Locoregional therapy in de novo metastatic breast cancer: Systemic review and meta-analysis

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ABSTRACT

Background: Locoregional therapy (LRT) in de novo metastatic disease is controversial with inconsistent results from randomized control trials (RCTs).
Methods: RCTs comparing LRT and systemic therapy to standard therapy alone in de novo metastatic breast cancer were identified. Hazard ratios (HRs) and their associated 95% confidence intervals (CIs) were computed and pooled in a meta-analysis using generic inverse variance. Overall survival (OS) and time to locoregional progression data were extracted for the intention to treat (ITT) population. Data on OS for pre-specified subgroups defined by tumor subtype and by site of metastases were also extracted.
Results: Analyses included 4 trials comprising 970 patients. LRT included standard surgery to the primary breast tumor in all studies, and adjuvant radiation per standard of care was required in 3 studies. Compared to standard treatment, LRT was not associated with improved OS in the ITT population (HR 0.97, 95% CI 0.72−1.29, p = 0.81). However, LRT was associated with improved time to locoregional progression (HR 0.36, 95% CI 0.14−0.95, p = 0.04). LRT was not associated with improved OS in any tumor subtypes, including hormone receptor positive (HR 0.96, 95% CI 0.65−1.43), triple negative (HR 1.4, 95% CI 0.50−3.91) and human epidermal growth factor receptor 2 positive disease (HR 0.93, 95% CI 0.68−1.28). Additionally, LRT did not improve OS in bone only disease (HR 0.97, 95% CI 0.58−1.62) and in visceral disease (HR = 1.02, 95% CI 0.77−1.35). Our critical appraisal has identified some methodological problems in the design and conduct of the studies included that could affect the meta-analysis result.
Conclusions: LRT in de novo metastatic breast cancer is not associated with improved OS. Results are consistent among different breast cancer subgroups. However, this conclusion should be interpreted with caution in view of the limitations identified in meta-analysis.

Contents

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1. Introduction

Despite changes to treatment of metastatic breast cancer over the last few decades, for most patients, the typical treatment is palliative systemic therapy with a median overall survival (OS) ranging between 1 and 5 years [1], depending on breast cancer subtype. *De novo* metastatic disease represents around 6% of breast cancer diagnosis [2].

Several retrospective studies have suggested a survival benefit for patients who underwent locoregional treatment (LRT) of the primary breast tumor in this setting [3,4]. Several mechanisms have proposed by which treatment of the primary tumor in metastatic disease may be beneficial. These include tumor burden reduction which may result in improved immunologic response [5,6], depletion of cancer stem cells and their tumor promoting functions [7] and disruption of self-seeding of the primary tumor [8].

In contrast to retrospective data, prospective data are limited and with conflicting results [9–12]. A recent meta-analysis which included 216,066 patients from 42 studies, including also retrospective studies, demonstrated a reduction of 32% in the risk of mortality in patients receiving LRT (surgery and/or radiotherapy) to the primary breast tumor in *de novo* metastatic disease [13]. Retrospective studies suffer from inherent selection bias, which could explain the apparent survival benefit in patients treated with surgery in these studies. Additionally, patients achieving excellent response to systemic therapy, patients with locally advanced breast cancer mistakenly classified as metastatic disease and oligometastatic disease, may be overly represented in surgery arms in retrospective studies [14], resulting in improved outcomes compared to those with more widespread or more refractory disease.

Treatment of metastatic breast cancer has evolved over the years with the introduction of new systemic therapies resulting in meaningful improvements in OS [1,15]. There is variability in the treatment and prognosis between the different molecular subtypes. Patients with hormone receptor positive metastatic breast cancer have a favorable prognosis compared to hormone receptor negative breast cancer [16]. The treatment of human epidermal growth factor 2 (HER2) enriched breast cancers has evolved dramatically during the twenty years [17–19] with some patients with metastatic disease achieving long term remissions even in the absence of loco-regional treatment [17]. With the improvement in systemic therapies, the proposed benefit of the addition of LRT remains uncertain [20]. Furthermore, little is known about whether the different molecular subtypes may be impacted differentially by LRT.

Patients with bone only disease have a favorable prognosis compared to patients with visceral metastases [21,22]. Bone only disease is more likely to have luminal subtype [23,24] and typically, endocrine therapy-based regimens are utilized initially [25]. In contrast, visceral involvement at presentation is often associated with triple negative or HER2 positive disease [26,27] and treatment is more likely to comprise chemotherapy-based regimes [25,28]. Compared to endocrine therapy, peri-operative interruption with systemic therapy are more likely to occur with chemotherapy, possibly resulting with inferior control or metastatic disease. This raises the question of whether management of loco-regional disease may actually result in inferior outcomes in patients requiring chemotherapy.

