

Do early HER2-overexpression breast cancer patients benefit from undergoing neoadjuvant trastuzumab and mastectomy? A meta-analysis

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Purpose: To assess the overall survival (OS) of early human epidermal growth factor receptor 2 (HER2)-enriched breast cancer patients after receiving neoadjuvant trastuzumab (NAT) compared to adjuvant trastuzumab (AT) treatment and the difference in local-regional relapse (LRR) rate with this tumor and treatment between women after mastectomy and women after breast-conserving therapy (BCT).

Methods: Articles were retrieved from PubMed, Embase, Web of Science, and Cochrane Library. A pooled odds ratio (OR) with a 95% confidential interval (CI) was calculated. The StataSE version 12.0 software was employed for meta-analysis.

Results: Twelve available clinical studies containing 2366 subjects were included. The OS of NAT compared with that of AT was not significantly different (pooled OR=1.04; 95% CI, 0.47–2.33). There was a significantly lower LRR rate for patients with mastectomy compared to those with BCT (pooled OR=0.58; 95% CI, 0.38–0.89); however, subgroup analysis revealed that the significant advantage of LRR for mastectomy compared to BCT was only represented in women without trastuzumab treatment (pooled OR=0.52; 95% CI, 0.31–0.88) compared to those who received trastuzumab treatment (pooled OR=0.71; 95% CI, 0.34–1.49).

Conclusion: Early stage HER2-overexpression breast cancer patients benefit with an equivalent OS from NAT treatment compared to AT. Patients who underwent mastectomy and BCT experienced a similar LRR rate if they received anti-HER2 targeted therapy of trastuzumab, but the LRR rate was discernibly reduced in patients who received mastectomy compared to BCT if they did not also receive trastuzumab treatment.

Keywords: human epidermal growth factor receptor 2, trastuzumab, mastectomy, breast conserving therapy, breast cancer

Introduction

Neoadjuvant systematic chemotherapy in breast cancer is a preoperative treatment, which is initially applied locally to advanced tumors to downgrade primary tumor and regional lymph nodes and enable their removal by operation. Currently, neoadjuvant chemotherapy is widely used in early resectable disease, mainly to allow breast-conserving therapy (BCT).^{1–3} Adjuvant chemotherapy is postoperative and attenuates breast cancer mortality by at least 15%.⁴ Many randomized clinical trials and meta-analyses confirm the equivalent overall survival (OS) of breast cancer women after receiving preoperative chemotherapy compared to those who undergo postoperative chemotherapy,^{5–9} however, these studies are imperfect, as they all failed to perform the subgroup analysis on different molecular subtypes of breast cancer.

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In the period before 1980, the modified radical mastectomy was the standard surgical method for breast cancer. In the early 1980s, two published randomized trials reformed this standard modality and confirmed that the survival benefits from BCT were equivalent to those of mastectomy.^{10,11} The Early Breast Cancer Trialists' Collaborative Group carried out a large-scale meta-analysis that further pooled the results from both randomized trials, finding the equality of OS and disease-free survival (DFS) between mastectomy and BCT.¹² Currently, instead of mastectomy, BCT has become the appropriate and preferred treatment for most early stage breast cancer patients,¹³ and it prevents the physical and psychological burden of sacrificing breast on women as much as possible.¹⁴

Human epidermal growth factor receptor 2 (HER2)-overexpression breast cancer accounts for approximately 15–25% of the primary breast tumors.¹⁵ Trastuzumab is currently indispensable for treating HER2-positive breast cancer. Prior to treatment with the anti-HER2 targeted drug, the local-regional recurrence (LRR) of this cancer molecular subtype is significantly greater than that of other phenotypes of disease, specifically Luminal A.¹⁶ Voduc et al¹⁶ found that the LRR rate of HER2-enriched breast cancer patients without trastuzumab treatment who underwent BCT and those who received trastuzumab was 21% and 17% at 10 years, respectively. After receiving trastuzumab, there is discernible reduction in the high LRR rate of HER2-positive breast tumors; a study from Debled et al¹⁷ showed that those women treated with BCT or mastectomy had a significantly reduced 4-year LRR rate of 2.9% or 0%, respectively. However, the LRR rates between these two surgical strategies in treating HER2-amplified breast carcinoma were not compared in these studies. Therefore, the aim of our article was to separately pool all clinical studies that concomitantly documented the OS outcomes of early HER2-overexpression breast cancer patients who received neoadjuvant trastuzumab (NAT) and adjuvant trastuzumab (AT) and that concurrently described the LRR rate of those women undergoing mastectomy and BCT. We aimed to identify the more applicable and preferably primary treatment strategy for this subtype of breast tumor. We included women treated with NAT or mastectomy as the study cohort and those with AT or BCT treatment as the control cohort.

