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Review

Impact of Local Treatment of the Primary Tumor on Overall Survival in *De Novo* Metastatic Breast Cancer: A Systematic Review and Meta-analysis

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Abstract

Background/Aim: The prognostic impact of local treatment (LT) of the primary tumor in patients with *de novo* metastatic breast cancer (dnMBC) remains unclear. We conducted a systematic review and meta-analysis to evaluate whether surgery and/or radiotherapy of the primary tumor improves overall survival (OS).

Materials and Methods: Electronic databases (PubMed, Embase, Cochrane) were searched up to March 2025 for studies comparing LT (surgery and/or radiotherapy) plus systemic therapy *versus* systemic therapy alone. Hazard ratios (HRs) for OS were pooled using a random-effects model. Subgroup analyses were performed by study design, treatment modality, biological subtype, and metastatic site. Heterogeneity was quantified using I^2, and meta-regression was used to explore potential moderators.

Results: Twenty studies, including randomized controlled trials (RCTs) and retrospective studies, were included. In pooled analyses, LT was associated with improved OS compared to systemic therapy alone. [HR=0.62; 95% confidence interval (CI)=0.52–0.75; $p<0.0001$; $I^2=97.3\%$]. In RCTs, the difference was not significant (HR=0.91; 95% CI=0.67–1.25; $p=0.57$). Surgery of the primary tumor was associated with improved OS (pooled HR=0.62; 95% CI=0.52–0.75). In the radiotherapy-only subgroup, based on a very limited number of heterogeneous retrospective studies, no survival benefit was observed (pooled HR=1.51; 95% CI=0.87–2.63). Given the very limited number of studies and the substantial heterogeneity ($I^2=91.5\%$), these findings need to be interpreted with caution. Subgroup analyses showed a non-significant trend in hormone receptor–positive disease (HR=0.78; 95% CI=0.58–1.04) and no benefit in HER2-positive (HR=0.90; 95% CI=0.61–1.33) or liver-limited disease (HR=1.17; 95% CI=0.77–1.78). No covariates were significantly associated with OS in meta-regression.

continued

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Conclusion: Although pooled analyses suggest an association between local treatment and improved OS, this effect appears largely driven by retrospective data and is not confirmed in randomized trials.

Keywords: Metastatic breast cancer, *de novo*, primary tumor surgery, radiotherapy, meta-analysis, overall survival, review.

Introduction

De novo metastatic breast cancer (dnMBC) represents 5–10% of all breast cancer cases and carries a poor prognosis. Traditionally, management is systemic, with local treatment (LT) reserved for symptom control. However, several retrospective studies suggest that resection or irradiation of the primary tumor may prolong survival, potentially by decreasing tumor burden or circulating tumor cells (1, 2).

Conversely, randomized trials, including Badwe *et al.* (3) and Khan *et al.* (4), failed to confirm a survival advantage, leading to ongoing controversy. In addition, the potential biological rationale underlying the use of locoregional treatment in the metastatic setting remains a topic of ongoing investigation. It has been hypothesized that removal of the primary tumor may reduce overall tumor burden, decrease the release of circulating tumor cells, and modulate tumor–host interactions, including immune responses. Conversely, other preclinical and clinical observations suggest that surgical intervention might disrupt tumor equilibrium or stimulate metastatic growth, thereby leading to uncertain clinical effects.

At the same time, the therapeutic landscape of metastatic breast cancer has evolved substantially with the introduction of more effective systemic therapies, including endocrine agents, CDK4/6 inhibitors, HER2-targeted therapies, and antibody–drug conjugates. As a result, survival outcomes are increasingly driven by tumor biology and responsiveness to systemic treatment rather than by local tumor control alone. This evolving scenario complicates the interpretation of earlier retrospective findings and may partly explain the discrepancies observed between observational studies and randomized clinical trials, further underscoring the need for a comprehensive and methodologically robust synthesis of the available evidence. The growing understanding of tumor biology and the availability of effective systemic agents necessitate re-evaluation of the role of LT in dnMBC. This study aimed to synthesize all available evidence to assess the impact of LT on OS and to identify potential subgroups benefiting from surgery or radiotherapy.