Here, we report on a meta-analysis of prospective randomized trials evaluating the role of LRT in *de novo* metastatic breast cancer. We also aimed to define the role of LRT in the different breast cancer subtypes. We hypothesized that LRT will not be associated with significant improvement is OS despite improvement in local control.

2. Methods

2.1. Literature review and study identification

A literature search utilizing MEDLINE (Host: PubMed) identified randomized clinical trials published between January 1, 2010 and June 30, 2020 which compared standard systemic therapy to systemic therapy and LRT (comprising of surgery with or without radiation) in *de novo* metastatic breast cancer patients. The terms "breast cancer", "metastatic", "*de novo*" and "surgery" and similar terms were cross-searched, using the following search algorithm: (((((((((metastatic) OR ("stage 4″)) OR ("stage iv")) OR (advanced)) OR (metastases)) OR ("*de novo*")) OR (denovo)) AND ((((surgery) OR (local*)) OR (lumpectomy)) OR (mastectomy))) AND ("breast cancer") AND ((clinicaltrial OR randomizedcontrolledtrial) AND (english))) AND (("2010/01/01": "2020/06/30″)). The search was restricted to the English language reports of prospective clinical trials. The search was supplemented by a review of abstracts from key conferences during the last 3 years (2018–2020) including the Annual Meetings of the American Society of Clinical Oncology (ASCO), the European Society of Medical Oncology (ESMO) and San Antonio Breast Cancer Symposium (SABCS).

2.2. Data extraction

Data were collected independently by two reviewers (DR and RM). Discrepancies were resolved by a third reviewer (HG). All data were extracted from primary publications and their associated online appendices.

Collected data included year of publication, number of patients, median follow-up, median age, proportion of pre-menopausal patients and proportion of patients who underwent surgery in the

control group. Trial level tumor characteristics were extracted including: proportions of HER2 positive, hormone receptor positive and triple negative disease and proportions of bone-only metastatic disease and visceral metastatic disease.

We then extracted the hazard ratios (HRs) and respective 95% confidence intervals (CI) for OS, time to locoregional progression and time to distant progression. When available, outcome data for subgroups were also collected based on tumor subtype and distribution of metastases (as categorized above).

2.3. Data synthesis and statistical analysis

The primary analysis compared OS between patients who were randomized to LRT to those who received standard therapy. The HR and associated 95% CI were computed for OS and then pooled in a meta-analysis using RevMan 5.3 (The Cochrane Collaboration, Copenhagen, Denmark). Statistical significance was defined as $p < 0.05$. No adjustment was made for multiple significance testing. Statistical heterogeneity was reported using Cochran Q and I^2 statistics. Statistically significant heterogeneity was defined as a Cochran Q $P < 0.10$ or I^2 greater than 50%. In the intention to treat (ITT) population, a subgroup analysis was performed to explore the difference between studies that randomized to upfront LRT to studies that randomized to LRT after initial clinical benefit from systemic therapy was achieved. Subgroup analyses was performed using methods described by Deeks et al. [29]. Additionally, the effect of LRT on OS was analyzed in different subgroups based on tumor subtypes and distribution of metastases (as categorized above). Multiple sensitivity analyses were performed: excluding studies in which post-operative radiation was not provided as part of LRT, excluding studies stoped prematurely due to poor enrolment, excluding studies where results were available only in an abstract form and excluding studies in which HER2 targeted therapy was not available to the majority of HER2 positive patients. Additionally, for OS leave-one-out sensitivity analysis (excluding one study at a time) was conducted. For the analysis for hormone receptor positive disease, sensitivity analysis excluding the study that included hormone receptor positive and HER2 negative disease (rather than hormone receptor positive with any HER2 status) was also performed.

The effect of trial-level characteristics on the natural log of HR for OS was evaluated using meta-regression which comprised a univariable linear regression weighted by individual study sample size using the weighted least squares (mixed effect) function [30]. Meta-regression analysis was performed on the following variables: median age, median duration of follow-up, proportion of pre-menopausal patients, proportion of patients with visceral disease and bone only disease, proportion of patients who underwent surgery in the control group and proportions of the different tumor subtypes. Meta-regression was performed using SPSS version 25 (IBM Corp, Armonk, NY, USA) using the weighted least squares (mixed effect) function. Due to the small number of included studies, meta-regression analyses were evaluated quantitatively using the Burnand criteria [31] rather than to inferring associations based of the p-value [32,33].