Methods

Search strategy

Based on the PRISMA-IDP Statement,¹⁸ electronic searches were performed in PubMed, Embase, Web of Science, and

Cochrane Library using the following retrieval strategy: ((HER2 OR (Human epidermal growth factor receptor 2)) AND ((“Breast Neoplasms”[Mesh]) OR (Breast cancer) OR (Breast tumour) OR (Breast tumour) OR (Breast carcinoma) OR (Breast Neoplasm))) AND (((Neoadjuvant therapy) OR (Neoadjuvant treatment)) AND ((Adjuvant therapy) OR (Adjuvant treatment)) AND (Trastuzumab OR Herceptin) AND (Overall Survival)) OR (Mastectomy AND ((Breast conservation surgery) OR (Breast conserving surgery) OR (Breast preservative surgery) OR (Breast preservation surgery) OR (Breast preserving surgery) OR (Breast preservative surgery) OR (Breast conservation therapy) OR (Breast conserving therapy) OR (Breast preservative therapy) OR (Breast preservation therapy) OR (Breast preserving therapy) OR (Breast preservative therapy) OR (Breast conservation treatment) OR (Breast conserving treatment) OR (Breast preservative treatment) OR (Breast preservation treatment) OR (Breast preserving treatment) OR (Breast preservative treatment)) AND ((Local-regional relapse) OR (Local-regional recurrence) OR (Local relapse) OR (Local recurrence)))). No restrictions were required during the retrieval. The searching of citation was terminated as of 28th May 2019.

Inclusion criteria

- Early HER2-enriched breast cancer patients;
- English publications which covered the number or the rate of event and the total sample size;
- Clinical trials which concurrently documented the data of LRR after BCT and that after mastectomy or OS after NAT and that after AT. LRR referred to the first recurrence of tumor in the ipsilateral breast, the chest wall or regional lymphatics, without evidence of distant metastasis. The definition of BCT was a combination of radiotherapy and surgery strategy involving lumpectomy, segmental mastectomy, quadrantectomy, or wedge resection. The methods of mastectomy included simple mastectomy and modified radical mastectomy. OS ranged from the date of diagnosis to the date of death or loss to follow-up.

Exclusion criteria

- Trials published in non-English;
- Patients with moderate-to-advanced stage disease;
- Male patients;
- Reviews, case reports, and conference papers;
- Other details that did not meet the inclusion criteria.

Two co-authors (Qian Wu and Jing Xiong) independently screened the retrieved citations and reserved the pertinent studies according to the titles, abstracts, and full-text articles. If some disagreements surfaced, they were resolved by the third reviewer (Zhumin Su).

Data abstraction

The following information was abstracted using Microsoft Excel version 2016 (Microsoft Corporation, Redmond, Washington, USA) by two authors (Jing Xiong and Zhumin Su): first author, publication year, study duration, original nation, median age, median follow-up, whether patients received trastuzumab treatment, the number of patients undergoing BCT or mastectomy and how many of them developed LRR, and the number of women who received NAT or AT and how many died from either treatment paradigms. Provided that there were any inconsistencies, they were resolved by discussion.

Statistical analysis

The included clinical studies were discussed by their differences of eligible criteria, chemotherapy strategy, and implementation of radiotherapy, as well as the risk of bias of study evaluation using the new version of the Cochrane tool. The crude odds ratio (OR) with its 95% confidence interval (CI) of LRR with respect to mastectomy compared to BCT or OS regarding NAT versus AT in each trial was calculated and then pooled together. If the event number was not shown in the publication, it was computed based on the end point percentages of LRR and OS or other information. A heterogeneity χ^2 test with a significance level of $P < 0.1$ was used to estimate the heterogeneity among different studies;¹⁹ when it was not significant ($P > 0.1$), a fixed-effect Mantel-Haenszel model was utilized to pool the data, otherwise, a random-effect Mantel-Haenszel model was applied.¹⁹ The publication bias was assessed by creating a Begg's funnel plot with 95% CI and Egger's test with a significance level of $P < 0.05$. All statistical tests were performed in StataSE version 12.0 (Stata Corporation, College Station, TX, USA).

