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Review

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Updated evidence of primary tumor resection in stage IV breast cancer: a systematic review and meta-analysis

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Abstract

Background: In stage IV breast cancer, surgical resection of the primary tumor was traditionally performed solely to palliate symptoms such as bleeding, infection, or pain. The ongoing discussion has shown that there are many research gaps in the current literature and differences in clinical practice. Thus, this systematic review and meta-analysis was designed to evaluate how primary tumor resection (PTR) affects the overall survival (OS) of patients with stage IV breast cancer. Method: A thorough literature search was completed using different databases (PubMed, Google Scholar, Scopus, ScienceDirect, and Cochrane Library) to find papers contrasting PTR with no PTR. The quality of research articles was evaluated using the Cochrane Risk of Bias 2.0 Tool and the Newcastle-Ottawa Scale (NOS). Review Manager 5.4 was used to determine how much demographic and clinical factors contribute to heterogeneity through subgroup and meta-regression analysis. Results: Data derived from 44 observational studies (OS) and four randomized controlled trials (RCTs) including 227,889 patients were analyzed. Of all cases, 150,239 patients were included in the non-PTR group, and 70,795 patients in the PTR group (37 observational studies and 4 randomized control trials). The pooled outcomes of four RCT studies (Hazard Ratio (HR) = 1.03, 95%CI: 0.67-1.58; I^2 = 88%; P < 0.0001; chi-square 24.57) favor non-PTR. While pooled outcomes of 43 observational studies showed PTR significantly improved OS (HR = 0.66, 95%CI: 0.61-0.71; I^2 = 87%; P < 0.00001; chi-square 359.12). Additionally, subgroup analysis that compared PTR with non-PTR in patients with

stage IV breast cancer for progression free-survival (HR = 0.89, 95%CI: 0.62-1.28; P = 0.03; I^2 = 71%) and locoregional progression-free survival (LPFS) (HR = 0.33, 95%CI: 0.14-0.74; P = 0.0004; I^2 = 87%) was found to be significant favoring the PTR group. Distant progression-free survival (DPFS) had a non-significant relationship (HR = 0.42, 95%CI: 0.29-0.60; P = 0.12; I^2 = 53%), while overall, there was a significant relationship (HR = 0.49, 95%CI: 0.32-0.75; P < 0.00001; I^2 = 90%). Subgroup analysis revealed that PTR is beneficial in patients with bone metastasis (HR = 0.83, 95%CI: 0.68-1.01; P = 0.01; I^2 = 56%), with one metastatic site (HR = 0.75, 95%CI: 0.63-0.59; P = 0.006; I^2 = 62%), but not in patients with positive margins (HR = 0.84, 95%CI: 0.67-1.06; P = 0.07; I^2 = 61%), negative margins (HR = 0.61, 95%CI: 0.59-0.63, P = 1.00; I^2 = 0%). Most of the patients in PTR and non-PTR groups belonged to white compared to other ethnic groups. Overall, observational studies were of high quality, while RCTs were of low quality. Conclusion: The current research suggests that PTR may be discussed as a possible option.

Keywords: PTR, primary tumor resection, breast cancer IV stage, breast cancer, overall survival, metastatic disease

INTRODUCTION

In 2020, around 685,000 females died worldwide due to breast cancer (BC), while diagnoses of BC were confirmed in 2.3 million women[1]. During that year, BC stood as the most prevalent cancer globally[2], and over the last five years, 7.8 million women have been alive after receiving a diagnosis[1]. Approximately 6% or more of newly diagnosed BC patients had distant metastases[3]. The effects of BC therapy can be detrimental to a woman's quality of life (QoL) and are linked to loss of working hours, depression, diminished sexual life quality, and the psychological impact of hereditary aspects[4,5]. One study evaluating the QoL of women with metastatic breast cancer (MBC) highlighted that patients value more therapies that increased disease-free survival (DFS) than therapies that increased overall survival (OS)[6]. Although the majority of BC survivors claim they have a good QoL, they frequently value adaptive and psychosocial issues rather than physical deficiencies[7].

Recent developments revealed the long-term control of metastasis symptoms and the extension of patient lives through the right use of new treatments that are becoming available[8]. Furthermore, BC in stage IV is still an incurable disease; however, current developments in medical technology and in research are extending the lifespan of women by approaching their conditions as chronic illnesses and prioritizing their QoL[9]. As a result, systemic therapy continues to be the mainstay of treatment and the importance of local therapy is still debatable.

According to the National Comprehensive Cancer Network (NCCN) guidelines (V4.2022) as previous publications noted, only women with stage IV BC who have completed systemic therapy and are experiencing impending problems, such as bleeding, skin ulceration, fungus, and pain should undergo surgery to remove the primary tumor[10]. Despite these warnings, research has revealed that up to 50% of women with metastatic disease have surgical excision of the primary tumor[11].

It is debatable whether surgery should be used to treat stage IV BC stage. The patient's reaction to induction systemic therapy (IST) has not been thoroughly examined in stage IV BC studies with regard to its impact on survival rates[12]. Guidelines do not actively promote surgery for stage IV primary tumors since there is insufficient data to support an increment of prognostic benefit[13]. Although clinical trials have produced mixed outcomes, it has been predicted that locoregional therapy for the primary tumor seems to increase OS[3]. Meanwhile, the degree of benefit from surgery may depend on prognostic factors, with those who have the best chances of surviving benefiting the most[14]. Surgical decisions should be decided on a case-by-case basis and may alter the survival of certain women, though a multidisciplinary approach is still

extremely significant[15]. In fact, a cohort study concluded that surgery within one year of a de novo MBC diagnosis was associated with considerably higher OS and progression-free survival (PFS)[16]. Another meta-analysis revealed that breast surgery might increase the OS of women[17]. However, prospective trials have not provided evidence to support a survival advantage for patients with primary tumors of IV stage BC who have surgically removed their primary tumors[18,19]. Additionally, several experts consider that removing primary tumors might possibly worsen survival[20,21].

Nevertheless, the best course of action for these patients is a thoughtful combination of systemic therapy such as chemotherapy, targeted or molecular therapy, hormone therapy, and immunotherapy either alone or in combination, local therapy with radiation, or surgery when necessary[22], which might enhance patients' survival[23]. Moreover, numerous precision medicines are presently in the midst of clinical trials, with several having already garnered Food and Drugs Authority (FDA) approval, either as standalone treatments or when used in conjunction with other medications, to address various manifestations of BC[24].

In the past, PTR was performed with palliative intent to treat or control symptoms such as bleeding, infection or pain. The underlying theory behind this therapeutic strategy was that local treatment did not increase OS in MBC. A wide range of unmet requirements shows that there are still significant difficulties for breast cancer patients regarding the quality of treatment and support[25]. Due to this ongoing discussion, a significant difference in clinical practice still exists. Thus, the present systematic review and meta-analysis were designed to assess how PTR affected stage IV BC patients' overall survival.

MATERIALS AND METHODS

This systematic review was in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines[26].

Search strategy

Various search terms were employed to retrieve pertinent original research papers from multiple databases, including Scopus, PubMed, The Cochrane Library, Web of Science, ScienceDirect, and Google Scholar (see Supplementary Table 1). The search was performed using the following terms: Primary resection, Stage IV, and Breast cancer. Research papers up to November 2022 were included.

Inclusion criteria

Randomized controlled trials (RCTs) and observational studies were conducted to assess the contrast between PTR and standalone systemic therapy in individuals diagnosed with stage IV *de novo* BC. Systemic therapy, encompassing radiotherapy for any location, chemotherapy, hormone therapy, and targeted therapy, was part of the comprehensive treatment strategy. Abstract-only studies meeting the inclusion criteria were also considered. Most recent studies were also included according to the sample size. Only English versions of research articles were included.