Materials and Methods

Search strategy and study selection. A comprehensive literature search was conducted in PubMed, Embase, and the Cochrane Library from inception to March 2025. The strategy combined MeSH terms and free-text keywords related to metastatic breast cancer and local treatment approaches. The search string included variations of "metastatic breast cancer," "stage IV breast cancer," and "*de novo* metastatic," combined with terms referring to surgical or radiotherapeutic management of the primary tumor and overall survival. Only studies conducted in humans and published in English were considered. In addition, the reference lists of eligible articles and relevant reviews were manually screened to identify further studies not captured through database searching. The full list of included studies and their main characteristics are reported in Table I (3–22).

Eligible studies were those enrolling patients with *de novo* metastatic breast cancer and comparing outcomes between individuals receiving local treatment of the primary tumor – through surgery, radiotherapy, or both – in addition to systemic therapy, versus systemic therapy alone. Studies were required to report hazard ratios (HRs)

Table I. *Baseline characteristics of the 20 studies included in the meta-analysis, including study design, treatment modality, patient distribution, and reported hazard ratios for overall survival.*

Study (Author, Year)	Study design	N (LT)	N (Control)	HR OS (95% CI)	*p*-Value
Badwe *et al.*, 2015 (3)	Open-label RCT	173	177	1.04 (0.81–1.34)	0.79
Li *et al.*, 2021(12)	Population-based cohort	3,825	10,192	0.56 (0.53–0.59)	<0.001
Zhu *et al.*, 2022 (8)	Retrospective SEER	4,238	10,774	0.60 (0.53–0.68)	<0.001
Gu *et al.*, 2020 (13)	Retrospective SEER	681	1,207	0.57 (0.51–0.64)	<0.001
Wang *et al.*, 2019 (11)	Retrospective SEER	1,891	6,251	0.76	<0.05
Lane *et al.*, 2019 (19)	NCDB cohort	10,510	13,505	0.56	<0.001
Drapalik *et al.*, 2024 (15)	NCDB PSM	305	744	0.39 (0.27–0.57)	<0.001
AlJohani *et al.*, 2016 (9)	Single-center	412	266	0.60 (0.48–0.87)	0.0003
Lin *et al.*, 2019 (16)	SEER cohort	3,138	5,444	0.67 (0.56–0.80)	<0.001
Partain *et al.*, 2021 (21)	Institutional cohort	52	45	0.52 (0.29–0.93)	<0.001
Mudgway *et al.*, 2020 (20)	NCDB HER2+	1,131	2,100	0.56 (0.40–0.77)	<0.002
van Uden *et al.*, 2020 (6)	NCR cohort	139	441	0.56 (0.42–0.75)	<0.001
Xie *et al.*, 2017 (18)	Retrospective	177	46	0.57 (0.33–0.98)	0.044
Soran *et al.*, 2018 (14)	RCT	138	136	0.66 (0.49–0.88)	0.005
Hotton *et al.*, 2023 (7)	ESME cohort	530	1,447	0.75 (0.61–0.92)	<0.05
Choi *et al.*, 2017 (10)	PSM cohort	82	163	0.36 (0.21–0.62)	0.02
Rhu *et al.*, 2014 (17)	Retrospective	40	222	0.51 (0.32–0.76)	<0.01
Soran *et al.*, 2021 (22)	Registry	265	240	0.40 (0.30–0.54)	<0.0001
Khan *et al.*, 2022 (E2108) (4)	RCT	125	131	1.11 (0.82–1.52)	0.57
Lian *et al.*, 2020 (5)	SEER cohort	918	2,319	1.97 (1.79–2.16)	<0.001

for overall survival or to provide sufficient information for their estimation. Both randomized and observational comparative designs were eligible. Conference abstracts, case series, preclinical work, and studies lacking survival data or a control arm were excluded.

Study selection followed PRISMA 2020 guidelines, and the full flow diagram is reported in Figure 1. The protocol for this systematic review was prospectively registered in PROSPERO (CRD420251168069).

