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Breast Surgery for De Novo Stage IV Breast Cancer: A Meta-Analysis of Randomized Trials Shows No Overall Survival Benefit

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Abstract

Retrospective evidence has suggested that removing the primary breast tumor in patients diagnosed with de novo metastatic breast cancer (MBC) might improve outcomes, yet randomized controlled trials (RCTs) have produced inconsistent findings. This analysis aimed to determine whether surgery of the primary tumor extends survival in this setting. We conducted a systematic literature search to identify RCTs comparing surgical excision of the primary breast tumor with no surgery in patients presenting with de novo MBC. Searches were performed in the Cochrane Library, Embase, Medline (OVID), and Web of Science, most recently updated in July 2023, and supplemented by manual review of conference abstracts. Extracted data included patient demographics, tumor features, and clinical outcomes. A random-effects meta-analysis was applied to account for heterogeneity across studies. Out of 3255 identified records, 5 RCTs met the inclusion criteria, encompassing 1381 patients. In the pooled intention-to-treat population, surgical removal of the primary tumor did not improve overall survival (HR = 0.93; 95% CI, 0.76–1.14). No subgroups defined by receptor status or metastatic pattern showed survival benefit, except for younger or premenopausal patients (HR = 0.74; 95% CI, 0.58–0.94). Surgery was associated with better local progression-free survival (HR = 0.37; 95% CI, 0.19–0.74). Overall, excision of the primary tumor does not confer a survival advantage in de novo MBC, though younger or premenopausal patients may benefit. The role of surgery should be explored within the context of rigorously designed clinical trials.

Keywords: Breast cancer, Primary tumor surgery, Metastatic disease, Meta-analysis, Overall survival

Introduction

Approximately 3%–10% of breast cancer patients present with metastatic disease either at diagnosis or within the first three months thereafter [1–3]. Patients with de novo MBC generally have better outcomes than those who develop distant metastases after treatment for early-stage disease [4, 5], likely because recurrent disease reflects expansion of therapy-resistant clones. Given the relatively slow progression in de novo MBC, locoregional interventions have been proposed to reduce ongoing tumor dissemination and subsequent metastasis driven by mesenchymal stem cells within primary tumors [6]. Retrospective studies suggest a potential survival benefit from breast surgery [7], but these analyses are prone to selection bias: younger, fitter patients with less aggressive disease are more likely to undergo surgery [8]. To rigorously evaluate the effect of surgical removal of the primary tumor in de novo MBC, five RCTs have been conducted [9–13]. However, variability in trial design—including timing of surgery, methodological differences, modest sample sizes, and conflicting outcomes—limits the certainty of conclusions. Individual trials were often underpowered to detect benefits within clinically relevant subgroups. Current guidelines reflect this uncertainty:

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while four of the five RCTs did not demonstrate a survival benefit, some recommend surgery for select patients [14], whereas others do not [15]. As a result, aggressive local treatment continues to be used in practice. For example, one large retrospective study in the era of modern systemic therapy found that roughly 25% of patients with de novo MBC underwent breast surgery within 12 months of diagnosis, and these patients showed improved overall survival in propensity score–matched analysis [16].

Taken together, the survival advantage of primary tumor excision in de novo MBC remains unresolved. It is possible that certain patient subgroups could benefit, but individual trials were not sufficiently powered to detect this. Retrospective studies carry inherent bias due to unknown confounders, and single RCTs may fail to detect modest survival gains. Pooling data from all available RCTs provides an opportunity to more definitively assess whether surgery improves outcomes in this population.

Materials and Methods

Literature search and study inclusion

We conducted a systematic literature review to identify RCTs comparing surgical excision of the primary breast tumor versus no surgery in patients presenting with de novo metastatic breast cancer (MBC). The review and meta-analysis were performed according to the PRISMA guidelines [17], and the study protocol was registered in PROSPERO (CRD42023430327).