Exclusion criteria

Studies containing fewer than 40 patients were excluded because of their limited reliability. Letters, case reports, comments, reviews, and meta-analyses were excluded, along with comparisons between surgery and no surgery, in stage IV de novo BC with upfront PTR If there is not enough data for thorough analysis or in the absence of comparative groups. Non-English articles were also excluded.

Study selection and assessment

An independent screening by article titles and abstracts, as well as the original publications, was completed. Initially, two independent reviewers evaluated whether the full-text content of studies met the inclusion

criteria, and then the findings of their evaluations were discussed to reach a decision. Disagreements were resolved by a third independent reviewer.

Data extraction

The studies meeting the predefined inclusion criteria were advanced to the data extraction stage. The screening was based on the paper's title, abstract, and full text. The information extracted from these studies was then recorded in a standardized data extraction template. Two reviewers separately documented specific details from each study, including the authors and publication year, the country, the average age, the total number of participants, and the median follow-up duration.

Primary outcomes

According to multivariate analysis, OS was the primary outcome, which was presented as Hazard Ratios (HRs).

Secondary outcomes

The secondary outcomes were the survival rate at 2, 3, and 5 years, distant progression-free survival (DPFS), PFS, and locoregional progression-free survival (LPFS). Using the technique described by Guyot, Ades[27], the HRs and their corresponding 95% confidence intervals (CIs) from studies that solely presented Kaplan-Meier (KM) survival curves were retrieved. Furthermore, we categorized the patient counts in each group based on specific criteria, including lymph nodes (N) status, Tumor size (T) status, Tumor grade (G), Progesterone Receptors (PR), Estrogen Receptors (ER), Human Epidermal growth factor Receptor 2 (HER2) status, locations of metastases, number of metastatic sites, presence of bone-only metastases, utilization of hormonal therapy, radiation, and targeted therapy. All these criteria are considered prognostic factors.

Quality assessment

The Newcastle-Ottawa scale (NOS) was used to evaluate observational studies, while the Cochrane tool was used for RCTs in order to evaluate the risk of bias (RoB). The elements of bias consist of randomization, deviation from intended intervention, missing outcome, measurement of outcomes, and reporting. These aspects were all included in the Cochrane risk of bias tool, which categorizes bias risk as low, high, or some concerns. Each research was assigned a maximum of nine points for NOS, which included considerations for selection, comparability, and results. Observational studies were categorized as low quality if their scores ranged from 0 to 4, and high quality if they scored between 5 and 9. When two reviewers disagreed, a third reviewer assisted in making the final judgment. Both observational research studies and RCTs were scored and reported.

Data analysis

The Review Manager 5.4 employed a random-effects model to collect and combine HRs and their corresponding 95%CI: from the included studies. An HR below 1 indicated an advantage for primary surgery in terms of survival. Heterogeneity was assessed using Cochran's *Q* test, which yielded a Chi-square (X^2) value and a P-value. Heterogeneity was considered significant if $P < 0.1$. The funnel plots were also examined and publication bias was evaluated using Begg's test[28]. Subgroup analysis was also performed to identify prospective patient subgroups and to address potential heterogeneity sources.

RESULTS

All the studies under scrutiny were published in peer-reviewed journals, resulting in a pool of 13,734 potential articles. Out of these, 1,964 were excluded (see Figure 1). Subsequently, after eliminating duplicate entries, a total of 11,770 papers underwent evaluation based on their titles and abstracts. Among these,

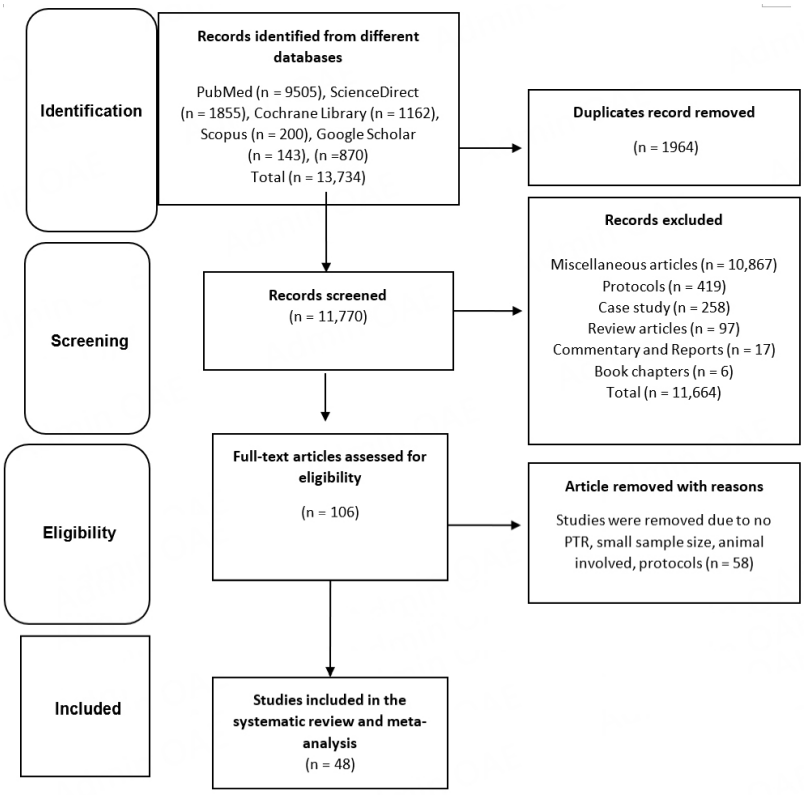

Figure 1. PRISMA flow chart.

11,664 articles were excluded due to their classification as review articles, editor letters, or editorial letters [Figure 1]. This systematic meta-analysis included 48 studies published between 2002 and 2022. Studies followed RCTs and observational study design[315,29-73]. The majority of the studies were reported from the United States of America (USA), while others from China, South Korea, India, Switzerland, Turkey, France, and Spain.

Baseline characteristics of the PTR group

In total, 227,889 patients enrolled in the included studies, while 70,795 patients were included in the PTR group. The mean age was found to be 50 years. The maximum value of positive HER-2 was 76% and the lowest was 4%. In terms of tumor grade, for G1-2, it was 84.90%, while the highest G3 was 55.80%. The highest visceral and bone-only metastasis was found to be 67% and 77%, respectively. In terms of hormone receptors, the average rates were: a PR positive rate of 68.9% and an ER positive rate of 82% in the PTR group [Supplementary Table 2].

Baseline characteristics of the non-PTR group

There were 150,239 patients and the mean age was over 40.02 years. HER-2 positivity ranged from 3% to 70%. In terms of tumor grade, the maximum G1-2 was 77%, while for G3 was 67%. The highest visceral and bone-only metastasis percentages were 77% and 84%, respectively. In terms of hormone receptors, the PR rate was 77%, while the ER in the non-PTR group was also 77% [Supplementary Table 3].

Tumor size

The T1 (43%), T2 (53%), T3 (57%) and T4 (93%) values of patients in the PTR group were lower than those in the non-PTR group that had T1 (57%), T2 (58%), T3 (43%) and T4 (81.8%) values [Table 1].