3. Results

Our search identified 603 studies published between January 2010 and June 2020. After exclusions, 4 studies comprising 970 patients were included in the analysis [9–12], see Fig. 1. The characteristics of the included studies in are shown in Table 1. In 2 studies patients who did not progress after systemic therapy were randomized between the experimental and the control arm [10,12] while in 2 studies no systemic treatment was given before randomization [9,11]. Post surgery adjuvant radiation in the experimental arm was mandatory per standard of care for early breast cancer in 3 studies [10–12]. One study was stopped prematurely due to poor enrollment [9]. Data on LRT in the control arm were reported in 3 studies [9,10,12] and it ranged between 11 and 19%. Most included patients had hormone receptor positive disease, and HER2 positive disease ranged between 22 and 32%. Visceral disease was present in the majority of the included patients in all studies.

3.1. Primary analysis

The mean weighted duration of follow-up was 37.1 ($\pm$0.38) months. Overall, in the 3 trials where number of deaths were reported, 60% (532/880) of patients had died during follow-up [10–12]. In the pooled analysis, compared to the control group, LRT was not associated with improved OS in the ITT population (HR = 0.97, 95% CI 0.72–1.29, Fig. 2A). There was a statistically significant heterogeneity (Cochran's Q p = 0.04, I^2 = 65%). Multiple sensitivity analyses for OS and leave-one-out sensitivity analysis for OS have shown similar result, see Table 2 and supplementary Figure 1. Similar magnitude of effect was seen in studies were patients received LRT as an upfront treatment (HR 0.92 95% CI 0.43–1.96, p = 0.83) and in studies were patients received LRT after systemic therapy (HR 1.06 95% CI 0.87–1.29, p = 0.56), p value for the subgroup difference = 0.72.

HRs data on time to locoregional progression were available in 3 studies [9,10,12]. Compared to the control group LRT was associated with significant improvement in time to loco-regional progression (HR = 0.36 95% CI0.14–0.95, p = 0.04, Fig. 2B). There was a statistically significant heterogeneity (Cochran's Q p = 0.002, I^2 = 84%). Sensitivity analyses for time to locoregional progression are shown in Table 2. Overall, the magnitude of effect on time to loco-regional progression was lower after excluding the study in which HER2 targeted therapy was not available and was higher after excluding the study in which adjuvant radiation was not mandated by the protocol (this study was also stopped prematurely). In one study, the number of events on locoregional progression was higher in the systemic therapy arm compared to the LRT arm (11% vs 1%), but HR for locoregional progression was not reported [11]. Only 2 studies reported data on time to distant progression or distant-progression free survival [9,10]. Pooling theses results showed LRT was associated with significantly worse time to distant progression (HR = 1.47 95% CI 1.15–1.86, p = 0.002).

3.2. Subgroup analysis

Data on OS by tumor subtype were available for hormone receptor positive disease and for HER2 positive disease in all studies [9–12] and for triple negative disease in 3 studies [9,11,12]. LRT was not associated with improved OS in any tumor subtypes, including hormone receptor positive (HR for OS = 0.96, 95% CI 0.65–1.43, Fig. 3A), triple negative disease (HR 1.4, 95% CI 0.50–3.91, Fig. 3B) and HER2 positive disease (HR 0.93, 95% CI 0.68–1.28, Fig. 3C). In the subgroup of hormone receptor positive disease, sensitivity analysis excluding the study that included only hormone receptor positive and HER2 negative disease showed similar results (HR = 1.00 95% CI 0.56–1.79).

Data on OS for bone only disease were available in 3 studies [9–11] and for visceral disease in 2 studies [9,10]. Compared to the control arm, LRT was not associated with improved OS in bone only disease (HR 0.97, 95% CI 0.58–1.62, p = 0.92, Fig. 3D) and in visceral disease (HR = 1.02, 95% CI 0.77–1.35, p = 0.90, Fig. 3E).
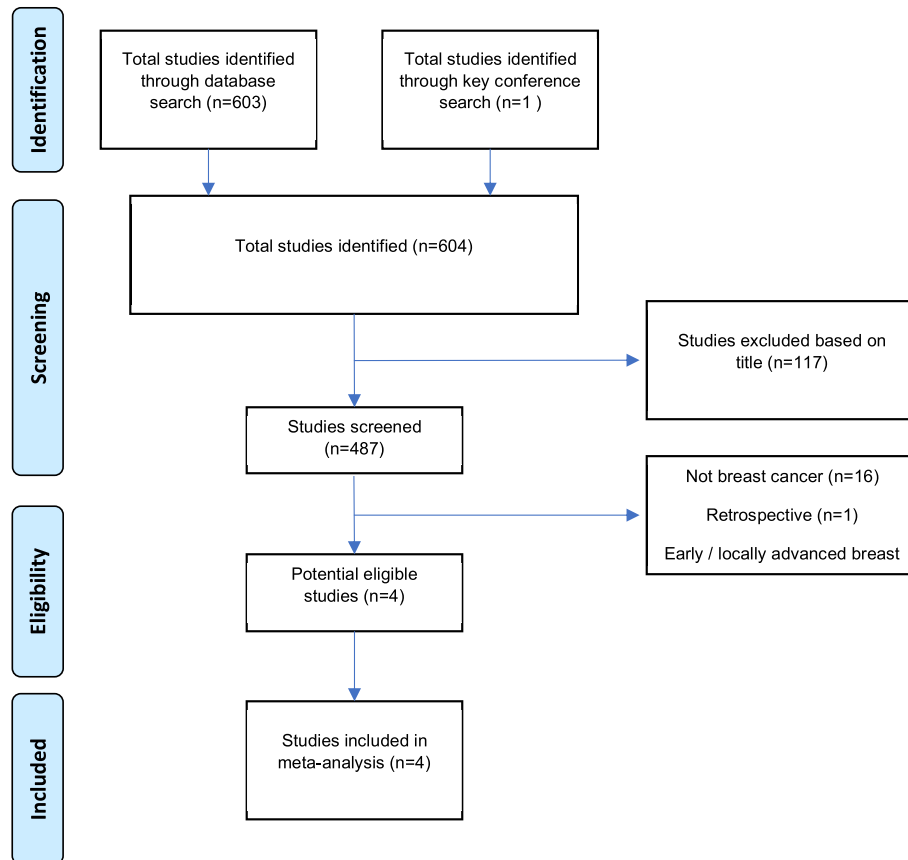
Fig. 1. Study selection scheme.