Data extraction and quality assessment. Data extraction was performed independently by two reviewers (L.S. and M.G.P.) using a predefined template. For each study, we collected information on study design, publication year, country, sample size, patient demographics, and distribution of biological subtypes, including hormone receptor–positive, HER2-positive, and triple-negative disease. Details regarding metastatic sites – such as visceral, bone-only, or liver-limited involvement – were recorded when available. Treatment characteristics, including whether patients underwent surgery, radiotherapy, or a combination of both, were also extracted. Reported hazard ratios for overall survival, along with their standard errors, were collected or reconstructed when necessary. When studies reported confidence intervals at levels different from 95%, these were harmonized to 95% confidence intervals for consistency across analyses. Discrepancies between reviewers were resolved through discussion or consultation with a third investigator.

To evaluate study quality, observational studies were assessed using the Newcastle–Ottawa Scale (NOS), while randomized trials were appraised using the Cochrane Risk of Bias tool (RoB 2). Each study was classified as having low, moderate, or high risk of bias based on criteria for participant selection, comparability of groups, and adequacy of outcome assessment.

Statistical analysis. HRs were analyzed on the log scale and pooled using a random-effects model (DerSimonian–Laird), acknowledging the anticipated heterogeneity across studies differing in design, populations, and treatment strategies. Statistical heterogeneity was

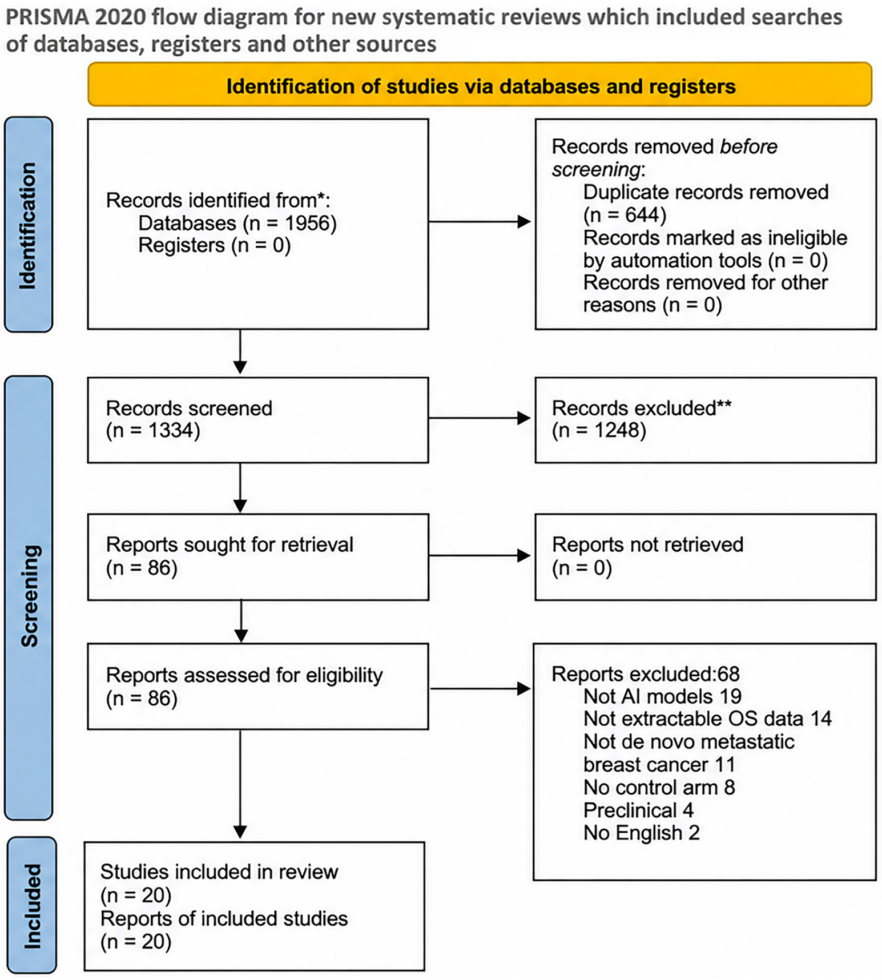

Figure 1. *PRISMA 2020 flow diagram showing identification, screening, eligibility assessment, and inclusion of studies in the systematic review and meta-analysis.*

quantified through the I^2 statistic, reflecting the proportion of variability attributable to between-study differences rather than chance, and by τ^2, estimating between-study variance (23).

