European Journal of Surgical Oncology xxx (2018) 1–9

Contents lists available at ScienceDirect

European Journal of Surgical Oncology

journal homepage: www.ejso.com

Review

Primary tumor resection in stage IV breast cancer: A systematic review and meta-analysis

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ARTICLE INFO

Article history:
Accepted 1 August 2018
Available online xxx

Keywords:
Primary tumor resection
Stage IV breast cancer
Systematic review
Meta-analysis

ABSTRACT

Objective: The impact of primary tumor resection (PTR) on survival is still controversial in stage IV breast cancer. This systematic review and meta-analysis aimed to evaluate the impact of PTR on overall survival (OS) in stage IV breast cancer.

Methods: Comprehensive literature search was conducted to identify studies comparing PTR with no PTR for stage IV breast cancer. The quality of the studies was assessed using Cochrane risk of bias tool and Newcastle-Ottawa Scale. We used subgroup and meta-regression analysis to assess the contribution of demographic and clinical factors to heterogeneity.

Results: Data on 714 patients in 3 randomized controlled trials (RCTs) and 67,272 patients in 30 observational studies were included. One RCT was terminated early due to poor recruitment, and the remaining two RCTs' design were different, thus RCTs were only performed systematic review without meta-analysis. The pooled outcomes of 30 observational studies showed PTR significantly improved OS ($HR = 0.65$; 95%*CI*, 0.61 to 0.70, $P < 0.001$, $I^2 = 80\%$). Additionally, PTR was associated with better distant progression-free survival ($HR = 0.42$; 95%*CI*, 0.29 to 0.60) but did not impact progression-free survival. Subgroup analysis showed PTR benefit in patients who had only one metastatic site ($HR = 0.62$, 95%*CI*. 0.48 to 0.81), bone-only metastasis ($HR = 0.61$, 95%*CI*. 0.37 to 1.00), with negative margin ($HR = 0.61$, 95% *CI*. 0.58 to 0.65).

Conclusions: PTR should not be part of routine clinical practice in stage IV breast cancer but might be performed in selected patients. Our findings highlight PTR might be valuable in patients with limited disease burden or attaining clear margin.

Introduction

About 6% of female breast cancer patients have distant metastasis at the time of diagnosis [1]. Traditionally, stage IV breast cancer is considered an incurable disease and the goal of treatment is to prolong life and reduce or prevent symptoms [2]. The current practice guidelines for the role of breast surgery in stage IV disease from the European Society for Medical Oncology (ESMO) Guidelines and the National Comprehensive Cancer Network (NCCN) Guidelines recommended different points [3]. NCCN guidelines suggested that the benefit from palliative PTR was unclear and PTR should be considered only after response to initial systemic therapy. ESMO Guidelines suggested that the true value of PTR is currently unknown and recommended that it can be considered in selected patients. Advances in systemic treatment have significantly improved the control of metastases and prolonged survival. In this context, the role of PTR in survival has therefore become a question worth considering. In recent years, some observational studies have shown that 35%–60% of breast cancer patients with stage IV disease at diagnosis receive treatment of the primary tumor and that this treatment was associated with a survival advantage [2,4,5]. However, preliminary reports from the prospective studies of Badwe et al. [6] and Soran et al. [7] failed to confirm the survival benefit of patients with primary stage IV breast

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https://doi.org/10.1016/j.ejso.2018.08.002
0748-7983/

cancer undergoing surgical resection of primary tumors. Furthermore, some researchers worried that the removal of primary tumors may actually have an adverse effect on survival [8–10]. In animal models, it has been demonstrated that excision of primary tumors can stimulate metastatic growth [10,11]. Presumably, this is mediated by disruption of tumor cell dormancy or induction of angiogenesis in metastases. In the human body, surgery and general anesthesia may actually affect the immune response [12]. Retsky et al. [13] found that surgery on primary tumors accelerated the recurrence of premenopausal lymph node positive women.

Because of this ongoing controversy, widespread clinical practice variation, and considerable deficiencies in the existing literature, we sought to use quantitative meta-analysis techniques based on the PRISMA guidelines to determine whether PTR was associated with prolonged overall survival compared to no PTR.

Methods

Search strategy

Several sources for relevant original publications were searched via the PubMed, Embase, Cochrane, Web of science databases and www.clinicaltrials.gov on February 5, 2018. We used following words as the literature search terms: ('stage IV' or metastatic) and ('breast cancer') and ('primary surgery' or surgery or resection). In order to broaden the search, we manually checked references from relevant primary studies, abstracts from meetings and review articles. No language limitation was imposed. All the search strategies were conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [14].

Inclusion and exclusion criteria

Randomized controlled trials (RCTs) or observational studies regarding patients with de novo stage IV breast cancer comparing PTR ± systemic therapy with systemic therapy alone were included. Systemic therapy consisted of at least one of the following treatment: chemotherapy, radiotherapy (any site), hormonal therapy and targeted therapy. Abstracts-only studies were also included if they met the selection criteria. Studies with less than 40 patients were excluded due to poor reliability. Exclusion criteria were case reports, letters, commentaries, review and meta-analyses, not comparison surgery with no surgery, not de novo stage IV breast cancer, not PTR, insufficient data for analysis, no comparison groups, preclinical experiment. Additionally, we chose the most recent study with the largest sample size if studies come from the same database (e.g. Surveillance, Epidemiology, and End Results database) with a cross time period.