Table 1. Different tumor sizes

Study ID	PTR				Non-PTR			
	T1 (%)	T2 (%)	T3 (%)	T4 (%)	T1 (%)	T2 (%)	T3 (%)	T4 (%)
Fields *et al.*, 2007[35]	NA	29	9	38	NA	22	11	42
Shien *et al.*, 2009[42]	43	52	57	93	57	48	43	57
Ruiterkamp *et al.*, 2009[41]	21	39	7	32	13	24	7	43
Ahn *et al.*, 2010[39]	9.4	27.4	34.9	28.3	8.5	35.5	24.4	29.3
Pathy *et al.*, 2011[45]	1.4	8.6	12.9	77	0.8	8.9	8.5	81.8
Lang *et al.*, 2013[48]	NA	44.1	27.1	20.4	NA	27.5	22.1	35.1
Anula *et al.*, 2015[50]	19	53	22	6	0	30	17	53
Quinn *et al.*, 2015[52]	19	12	8	10	13	7	17	8
Wang *et al.*, 2016[73]	NA	43.9	22.7	16.7	NA	26.4	16.5	35.1
Muzaffar *et al.*, 2016[56]	NA	NA	26.5	NA	NA	NA	32.7	NA
Yoo *et al.*, 2017[57]	16.4	39.3	21.2	19.8	5.1	15.1	12.8	36.4
Barinoff *et al.*, 2017[58]	16	38	15	25	35	48	9	8
Desille-Gbaguidi *et al.*, 2018[60]	7.2	31.8	18.8	42	2.8	30	14.3	50
Soran *et al.*, 2018[31]	8.7	52.2	21.7	17.4	8.1	42.7	22.1	27.2
Fitzal *et al.*, 2018[30]	22	18	22	18	16	58	7	18
Lopez-Tarruella *et al.*, 2019[62]	10.6	37.8	10.1	35.8	5.3	16.8	11.4	50.2
Lane *et al.*, 2019[15]	12.1	26.7	13.8	33.1	11.1	24.4	13	34.9
Yao *et al.*, 2020[66]	11.5	36.4	18.5	29.7	10.1	23.5	13.6	33.3
Xie *et al.*, 2022[71]	11	36.5	17.9	31	9.5	23.5	13.6	30.9
Khan *et al.*, 2022[3]	52.9			47.1	51.2			48.8

PTR: Primary tumor resection.

Regional lymph nodes

With N0 (50.7%), N1 (61%), N2 (39.1%), and N3 (33.33%) in the PTR group and N0 (36%) N1 (47%), N2 (30%), and N3 (28.6%) in the non-PTR group, there was a light variation in the proportion of N0 stage in each group [Table 2].

Treatment options

In different studies there were four types of therapies used for both PTR and non-PTR groups. Most studies included chemotherapy and radiotherapy as an initial treatment for metastatic breast cancer along with PTR or without PTR [Table 3].

The majority of the patients in PTR and non-PTR groups were Caucasians (> 70%), as shown in Figure 2.

Overall survival rate

A significant increase and decrease in OS following PTR, with a high degree of heterogeneity, was seen in pooled analysis for four RCT studies (HR = 1.03, 95%CI: 0.67-1.58; I^2 = 88%; P < 0.0001; chi-square 24.57) [Figure 3]. Two studies favor PTR[30,31] and two favor non-PTR[29,74].

A pooled analysis of 43 observational studies showed a notable rise in the OS rate after PTR. However, there was a considerable variation in the outcomes (HR = 0.66, 95%CI: 0.61-0.71; I^2 = 87%; P < 0.00001; chi-square 359.12) [Figure 3]. Most of the studies favor PTR, and overall, subgroup analysis favored PTR (HR = 0.68, 95%CI: 0.64-0.74; I^2 = 89%; P < 0.00001; chi-square 459.12).

Table 2. The number of lymph nodes affected

Study ID	PTR-group				Non-PTR group			
	N0	NI	N2	N3	N0	NI	N2	N3
Lang *et al.*, 2013[48]	40	NA	NA	NA	22.5	NA	NA	NA
Anula *et al.*, 2015[50]	33	61	6	0	13	43	30	13
Wang *et al.*, 2016[73]	6.1	30.3	30.3	33.33	13.2	34.1	24.2	28.6
Muzaffar *et al.*, 2016[56]	19.4	27.5	39.1	NA	16.6	38.6	26.7	NA
Yoo *et al.*, 2017[57]	16.1	40.5	19.3	20.6	3.7	20.1	12.8	23.8
Barinoff *et al.*, 2017[58]	15	36	24	26	36	45	12	7
Desille-Gbaguidi *et al.*, 2018[60]	50.7	29	2.9	2.9	18.6	34.3	25.7	4.1
Fitzal *et al.*, 2018[30]	22	44	16	9	22	47	4	4
Lane *et al.*, 2019[15]	20.1	34.5	13.6	12.2	19.2	35.6	12.7	11.9
Yao *et al.*, 2020[66]	16.9	36.5	19.4	24.1	22.8	46	8	11.5
Bilani *et al.*, 2020[67]	25.8	37.1	13.1	14.3	23.5	38.9	9.5	11.4
Xie *et al.*, 2022[71]	16.5	38.1	18.9	23.7	25	44.6	7	10.6
Khan *et al.*, 2022[3]	52.9		47.1		51.2		48.8	

PTR: Primary tumor resection.

Subgroup analysis was performed and the results showed there was no significant difference between PTR and non-PTR groups in relation to positive margins (HR = 0.84, 95%CI: 0.67-1.06, $P = 0.07$; $I^2 = 61\%$) over negative margins (HR = 0.61, 95%CI: 0.58-0.63, $P = 0.96$; $I^2 = 0\%$)[32,33,45]. Overall, there was 90% heterogeneity ($P < 0.00001$) with HR = 0.69, 95%CI: 0.61-0.79 among the positive and negative margins [Figure 4].

Subgroup analysis of bone and visceral metastasis showed significant difference and favored the PTR in which there was only bone metastasis[29,31,36,39,44,46,47,51,54,62] (HR = 0.83, 95%CI: 0.68-1.01; $P = 0.01$; $I^2 = 56\%$) over visceral metastasis[36,39,41,42,44,47,50,54,58,62,70,71] (HR = 1.16, 95%CI: 0.93-1.43; $P < 0.00001$; $I^2 = 81\%$) as shown in Figure 5. Overall high heterogeneity among patients with bone and visceral metastasis was found (HR = 0.99, 95%CI: 0.84-1.16; $P < 0.00001$; $I^2 = 79\%$).

Subgroup analysis in terms of number of metastatic sites showed PTR benefits patients who had only one metastatic site[45,47,48,50,51,54,60,62,67] (HR = 0.75, 95%CI: 0.63-0.59; $P = 0.006$; $I^2 = 62\%$), while patients with number of metastatic sites - more than 3 - showed a non-significant relationship, and there were no difference between PTR and non-PTR groups[45,50,51,54,60,67,70] (HR = 1.17, 95%CI: 0.70-7.95; $P = 0.02$; $I^2 = 61\%$) [Figure 6]. Overall non-significant heterogeneity (60%) was found with HR = 0.79, 95%CI: 0.69-0.90; $P = 0.02$.

When subgroup analysis was performed to compare PTR with no PTR patients with stage IV BC for PFS, DPFS, and LPFS: PFS[35,38,58] (HR = 0.89, 95% 0.62-1.28; $P = 0.03$; $I^2 = 71\%$) and LPFS[29,59,65] (HR = 0.33, 95%CI: 0.14-0.74; $P = 0.0004$; $I^2 = 87\%$) were found to be significant favoring the PTR group, while DPFS[3,34,49] had non-significant relationship with HR = 0.42, 95%CI: 0.29-0.60; $P = 0.12$; $I^2 = 53\%$. Overall, there was a significant difference as HR = 0.49, 95%CI: 0.32-0.75; $P < 0.00001$; $I^2 = 90\%$ [Figure 7].