To explore whether the treatment effect varied across clinically relevant subsets, we performed predefined subgroup analyses according to study design (randomized *vs.* retrospective), type of local therapy (surgery *vs.* radiotherapy), biological subtype (hormone receptor–positive *vs.* HER2-positive), and metastatic pattern (liver-limited *vs.* other presentations). In addition, a meta-regression analysis was conducted to assess whether receptor status, metastatic distribution, or design features influenced the magnitude of benefit associated with local treatment.

Results were expressed as pooled hazard ratios with 95% confidence intervals (CI), with HR values below 1 indicating improved survival associated with local treatment. A *p*-value <0.05 was considered statistically significant. All analyses were performed using R version 4.3 and RevMan 5.4.

Given the relatively limited number of studies included in the meta-regression analyses in relation to the number of covariates explored, the risk of overfitting cannot be

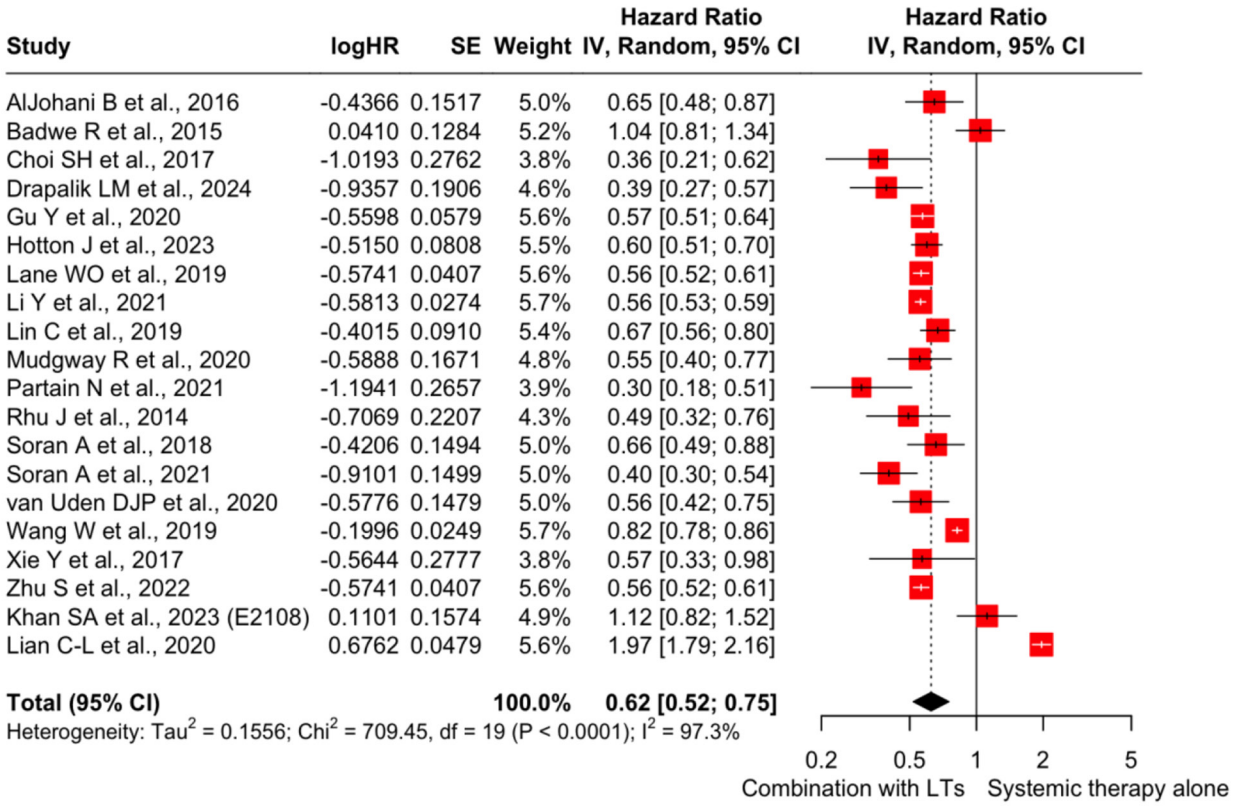

Figure 2. *Forest plot showing the pooled hazard ratio for overall survival comparing local treatment of the primary tumor versus systemic therapy alone in patients with de novo metastatic breast cancer.*

excluded. In addition, the high degree of between-study heterogeneity and the predominance of retrospective studies may further compromise the stability and interpretability of these models. Therefore, the meta-regression findings should be interpreted with caution and regarded as hypothesis-generating rather than confirmatory.