Study selection

All the title and abstract citations were inspected by two authors (WKX and YTZ) independently with conflicts consulted by a third reviewer (SQZ). Criteria of selection were applied by reviewers after screening the potentially included studies. Duplicates were eliminated using Endnote X8 or manually.

Data extraction

Two reviewers independently recorded the following information from each study: authors, year of publication, database, years of inclusion, mean age, country and median follow-up. Primary outcome was overall survival (OS) reported as hazard ratios (*HRs*) according to multivariate analysis while secondary outcome was 2/3/5-year survival rate, progression-free survival (PFS), distant progression-free survival (DPFS) and locoregional progression-free survival (LPFS). PFS was defined as the interval between start of systemic/surgical therapy and disease progression, either local or distant. DPFS and LPFS were defined as the time from the start of systemic/surgical therapy to locoregional progression or distant progression respectively. All the above survival were also censored at point died of any cause. Besides, we extracted the *HRs* and 95% confidence interval (*CI*) from the studies only presented Kaplan-Meier (KM) survival curves through the method provided by Guyot et al. [15] We also collected the number of patient in both group based on following items: T status, N status, grade, ER: estrogen receptor status, PR: progesterone receptor status, HER2: human epidermal growth factor receptor 2 status, number of metastatic sites, sites of metastases, bone-only metastases, comorbidity, radiotherapy, hormonal therapy and targeted therapy. We used the odds ratio (*OR*) and 95% confidence interval (*CI*) to describe above information.

Methodology quality assessment

The quality of each RCT and observational study was assessed by using the Cochrane risk of bias tool [16] and the Newcastle-Ottawa Scale (NOS) respectively. Cochrane risk of bias tool expressed risk of bias as low, high, or unclear risk including the aspects of selection, performance, detection, attrition, reporting and other bias. As for NOS, a maximum of nine points was assigned to each research and the aspects including selection, comparability, and outcomes. Observational studies which scored 0–4 were defined as low-quality evidence while scored 5–9 was defined as high-quality evidence. Two reviewers made the assessment with disagreements consulted by a third reviewer. All RCTs and observational studies were scored and recorded.

Data synthesis and analysis

HRs, *ORs* and 95% *CI* for each of comparisons in the studies were extracted and pooled using the random-effects model in Review Manager (version 5.3; Cochrane Collaboration [http://www.cochrane.org]). A *HR* of less than one indicated a survival benefit favoring primary surgery. Study heterogeneity was estimated through Cochran's Q test which reported with a χ^2 value and *P* value. Heterogeneity was considered if $P < 0.1$. Another form of *Q* test, I^2 statistic ($I^2=(Q-df)/Q$), was also used with values over 50% suggesting high heterogeneity. Additionally, we inspected the funnel plots and used Begg's test [16] to assess publication bias. In order to address the possible sources of heterogeneity and figure out potential subsets of patients, we conducted subgroup analysis. Sensitivity analyses were done by omitting every study one-by-one from the meta-analysis so as to determine the influence of individual study exerting on the combined result. Begg's test and meta-regression were performed with Stata 12.0 (Stata Corp, College Station, Tex).

Results

Overall, search strategy identified 27,797 articles. PRISMA flow diagram depicts the process of study selection (Supplemental Fig. 1). A total of 3 RCTs and 30 observational studies, including 67,986 patients that met the established study criteria, were included in this study. Among them, three RCTs [6,17,53] were only included in the systematic review but not in the meta-analysis because one [17] was stopped early due to poor recruitment while the remaining two RCTs [6,53] were not the same design. 30 observational studies [2,5,18–45] reporting data from 67,272 patients were included in the final comprehensive meta-analysis. Main baseline characteristics of the included studies are revealed in detail (Supplemental Table 1). Totally, 30,969 patients (45.6%)

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underwent PTR ± systemic therapy, and 36,927 patients (54.4%) received systemic therapy alone. In addition, the excluded study (repeated database) by Akay et al. [46] was included in the synthesis of DPFS (distant progression-free survival) because the other study from the same database did not report. Methodology quality of included studies was evaluated in both RCTs and observational studies. For RCTs (Supplemental Fig. 2a) and 2 studies reported complete outcome data. 3 studies reported random sequence generation, selective reporting and allocation concealment. None of the study reported blinding of the participants and personnel, the same was to blinding of the outcome assessment (Supplemental Table 2). As for observational studies (Supplemental Fig. 2b), overall bias risk is moderate due to unclear or high risk of bias in adequacy of follow-up and comparability of cohorts on the basis of the design or analysis. According to NOS, 2 studies scored 3 points, 13 studies scored 4 points, 12 studies scored 5 points, 3 studies scored 6 points (Supplemental Table 3).

Symmetrical funnel plots (Supplemental Fig. 3) and Begg's test ($P = 0.602$) indicate little publication bias existence in this meta-analysis for OS among observational studies and RCTs respectively.

Baseline characteristics

Of all reported patients, 67,457 patients (99.4%) were female and 439 patients (0.6%) were male. Data for the mean age were available for 54,653 patients but the standard deviation (SD) was only showed in nine studies. Patients who underwent PTR were slightly younger than patients who did not (mean age 58.5 vs 60.8 years). Patients in PTR group tended to have lower T status than those who did not have surgical intervention: 55% of patients in surgical group had a T2 or lower tumor compared with 47% in systematic treatment group. A slight difference was found in proportion of N0-2 stage in PTR group and no PTR group with 84% and 83% respectively. The grade of tumor was lower in no PTR: 50% of patients in PTR group had low & moderate tumor while 61% in no PTR group. Estrogen receptor positive rate was lower in PTR group (70% PTR, 77% no PTR). 57% of the PTR group was progesterone receptor positive compared with 63% of the no PTR group. HER2 positive tumor was more often in PTR group (52%) compared with no PTR group (36%). Patients with only 1 metastatic site were more likely to undergo PTR (59%) compared with no PTR group (42%). Visceral metastases were more often in no PTR group (52%) than PTR group (48%). 16% of the PTR group was bone-only metastases compared with 15% of the no PTR group. Morbidities were similar for both two groups (Table 1).

