Systematic Review and Meta-Analysis

Medicine®

OPEN

The reciprocal influences of prognosis between two types of surgical interventions and early breast cancer patients with diverse luminal subtypes

A meta-analysis

Lin He, PhD[a], Shengnan Zhao, MM[b], Min Liu, MM[c], Zhumin Su, PhD[d], Yuanzhong Ren, MM[e], Yuhua Song, MD[a,*]

Abstract

Background: To investigate and compare the effects of breast-conserving therapy (BCT) and mastectomy on the disease recurrence and long-term survival in early-stage luminal breast cancer and the difference in prognosis across diverse luminal subtypes receiving single surgical modality.

Methods: The databases of PubMed and Embase were retrieved to select eligible trials that were published from inception to 13 November 2018. The clinical trials that offered the details about recurrent disease and/or survival in luminal tumors underwent BCT or mastectomy met the inclusion criteria (n=24). With the random- or fixed-effect model basing on heterogeneity Chi^2 test with its significant level of $P < .1$, pooled odds ratio (OR) with its 95% CI, and P value were identified for endpoints.

Results: The analyzed data were constituted of 25 qualified trials with 13,032 unique women suffered from luminal cancers. The fixed-effect models were utilized. On the LRR regarding BCT versus mastectomy, the pooled data indicated no significant difference in luminal carcinomas (OR, 0.84; 95%CI, 0.43–1.64; $P = .61$; n=867). In BCT cohort, the pooled data showed that there were some significant benefits favoring luminal A over luminal B in LR (OR, 0.61; 95%CI, 0.46–0.81; $P = .0007$; n=5406), DM (OR, 0.53; 95%CI, 0.41–0.69; $P < .00001$; n=4662), DFS (OR, 0.59; 95%CI, 0.36–0.96; $P = .03$; n=776) and OS (OR, 0.65; 95%CI, 0.42–0.99; $P = .05$; n=1149), but not in LRR (OR, 0.74; 95%CI, 0.48–1.13; $P = .16$; n=3732), coupled with luminal A/B over luminal-HER2 in LRR (OR, 0.43; 95%CI, 0.25–0.76; $P = .004$; n=890), DM (OR, 0.56; 95%CI, 0.35–0.90; $P = .02$; n=1396), DFS (OR, 0.47; 95%CI, 0.27–0.83; $P = .009$; n=532); in mastectomy cohort, there were apparent advantages of LRR (OR, 0.58; 95%CI, 0.36–0.92; $P = .02$; n=1768), LR (OR,0.56; 95%CI, 0.38–0.83; $P = .004$; n=1209), DM (OR, 0.58; 95%CI, 0.40–0.84; $P = .004$; n=652) and OS (OR, 0.62; 95%CI, 0.43–0.89; $P = .009$; n=652) in luminal A vs luminal B.

Conclusion: For early luminal breast cancer, the equality of LRR was achieved in BCT and mastectomy. In comparison, luminal A cancers benefit the most improved tumor re-appearence and survival in luminal diseases regardless of the option of surgical modality, whereas luminal-HER2 is affected by the worst clinical outcomes in them who follows BCT.

Abbreviations: BCT = breast-conserving therapy, CI = confidence interval, DFS = disease-free survival, DM = distant metastasis, ER = estrogen receptor, HER2 = human epidemic growth factor receptor 2, LR = local recurrence, LRR = localregional relapse, OR = odds ratio, OS = overall survival, pCR = pathological complete response, PFS = progress free survival, PR = progesterone receptor, TNBC = triple negative breast cancer.

Keywords: breast-conserving therapy, mastectomy, meta-analysis, molecular subtype

Editor: Kou Yi.

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

Informed consent was obtained from all individual participants included in the selected studies.

The authors have no conflicts of interest to disclose.

Supplemental Digital Content is available for this article.

[a] *Breast Center B Ward,* [b] *Tumor-Comprehensive Treatment Department,* [c] *Department of Geriatrics, The Affiliated Hospital of Qingdao University, Qingdao, Shandong Province,* [d] *Department of Neurology, The People's Hospital of China Medical University, Shenyang, Liaoning Province,* [e] *Department of Joint Surgery, The Affiliated Hospital of Qingdao University, Qingdao, Shandong Province, China.*

[*] *Correspondence: Yuhua Song, Breast Center B Ward, The Affiliated Hospital of Qingdao University, Qingdao, Shandong Province, China (e-mail: qdsongyh@126.com).*

Medicine (2019) 98:11(e14912)

Received: 30 November 2018 / Received in final form: 22 February 2019 / Accepted: 25 February 2019

http://dx.doi.org/10.1097/MD.0000000000014912

KEY POINTS

- Breast conservative therapy and mastectomy, which are distinctly different treatment scenarios, complete a similar localregional reappearence in luminal tumors.
- Luminal A carcinoma utmost curtails the risk of disease recurrence and possesses the benefit of long-time survival among all breast cancer with luminal phenotypes no matter how to select surgical modality.
- The patients with luminal-HER2 phenotype entail the most inferior clinical prognosis of all luminal cancers following breast conservation therapy.