Results

Search results

After systematic retrieval in the databases described earlier, 3078 citations were obtained. After deleting the duplicates ($n=903$), citations categorized as reviews ($n=244$), conference papers ($n=702$), and case reports ($n=34$), 1195 records

were remained for the title and abstract screening. An additional 1139 citations were removed by this step, and 56 articles qualified for full-text article assessment; we excluded the nonmatched documents that were reviews ($n=8$) or covered non-HER2-overexpression breast tumors ($n=9$) as well as those with no valid control cohort ($n=12$) or no prognosis ($n=15$). Ultimately, 12 satisfactory studies^{16,17,20–23} were involved in the meta-analysis. The PRISMA flow diagram of selecting qualified clinical trials is outlined in Figure 1.

Characteristics of included studies

The original nations of the included articles were USA ($n=2$), France ($n=1$), Canada ($n=3$), the Netherlands ($n=1$), Spain ($n=1$), the UK ($n=1$), India ($n=1$), China ($n=1$), and Japan ($n=1$). The sample size ranged from 43 to 748 (median: 81.5), with a total number of 2366 subjects. The year range of included studies was 2008 to 2018. The other details including study duration, whether trastuzumab was received or absent, chemotherapy strategy, and which cohort (study cohort or control cohort) received radiotherapy are presented in Table 1.

Meta-analysis results

Four eligible trials with 960 subjects were included to analyze the OS between NAT and AT. As shown in Figure 2, the pooled data indicated that there was no significant difference in the OS of HER2-overexpressing breast tumors after receiving NAT compared to AT (pooled OR=1.04; 95% CI, 0.47–2.33).

There were 8 valid studies with 1406 patients who were collected to investigate the comparison of the LRR rate between mastectomy and BCT in treating HER2-amplified breast cancer. The data analysis suggested that women with this tumor undergoing mastectomy benefited from a lower LRR rate than those in the treatment of BCT (pooled OR=0.58; 95% CI, 0.38–0.89) (Figure 3A). We further divided the included trials into subgroups based upon whether trastuzumab administration to patients was documented. Interestingly, the subgroup with absent trastuzumab still showed a lower LRR rate with mastectomy than with BCT (pooled OR=0.52; 95% CI, 0.31–0.88), while the LRR rate between these two surgical interventions was not significantly different in the subgroup that received trastuzumab (pooled OR=0.71; 95% CI, 0.34–1.49) (Figure 3B).

Risk of bias in analyzed studies

All included trials referencing the OS of NAT versus AT and the LRR of mastectomy versus BCT were combined to judge

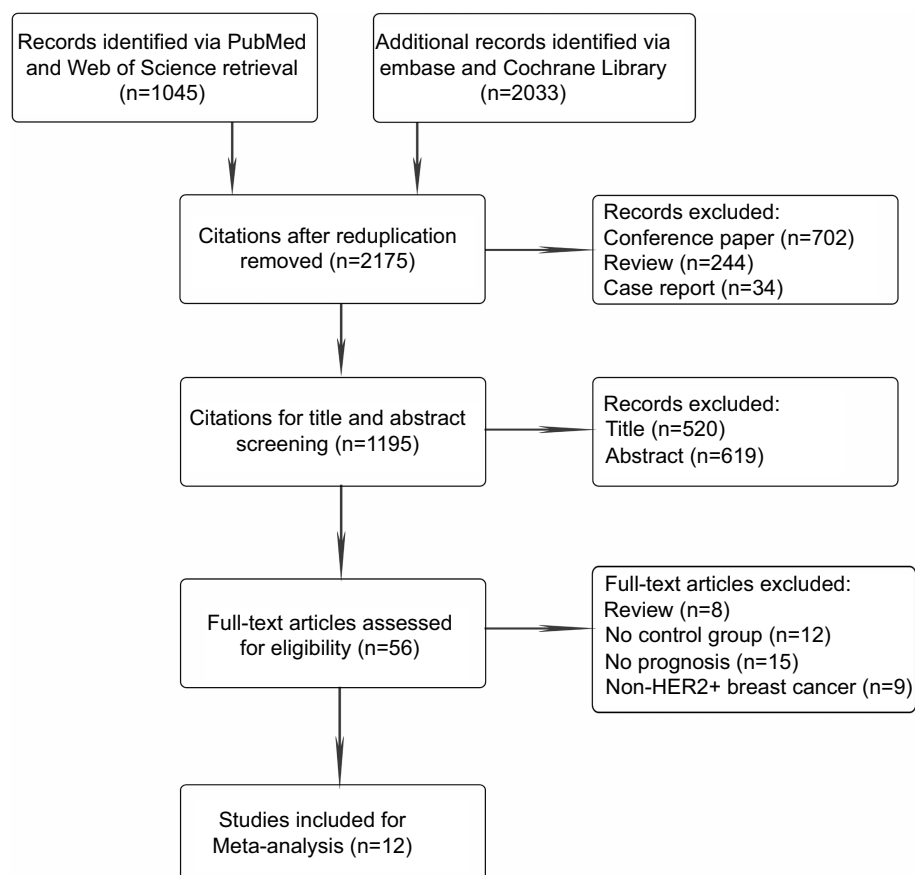


Figure 1 The study selection procedure.