Table 1
Trial characteristics.

Trial	Median Follow up (months)	Number of patients	Treatment before randomization	Post- surgery adjuvant RT to breast (%)	HR positive	HER2 positive	Triple Negative	Pre-menopausal	Visceral disease	Bone only disease	Surgery in control arm
Badwe 2017 [10]	23	350	Systemic Therapy	80%	60%	31%	NA	46%	71%	29%	11%
Soran 2018 [11]	40	274	Upfront surgery	58%	78%	31%	12%	58%	54%	46%	6%
Fitzal 2019 [9]	37.5	90	Upfront surgery	20%	81%	22%	9%	13%	62%	38%	15%
Khan 2020 [12]	53	256	Systemic Therapy	60%	58%	32%	8%	36%	65%	38%	19%

Abbreviations: HER2 — human epidermal growth factor receptor 2, HR — hormone receptor, RT-radiotherapy.

3.3. Meta-regression

Results of the meta-regression analysis are shown in Table 3. In quantitative assessment, higher proportions of pre-menopausal women, of triple negative disease and of bone-only disease were associated with highly quantitatively significant lower HR for OS (i.e. increased benefit from experimental therapy). Higher proportion of visceral disease were associated with highly quantitatively significant higher HR for OS (i.e. lower benefit or harm from experimental therapy). Older age was associated with substantially quantitatively significant higher magnitude of effect of OS and higher proportion of hormone receptor positive disease were associated with highly quantitatively significant lower magnitude

of effect on OS.

4. Discussion

The role of LRT of the breast in *de novo* metastatic breast cancer has been controversial with inconsistent results [34]. Numerous retrospective analyses have demonstrated a survival benefit in this setting [3,13,35,36], while results from prospective have been inconsistent [9–12]. The improvement in systemic treatment further increases the uncertainty regarding to role of LRT in metastatic disease.

In this meta-analysis, comprising only randomized prospective trials, no survival advantage for LRT in *de novo* metastatic disease
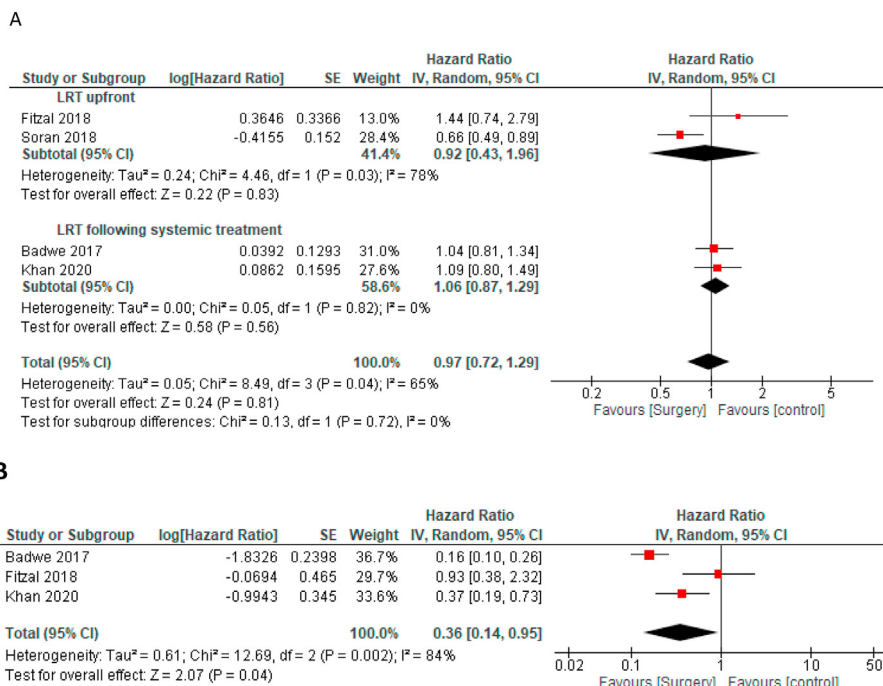
A