Treatment differences

Patients in the surgical group were more likely to undergo neoadjuvant or adjuvant radiotherapy (*OR* = 3.25, *95% CI*. 2.31 to 4.57; $P < 0.001$; $I^2 = 96\%$). However, no significant differences between PTR group and non-PTR group were identified regarding the hormonal therapy and targeted therapy (Table 1).

Surgery details

Information about type of resection was recorded in 22 studies for 24,445 patients. 67% underwent a mastectomy and 33% were performed with a breast conserving surgery. The management of axillary lymph node was reported in 12 studies representing for 3385 patients. The majority of the patients underwent axillary lymph node dissection (79%) while others had a sentinel node biopsy (11%) or did not perform axillary lymph node dissection (10%). Indication of the surgery was available in 4 studies for 485 patients: 26% for establishment of diagnosis, 22% for a definitive treatment, 43% for a palliative therapy and 9% for other reasons.

Survival

OS was indicated as univariate *HRs* in 6 studies [23–25,29,30,32] extracted from KM survival curves, and multivariate heterogeneously for age, T status, N status, ER, PR, metastatic site, visceral metastases and other factors in 27 studies. All studies were published after 2000.

Comparing PTR group with no PTR group, three RCTs reported different survival outcomes. No benefit was found in Badwe et al.'s [6] study (350 patients) which included patients who responded to chemotherapy and underwent PTR subsequently (*HR* = 1.04, 95% *CI*. 0.81 to 1.34). Trial by Fizal [17] et al. enrolled 90 patients from 15 centers but was stopped early due to poor recruitment. The prognosis of patients in the surgical group had a worse trend, but the results were not statistically significant (*HR* = 1.45, 95% *CI*. 0.74 to 2.82). In Soran et al.'s [53] MF07-01 trial (274 patients), PTR was done prior to systemic therapy which showed a significant benefit after 40 months follow-up (*HR* = 0.66, 95% *CI*. 0.49 to 0.89). Details of three RCTs was showed as follows (Supplemental Table 4).

Pooled analyses for 30 observational studies revealed a great improvement in overall survival after resection of the primary tumor with a high level of heterogeneity (*HR* = 0.65, 95% *CI*. 0.61 to 0.70; $P < 0.001$; $I^2 = 80\%$) (Fig. 1). Sensitivity analyses showed PTR benefit in patients who had only one metastatic site [26,30,36,37] (*HR* = 0.62, 95% *CI*. 0.48 to 0.81; $P < 0.001$), bone-only metastatic [30,36,37] (*HR* = 0.61, 95% *CI*. 0.37 to 1.00; $P = 0.05$), with negative margin [20,21,26] (*HR* = 0.61, 95% *CI*. 0.58 to 0.65; $P < 0.001$), hormone-receptor positive [30,36] (*HR* = 0.65, 95% *CI*. 0.61 to 0.70; $P = 0.01$) and hormone-receptor negative [30,36] (*HR* = 0.54, 95% *CI*. 0.32 to 0.92; $P = 0.02$) (Fig. 2). No significant difference was found in visceral-only metastatic [30,36] (*HR* = 0.58, 95% *CI*. 0.28 to 1.20; $P = 0.14$), with positive margin [20,21,26] (*HR* = 0.84, 95% *CI*. 0.67 to 1.05; $P = 0.13$) and at least 3 metastatic site [26,30,37](*HR* = 0.98, 95% *CI*. 0.44 to 2.15; $P = 0.95$) patients between PTR and no PTR group (Table 2). The benefit of surgery was consistent among studies with at least 2 and 3 years of follow up period. Leaving of low quality studies resulted in a significant decrease of heterogeneity in the remaining studies (*HR* = 0.60, 95% *CI*. 0.55 to 0.64; $P < 0.001$; $I^2 = 33\%$). When regarding the order of surgery and systematic therapy, it had adverse outcomes to RCTs. Surgery before systematic therapy group failed to achieve the significant benefit compared with systematic therapy alone group (*HR* = 0.79, 95% *CI*. 0.57 to 1.10; $P = 0.16$; $I^2 = 94\%$). Only one study demonstrated the result comparing surgery after systematic therapy group to systematic therapy alone group, showing a 44% decrease in mortality (*HR* = 0.56, 95% *CI*. 0.52 to 0.61; $P < 0.001$) (Table 2). Subgroup analysis was also conducted (Table 3). Overall survival was improved better comparing high quality studies with low quality studies in subgroup analysis ($P = 0.007$). No significant difference was showed in multicenter/single-center subgroup ($P = 0.20$) and large/small sample size subgroup ($P = 0.36$). Difference was found in three published periods ($P = 0.01$) but not in three races ($P = 0.53$). Both univariate analyses and multivariate analyses provided significant evidence of improved survival in PTR group (unadjusted analysis: *HR* = 0.57, 95% *CI*. 0.50 to 0.64; $P < 0.001$; $I^2 = 32\%$; adjusted analysis: *HR* = 0.67, 95% *CI*. 0.62 to 0.70; $P < 0.001$; $I^2 = 80\%$).