Abbreviation: HER2, human epidermal growth factor receptor 2.

each risk of bias domain. The risk of bias summary and the risk of bias graph are presented in [Figure 4A](#) and [B](#), respectively.

Publication bias

In the Begg's funnel plots of the OS of NAT versus AT and the LRR of mastectomy versus BCT, data were uniformly arranged above and below the axis. Consistently, their publication bias in light of Egg's test was not statistically significant ($p=0.844$ and 0.515 , respectively), suggesting that the moderate heterogeneity in the OS of NAT versus AT was not by virtue of bias ([Figure S1](#) and [S2](#) in Supplementary, page 1 and 2).

Discussion

HER2-positive breast cancer necessitates at least 1 year of continuous trastuzumab treatment to achieve optimal therapeutic efficacy. Our results demonstrate that the early stage HER2-enriched breast tumor patients who receive NAT have a comparative OS to those who undergo AT.

Additionally, greater local-regional control is attained in those who receive mastectomy compared to those who receive BCT before the era of trastuzumab administration; nevertheless, women with this disease who receive trastuzumab treatment derive an equivalent LRR rate with the two surgical approaches.

In agreement with our results, some trials ascertain no differences between patients with early HER2-positive breast cancer following treatment with NAT compared to AT in the local relapse-free survival, event-free survival, relapse-free survival as well as breast cancer-specific survival.^{24–26} However, the study of Chatterjee et al²⁴ indicated that the DFS of patients in AT cohort was significantly longer than that in NAT cohort. Trastuzumab emtansine (T-DM1) is an antibody-cytotoxic drug conjugate of trastuzumab and the cytotoxic agent emtansine; it has efficacious antitumor effects in trastuzumab-sensitive and trastuzumab-resistant HER2-amplified breast tumors and was initially approved for advanced HER2-positive breast cancer patients who have previously received

Table 1 The details of eligible articles

First author	Publication year	Study duration	Original nation	Median age, y ^a	Median follow-up	Trastuzumab	No. of patients	CT strategy	Radiotherapy	
									Study gr.	Control gr.
Mastectomy vs BCT										
Herrero-Vicent ¹	2016	1998–2014	Spain	49; 50	72 ms	Received	48	NAT	Both	
Ihemelandu ²	2008	1998–2005	USA	NA	NA	Absent	43	AT	No	Yes
Gabos ³	2010	1998–2003	Canada	NA	4.8 ys	Absent	88	AT	Both	
Debled ⁴	2015	2005–2012	France	49; 51	46.5 ms	Received	152	NAT	Both	
Straver ⁵	2010	2000–2007	The Netherlands	45	35 ms	Received	56	NAT + AT	Both	
Voduc ⁶	2010	1986–2004	Canada	59	12 ys	Absent	227	AT	Both	
Tanioka ⁷	2010	1996–2006	Japan	54.5	46 ms	Received	44	NAT	Both	
Peterson ⁸	2014	2003–2009	Canada	NA	4.4 ys	Received	748	AT	No	Yes
NAT vs AT										
Chatterjee ⁹	2016	2011–2013	India	53	23.5 ms	Received	75	NAT + AT	Both	
Gonzalez-Angulo ¹⁰	2015	2001–2012	USA	NA	45 ms	Received	589	NAT + AT	Both	
Yang ¹¹	2018	2000–2008	China	NA	6.5 y ^b	Received	60	NAT + AT	Both	
Palmeri ¹²	2015	2006–2011	UK	50.4	53.7 ms	Received	236	NAT + AT	Both	

Notes: ^aThe value before the semicolon belongs to the study cohort; the value after it belongs to the control cohort. ^bMean value of follow-up.

Abbreviations: CT, chemotherapy; BCT, breast-conserving therapy; NAT, neoadjuvant therapy; AT, adjuvant therapy; ys, years; ms, months; gr., group; NA, not assessed in publication.