1. Introduction

The discernible landscape that radiotherapy following breast-conserving therapy (BCT) and mastectomy achieve equivalent disease-free survival (DFS) and overall survival (OS) for early breast cancer has been well confirmed by a myriad of large randomized controlled trials.[1,2] Approximately 5% to 10% of operable patients undergo mastectomy and 10% to 20% of early invasive breast cancer receiving BCT will gradually develop a tumor recurrence within 10 years,[3–5] thus increasing the risk of distant metastasis (DM) and mortality. In this context, BCT has become an adequate surrogate of local regional treatment for mastectomy in patients with early breast cancer in that it maximum downsizes the physiological and psychological burden of sacrificing the breast.

Even if the gross mass tumor is successfully excised and the surgical margin is negative, as the breast cancer is multifocal,[6] thus will remaining microscopic residual lesions, if left untreated, 30% to 40% of these women are still in the detriment of disease recrudesce.[1,7] Many signaling pathways are relative to the reappearance of breast tumor, including the destruction of estrogen-receptor-related signaling pathways, and the amplification or overexpression of proto-oncogenes such as human epidemic growth factor receptor 2 (HER2).[8] Recently, according to the expression level of these receptors and tumor grade, breast cancer can be divided into the following five subtypes: luminal A, estrogen receptor (ER) positive or progesterone receptor (PR) positive and HER2 negative with grade 1 or 2; luminal B, ER positive or PR positive and HER2 negative with grade 3; luminal-HER2, ER positive or PR positive and HER2 positive; HER2-enriched, ER negative, PR negative and over-expression of HER2; triple negative breast cancer (TNBC), negativity of ER, PR and HER2.[9–11]

Historically, the luminal breast cancers are always prone to benefit a favorable prognosis, with a recurrent tumor rate 2 to 3 times less than HER2-amplified and TNBC that are wildly recognized as the high-risk tumors.[12,13] In 2012, a systematic review was implemented by Lowery and colleagues who investigated and compared the local regional relapse (LRR) of breast cancer patients with different molecular subtypes after BCT or mastectomy,[14] reaffirming this conception. Inadequately, this ingenious study fails to investigate whether the surgical decisions could impact on the disease recrudesce and long-term survival of luminal cancers and what the influence of different luminal subtypes undergo single modality of surgical intervention on these clinical outcomes. To settle this issue, herein, we performed a meta-analysis to establish and compare the prognosis in two types of treatment scenarios followed by luminal disease and the difference across various luminal subtypes, including luminal-HER2 if applicable, who were treated with either BCT or mastectomy.

2. Methods

2.1. Search strategy

Using the accurate retrieval strategy: luminal AND (mastectomy OR (breast conserving surgery) OR (breast preserving surgery) OR (breast conservation surgery) OR (breast conserving treatment) OR (breast preservation treatment) OR (breast conservation treatment) OR (breast conserving therapy) OR (breast preserving therapy) OR (breast conservation therapy)) AND ((breast cancer) OR (breast tumor) OR (breast neoplasms)) AND ((local regional recurrence) OR (local regional relapse) OR (pathological complete response) OR (overall survival) OR (disease free survival) OR (progress free survival) OR (disease metastasis) OR (metastasis free survival) OR LRR OR pCR OR OS OR DFS OR PFS), electronic searches were conducted in databases of PubMed and Embase. In the course of the retrieval procedure, no restrictions were required. Citation searching was finished as of 9 November 2018.

2.2. Inclusion criteria

- Clinical trials;
- Early stage breast cancer female patient with luminal phenotype;
- Delineating the outcomes of disease recurrence and/or long-time survival in BCT arm and/or mastectomy arm;
- The precise number of events or event ratio coupled with total sample size was provided.

2.3. Exclusion Criteria

- Not published in English;
- Review, case report, conference abstract, or conference paper;
- Be incapable of meeting the inclusion criteria.

The retrieved citations were independently screened by two co-authors (Qian Wu and Zhumin Su) on the basis of titles, abstracts and full-texts, and only the satisfactory studies that met the inclusion criteria were reserved. Provided comprising of any discordance, it was addressed by discussion.