When subgroup analysis was performed to compare PTR with no PTR patients with stage IV BC for immunohistochemistry characteristics, it was found that high PR (HR = 0.95, 95%CI: 0.29-3.06; $P < 0.00001$; $I^2 = 86\%$), high ER (HR = 0.67 95%CI: 0.47-0.93; $P > 0.01$; $I^2 = 18\%$) and HER2 positive (HR = 1.13, 95%CI: 0.84-1.53, $P = 0.05$; $I^2 = 58\%$) groups present higher PFS and DFS but not LPFS [Figure 8].

Table 3. Treatment options in PTR and non-PTR groups

Study ID	PTR								Non-PTR							
	Radiotherapy (%)		Hormonal therapy (%)		Targeted therapy (%)		Chemotherapy (%)		Radiotherapy (%)		Hormonal therapy (%)		Targeted therapy (%)		Chemotherapy (%)	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Rapiti *et al.*, 2006[33]	21	79	43	57	NA	NA	53	47	5	95	40	60	NA	NA	74	26
Babiera *et al.*, 2006[34]	NA	NA	23.17	2.43	NA	NA	73.17	2.43	NA	NA	43.66	2.81	NA	NA	52.81	2.81
Hazard *et al.*, 2008[38]	67	33	NA	NA	NA	NA	NA	NA	29	71	NA	NA	NA	NA	NA	NA
Shien *et al.*, 2009[42]	NA	NA	51	39	NA	NA	NA	NA	NA	NA	49	61	NA	NA	NA	NA
Ruiterkamp *et al.*, 2009[41]	34	66	NA	NA	NA	NA	89	11	10	90	NA	NA	NA	NA	79	21
McGuire *et al.*, 2009[40]	NA	NA	54	46	NA	NA	34	66	NA	NA	56	44	NA	NA	35	65
Leung *et al.*, 2010[43]	NA	NA	55	45	NA	NA	65	35	NA	NA	49	51	NA	NA	53	47
Ahn *et al.*, 2010[39]	30	70	53.60	46.40	23.6	76.4	98.20	1.80	4.50	95.50	33	67	20.5	79.50	94.30	5.70
Dominici *et al.*, 2011[72]	NA	NA	74	26	NA	NA	78	22	NA	NA	67	NA	NA	NA	84	16
Pérez-Fidalgo *et al.*, 2011[46]	NA	NA	15.60	84.40	NA	NA	NA	NA	NA	NA	23.50	76.50	NA	NA	NA	NA
Lang *et al.*, 2013[48]	32.40	67.60	23	77	NA	NA	73	27	11.90	88.10	43.30	56.70	NA	NA	53	47
Akay *et al.*, 2014[49]	NA	NA	57	43	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	77	23
Badwe *et al.*, 2015[29]	80	5	NA	NA	0	100	82	18	NA	NA	NA	NA	15	85	72	28
Rhu *et al.*, 2015[51]	53	47	55	45	NA	NA	88	12	53	47	43.20	56.80	NA	NA	80	20
Quinn *et al.*, 2015[52]	64	36	NA	NA	NA	NA	77	23	54	46	NA	NA	NA	NA	49	51
Kolben *et al.*, 2016[54]	NA	NA	44.40	45.60	NA	NA	56	44	NA	NA	55	45	NA	NA	45	55
Wang *et al.*, 2016[73]	52	49	56.10	43.90	24.2	75.8	NA	NA	19.80	80.20	56	44	15.40	84.60	NA	NA
Muzaffar *et al.*, 2016[56]	38	61	NA	NA	NA	NA	NA	NA	32.30	65.40	NA	NA	NA	NA	NA	NA
Xie *et al.*, 2017[55]	41	55	54.80	44.10	NA	NA	NA	NA	4	96	13	87	NA	NA	NA	NA
Barinoff *et al.*, 2017[58]	43	57	NA	NA	NA	NA	32	68	17	83	NA	NA	NA	NA	23	77
Desille-Gbaguidi *et al.*, 2018[60]	79.70	20.30	81.10	18.90	NA	NA	76.80	23.20	8.60	91.40	58.60	41.40	NA	NA	54.20	45.80
Lim *et al.*, 2018[61]	54	40	49	45.70	NA	NA	92	20.2	34.90	61.50	48	48	NA	NA	93	4
Fitzal *et al.*, 2018[30]	60	40	67	33	NA	NA	34	66	31.40	68.60	62	38	NA	NA	37	63
Wang *et al.*, 2019[63]	NA	NA	NA	NA	NA	NA	68	33	NA	NA	NA	NA	NA	NA	54	46
Si *et al.*, 2020[65]	78.80	35.40	NA	NA	NA	NA	NA	NA	21.20	64.60	NA	NA	NA	NA	NA	NA
Mudgway *et al.*, 2020[64]	47.40	28.80	41.30	31.30	NA	NA	36.50	22.20	52.60	71.20	58.70	68.70	NA	NA	63.50	77.80
Çöpelci *et al.*, 2021[69]	NA	NA	5.20	95.80	NA	NA	34.20	65.80	NA	NA	4.30	96.70	NA	NA	36.80	63.20
Huang *et al.*, 2021[70]	27.20	72.80	46.40	53.60	20	80	98.20	4.80	11.90	88.10	24.60	75.40	17.80	82.20	79.70	20.30
Khan *et al.*, 2022[3]	11.5	NA	NA	NA	NA	NA	NA	NA	57.6	NA	NA	NA	NA	NA	NA	NA

When subgroup analysis was performed to compare PTR with non-PTR patients with stage IV BC for T and nodal involvement, HR = 1.43 95%CI:1.07-1.91; $P < 0.05$; $I^2 = 73\%$ presented higher PFS and DFS but not LPFS [Figure 9], and as indicated in Figure 9, they did not favor PTR.

Quality assessment

No evidence for publication bias was found in observational studies and RCTs, as indicated by visual inspection of the funnel plot [Figure 10], as all studies fall close to the vertical line. Newcastle-Ottawa Scale (NOS scores for the observational studies and RoB-2.0 for RCTs are shown in Supplementary Table 4 and Supplementary Figure 1).

DISCUSSION

The present meta-analysis supports the idea that excision of the primary tumor improves OS and reduces mortality in patients with metastatic disease. This conclusion is drawn from a comprehensive analysis of data pooled from multiple observational studies, which collectively demonstrated a noteworthy reduction in the death risk (as indicated by an HR of 0.66) following the PTR. Despite some heterogeneity in the study results, the consensus among the majority of these studies supports the notion that PTR offers substantial benefits to patients with MBC, thereby underscoring its therapeutic value in this clinical setting. Meanwhile, RCTs favored non-PTR (HR = 1.03). It was originally thought that once cancer metastasized, there was no therapeutic reason to remove the primary tumor. However, there is increasing evidence that the primary tumor still contributes to the development of metastatic disease, which may explain the advantages of PTR. To support this idea, several theories have been developed. The best-case scenario is that removing the primary tumor will decrease the overall tumor burden, improving the effectiveness of systemic treatment. A complete response to treatment is more favorable when the biggest amount of malignant tissue is reduced[74].