Only three studies [31,42,45] reported progression-free survival (PFS), three [22,43,46] for distant progression-free survival (DPFS) and one [40] for locoregional progression-free survival (LPFS) which were also synthesis although a high level of heterogeneity was presented (Fig. 3).

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Table 1
The difference of tumor and treatment characteristics comparing PTR and no PTR in patients with stage IV breast cancer.

	PTR group	non-PTR group	No. of studies	No. of patients	Odds ratio/Weighted Mean Difference (95% CI)	*p*	I^2 (%)
Mean age (years)	58.5	60.8	27	54,653	−1.37 (−4.02, 1.29)	0.31	87
T status							
T0-2	55%	47%	19	54,107	1.64 (1.22, 2.20)	0.001	98
T3-4	45%	53%			1 [Reference]		
N status							
N0-2	84%	83%	9	33,906	1.37 (1.01, 1.84)	0.04	91
N3	16%	17%			1 [Reference]		
Grade							
Low & Moderate	50%	61%	8	3284	0.58 (0.46, 0.73)	<0.001	34
High	50%	39%			1 [Reference]		
ER status							
Positive	70%	77%	17	38,159	0.86 (0.71, 1.04)	0.12	84
Negative	30%	23%			1 [Reference]		
PR status							
Positive	57%	63%	16	38,093	0.97 (0.80, 1.18)	0.77	87
Negative	43%	37%			1 [Reference]		
HER2 status							
Positive	52%	36%	17	5046	1.08 (0.83, 1.40)	0.80	64
Negative	48%	64%			1 [Reference]		
Metastatic site							
1	59%	42%	12	3363	2.63 (2.03, 3.41)	<0.001	54
> 1	41%	58%			1 [Reference]		
Visceral metastases							
Yes	52%	48%	14	4101	0.74 (0.57, 0.95)	0.02	69
No	48%	52%			1 [Reference]		
Bone-only metastases							
Yes	16%	15%	10	40,235	1.29 (1.03, 1.60)	0.03	82
No	84%	85%			1 [Reference]		
Comorbidity							
Yes	16%	16%	4	25,360	0.89 (0.64, 1.24)	0.49	94
No	84%	84%			1 [Reference]		
Hormonal therapy							
Yes	27%	41%	13	41,383	1.19 (0.66, 2.15)	0.56	99
No	73%	59%			1 [Reference]		
Targeted therapy							
Yes	15%	25%	5	1508	0.76 (0.34, 1.66)	0.49	69
No	85%	75%			1 [Reference]		
Radiotherapy							
Yes	49%	30%	16	41,556	3.25 (2.31, 4.57)	<0.001	96
No	51%	70%			1 [Reference]		

Abbreviations: PTR, primary tumor resection; No., number.

Mortality

2- and 3-year overall survival rate was reported in 3 RCTs and 24 observational studies. 5-year overall survival rate was reported in 2 RCT and 24 observational studies.

Pooled analysis of observational studies manifested an increase of 2-, 3-, 5-year overall survival rate in PTR group (PTR vs no PTR, 2-year survival *OR* = 2.00, 95% *CI*. 1.80 to 2.23; 3-year survival *OR* = 1.97, 95% *CI*. 1.75 to 2.21; 5-year survival *OR* = 2.32, 95% *CI*. 2.01 to 2.67). (Supplemental Figs. 4, 5, 6).

Meta-regression analysis

Given that the overall heterogeneity was significant, the heterogeneity contribution of median age, publication year, pathological grade, quality score, and the proportion of early T stage, early N stage, mastectomy, ER-positive, HER2-positive, median follow-up time, bone-only metastasis, multiple visceral metastases were analyzed by meta regression analysis (Supplemental Fig. 7). Contribution estimates for different study characteristics were computed. The quality scores showed a significant contribution to overall heterogeneity (R^2 = 34.95%, τ^2 = 0.01893, $P < 0.05$) (Supplemental Fig. 8). Other characteristics shows a trend but it is not statistically significant (all $P > 0.05$) and it showed no significant contribution of these characteristics to overall heterogeneity level, as the heterogeneity proportion was between 19.85% and 12.62% and the remaining heterogeneity (τ^2) ranged from 0.0233 to 0.0598.

Discussion

The main findings of this systematic review and meta-analysis about the role of PTR in patients with stage IV breast cancer are as follows. First, there are currently three RCTs on the prognostic role of PTR in stage IV breast cancer. One RCT [17] stopped early due to poor recruitment, and the remaining two RCTs [6,53] came to inconsistent conclusions due to design inconsistencies. The RCT of Badwe et al. [6] found that PTR did not improve survival for patients who have responded to front-line chemotherapy. In contrast, in the MF07-01 trial [53], patients were given PTR prior systemic therapy and found a statistically significant improvement in median survival in patients undergoing primary tumor resection. Second, in observational studies, non-randomized use of PTR significantly improved the OS, but with high level of heterogeneity between studies. In addition, PTR was associated with better distant progression-free survival (*HR* = 0.42; 95%*CI*, 0.29 to 0.60, $P < 0.001$, I^2 = 53%) but did not impact progression-free survival. Subgroup analysis showed PTR benefit in patients who had only one metastatic site (*HR* = 0.62, 95% *CI*. 0.48 to 0.81; $P < 0.001$), bone-only metastatic (*HR* = 0.61, 95% *CI*. 0.37 to 1.00; $P = 0.05$), with negative margin (*HR* = 0.61, 95% *CI*. 0.58 to 0.65; $P < 0.001$), but not in patients with positive margin or more than 3 metastases.