Studies were considered eligible if they met the following criteria: (1) randomized controlled design, (2) included patients with de novo MBC, (3) at least one arm involved primary breast tumor surgery, (4) reported any efficacy outcomes, and (5) published in English. Retrospective, single-arm prospective studies, meta-analyses, and ongoing studies without published results were excluded. Two librarians at the Karolinska Institute Library conducted the database searches in December 2022, with an update in July 2023. Databases included Cochrane Library, Embase, Medline (OVID), and Web of Science. The Medline (Ovid) strategy used both MeSH terms and free text, and was adapted to other databases via the Polyglot Search Translator [18]. Searches were conducted from database inception, with peer review of strategies by a second librarian. De-duplication followed the method described by Bramer *et al*. [19], with an additional check comparing DOIs. Complete search strategies for all databases are provided in the Supplementary Material. Conference abstracts from ESMO, ASCO, and the San Antonio Breast Cancer Symposium were also reviewed to capture unpublished or recent data. Full-text articles were screened by A.M., and risk of bias for the primary outcome (overall survival) was assessed using the revised Cochrane RoB2 tool [20].

Data extraction

A predefined form was used to extract data, including study name, ClinicalTrials.gov identifier, first author, journal and year, total sample size, sample size per arm, timing of randomization (at enrollment or post-systemic therapy), median follow-up, methods for disease progression assessment, and hazard ratios (HR) with 95% confidence intervals (CI) for OS, LPFS, and PFS. Additional variables included HRs for subgroups defined by metastatic site (bone vs. visceral), hormone receptor and HER2 status, age categories, and number of metastatic sites. Data on patients allocated to systemic therapy who underwent surgery or patients randomized to surgery who did not receive it were also collected. Data extraction was performed independently by A.P. and A.M., with discrepancies resolved by consensus.

Endpoints

The primary endpoint was overall survival (OS), defined as the interval from randomization to death from any cause. Subgroup analyses assessed OS by age (younger vs. older), tumor characteristics (hormone receptor and HER2 status), and metastatic pattern (visceral vs. bone-only; oligometastatic vs. non-oligometastatic). Age definitions varied between studies, with some using an age cutoff [10, 12] and others using menopausal status [9, 12, 13], while ABCSG-28 provided no subgroup analyses [11]. For this analysis, premenopausal and younger-than-study-specific age cutoff patients were pooled, as were postmenopausal and older-than-cutoff patients. Secondary endpoints included locoregional progression-free survival (LPFS), defined as time from randomization to first locoregional recurrence or death, and progression-free survival (PFS), which combined overall and distant PFS endpoints reported in three of five trials [9, 11, 13].

Statistical analysis

Trial-level meta-analyses summarized HRs with 95% CIs for OS, LPFS, and PFS. HR < 1 indicates a survival

benefit for surgery. Random-effects models (DerSimonian-Laird method) were used to pool estimates, assuming variability in true intervention effects between trials (e.g., upfront surgery vs. induction chemotherapy). Sensitivity analyses were performed by sequentially omitting each trial and repeating the meta-analysis to examine study influence. Heterogeneity was quantified using I^2, representing the proportion of total variance due to between-study differences. Publication bias was evaluated with funnel plots and Egger's test. All analyses were conducted in R version 4.1.2 using the metafor and meta packages.

Results and Discussion

Study and patient characteristics

The systematic literature search, detailed in the Supplementary Materials, initially identified 5581 records, which decreased to 3255 after duplicates were removed. In addition, 328 studies were identified from conference proceedings. After screening against the predefined inclusion criteria, 5 randomized controlled trials (RCTs) examining the effect of primary breast surgery on survival in patients with de novo metastatic breast cancer (MBC) were included. Four trials were published in full, and one was reported as a poster at the ASCO 2023 Annual Meeting. For the MF07-01 trial, the most recent 10-year follow-up was included in this analysis [21]. **Table 1** summarizes the study designs and participant characteristics.