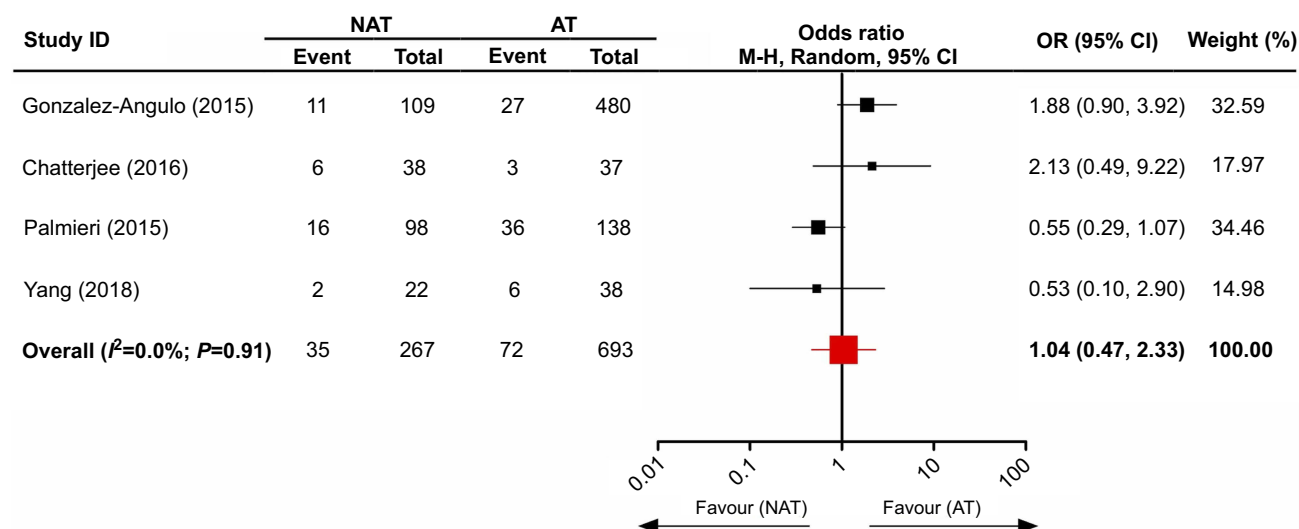


Figure 2 The comparison of overall survival between neoadjuvant trastuzumab and adjuvant trastuzumab.

Abbreviations: NAT, neoadjuvant trastuzumab; AT, adjuvant trastuzumab.

trastuzumab treatment.^{27,28} The articles of Hurvitz²⁹ and Minckwitz,²⁸ respectively, assessed the tumor response and the survival prognosis of early stage HER2-enriched subtype of breast tumors after treatment with T-DM1 and trastuzumab. Their findings demonstrated that women with this disease subset who received T-DM1 had significantly superior DFS and distant relapse-free survival and reduced pathological complete response (pCR) rates compared to those who received trastuzumab, but the OS was not significantly different. The mechanisms of action of T-DM1 eradicating HER2-positive breast tumor foci contrast to those of trastuzumab. T-DM1 activates caspase-3/caspase-7 to induce apoptotic cell death and releases the intracellular enzyme adenylate kinase which contributes to the cellular lysis. Trastuzumab antagonizes the constitutive growth-signaling properties of the HER2 system, mobilizes immune cells to kill the tumor target, and reinforces chemotherapy-induced cytotoxicity.^{27,30}