B

Fig. 2. Forest plots - a: Overall survival in ITT group, b: Time to locoregional progression in ITT group.

Table 2
Sensitivity analyses for outcomes.

Analysis	Primary analysis HR, 95% CI	Excluding study radiotherapy was not mandatory/ stopped prematurely HR, 95% CI	Excluding study available only in abstract form HR, 95% CI	Excluding study HER2 targeted therapy were not available HR, 95% CI
Overall survival	0.97 (0.72–1.29)	0.91 (0.67–1.24)	0.94 (0.63–1.40)	0.96 (0.62–1.48)
Time to locoregional progression	0.36 (0.14–0.95)	0.23 (0.10–0.53)	0.37 (0.07–2.07)	0.56 (0.23–1.37)

Abbreviations: CI- confidence interval, HER2 — human epidermal growth factor receptor 2, HR-hazard ratio.

was identified, despite achieving significant improvement in locoregional control. Additionally, focusing on different subgroups, based on both cancer subtype by receptors expression and based on the site of metastases, did not reveal any subgroup that might benefit for LRT. Of note, as OS data for visceral disease were available only from 2 studies the interpretation that can be made for this subgroup is limited. Given the inconsistent results form prospective studies, our results suggest a limited role for LRT in *de novo* metastatic disease. In the presence of what seems to be robust retrospective data, our findings highlight the importance of randomized prospective trials to answer meaningful clinical decisions.
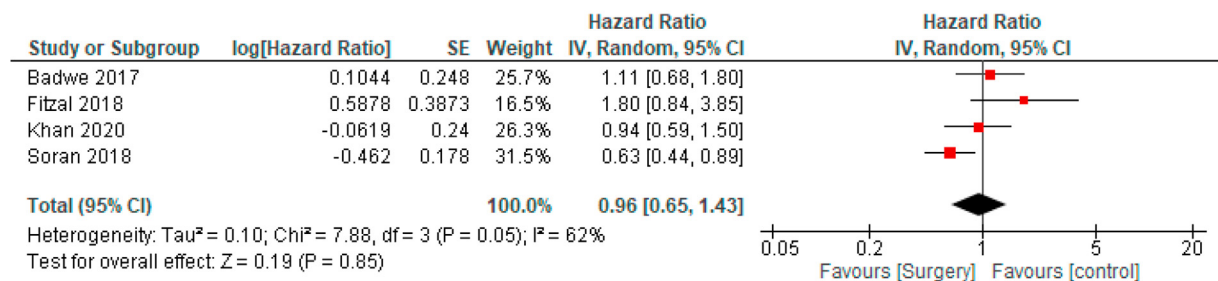
A possible explanation for the discrepancy between retrospective and prospective results is an inherent selection bias in retrospective data. Such bias is likely difficult to adjust/control for and will likely result in residual bias in most analyses. In retrospective studies patients who responded better to initial systemic therapy may have been more likely to be offered LRT, hence representing subpopulation with favorable prognosis compared to patients without initial response to systemic therapy. In some retrospective studies arms were not adequately adjusted and patients in surgery arms were also younger, had smaller tumors and lower metastatic burden [3], highlighting the selection of patients that were more likely to have longer survival regardless to treatment selection.