Inclusion criteria differed across trials: two studies required an initial systemic therapy phase and enrolled only patients without disease progression [8, 13], two allowed surgery upfront [10, 11], and one trial offered chemotherapy first for initially unresectable tumors, whereas resectable tumors underwent surgery followed by endocrine therapy [9]. Among trials that used initial systemic therapy, treatment regimens varied: in EA2108, approximately one-third of participants received chemotherapy alone, endocrine therapy alone, or chemotherapy combined with HER2-targeted therapy [12]; in Badwe *et al*., all patients with initially unresectable tumors were treated with chemotherapy [9]; and in PRIM-BC, systemic therapy was tailored based on receptor status and presence of life-threatening disease [13].

Table 1. Key features of the studies incorporated in the meta-analysis.

First Author (Year)	Study Name / Identifier	Enrollment Years	Sample Size	Median Follow-Up (Months)	Bone-Only Disease	HER2 Positive	ER Positive	Timing of Surgery	Clear Surgical Margins	Primary Endpoint
Badwe, 2015	Badwe *et al* NCT00193778	2005–2013	350	23	28.5%	30.5%	59.4%	At enrollment if resectable; after systemic therapy if initially unresectable	NR	Overall survival
Soran, 2021 (previously reported 2018)	MF07-01 NCT00557986	2007–2012	278 (265 in most recent analysis)	120	46.0%	29.0%	79.2%	At enrollment	NR	Overall survival
Fitzal, 2019	ABCSG-28 NCT01015625	2011–2015	90	37.5	37.8%	22.2%	81.1%	At enrollment	76.2%	Overall survival

Khan, 2022	EA2108 NCT01242800	2011–2015	256	53	32.2%	*	59.6%	After 16–32 weeks of systemic therapy	91.5%	Overall survival
Shien, 2023	PRIM-BC UMIN000005586	2011–x	407	60	28.7%	29.7%	71.9%	After 3 months of systemic therapy	87.3%	Overall survival

*ER-positive/HER2-negative.

Abbreviations: NR: not reported; HER2: human epidermal growth factor receptor 2; ER: estrogen receptor.

Across all included studies, 1381 patients were analyzed: 685 (49.6%) underwent surgery of the primary tumor, and 696 (50.4%) did not. Bone-only metastases were present in 34.9% of patients (range 28–46% across trials), while visceral metastases occurred in 61.3%. Hormone receptor–positive and HER2-positive disease were observed in 67.9% and 25.3% of patients, respectively. Notably, 11.4% of patients randomized to systemic therapy alone eventually received surgery, while 10.6% of those assigned to surgery did not undergo the procedure. OS was the primary endpoint in all trials.

Risk-of-bias assessment for the four fully published RCTs indicated one study with a high risk of bias. Funnel plot inspection and Egger's test did not reveal evidence of publication bias.

Overall survival

The pooled meta-analysis for OS (n = 1381) in the intention-to-treat (ITT) population demonstrated no survival benefit from primary breast tumor surgery (HR = 0.93; 95% CI, 0.76–1.14); **(Figure 1)**. Between-study heterogeneity was moderate (I^2 = 64%). Sensitivity analyses, in which studies were sequentially excluded, confirmed the stability of this result.

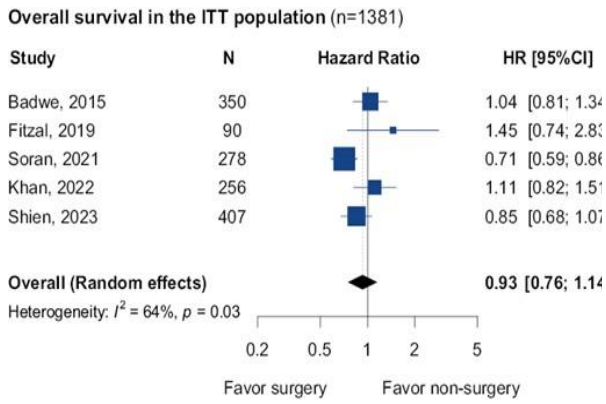
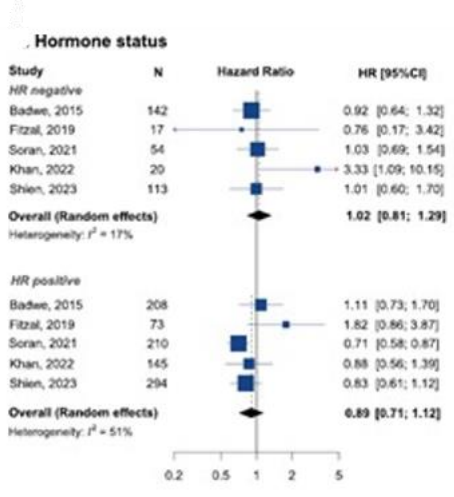