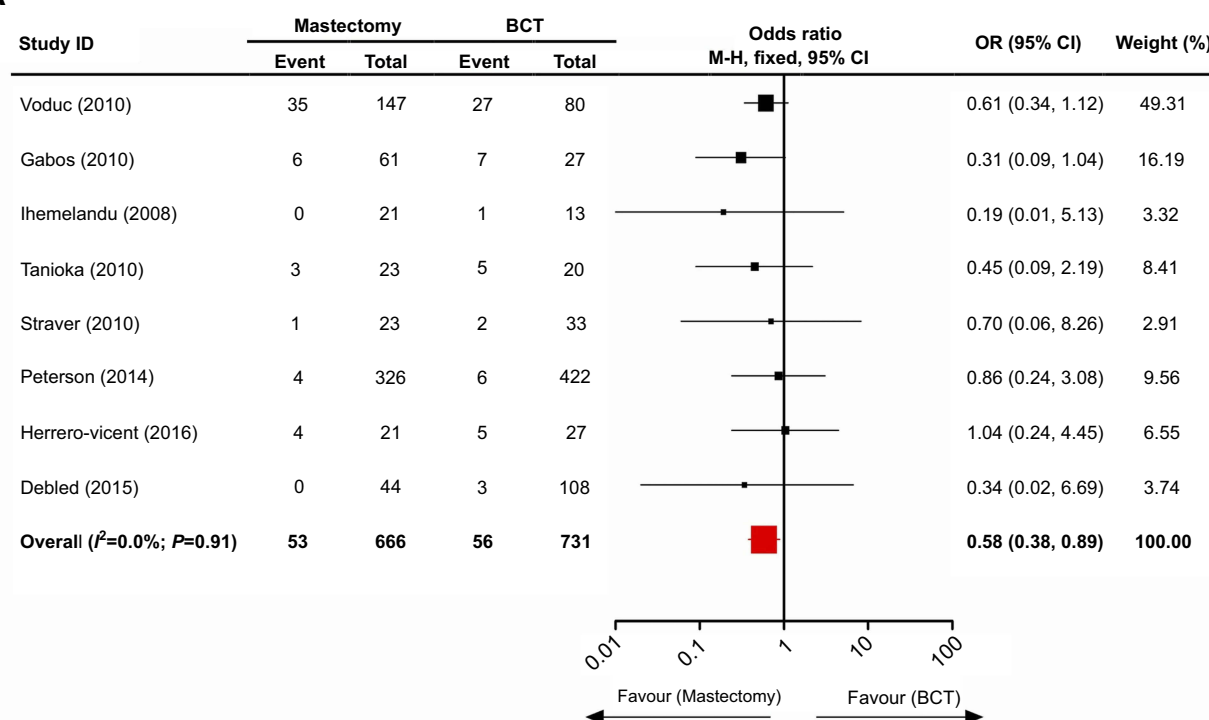
For breast cancer patients with the HER2-enriched subtype, there are two distinct eras determined by the usage of trastuzumab in the adjuvant setting. In the period preceding the use of anti-HER2 targeted therapy, the LRR rate of this tumor ranges from 4% to 15%.^{16,31} The natural process of this phenotype of breast cancer has been positively influenced by trastuzumab.³² Yin et al³³ analyzed six relevant studies and indicated that trastuzumab reduced the LRR rate of HER2-positive breast cancer by 50%. This conclusion was supported by a retrospective study

performed by Panoff and colleagues,³⁴ which found that the LRR rate of women with this disease who underwent mastectomy plus trastuzumab was 1.7%. Our article finds the different LRR rates between HER2-amplified breast tumors undergoing mastectomy and those undergoing BCT before the application of trastuzumab coupled with the identical LRR rate among both surgical scenarios after its administration, which mirrors the trastuzumab-adjusted alteration of the natural course of this disease.

There is a viewpoint suggesting that the prognosis of HER2-enriched breast cancers primarily depends on the biological characteristics of the disease rather than the content of surgical approach.³⁵ Nevertheless, it may be somewhat confined and not comprehensive. A study enrolled 618 breast cancer patients that underwent either BCT or mastectomy, 92 of whom were classified as the HER2 subtype.²¹ In the BCT cohort, HER2 subtype of breast cancer and lymph node positivity were independent prognostic factors associated with high-risk of LRR. This cancer subset was not associated with increased risk of LRR in the mastectomy cohort. Similarly, our results reaffirm that the different extents of surgery may be related to the prognosis of HER2-overexpression breast carcinoma devoid of trastuzumab treatment.

There are some limitations of this article that deserve mention. First, despite the absence of publication bias, only English literature was included which might give rise to selection bias. Second, the included studies in