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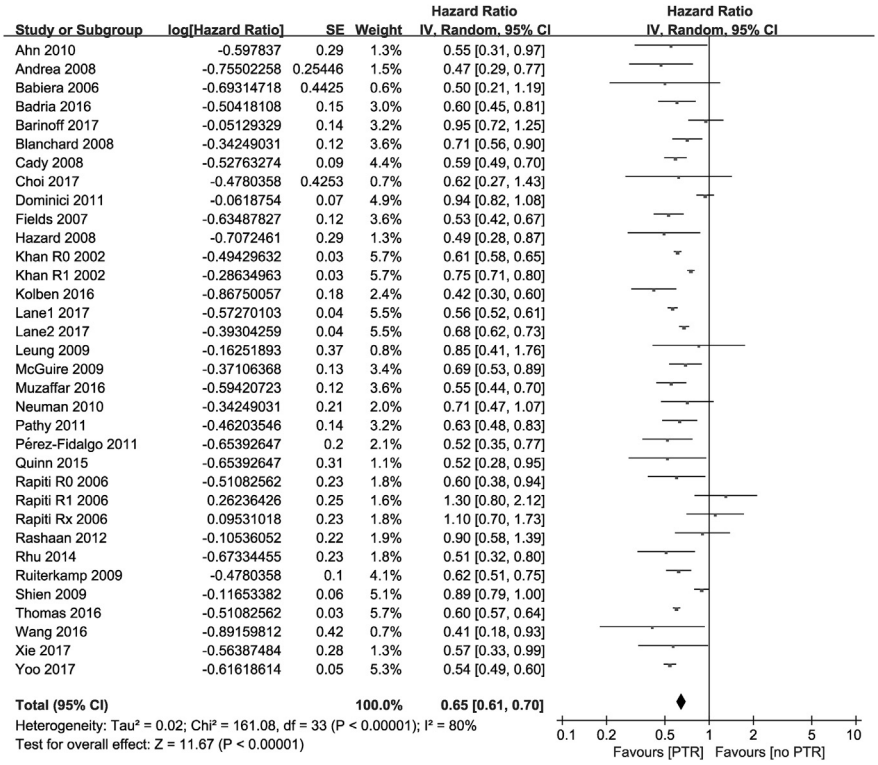

Fig. 1. Forest plot comparing PTR with no PTR in patients with stage IV breast cancer for OS among observational studies; Abbreviations: OS, overall survival; PTR, primary tumor resection; R0, patients with negative margin; R1, patients with positive margin; Rx, patients with unknown margin; Lane 1, surgery following systemic therapy; Lane 2, surgery prior to systemic therapy.

When we searched for other relevant meta-analyses on the topic on PubMed on February 5, 2018, we found that there are 3 meta-analysis on this topic to date. Petrelli et al. [47] reported that the first meta-analysis compared survival outcomes in patients with stage IV breast cancer who received PTR or no PTR. They analyzed 15 observational studies and found that PTR provided survival benefits for stage IV breast cancer patients ($HR = 0.69$; 95% *CI*. 0.63 to 0.77; $P < 0.001$). Harris et al. [48]investigated the survival outcome of PTR compared to system treatments alone in stage IV breast cancer patients. They revealed a significantly higher 3-year survival rates PTR compared to system treatments alone by analyzing 10 observational studies involving 28,693 patients ($OR = 2.32$; 95%*CI*. 2.08 to 2.6; $P < 0.01$). Headon et al. [49] performed the third meta-analysis including 16 observational studies comparing PTR and system treatment alone in stage IV breast cancer patients. They also showed a survival benefit for PTR compared to system treatment alone in stage IV breast cancer patients ($HR = 0.60$; 95%*CI*. 0.51–0.69; $P < 0.001$). These three meta-analyses included only observational studies and concluded that the survival rate of stage IV patients undergoing PTR was significantly higher than system treatment alone. However, our study is very different from these three previous meta-analyses. First, we included three RCTs that were less biased than observational studies and found discrepancies between the results of RCTs and that of observational data. Second, our comparative analysis was the largest, comprising data from 3 RCTs and 30 observational studies with a total of 67,896 patients. Thirdly, we conducted a detailed subgroup analysis and found that PTR might be valuable in patients with limited disease burden or attaining clear margin, but not in patients with positive margin or more than 3 metastases.