Figure 1. Pooled overall survival outcomes in the intention-to-treat (ITT) cohort comparing breast surgery to no breast surgery. Abbreviations: HR: hazard ratio; 95% CI: 95% confidence interval.

Subgroup analyses were performed according to hormone receptor status, HER2 status, age group, number of metastatic sites, and metastasis location **(Figure 2).** No benefit was observed in patients with hormone receptor negative disease (HR = 1.02; 95% CI, 0.81–1.29) or hormone receptor positive disease (HR = 0.89; 95% CI, 0.71–1.12). Similarly, HER2-negative (HR = 1.05; 95% CI, 0.77–1.43) and HER2-positive patients (HR = 0.94; 95% CI, 0.69–1.28) did not show improved OS with surgery. Metastasis location (bone versus visceral) and the number of metastatic sites (solitary/few versus multiple) did not alter survival outcomes. The only subgroup showing improved survival was younger or premenopausal women (HR = 0.74; 95% CI, 0.58–0.94).



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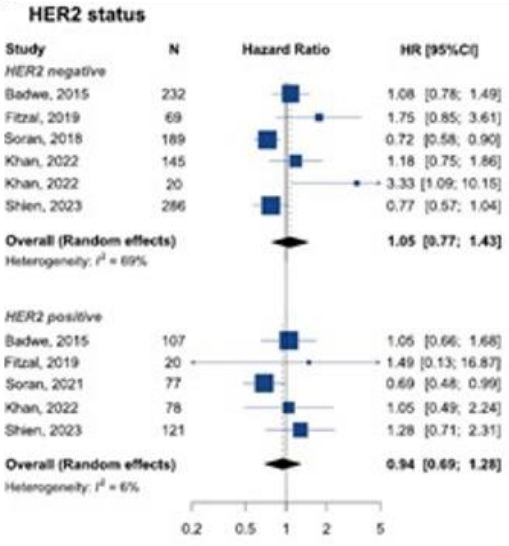

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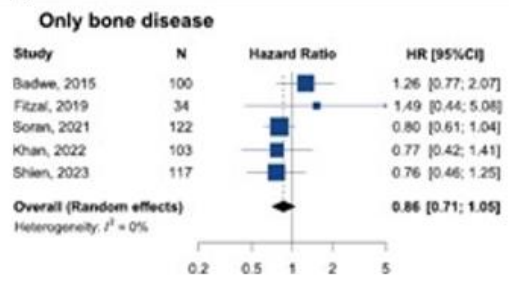

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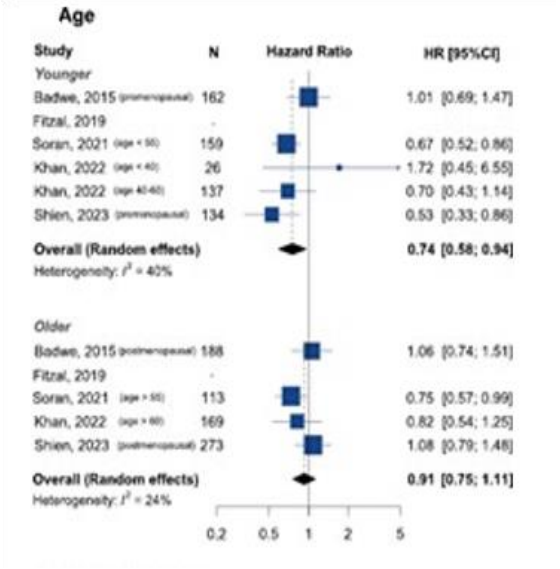