The predictive value of PTR in stage IV BC is currently the main subject of four RCTs and supports the non-PTR approach (HR = 1.03). Due to different designs, the two RCTs[29,31] had conflicting conclusions, while one RCT[30] was suspended early due to inadequate enrollment. PTR did not increase survival in patients who responded to front-line chemotherapy, according to the RCT led by Badwe *et al.*[29]. In contrast, the MF07-01 trial revealed that patients who underwent PTR had a statistically significant increase in survival when PTR was performed prior to systemic therapy[31] [Supplementary Figure 1]. In addition, meta-analyses of the studies revealed a significant improvement in OS after PTR with a high degree of heterogeneity (HR = 0.66, 95%CI: 0.61-0.71; $I^2 = 87\%$; $P < 0.00001$) in observational studies. These findings are well supported by the conclusions of Petrelli and Barni[75], in which they assess the survival rates of stage IV BC patients who received PTR vs those who did not. They examined 15 observational studies and found that PTR improved stage IV BC patients' survival outcomes (HR = 0.69; 95%CI: 0.63 to 0.77; $P < 0.001$). Similarly, in another meta-analysis, 28,693 patients in stage IV BC were included in the data from 10 trials, and 52.8% of them underwent PTR. Those patients who underwent PTR had a higher 3-year survival rate (40%) compared to those who did not (22%) (Odd Ratio (OR) 2.32, 95%CI: 2.08-2.6, $P < 0.01$)[76]. In addition, PTR significantly increased OS according to the results of 30 observational studies combined (HR = 0.65; 95%CI: 0.61-0.70; $P < 0.001$, $I^2 = 80\%$)[77]. Our meta-analysis is different from other published papers as it encompasses RCT in addition to observational studies. Furthermore, we also performed subgroup analysis using other important variables such as bone-only metastasis, visceral metastasis, positive and negative margins, number of metastatic sites and DFS, LRSF, DPFS.

In the present study, subgroup analysis showed PTR in patients with bone metastasis (HR = 0.83, 95%CI: 0.68-1.01; $P = 0.01$; $I^2 = 56\%$), with one metastatic site (HR = 0.75, 95%CI: 0.63-0.59; $P = 0.006$;

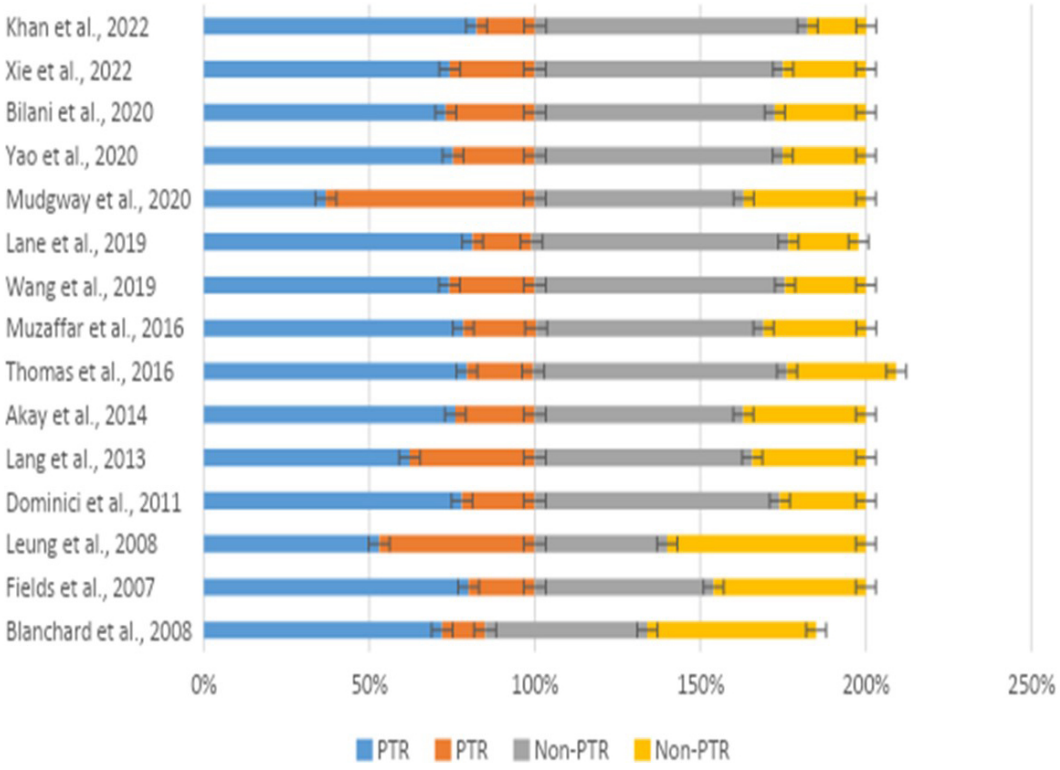

Figure 2. Race wise distribution of patients in PTR and non-PTR groups.

I^2 = 62%), but no benefit has been found concerning the resection margins, positive margins (HR = 0.84, 95%CI: 0.67-1.06, P = 0.07; I^2 = 61%) or negative margins (HR = 0.61, 95%CI: 0.59-0.63, P = 1.00; I^2 = 0%) and > 1 metastatic sites (HR = 1.17, 95%CI: 0.70-7.95; P = 0.02; I^2 = 61%). These findings are well supported by the conclusions of Pathy *et al.*[45], in which patients with positive margins did not benefit from resection in terms of OS. Similar results were discovered by Rapiti *et al.*[33]. If surgery can offer advantages, then this raises the subsequent question: which type of surgery might be more beneficial, mastectomy or conserving surgery? Finally, there is still disagreement regarding the ideal timing of surgery in relation to neoadjuvant therapy. These issues merit further investigation in subsequent prospective trials but fall outside the scope of this meta-analysis.

In the current study, another subgroup analysis was also performed for PFS, DPFS and LPFS and revealed that, overall, there was a non-significant relationship (HR = 0.49, 95%CI: 0.32-0.75; P < 0.00001; I^2 = 90%), which are well supported by the subgroup analysis findings of Mohanty *et al.*[78].

In the present study, four distinct therapeutic approaches were identified and applied to PTR and non-PTR groups. In most studies, chemotherapy and radiotherapy were used as a last resort for the treatment, either with or without PTR. However, early surgery is more likely to benefit patients based on metastasis and tumor biology hypothesis. This finding is supported by three reasons. Firstly, the primary tumor might be the source of new metastases; secondly, PTR might make distant metastases more responsive to chemotherapy; and thirdly, PTR can remove non-vascularized and necrotic tumor areas, thereby improving the efficiency of systemic treatment.