Results

A total of 20 studies, including approximately 70,000 patients with *de novo* metastatic breast cancer, were eligible for quantitative synthesis. The pooled analysis demonstrated a statistically significant overall survival (OS) benefit associated with local treatment of the primary tumor combined with systemic therapy. Overall, local treatment was associated with a 38% reduction in the risk of death compared with systemic therapy alone (pooled HR=0.62, 95% CI=0.52–0.75, $p<0.0001$; Figure 2). This effect was accompanied by extreme between-study heterogeneity (I^2=97.3%), indicating considerable variability across included studies. Therefore, the pooled estimate should be interpreted with caution, as differences in study design, patient selection, systemic therapy era, and analytical adjustments may substantially influence the observed effect size. When the analysis was restricted to randomized controlled trials, no statistically significant survival benefit was observed (HR=0.91, 95% CI=0.67–1.25, p=0.57; Figure 3). This discrepancy suggests that the apparent global benefit in the overall cohort is largely driven by retrospective studies, in which patients selected for local treatment tend to be younger, fitter, and more

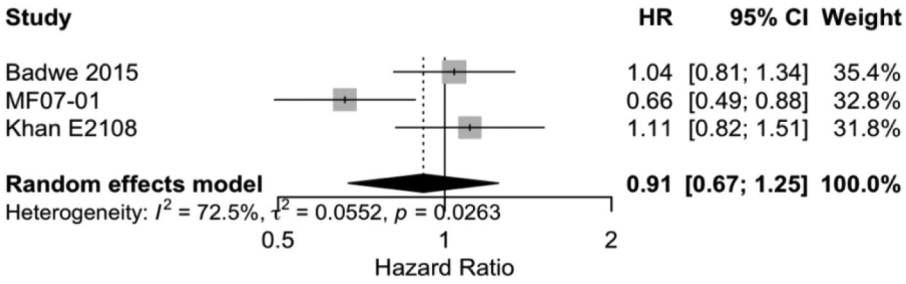

Figure 3. *Forest plot of overall survival including only randomized controlled trials [(3), MF07-01, and ECOG E2108]. A random-effects model was used. No statistically significant overall survival benefit was observed for locoregional treatment (HR=0.91, 95% CI=0.67–1.25).*

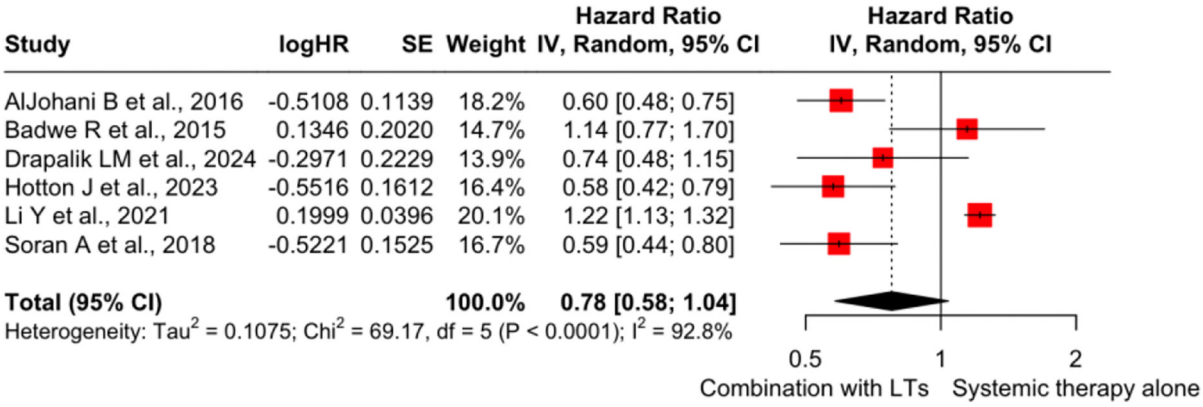

Figure 4. *Forest plot of overall survival in patients with hormone receptor–positive de novo metastatic breast cancer receiving local treatment of the primary tumor versus systemic therapy alone. Although a trend toward improved survival was observed, the effect did not reach statistical significance (HR=0.78, 95% CI=0.58–1.04).*