2.4. Data abstraction

With the application of Excel vision 2016, the following information was respectively abstracted by two reviewers (Qian Wu and Biyuan Zhang) from eligible trails: the first author, original nation, publication year, study duration, median follow-up, the regimen of adjuvant therapy and radiotherapy, total sample size as well as the number of events. If some inconformities surfaced, they were resolved by the third reviewer (Lijiu Zhang).

2.5. Statistical analysis

The crude odds ratio (OR) with its 95% confidence interval (CI), and *P* value regarding to all valid relapsing disease and survival

benefit for each included study was calculated. Provided that the number of events was not described, its computation was obtained in light of the endpoint percentage or other information seen in the publication. The Heterogeneity Chi^2 test with its significant level of $P < .1$ was employed to evaluate the heterogeneity among different studies.[15] A random-effect model was used to integrate the data when heterogeneity test appeared to no statistically significant ($P < .1$); if with a drastically different situation, a fixed-effect model was utilized.[15] The publication bias was assessed by creating a funnel plot with its 95% CI. If the data were uniformly arranged at the left and right of the plot, it denoted no major asymmetry that signified a likelihood of publication bias. The difference of eligibility criteria, sample size, potential bias, as well as treatment regimen in selected trials was discussed, and their qualities were estimated in terms of the instrument provided by Jadad and colleagues[16] (Supplemental Table 2, http://links.lww.com/MD/C883 in *Appendix, page 6*). All statistical tests were analyzed by using Revman Manager software version 5.3 and tracked once more.

3. Results

3.1. Search results

Following the path of the systematic retrieval, we collected 753 potential citations, of which classified as duplications (n = 123), reviews (n = 35), case reports (n = 13), as well as conference abstracts (n = 229) coupled with conference papers (n = 7) were deleted. The remainder articles (n = 346) were selected by applying title and abstract screening. After the previous procedure, a total of 53 studies were entered into full-text scrutinization, and 28 of them were excluded by virtue of no association between luminal cancer with surgical paradigm (n = 19), containing males (n = 1), no prognosis (n = 2), without comparison of luminal subtypes in mastectomy arm (n = 4) or in BCT arm (n = 2). Ultimately, 25 eligible clinical trials[13,17–40] with 13,032 unique patients were involved for data extraction after removal of ineligible studies that were unable to meet the inclusion criteria. The PRISMA flow diagram was outlined in Figure 1.

