the MF07-01 study in the peer-reviewed publication showed that local control provides a significant survival advantage in all subgroups except for the patients with triple negative (TN) BC in both 5-year and 10-year OS.

### Oligometastatic Disease

The majority of randomized studies did not show a survival benefit of LRT in dnMBC, but these trials are heterogeneous in design and there are subgroups of patients that deserve detailed analysis. When addressing primary surgery for dnMBC patients, detailed information about oligometastatic disease (OMD) is important. Though this term has no formal definition, OMD often refers to less than five metastases (28).

Unfortunately, literature regarding the survival impact of surgical resection of the primary tumor in oligometastatic BC patients is lacking. In the E2108 and Indian studies, no survival difference was reported for oligometastatic patients, which represented 16.3% and 25% of the study population, respectively (23, 27, 29). It is also important to address metastases-directed treatment when assessing

the impact of local treatment of the primary tumor in oligometastatic BC. The combination of LRT of the primary tumor and metastasis-directed therapy, aimed at complete eradication of detectable disease, should be investigated. 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.

The IMET study published in 2022 enrolled 200 patients with luminal A/B and/or human HER2-positive patients with operable lung and/or liver metastases in the follow-up assessment after completion of primary BC treatment. The median follow-up time was 77 months in the intervention (IT) group (n = 119; 59.5%) and 57 months (range 39–84) in the ST-only group (n = 81; 40.5%). The median (range) metastasis detection-free interval (MDFI) was 40 (23–70) months in the IT group, and 35 (13–61) months in the ST-only group (p = 0.47). The groups had similar surgeries for the primary tumor and axilla. Nearly half 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 HR positive in 75% (n = 150) of the patients, and 32% (n = 64) of the patients had HER2 positive 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 HoD was 56% lower in the IT group than in the ST-only group (hazard ratio HR 0.44; 95% 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 (28).

### Bone-only Disease

The dnMBC patients with bone-only disease usually have a better prognosis. BOMET MF14-01 is a prospective, multicenter registry study that evaluated the role of LRT of the primary tumor in addition to ST in dnMBC patients with bone-only disease. This study included 505 patients and concluded a better survival in the median 3-year follow-up in favor of LRT (HR 0.40, p<0.0001) (30).

In a large cohort retrospective study including 3956 BC patients with bone metastases, surgery of the primary tumor in addition to ST significantly improved OS with a median survival of 50 months versus 31 months in ST-only patients (p<0.001) (31).

Regarding randomized trials, in the MF07-01 study, 51% and 40% of patients presented with bone-only metastases in the LRT group and ST group respectively. Notably, 23% and 15% of patients had a solitary bone metastasis in the LRT and ST groups, respectively. In unplanned subgroup analysis, solitary bone metastasis was associated with a lower risk of death if treated with LRT in addition to ST (24). Conversely, in the E2108 trial, patients with bone-only disease (37.7%) were under-represented (27).

### Molecular Subtypes

HR-positive tumors have the best prognosis among the subtypes of breast cancer (32). According to retrospective studies, HR-positive dnMBC patients benefit the most from LRT (33-35). In the subgroup

analysis of the MF07-01 study, HR-positive status was also a relevant factor for surgical decision making (25). One of the pitfalls of this study was that HR-positive patients are over-represented in the LRT arm, which results in uncertainty regarding the results of this trial. In the ABCSG-28 POSITIVE study, luminal B subtype did not show a statistically significant benefit from primary tumor surgery. In contrast, surgery adversely affected survival in the luminal A subgroup (26). The E2108 trial showed that the TN immunohistochemical subtype was associated with poor prognosis in dnMBC patients undergoing surgery. Similar findings were seen in the MF07-01 trial. Some retrospective evidence also seems to support the use of LRT in the HER2-positive subtype. Even if HER2 expression results in a more aggressive disease with a poor prognosis, the use of HER2-targeted therapy led to outstanding survival benefit in these patients. According to retrospective observational studies, 13–32% of patients with HER 2 positive dnMBC who received LRT and had no evidence of disease lived for more than ten years (36, 37).

### Quality of Life

While primary surgery in dnMBC patients appears to improve OS, the impact on quality of life (QoL) must also be explored. In their MF07-01Q study, Soran et al. concluded that LRT had no detrimental effect on QoL compared to ST only in a cohort of patients who lived longer than three years, but the toxic effects of continued ST might be the cause of lower physical QoL scores compared to those of the general population and stage I-III BC patients (38). In the E2108 trial, Khan et al. (27) assessed health-related quality of life (HRQoL) using the FACT-B study assessment (Trial Outcome Index), which encompasses depression, anxiety, and well-being. Although HRQoL outcomes in the LRT group worsened at 18-month follow-up, results were comparable at the 6 and 30-month follow-ups. In conclusion, the EA2108 study found neither an improvement in OS nor a change in the QoL scale in patients who underwent LRT.

Although modified radical mastectomy (MRM) is associated with higher morbidity than BCS, retrospective studies of primary surgery in *de novo* metastatic inflammatory BC (IBC) found that MRM was an independent factor associated with OS in patients with dnMBC metastatic IBC (39). Chen et al. (40) Also noted that MRM may improve disease specific survival in a subset of dnIBC patients. A randomized clinical study, JCOG 1017, is currently underway and this study will add more valuable evidence to this cohort of patients' survival and QoL (41).

### Conclusion

Survival in dnMBC patients is currently higher than in the past decade. Typically, patients with dnMBC have more favorable disease characteristics and longer OS compared to metachronous patients (42). Stage IV BC is an extremely heterogenous disease and prognosis for these patients may vary according to the treatment choice. ST for dnMBC patients has dramatically evolved over the last two decades for every molecular subtype. LRT of the primary tumor and modern ST seem to be the perfect partners for better DFS and OS. Current guidelines offer LRT in selected cases due to the lack of clear evidence. However, there may be a subgroup of patients that may benefit more from LRT, including younger age, less tumor burden (oligometastatic disease, bone-only disease) and favorable molecular subtype (HR positive patients). Meanwhile, LRT of the primary tumor should be discussed in a multidisciplinary context for every patient with dnMBC.

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### Authorship Contributions

Surgical and Medical Practices: S.O., A.S.; Concept: B.D., B.G., H.M., S.O., A.S.; Design: B.D., B.G., H.M., S.O., A.S.; Data Collection and/ or Processing: B.D., B.G., H.M., S.O., A.S.; Analysis and/or Interpretation: B.D., B.G., H.M., S.O., A.S.; Literature Search: B.D., B.G., S.O., A.S.; Writing: B.D., B.G., H.M., S.O., A.S.

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