likely to have hormone receptor–positive disease or limited metastatic burden.

When examining treatment modality, surgical resection of the primary tumor emerged as the component most consistently associated with improved survival across studies. In contrast, non-surgical local approaches did not show a clear effect on overall survival and contributed minimally to the observed pooled benefit.

Subtype-specific analyses highlighted further heterogeneity. In hormone receptor–positive disease, local treatment showed a favorable – but non-significant – trend toward improved OS (HR=0.78, 95% CI=0.58–1.04, p=0.0885; Figure 4). No survival advantage was observed in HER2-positive tumors (HR=0.90, 95% CI=0.61–1.33) (Figure 5).

Meta-regression analyses explored potential modifiers of treatment effect, including study design, metastatic pattern, hormone receptor status, and HER2 status. None of these variables demonstrated a statistically significant association with OS benefit (all p>0.1), indicating that no single factor reliably predicts which patients derive benefit from local treatment. The substantial heterogeneity observed across studies likely reflects differences in patient selection, systemic therapy era, and methodological design. In summary, the pooled evidence suggests that local treatment of the primary tumor is associated with improved survival in *de novo* metastatic breast cancer; however, this association is not confirmed in randomized trials. No specific clinical or biological subgroup demonstrated a consistent survival benefit, and heterogeneity remained high across analyses.

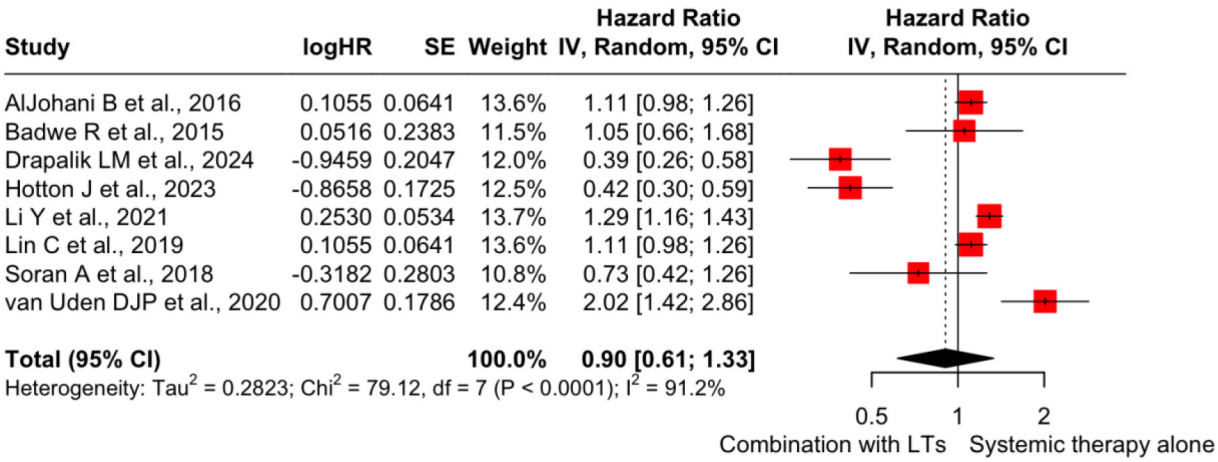

Figure 5. *Forest plot of overall survival in HER2-positive patients. A random-effects model was used. No statistically significant difference in overall survival was observed between locoregional treatment and systemic therapy alone (HR=0.90, 95% CI=0.61–1.33).*

Discussion

This meta-analysis demonstrates an apparent OS advantage associated with LT of the primary tumor in patients with dnMBC. Across more than 70,000 patients, local treatment was linked to a significant 38% reduction in the risk of death compared with systemic therapy alone. However, this benefit was not confirmed in randomized controlled trials (RCTs), highlighting the central role of study design and patient selection in shaping observed outcomes.