Heterogeneity between the included studies in this meta-analysis exists. In 2 studies randomization to LRT occurred after achieving clinical benefit from systemic therapy [10,12] while in 2
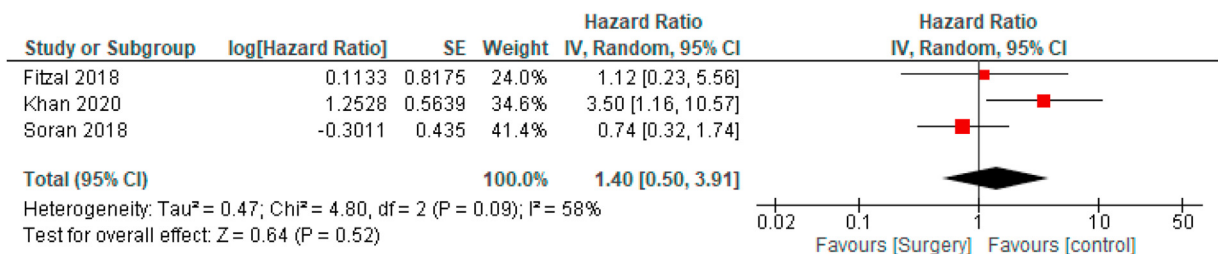
studies patients in the experimental arm were treated with an upfront surgery [9,11]. The strategy of delayed surgery has the advantage of preventing patients with rapidly progressive disease refractory to systemic treatment to undergo surgery further delaying exposure to potentially effective systemic therapy. Additionally, initial systemic treatment can potentially reduce tumor burden and prevent life threatening complications that could be associated with distant metastases. However, our analysis shows that timing of LRT had no impact on the magnitude of effect on OS in this meta-analysis. Compared to the control arm, LRT for triple negative disease had worse OS (HR = 1.4). Although this finding was not statistically significant, this trend might support the importance of systemic treatment, especially in a disease with aggressive biology, such as triple negative subtype. Of note, time to distant progression was significantly shorter with LRT, but this analysis is limited as only 2 studies reported these results [9,10].

The only positive trial which showed a survival advantage for LRT was that by Soran et al. [11] with a HR of 0.66 for survival and a 5 year overall survival improvement (46.4% versus 26.4%). However, this trial has limitations. Despite randomization, there were differences in characteristics between the treatment arms - patients in the surgical group had lower rates of triple negative disease (7% vs 17%), higher rates of hormone positive disease (85.5 vs 71.8%) and were more likely to have solitary bone metastases (34% vs 24%). These differences may have resulted in biased results. One other drawback of this study was that there was no histologic
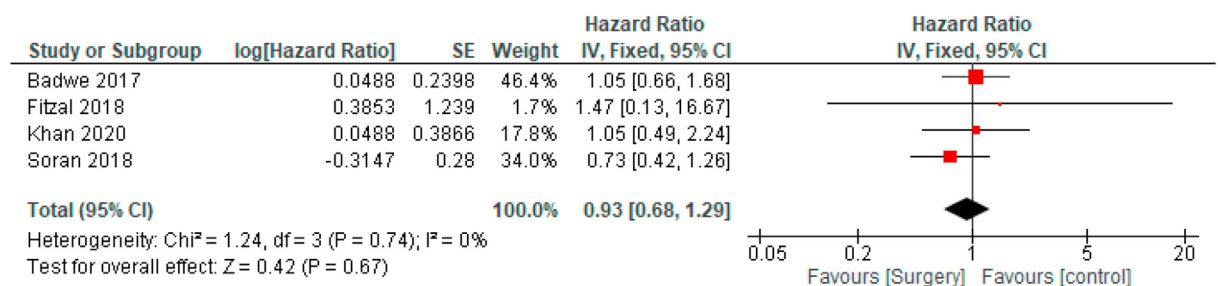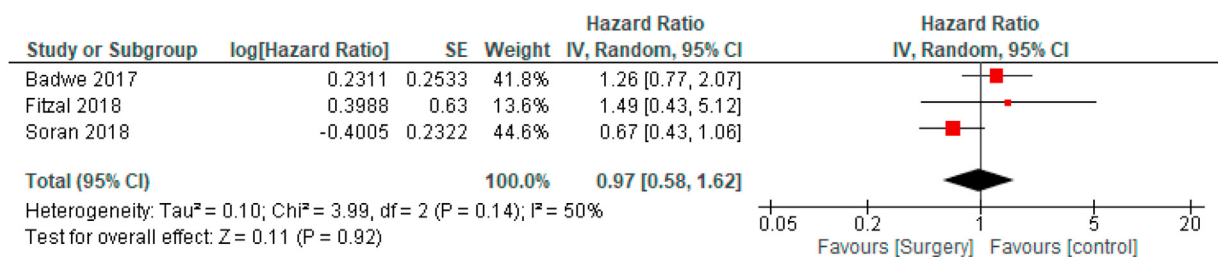
A

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Badwe 2017	0.1044	0.248	25.7%	1.11 [0.68, 1.80]
Fitzal 2018	0.5878	0.3873	16.5%	1.80 [0.84, 3.85]
Khan 2020	-0.0619	0.24	26.3%	0.94 [0.59, 1.50]
Soran 2018	-0.462	0.178	31.5%	0.63 [0.44, 0.89]
Total (95% CI)			100.0%	0.96 [0.65, 1.43]

Heterogeneity: Tau² = 0.10; Chi² = 7.88, df = 3 (P = 0.05); I² = 62%
Test for overall effect: Z = 0.19 (P = 0.85)