A



B

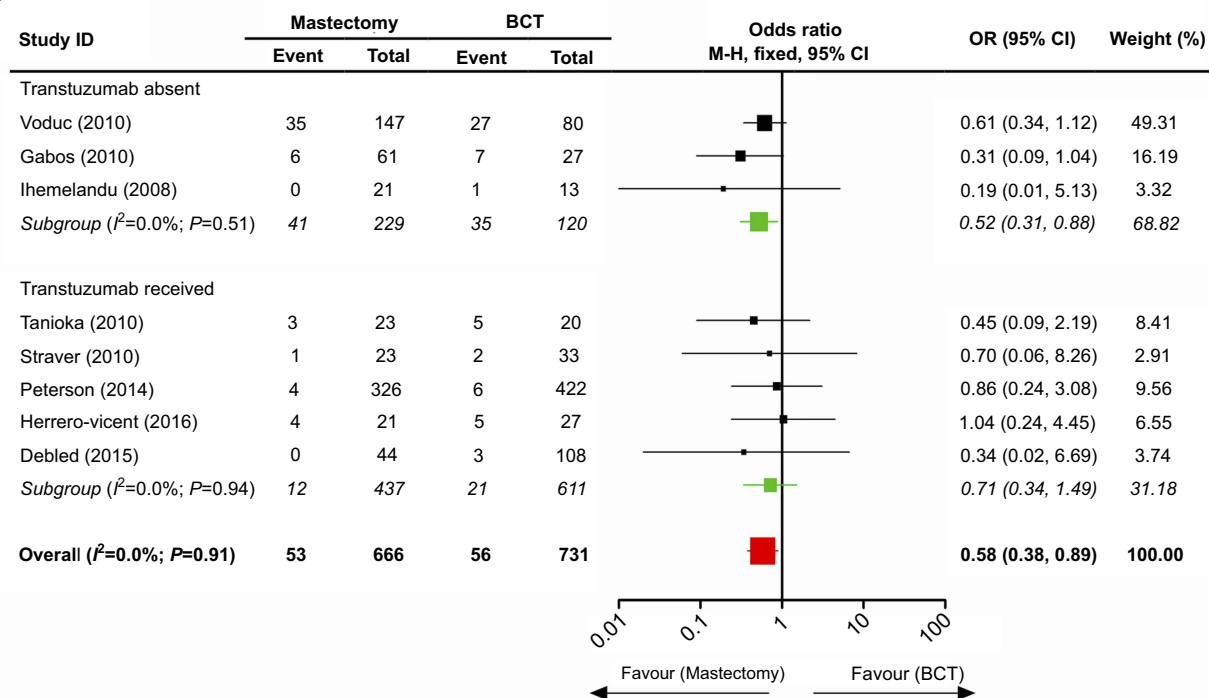


Figure 3 The comparison of local-regional relapse between mastectomy and BCT. (A) Whole group analysis; (B) Subgroup analysis.

Abbreviation: BCT, breast-conserving therapy.

partial meta-analyses were limited, which might lead to result bias. More importantly, we did not investigate other factors that might affect the outcome of LRR in women

because of insufficient information provided by the publications, such as chemotherapy regimen, fractionated mode, and dose of radiotherapy.

A

	Yang2018	Voduc2010	Tanikaka2010	Straver2010	Peterson2014	Palmeri2015	Ihemelandu2008	Herrero-Vicent2016	Gonzalez-Angulo2015	Gabos2010	Debled2015	Chatterjee2016	
Random sequence generation (selection bias)	+	+	+	+	?	+	+	+	+	+	+	+	
Allocation concealment (selection bias)	+	+	+	+	+	+	+	+	+	+	+	+	
Blinding of participants and personnel (Performance bias)	+	+	+	+	+	+	+	+	+	+	+	+	
Blinding of outcome assessment (detection bias)	+	+	+	+	+	+	+	+	+	+	+	+	
Incomplete outcome data (attrition bias)	+	+	+	+	+	+	+	+	+	+	+	+	
Selective reporting (reporting bias)	+	+	+	+	+	+	+	+	+	+	+	+	
Other bias	+	+	+	+	+	+	+	+	+	+	+	+	

B

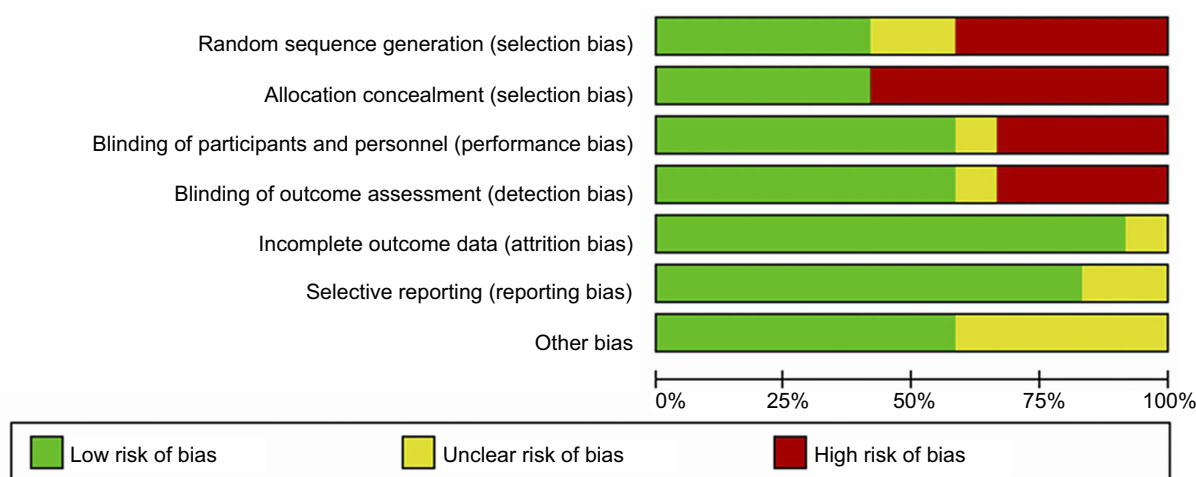


Figure 4 The assessment of risk of bias by the new Cochrane tool. (A) The risk of bias summary; (B) The risk of bias graph.