The high heterogeneity observed across analyses likely reflects variations in patient selection, timing and extent of local treatment, and systemic therapy availability across different study eras, rather than a uniform treatment effect.

The divergence between retrospective and prospective evidence underscores the influence of selection bias. Patients undergoing surgery in observational cohorts are typically younger, fitter, and more likely to have favorable disease features, such as limited metastatic burden or hormone receptor–positive biology, factors independently associated with prolonged survival. In contrast, randomized controlled trials such as those by Badwe *et al.* (3), Soran *et al.* (14) and Khan *et al.* (4) balanced baseline characteristics and did not demonstrate a consistent overall survival benefit, despite improvements in locoregional control. Taken together, these prospective data suggest that the survival advantage observed in retrospective analyses is likely influenced by selection bias rather than reflecting a clear causal effect of local treatment. The evolving landscape of systemic therapy may further explain the discrepancy between historical retrospective analyses and contemporary randomized trials. The introduction of CDK4/6 inhibitors, antibody–drug conjugates, and increasingly effective HER2-targeted therapies has substantially prolonged survival in selected subtypes of metastatic breast cancer. In this context, disease trajectory is primarily dictated by systemic treatment responsiveness and intrinsic tumor biology rather than by the presence of the intact primary tumor. As systemic control improves, the relative impact of local tumor removal on overall survival may become progressively attenuated.

Several biological theories have been proposed to explain why removal of the primary tumor might influence survival, including the reduction of tumor-driven immunosuppression, interruption of metastatic seeding, and enhancement of systemic therapy efficacy by reducing overall tumor burden (24). Yet, the natural history of

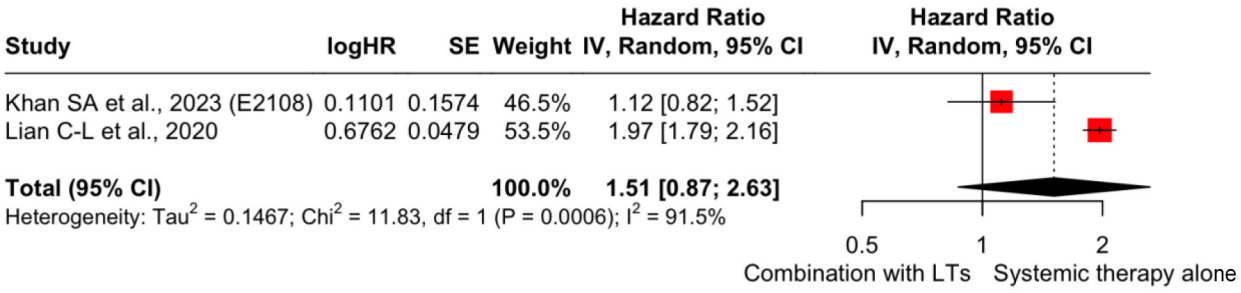

Figure 6. *Forest plot of overall survival evaluating the addition of radiotherapy to locoregional treatment. A random-effects model was used. No statistically significant difference in overall survival was observed between treatment strategies (HR=1.51, 95% CI=0.87–2.63).*

metastatic breast cancer has evolved substantially with modern therapies, including endocrine agents and HER2-targeted treatments (25). In this contemporary context, systemic disease progression remains the dominant driver of mortality, and local control may exert only a modest or negligible impact.