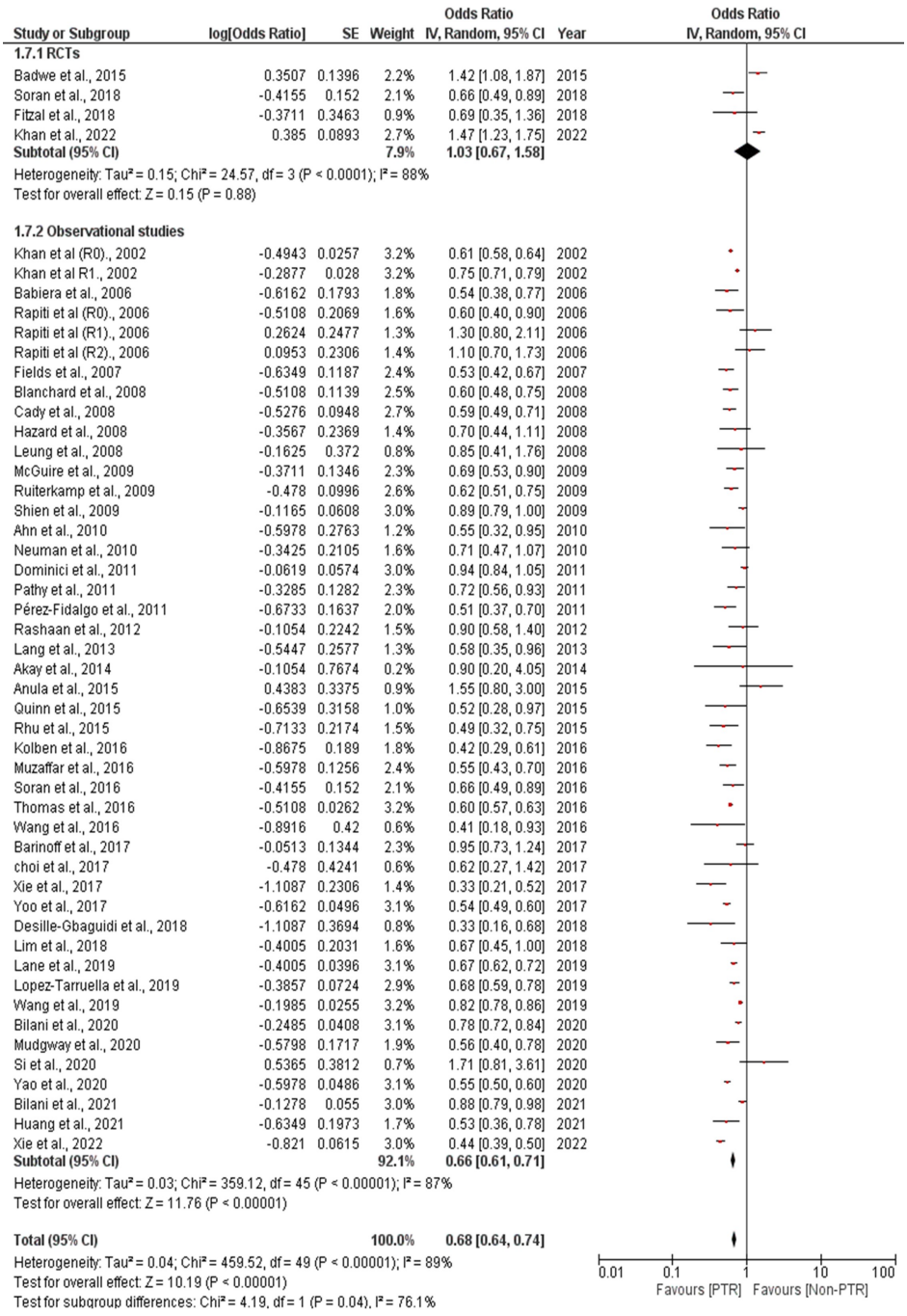

Figure 3. Forest plot for OS (Patients with stage IV breast cancer underwent PTR or without PTR).

In another subgroup analysis, PR (HR = 0.95, 95%CI: 0.29-3.06; $P < 0.00001$; $I^2 = 86\%$), ER (HR = 0.67, 95%CI: 0.47-0.93; $P > 0.01$; $I^2 = 18\%$) and HER2 positive (HR = 1.13, 95%CI: 0.84-1.53, $P = 0.05$; $I^2 = 58\%$) groups present higher PFS and DFS but not DPFS. These findings can be very helpful in finding appropriate treatment options. Indeed, the fundamental molecular markers that are acknowledged and established as prognostic indicators and predictors of response for therapeutic practice are hormone receptors, specifically ER, PR, and HER2[79]. In addition, N status and T are statistically very important prognostic indicators for

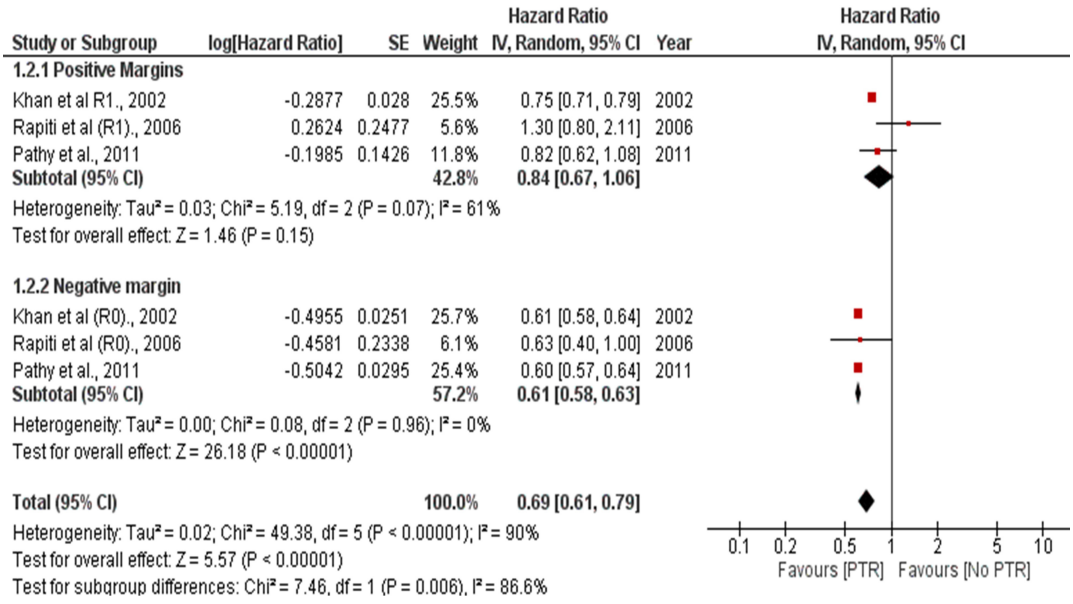

Figure 4. Forest plot depicting OS comparing patients with stage IV breast cancer who underwent PTR with those who did not, stratified by margin status. PTR: Primary tumor resection.