Conclusion

The OS of HER2-amplified breast tumor patients treated with NAT is equivalent to those with AT treatment. The LRR rate of those women who undergo mastectomy compared to BCT is identical in the absence of trastuzumab treatment, but mastectomy reduces the LRR rate compared to BCT in women who receive trastuzumab treatment.

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

Disclosure

The authors report no conflicts of interest in this work.

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Supplementary materials

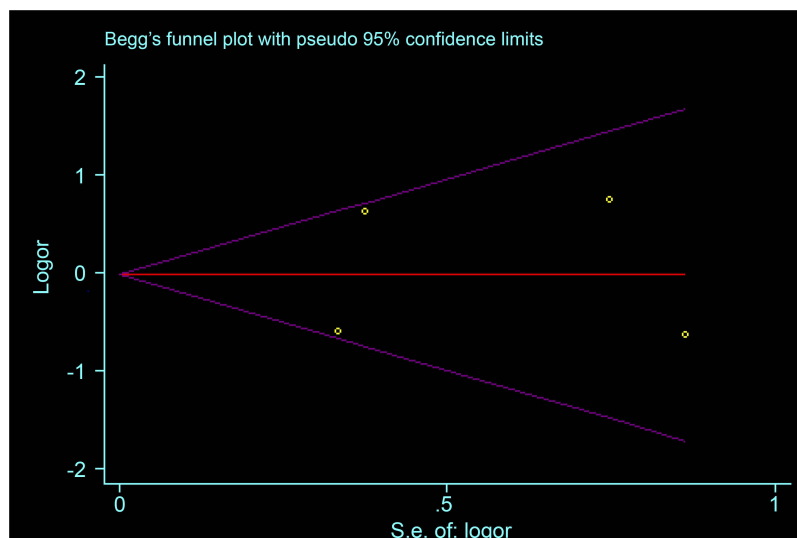


Figure S1 The Begg's funnel plot with a 95% confidence interval was created to assess the presence of publication bias OS of neoadjuvant therapy versus adjuvant therapy. $p=0.844$ according to the Egg's test.

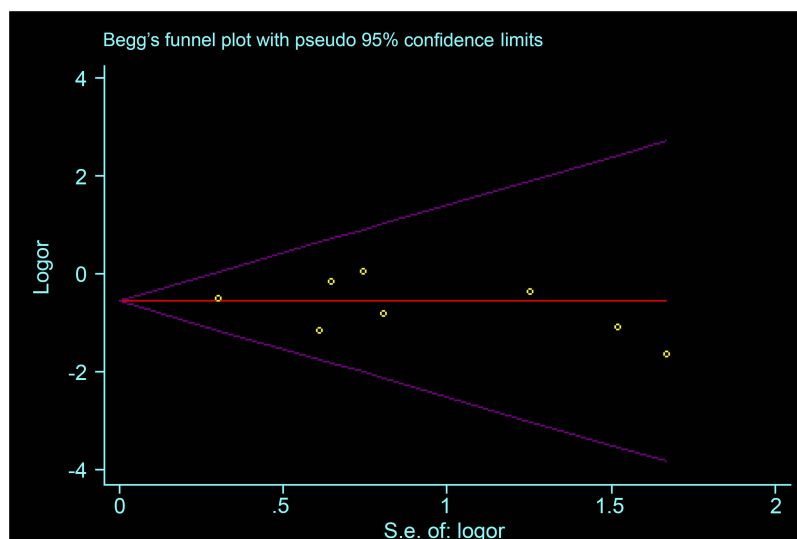


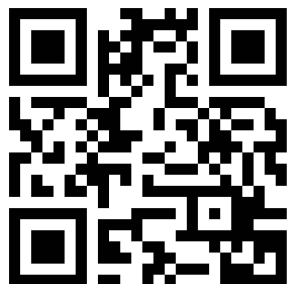
Figure S2 The Begg's funnel plot with a 95% confidence interval was created to assess the presence of publication bias in LRR of mastectomy versus breast-conserving therapy. $p=0.515$ according to the Egg's test.

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