Favours [Surgery]   Favours [control]

B

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Fitzal 2018	0.1133	0.8175	24.0%	1.12 [0.23, 5.56]
Khan 2020	1.2528	0.5639	34.6%	3.50 [1.16, 10.57]
Soran 2018	-0.3011	0.435	41.4%	0.74 [0.32, 1.74]
Total (95% CI)			100.0%	1.40 [0.50, 3.91]

Heterogeneity: Tau² = 0.47; Chi² = 4.80, df = 2 (P = 0.09); I² = 58%
Test for overall effect: Z = 0.64 (P = 0.52)

Favours [Surgery]   Favours [control]

C

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
Badwe 2017	0.0488	0.2398	46.4%	1.05 [0.66, 1.68]
Fitzal 2018	0.3853	1.239	1.7%	1.47 [0.13, 16.67]
Khan 2020	0.0488	0.3866	17.8%	1.05 [0.49, 2.24]
Soran 2018	-0.3147	0.28	34.0%	0.73 [0.42, 1.26]
Total (95% CI)			100.0%	0.93 [0.68, 1.29]

Heterogeneity: Chi² = 1.24, df = 3 (P = 0.74); I² = 0%
Test for overall effect: Z = 0.42 (P = 0.67)

Favours [Surgery]   Favours [control]

D

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Badwe 2017	0.2311	0.2533	41.8%	1.26 [0.77, 2.07]
Fitzal 2018	0.3988	0.63	13.6%	1.49 [0.43, 5.12]
Soran 2018	-0.4005	0.2322	44.6%	0.67 [0.43, 1.06]
Total (95% CI)			100.0%	0.97 [0.58, 1.62]

Heterogeneity: Tau² = 0.10; Chi² = 3.99, df = 2 (P = 0.14); I² = 50%
Test for overall effect: Z = 0.11 (P = 0.92)

Favours [Surgery]   Favours [control]

E

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
Badwe 2017	-0.0305	0.1558	86.5%	0.97 [0.71, 1.32]
Fitzal 2018	0.3365	0.3947	13.5%	1.40 [0.65, 3.03]
Total (95% CI)			100.0%	1.02 [0.77, 1.35]

Heterogeneity: Chi² = 0.75, df = 1 (P = 0.39); I² = 0%
Test for overall effect: Z = 0.13 (P = 0.90)
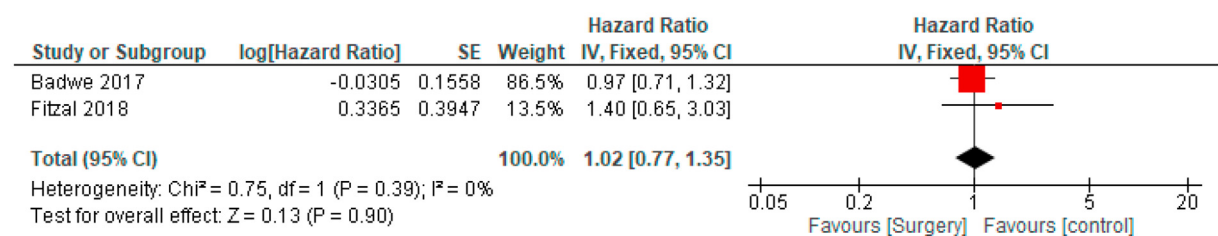
Favours [Surgery]   Favours [control]

Fig. 3. Forest plots for overall survival according to subgroups - a: Hormone positive disease, b: Triple negative disease, c: HER2 positive disease, d: Bone only disease, e: Visceral disease. Hazard ratios for each trial are represented by the squares, the size of the square represents the weight of the trial in the meta-analysis, and the horizontal line crossing the square represents the 95% confidence interval. The diamonds represent the estimated pooled effect. All P values are two-sided.

Table 3
Results of meta-regression analysis for overall survival.

Variable	B	P
Median age	0.452	0.548
Duration of follow-up	−0.056	0.944
Proportion pre-menopausal	−0.903	0.097
Proportion with visceral disease	0.723	0.277
Proportion with bone only	−0.651	0.349
Proportion LRT in control group	0.268	0.827
Proportion of HR positive	−0.475	0.525
Proportion of HER2 positive	−0.411	0.589
Proportion of triple negative	−0.883	0.311

Abbreviations: HER2 — human epidermal growth factor receptor 2, HR — hormone receptor, LRT-locoregional therapy.

conformation of solitary bone metastases [11], which might increase the possibility of mis-diagnosis of metastatic disease and thereby result in substandard treatment in the control arm.