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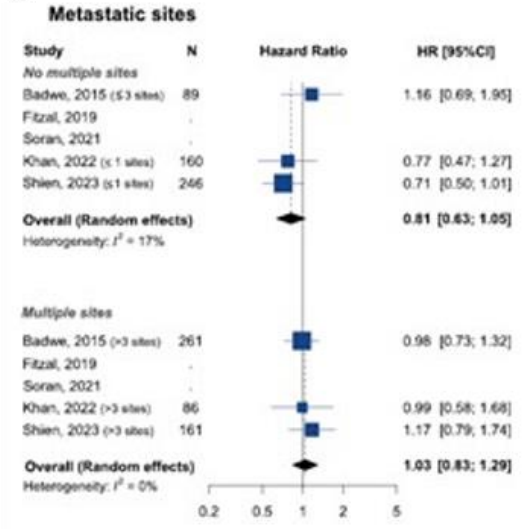

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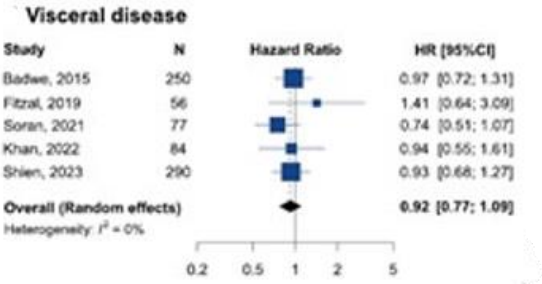

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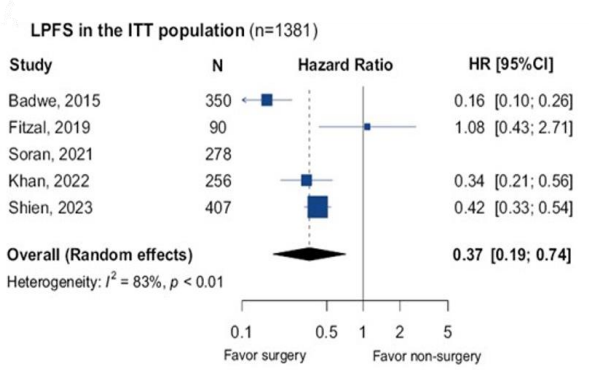
Figure 2. Pooled overall survival according to subgroup comparisons: (a) hormone receptor status, (b) HER2 status, (c) patients with bone-only metastases, (d) age groups, (e) number of metastatic sites, and (f) presence of visceral metastases. Abbreviations: HR: hazard ratio; 95% CI: 95% confidence interval.

Local progression-free survival and progression-free survival

Data on local progression-free survival (LPFS) were reported in four RCTs. Patients undergoing surgical excision of the primary tumor exhibited markedly better LPFS (HR = 0.37; 95% CI, 0.19–0.74); **(Figure. 3a)**, although trial-to-trial variability was substantial (I^2 = 83%). For progression-free survival (PFS), three RCTs reported outcomes, showing that breast surgery did not confer a benefit (HR = 1.14; 95% CI, 0.65–1.99); **(Figure 3b)**, with high heterogeneity among studies (I^2 = 91%).