Although RCTs seem to outperform observational studies because they eliminate selection bias, RCTs may have some limitations as well, and these limits must be carefully evaluated when evaluating RCT results. Fitzal's [17] RCT included a total of 90 patients in 15 centers to evaluate the survival difference between sequential surgical sequential and systemic treatment in newly diagnosed stage IV breast cancer. The median OS of the two groups was 34.6 and 54.8 months, respectively. The prognosis of patients in the surgical group had a worse trend, but the results were not statistically significant ($HR = 1.45$, $P = 0.267$). The study also compared the quality of life of the two groups of patients. The results showed that removal of the primary lesion failed to improve quality of life in the patient, and the symptoms of insomnia, breast and arm reported 6 months after surgery were higher than those in the non-PTR group. However, these differences in quality of life will disappear during long-term follow-up. Due to poor recruitment, the trial was stopped early, and the study was only systematically reviewed and not included in the final meta-analysis. Soran et al. [53]'s MF07-01 trial is another prospective RCT to evaluate the impact of primary surgery on the overall survival of newly diagnosed stage IV breast cancer. In the experimental design, one group received surgical resection of the primary tumor followed by sequential system therapy; the other group received only systemic therapy. Among the 274 patients that could be evaluated, the results showed that OS was significantly longer in the patients who received surgery followed by chemotherapy ($HR = 0.66$, $P = 0.005$). Subgroup analysis showed that patients with isolated bone metastases, age <55 years, ER/PR+ and HER2-patients had significant survival benefits. This study shows the therapeutic value of local surgical resection of stage IV breast cancer. It also suggests that factors such as metastatic site and tumor burden should be fully considered. Badwe et al. [6] randomly assigned 350 patients with objective remission to the surgical treatment group (n = 173) and non-surgical treatment group (n = 177). The median follow-up time was 23 months. There was no significant difference in median OS time between the two groups (19.2 months vs. 20.5

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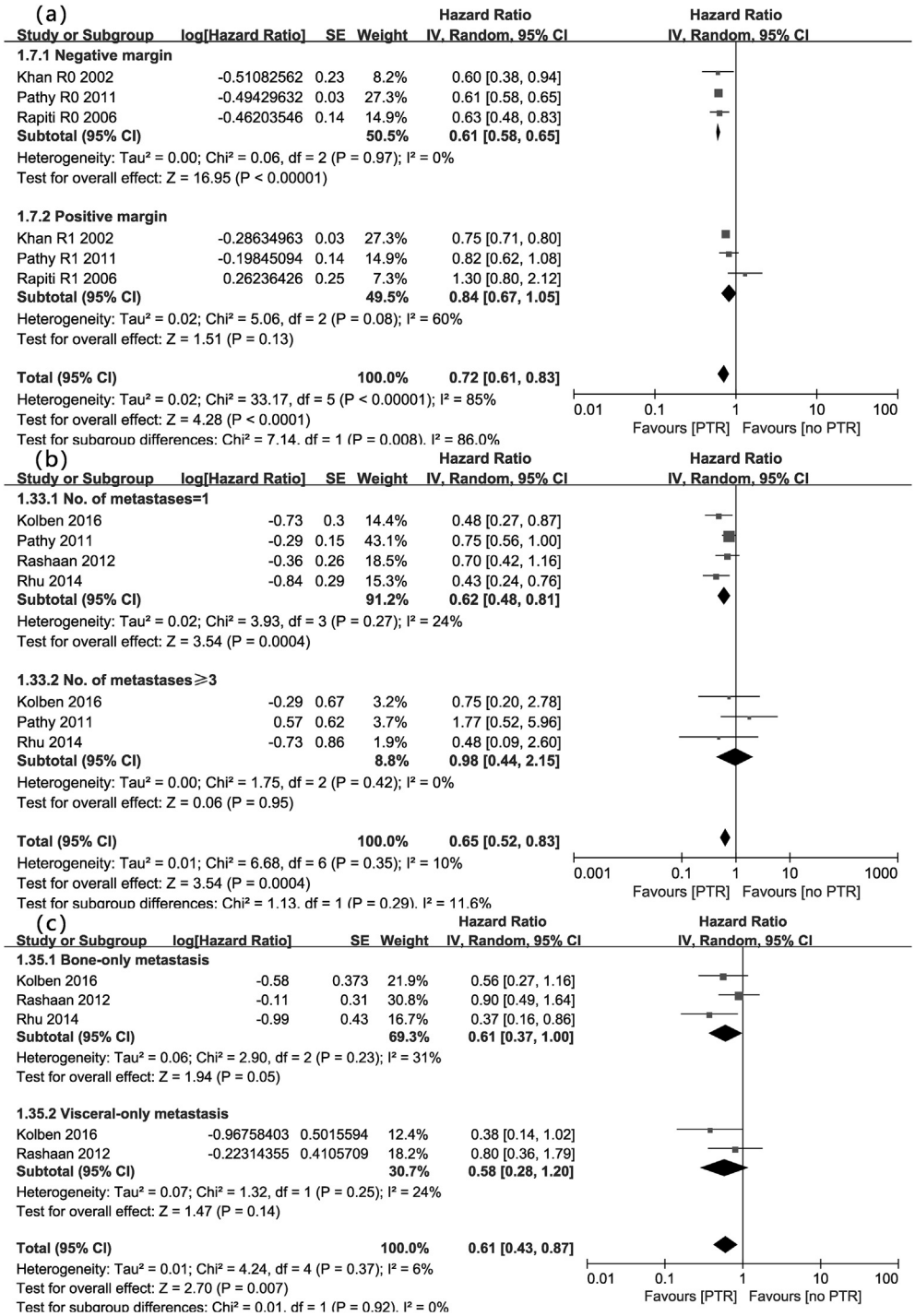

Fig. 2. Forest plot for OS comparing PTR with no PTR in patients with stage IV breast cancer according to margin status (**a**), No. of metastases (**b**) and bone/visceral-only metastasis (**c**); Abbreviations: OS, overall survival; PTR, primary tumor resection; No., number; R0, patients with negative margin; R1, patients with positive margin.

months), suggesting that surgery did not improve survival. However, this RCT has some limitations: First, most patients have clinical symptoms when they are diagnosed, which means a more severe disease burden. Second, 31% of patients were HER2 positive, however, only 15% received targeted therapy. In particular, none of the HER2-positive patients in the locoregional treatment group received targeted therapy. Third, only some patients received paclitaxel-based chemotherapy. These factors led to only about 20 months of median OS in both groups, which are lower than those of developed countries.