Other included studies in this meta-analysis also have several important limitations. Badwe et al. conducted a randomized prospective study in India [10] in patients who responded to systemic therapy and showed no survival benefit for LRT. They reported an improved locoregional control but with a significantly worse distant PFS. This may explain the results of comparable OS despite improvement in loco-regional control. The detrimental effect of LRT on distant PFS could be explained by an enhanced metastatic growth after tumor resection. This phenomenon has been demonstrated in animal and human studies [37—39]. Furthermore, potential delays in systemic therapy delivered perioperatively could also hamper systemic control. An important limitation of this study was that some patients may have been undertreated, for example only a small minority (8%) of patients with HER2 positive disease received directed anti-HER2 therapy. As there were more women with HER2 positive disease in the control arm (36% vs. 25%), this inferior systemic therapy is unlikely to explain lack of OS benefit with LRT therapy. Also, as this study enrolled women in a low-middle income country with low screening rates, it likely included patients with delayed presentation rather than tumor biology consistent with early metastatic potential. This may limit generalizability to higher income settings.

The study conducted by Fitzal et al. was planned to recruit 254 patients but was closed after 5 years when only 90 patients were recruited. Consequently, the study was under-powered to detect differences between treatment arms. However, despite not reaching statistical significance a trend for inferior OS was observed in the surgery arm with an absolute survival difference of 20.2 months [9]. Khan et al. presented the initial results of the phase 3 ECOG ACRIN 2108 trial during ASCO 2020 virtual conference [12]. Several concerns regarding the results of this trial have been raised [40]. Three-year survival rates were much higher than expected, decreasing the power of this study. Although one of the inclusion criteria was free surgical margins, only 80% of patients in the LRT arm achieved clear margins and a there was a high percentage of skin or fascia involvement. Some of the included patients had very short duration of follow-up, limiting the ability to capture a potential benefit from LRT in patients with relatively longer survival. Also, no subgroup analysis regarding metastatic sites were presented. To address the weakness of the includes studies multiple sensitivity analysis were done, with no effect of OS. Additionally, the results of leave-one-out sensitivity analysis support OS results are not driven by any one the individual study.

This study has limitations. First, this is a literature-based rather than an individual patient-based meta-analysis. Consequently, it is subject to publication bias. Second, there were several differences in the protocol of treatment of included studies. Systemic treatment prior randomization was not given in 2 studies, and there was both intra- and inter-study variability in the type of the systemic treatment that was given. Additionally, data of subsequent lines of systemic treatment were not reported and the impact of this on OS could not be assessed. Additionally, there was evidence of contamination with LRT given to some of the patients in the control arm. As only the minority in the control group was treated with LRT the impact on the results is limited. However, this was explored in meta-regression with no quantitive difference observed on the magnitude of effect on OS. Third, there was heterogeneity between studies populations, which may also affect the results, as there is a high variability in metastatic breast cancer outcome, mainly related to receptors expression and tumor burden. Of note, the effect of LRT was evaluated on different subgroups with overall similar magnitude of effect. Moreover, there was heterogeneity in the quality of data available from the studies, with one trial closed prematurely due to poor accrual and another trial which was presented only in abstract form. Finally, the studies that reported quality of life used different scales and therefore could not be pooled.

In conclusion, this meta-analysis shows no survival advantage for LRT in *de novo* metastatic breast cancer despite significant improvement in locoregional control. Comparable OS results were consistent among different subgroups based on tumor biology or burden of disease. Systemic treatment remains the core treatment in metastatic breast cancer and efforts to improve anti -cancer drugs in order to improve survival and quality of life should continue. LRT for *de novo* metastatic disease should not be offered routinely. Current data did not identify specific subgroups that may benefit form LRT treatment. However, further research is desired to investigate to role of local treatment in some clinical circumstances such as oligometastatic disease or when the primary site is the sole active site after systemic therapy.

Declarations

Conflict of interest

Dr. Yerushalmi reports personal fees from: Roche (Consulting, Invited speaker), Pfizer (Consulting), Novartis (Consulting), Teva (Invited speaker), Medison (Invited speaker), MSD (Invited speaker), Astra-Zeneca (Invited speaker) and Novartis (Invited speaker), all outside the submitted work.

Dr. Moore reports personal fees from Roche (invited speaker), MSD (invited speaker), all outside the submitted work.

Dr. Amir reports personal fees from Genentech/Roche (expert testimony), Apobiologix (consulting). Novartis (consulting), Sandoz (consulting), Exact Sciences (consulting) and Agendia (consulting).

Dr. Goldvaser reports personal fees from: Roche (honorarium), Pfizer (honorarium), Novartis (honorarium and consulting) and Oncotest (honorarium) all outside the submitted work.

All other authors have no conflicts of interest.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author contributions

Daniel Reinhorn: Investigation, data curation, writing—original draft, writing—review and editing, final approval of the version to be submitted.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2021.05.003.

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