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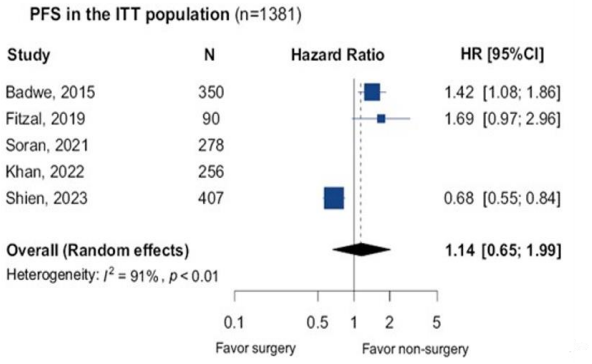

b)

Figure 3. (a) LPFS pooled results in the ITT population comparing breast surgery vs no surgery. (b) PFS pooled results in the ITT population comparing breast surgery vs no surgery. Abbreviations: HR: hazard ratio; 95% CI: 95% confidence interval.

Patient-reported quality of life

Two trials, ECOG EA2108 [12] and ABCSG-28 [22], reported patient-reported quality of life, while MF07-01 [23] included only a subgroup surviving at least three years post-randomization. Across all studies, no improvement in quality of life was associated with surgical removal of the primary tumor. Due to the heterogeneity of questionnaires used, a pooled meta-analysis was not feasible.

The benefit of excising the primary breast tumor in de novo metastatic breast cancer remains unresolved. In this meta-analysis encompassing five RCTs with 1381 patients, no overall survival (OS) advantage was observed for surgery in the general population or among subgroups defined by receptor status or metastatic pattern. The exception may be younger or premenopausal women, but variable definitions and inconsistent trial results indicate this finding is preliminary and hypothesis-generating. Nevertheless, surgery consistently improved locoregional disease control.

Arguments in favor of surgery include potential reduction of tumor burden in oligometastatic patients and prevention of local complications such as pain, ulceration, bleeding, and infection. However, the NRG-BR002 randomized phase II trial questions the benefit of complete local treatment of oligometastatic sites [24], suggesting that aggressive local therapy outside of clinical trials should be approached with caution.

Interestingly, exploratory data from PRIM-BC indicated that metastatic progression might accelerate within three months post-surgery [13], highlighting gaps in the understanding of metastatic dynamics and reinforcing the need for rigorous trial design. Regarding quality of life, none of the included studies demonstrated improvement despite enhanced local tumor control. This could be explained by the surgical burden in palliative patients [25] and the ongoing psychosocial challenges of metastatic disease [26], indicating that routine breast surgery in this context may not be justified.

Our meta-analysis represents the most comprehensive evaluation to date of the impact of breast surgery in patients with de novo MBC, offering sufficient statistical power to examine all clinically relevant subgroups. Nonetheless, limitations inherent to the individual RCTs must be acknowledged, as they constrain the interpretability of their findings. For instance, in the MF07-01 trial, imbalances such as higher rates of triple-negative tumors and lack of histologic confirmation for solitary bone lesions favored the surgery group [10], potentially biasing reported outcomes. Protocol deviations were also noted, for example, in the EA2108 trial, where more than 10% of patients did not follow the planned treatment [12], and per-protocol analyses were not presented. Furthermore, most RCTs did not report on the relationship between surgical margin status and outcomes, despite an exploratory subgroup analysis from PRIM-BC indicating that patients with tumor-free margins experienced better OS [13]. In addition, systemic therapy regimens have evolved substantially since the conduct of these trials, as reflected by differences in median OS between the earliest trial (~20 months) [9] and the most recent (~70 months) [13]. Despite these individual study limitations, the pooled evidence from this meta-analysis clearly indicates that routine surgical removal of the primary tumor in de novo MBC is not supported, except for symptomatic palliation of local tumor-related complications.

Conclusion

By aggregating data from all available RCTs, no improvement in OS with breast surgery for patients with de novo MBC was observed. Ongoing trials continue to explore this question (Clinicaltrials.gov identifier NCT05285332), although other studies have faced challenges, including low recruitment and early termination (NCT01392586). At present, surgical removal of the primary tumor should not be routinely recommended, except when required for symptom control in local disease, with the possible exception of carefully selected premenopausal patients, and should primarily be performed within the framework of rigorously designed clinical trials.

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