At present, the optimal timing of surgery is controversial, although according to the theory of metastasis and tumor biology, patients are more likely to benefit from early surgery. Because, first, the primary tumor is the source of new metastases; second, primary tumor resection may enhance the sensitivity of distant metastases to chemotherapy; third, systemic therapy may be more effective after tumor burden reduction, because surgery can remove necrotic and non-vascularized tumors areas which drug cannot reach. The RCT of Badwe et al. [6] found that PTR did not improve survival for patients who have responded to front-line

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Table 2
Summary of sensitivity analysis for OS comparing PTR and no PTR in patients with stage IV breast cancer.

	No. of studies	No. of patients	Hazard ratios	p	I^2 (%)
RCTs					
Trials with ≥ 3 y of follow- up [53]	1	274	0.66 (0.49, 0.89)	0.006	/
Surgery after responding to chemotherapy [6]	1	350	1.04 (0.81, 1.34)	0.79	/
Observational studies					
Overall	30	67,272	0.65 (0.61, 0.70)	<0.001	80
Studies with ≥ 2 y of follow- up	19	31,315	0.61 (0.54, 0.68)	<0.001	81
Studies with ≥ 3 y of follow- up	10	29,374	0.62 (0.55, 0.71)	<0.001	83
Studies with ≥ 4 y of follow- up	2	848	0.56 (0.48, 0.64)	<0.001	0
Hormone-receptor positive	2	NA	0.65 (0.47, 0.91)	0.01	0
Hormone-receptor negative	2	NA	0.54 (0.32, 0.92)	0.02	0
No. of metastases = 1	4	NA	0.62 (0.48, 0.81)	<0.001	24
No. of metastases ≥ 3	3	NA	0.98 (0.44, 2.15)	0.95	0
Bone-only metastases	3	NA	0.61 (0.37, 1.00)	0.05	31
Visceral-only metastasis	2	NA	0.58 (0.28, 1.20)	0.14	24
Negative margin	3	8379	0.61 (0.58, 0.65)	<0.001	0
Positive margin	3	7544	0.84 (0.67, 1.05)	0.13	60
Surgery prior to systemic therapy	2	18,608	0.79 (0.57, 1.10)	0.16	94
Surgery following systemic therapy	1	19,463	0.56 (0.52, 0.61)	<0.001	/

Abbreviations: OS, overall survival; PTR, primary tumor resection; NA, not available.

Table 3
Summary of subgroup analysis for OS comparing PTR and no PTR in patients with stage IV breast cancer.

	No. of studies	No. of patients	Hazard ratios (95% CI)	P (Subgroup)	P	I^2 (%)
RCTs						
Surgery prior to systemic therapy [53]	1	274	0.66 (0.49, 0.89)	0.02	0.006	/
Surgery following systemic therapy [6]	1	350	1.04 (0.81, 1.34)		0.79	/
Observational studies						
Overall	30	67,272	0.65 (0.61, 0.70)		<0.001	80
Studies with 3-year survival rate < 30%	5	8872	0.76 (0.62, 0.93)	0.11	0.009	66
Studies with 3-year survival rate ≥ 30% and < 50%	16	6201	0.62 (0.54, 0.72)		<0.001	79
Studies with 3-year survival rate ≥ 50%	4	26,566	0.59 (0.52, 0.66)		<0.001	75
Studies with ≥ 1000 patients	4	58.676	0.62 (0.56, 0.68)	0.36	<0.001	91
Studies with < 1000 patients	26	8596	0.66 (0.60, 0.74)		<0.001	68
High quality study	15	30,163	0.60 (0.55, 0.64)	0.007	<0.001	33
Low quality study	15	37,109	0.71 (0.64, 0.79)		<0.001	87
Multicenter	13	62,597	0.67 (0.62, 0.74)	0.20	<0.001	86
Single-center	17	4675	0.60 (0.52, 0.72)		<0.001	61
Published between 2002 and 2008	8	12,368	0.66 (0.58, 0.75)	0.01	<0.001	78
Published between 2009 and 2012	10	3484	0.75 (0.65, 0.86)		<0.001	62
Published between 2013 and 2017	12	51,420	0.59 (0.55, 0.64)		<0.001	63
Univariate analysis	6	3819	0.57 (0.50, 0.64)	0.02	<0.001	32
Multivariate analysis	24	63,453	0.67 (0.62, 0.70)		<0.001	80
American patients	22	60,354	0.64 (0.59, 0.70)	0.53	<0.001	83
Asian patients	10	4707	0.61 (0.50, 0.75)		<0.001	80
European patients	8	2211	0.74 (0.57, 0.95)		0.02	75

Abbreviations: OS, overall survival; PTR, primary tumor resection.