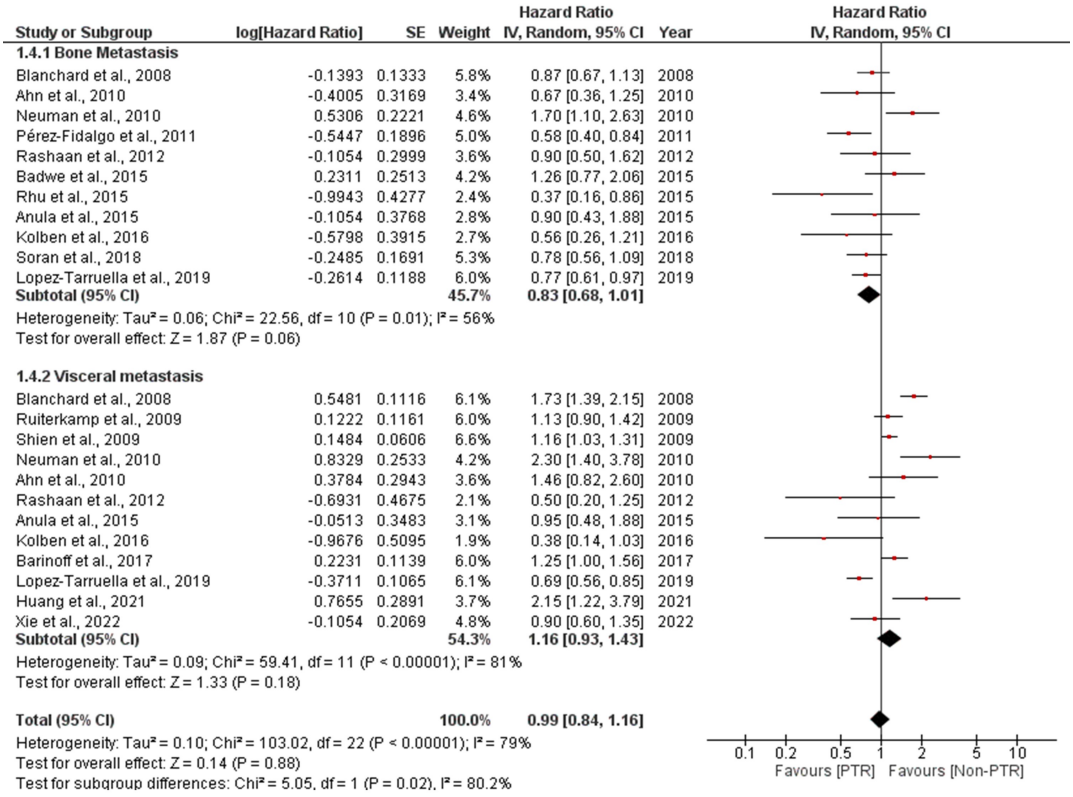

Figure 5. Forest plot comparing PTR with non-PTR patients with stage IV breast cancer for OS according to the type of metastasis. PTR: Primary tumor resection.

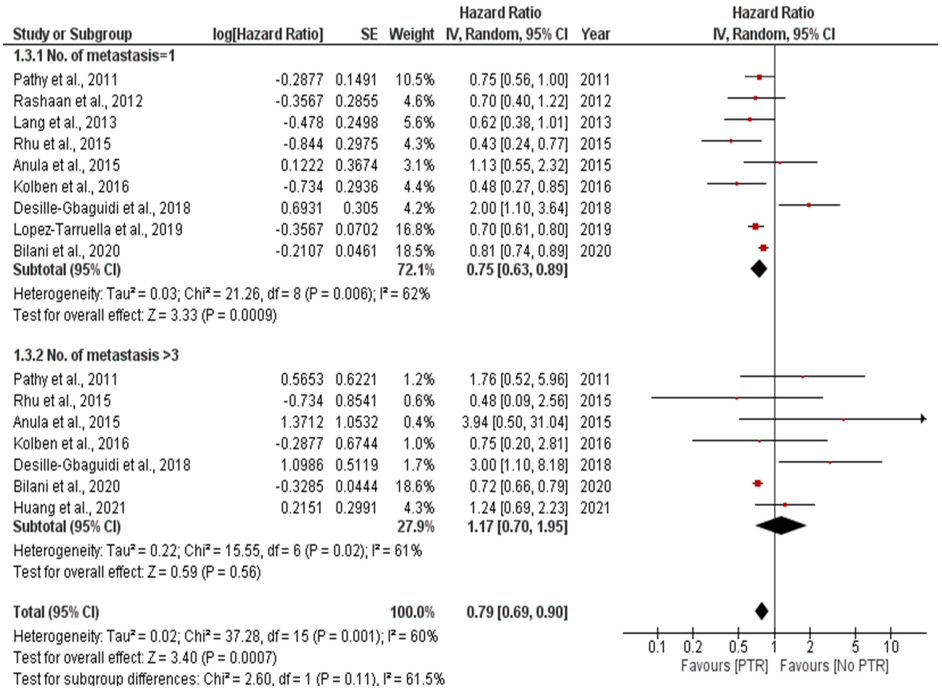

Figure 6. Forest plot for OS comparing PTR with non-PTR patients with stage IV breast cancer according to number of metastases. PTR: Primary tumor resection.

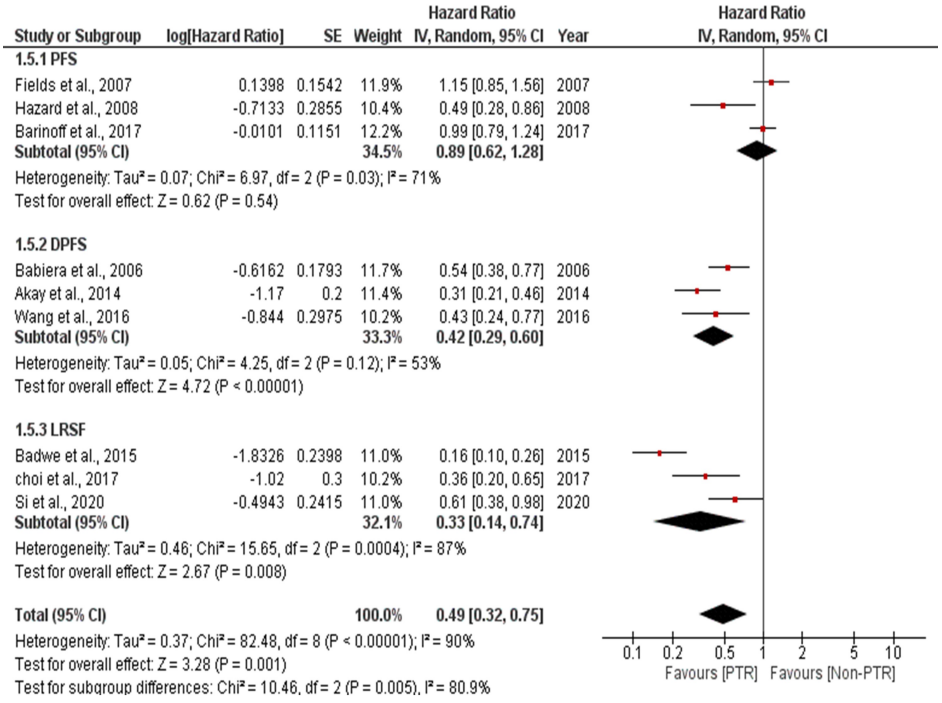

Figure 7. Forest plot comparing PTR with non-PTR patients with stage IV breast cancer for PFS, DPFS and LPFS. PTR: Primary tumor resection.