Our subgroup analyses further contextualize these observations. Hormone receptor–positive patients showed a non-significant trend toward improved survival with LT, potentially reflecting the indolent trajectory of luminal disease and the prolonged effectiveness of endocrine therapy. Conversely, no benefit was observed in HER2-positive tumors or in patients with liver-limited metastases, where outcomes are more closely dictated by disease biology and responsiveness to systemic therapy. These findings reinforce the notion that intrinsic tumor characteristics, rather than local–regional management, primarily determine prognosis in dnMBC. Recent evidence further supports the complexity of treatment decision-making in *de novo* metastatic breast cancer. Kitsuya *et al.* (26) reported that surgical resection of the primary tumor was associated with improved survival in patients with bone-only metastatic disease across most biological subtypes, although no benefit was observed in HR−/HER2+ tumors, highlighting the heterogeneity of treatment effects. Similarly, Gorobets *et al.* (27) demonstrated the long-term prognostic value of the lymph node ratio in patients with *de novo* metastatic breast cancer, underscoring the critical role of disease burden and biological characteristics in determining outcomes. Together, these findings reinforce the notion that prognosis in dnMBC is primarily driven by tumor biology and disease extent, and that the potential benefit of local treatment is likely confined to carefully selected patient subgroups rather than representing a universally applicable strategy.

The distinction between surgical resection and radiotherapy warrants careful interpretation. Surgical removal achieves complete excision of the primary tumor and may be preferentially offered to patients with limited metastatic burden, good performance status, and favorable biology, thereby reflecting a selection phenomenon rather than a direct therapeutic survival effect. In contrast, radiotherapy is frequently delivered for local control or palliation and may not sufficiently influence systemic disease kinetics to translate into overall survival improvement. These differences likely reflect both biological and selection-related mechanisms rather than a clear causal advantage of surgery itself. Moreover, the radiotherapy-only subgroup analysis was based on a very small number of heterogeneous studies and therefore cannot support definitive conclusions regarding the independent effect of radiotherapy (Figure 6).

Meta-regression analyses did not identify any clinical or biological predictors of benefit. Neither receptor subtype, metastatic distribution, nor study design was associated with the magnitude of treatment effect. The substantial heterogeneity observed across all analyses

(I^2>90%) likely reflects differences in patient selection, systemic therapy era, timing and extent of surgery, and incorporation of radiotherapy or multimodality strategies.

Overall, this meta-analysis suggests that local treatment of the primary tumor is associated with improved survival in dnMBC, but this association is largely driven by retrospective data, and causality is not supported by randomized evidence. Therefore, local treatment should not be adopted as routine curative practice but may be considered on an individual basis – particularly for patients with limited metastatic burden, favorable biology, and well-controlled systemic disease – within a multidisciplinary framework.

The very high heterogeneity represents a major limitation of this meta-analysis and underscores the influence of retrospective data and unmeasured confounding.

Future research should not simply replicate previous randomized designs but instead focus on biologically and clinically selected populations. Trials restricted to patients demonstrating durable response to first-line systemic therapy, those with oligometastatic presentation, or those stratified by molecular subtype in the era of modern targeted therapies may provide more definitive answers. Incorporating contemporary systemic regimens is essential to clarify whether any true subgroup derives meaningful survival benefit from locoregional intervention.

Conclusion

This meta-analysis indicates that the apparent survival benefit of local treatment in *de novo* metastatic breast cancer is predominantly driven by retrospective evidence and is not supported by randomized trials. Although pooled analyses demonstrate a consistent direction of effect, causality cannot be established due to substantial heterogeneity and the inherent risk of selection bias. These findings suggest that local treatment should not be adopted as routine practice but may be considered for carefully selected patients, particularly those with limited metastatic burden, favorable biology, and good response to systemic therapy, within a multidisciplinary framework.

Conflicts of Interest

Giuseppe Tonini reports participation in advisory boards for Molteni, Novartis, PharmaMar, and MSD. Francesco Pantano reports participation in advisory boards for Lilly, Gilead, AstraZeneca, Novartis, and Daiichi Sankyo. All other Authors declare no conflicts of interest.

Authors' Contributions

L.S. and M.G.P. conceived the study and performed data extraction. L.S., M.G.P., and M.I. conducted the statistical analyses. G.T. and F.P. supervised the study and contributed to data interpretation. All authors contributed to manuscript writing, critically revised the content, and approved the final version.

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Artificial Intelligence (AI) Disclosure

During the preparation of this manuscript, the authors used ChatGPT (GPT-5, OpenAI) solely to improve the readability and clarity of the text. The authors reviewed and edited the content and take full responsibility for the final version of the manuscript.

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