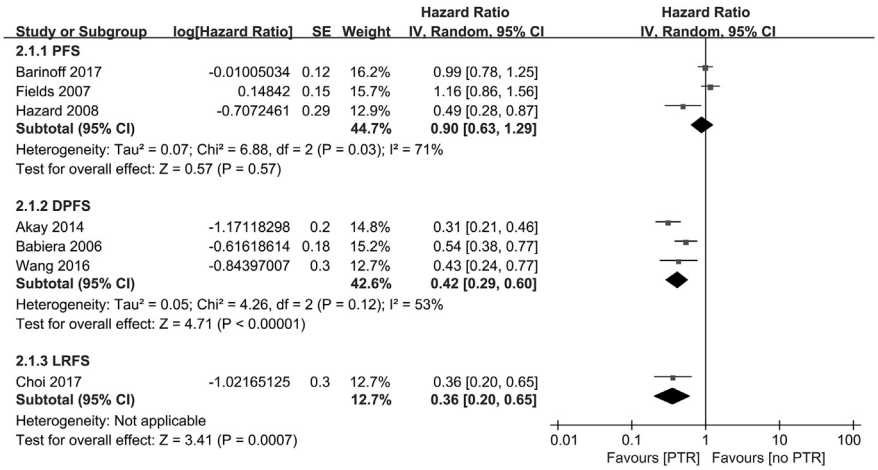

Fig. 3. Forest plot comparing PTR with no PTR in patients with stage IV breast cancer for PFS, DPFS and LPFS among observational studies; Abbreviations: PTR, primary tumor resection; PFS, progression-free survival; DPFS, distant progression-free survival; LPFS, locoregional progression-free survival.

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chemotherapy. In contrast, in the MF07-01 trial [53], patients were given PTR after surgical removal of the intact primary tumor and found a statistically significant improvement in median survival in patients undergoing primary tumor resection. Surgery prior systemic therapy includes all patients whom might and might not respond systemic therapy, but surgery following systemic therapy eliminates patients who had no respond to systemic therapy; this may be the group who gets benefit by resecting primary tumor. The results of these two RCTs suggest that the timing of surgery may affect the patient's prognosis. Therefore, it is expected to design a more complete RCT to explore whether surgery should be performed initially or after first-line chemotherapy.

It is expected that patients with better prognostic factors more likely to have underwent PTR. The current analysis also confirmed these doubts. Indeed, patients with smaller primary tumor volumes, single metastatic sites, or only bone metastases are more likely to undergo PTR. Interestingly, patients in the PTR group had a higher proportion of visceral metastases ($OR = 2.63$; 95%*CI*. 2.03 to 3.41; $P < 0.01$) than did the non-surgical group. However, there is no detailed information on specific metastatic sites in the original study despite that the prognosis of different metastatic sites is very different. For example, the prognosis of patients with brain metastases is worse than that of liver or lung metastasis [50]. In addition, the size and number of metastases may also lead to different prognosis, however, these data information are not provided in the original study. Finally, the PTR group received a higher proportion of adjuvant radiotherapy ($OR = 3.25$; 95%*CI*. 2.31 to 4.57; $P < 0.01$), which indicated that patients in the surgery group may have experienced more aggressive multimodal treatment (treatment bias). In fact, Le Scodan et al. [51] have reported that local radiotherapy of primary tumors is associated with improved survival in Stage IV breast cancer patients.

Stage IV breast cancer is actually a group of highly heterogeneous diseases. Theoretically, PTR is unlikely to improve the prognosis of all metastatic breast cancer. Therefore, identifying which patients are most likely to benefit from PTR is the most clinically interesting part. Modern systemic therapy with a remarkable response rate results in prolonged survival of patients with metastatic breast cancer. The 5-year cancer special survival of de novo breast cancer has been improved from 28% (1990–1998) to 55% (2005–2010) [52]. Therefore, local control may become more and more important in the management of patients with distant metastatic disease. Due to advances in surgical techniques and improved anesthesia and care, the effect of primary tumor resection on immune stress is gradually diminishing. Lane et al. [2] found that PTR occurred in almost half of women with stage IV breast cancer, especially after systemic treatment, based on a study based on a US population study.

We acknowledge that there are several limitations to the existing data and our analysis. First, there are limitations on the quality and quantity of RCTs included. This study included only three RCTs. Half of the observational studies were classified as low quality rather than high quality. Despite this, high-quality observational studies tend to report greater benefits. Second, some studies do not describe the type and timing of PTRs in sufficient detail to allow them to be applied in practice. For example, there were 30 observational studies but only 3 of them had explanations either surgery prior systemic therapy or surgery following systemic therapy. Third, the heterogeneity of the research results is very large. The most effective area for further research may be to assess the role of patient selection, the type and timing of PTR, to explain the heterogeneity of the treatment effect. Fourth, the smallest clinically important differences in these results have not been well defined, raising questions about the scale of clinical benefit. Fifth, there is a possibility of publication bias, although no statistical evidence is detected. Sixth, the follow-up time and survival heterogeneity between different studies have been shown to be significant. Distinction in patient age structure, tumor volume, sample size, type of surgery, tumor staging and grading, neo-adjuvant and adjuvant drug, and other factors in these studies may be responsible for the high degree of heterogeneity. The calculation of the overall rate estimate using a random effects model may minimize the heterogeneity, but this cannot be eliminated. Several other limitations are heterogeneous study cohorts (age and race), small sample size, use of different surgery types, effect of various systemic therapies, etc.

Conclusions

PTR should not be part of routine clinical practice in stage IV breast cancer but might be performed in selected patients. Our findings also highlight that PTR might be valuable in patients with limited disease burden or attaining clear margin. The results of a multicenter, large-scale RCT involving long-term follow-up of different subgroup patients are important for confirming the effect of PTR on the survival of patients with stage IV breast cancer and identifying the patients most likely to benefit from PTR.

Declarations of interest

None.

Acknowledgements

None.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ejso.2018.08.002.

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