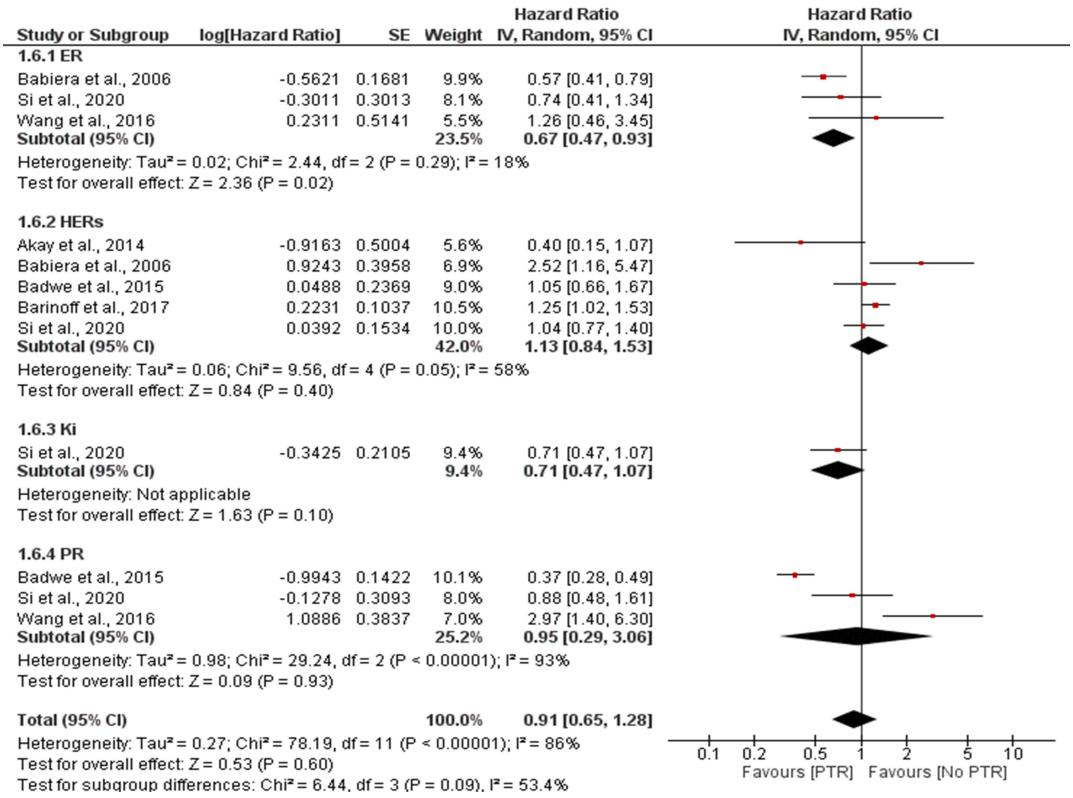

Figure 8. Forest plot comparing PTR with non-PTR patients with stage IV breast cancer for ER, HER2, Ki and PR. PTR: Primary tumor resection.

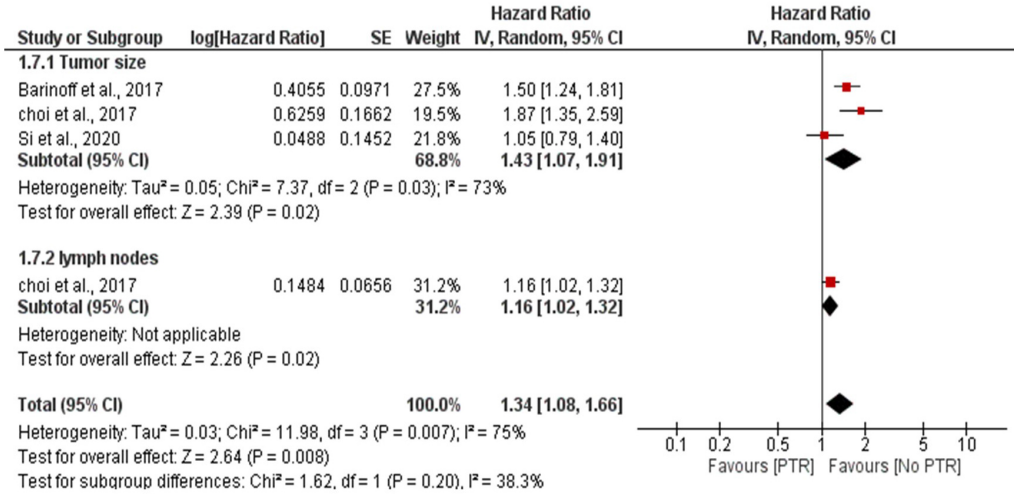

Figure 9. Forest plot comparing PTR with non-PTR patients with stage IV breast cancer for tumor size and lymph nodes. PTR: Primary tumor resection.

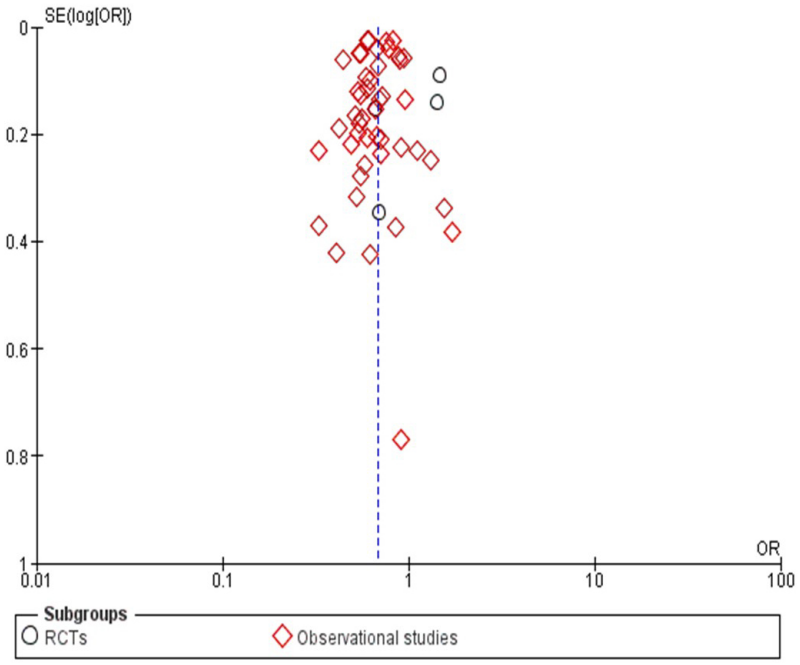

Figure 10. Publication bias funnel plot for the primary outcome. LogHR and HR ratio.

predicting the outcome of BC patients[79], as in the present study, HR values were higher than 1, which indicates high risk, and it did not favor PTR [Figure 9]

One of the most crucial prognostic markers predicting survival and recurrence in BC is the nodal status[80]. The likelihood of distant recurrences is directly correlated with the number of affected axillary lymph nodes[81]. In the present studies, HR ratios are different and subgroup analysis does not favor PTR. Unfortunately, the data needed from included studies regarding radical axillary surgery were not available, and we were unable to perform any analysis, even though this procedure ensures correct clinical staging and offers excellent local control with few side effects[82].

Limitations

Our meta-analysis had several limitations, notably the restriction to a small number of RCTs, possibly due to the unavailability of such trials. Secondly, some studies lacked comprehensive information about the type and timing of PTRs, hindering the provision of substantial evidence for their clinical application. For instance, only a small number of the 44 observational studies registered the exact timing of surgery, either prior to systemic therapy or after systemic therapy, so this variable was not included in the analysis. Thirdly, the length of follow-up and the treatment methods used in the studies varied considerably, and we included the information from multivariate and univariate analyses, depending on result availability. Last but not least, the research findings exhibit significant heterogeneity, making it challenging to comprehend the results and consequently apply suitable treatment options.

Evaluating patient selection criteria, the specific timing and type of PTR, and the diversity within treatment approaches could offer promising avenues for future research.

Such limitations underline the requirement for additional prospective research on applying PTR in metastatic settings.

CONCLUSIONS

Patients with stage IV BC usually should not undergo PTR. However, in some situations, PTR is feasible. The current findings prompt discussions about the inclusion of PTR in the treatment options offered to the patient and suggest a considerable advantage in removing the primary tumor for selected advanced MBC patients. Our findings also show that PTR may be useful in patients with mild disease load or those who can achieve clear margins. More research is needed to determine the molecular mechanism by which primary tumors affect the location and development of metastatic disease. Utilizing this information can assist in identifying patients who might most benefit from PTR.

The establishment of a standardized and multicentric data collection base is vital, which will enable researchers to draw reliable conclusions about the role of PTR in metastatic breast cancer settings.

DECLARATIONS

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Authors' contributions

Study conception and supervising: Sidiropoulou Z, Fonseca V

Systematic review; writing and revising: Sidiropoulou Z, Martins AR, Amaral P, Cardoso V, Boligo S, Fonseca V

Availability of data and materials

All of the included material and raw data are in possession of Sidiropoulou Z, Fonseca V.

Financial support and sponsorship

None.

Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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