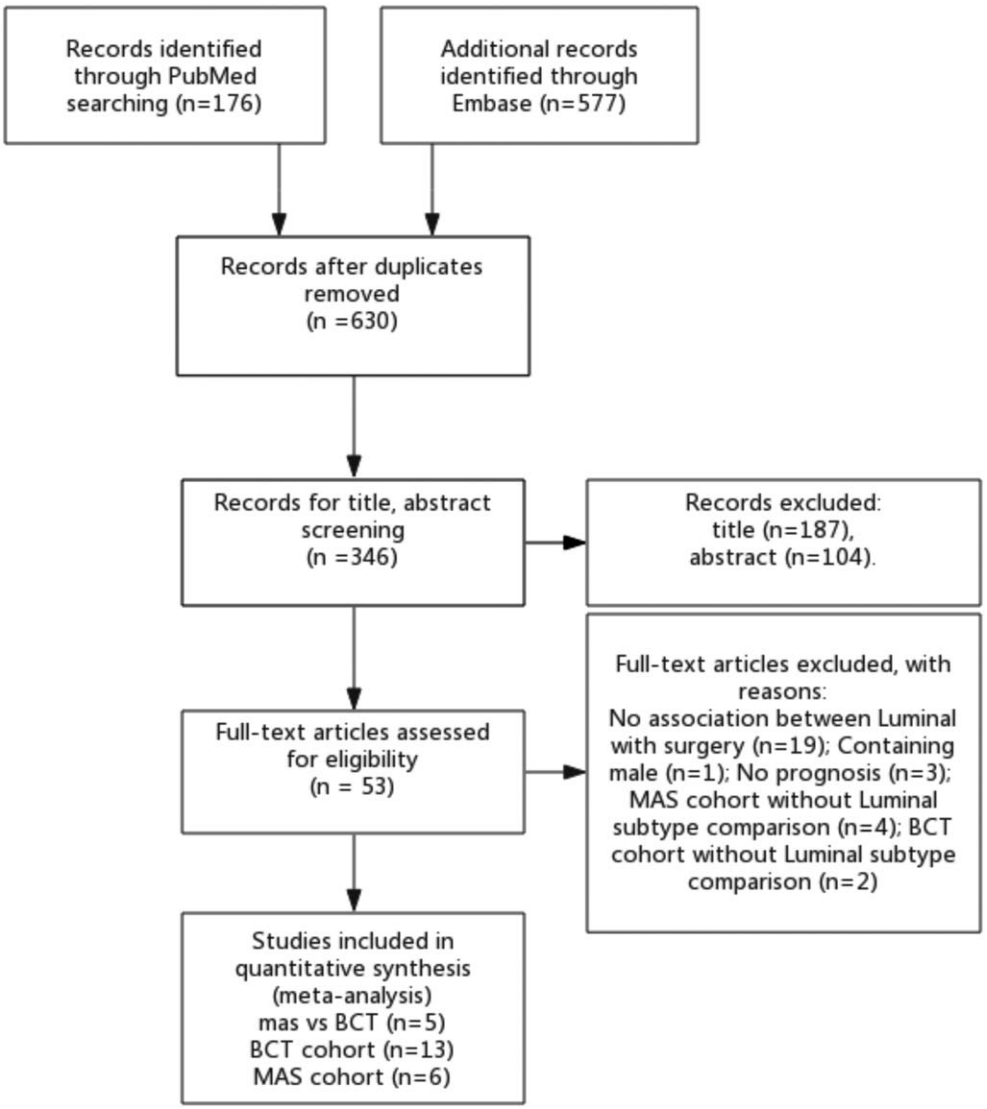


Figure 1. The flow diagram of selecting trials. BCT = breast conserving therapy, MAS = mastectomy.

Table 1

The details of radiotherapy and adjuvant therapy details in analyzed studies.

First author	Publication year	Total sample size (n)	BCT (RT dose‡/CT regimen)	RT fraction†/CT duration of BCT	Mastectomy (RT dose‡/CT regimen)	RT fraction†/CT duration of mastectomy
Gabos	2010	442	WBI: 42.5–50 Gy, regional LN irradiation offered if with ≥4 LN+	16–25 fractions	WBI: 45–50 Gy, chest wall and regional LN irradiation offered if with ≥1 LN+ or locally advanced disease	20–25 fractions
Ihemelandu	2008	207	Irradiation dose and adjuvant therapy details not provided	*	Irradiation dose and adjuvant therapy details not provided	*
Meyers	2011	80	Irradiation dose and adjuvant therapy details not provided	*	Irradiation dose and adjuvant therapy details not provided	*
Straver	2010	138	Dose dense AC and/or DC	6 cycles	dose dense AC and/or DC	6 cycles
Voduc	2010	2202	Irradiation dose and adjuvant therapy details not provided	*	Irradiation dose and adjuvant therapy details are provided	*
Bane	2014	730	WBI: 42.5–50Gy	16–25 fractions		
Braunstein	2016	1037	Irradiation dose and adjuvant therapy details not provided	*		
Jwa	2016	229	AC or DC or GP or AC-T	4 cycles		
Demirci	2011	370	WBI: 36–50.4 Gy with 6–24 Gy tumor bed boost if required; PBI: 37.6–38.5 Gy	*		
Gangi	2014	1553	WBI without dose details	*		
Kaiser	2018	604	WBI: 54 Gy	*		
Mazouni	2012	631	Irradiation dose and adjuvant therapy details not provided			
Jia	2014	486	WBI: 50 Gy	25 fractions		
Millar	2009	417	WBI: 50Gy or 45 Gy plus a tumor bed boost /CMF or AC or adjuvant tamoxifen.	25 fractions		
Sanpaolo	2011	485	WBI: 50 Gy plus tumor bed boost /CMF or doxorubicin-based	*		
Wong	2011	323	WBI:50 Gy plus tumor bed boost /CMF or DC or FEC	25 fractions / 4–6 cycles		
Yamazaki	2015	139	WBI: 50 Gy plus tumor bed boost	*		
Braunstein	2015	46	WBI: 61Gy	*		
Wen	2016	555			Irradiation dose and adjuvant therapy details not provided	*
Ragaz	1997	79			36 patients received 37.5 Gy, 43 patients without RT /CMF	16 fractions /6–12 months
Overgaard	1997	45			24 patients received 50 Gy or 48 Gy, 21 patients without RT /CMF	22–25 fractions /8–9cycles
Mersin	2011	913			Irradiation dose and adjuvant therapy details not provided	*
Wu	2012	534			475 patients received 40–50Gy RT; 229 patients without RT	23–25 fractions
Nakamura	2016	74			WBI: 50Gy /AC-T or FEC-T or AC or FEC or others.	25 fractions /*
Moo	2014	713			Irradiation dose and adjuvant therapy details not provided	*

AC = doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 every 3 weeks, AC-T = doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 followed by docetaxel 100 mg/m^2 every 3 weeks, BCT = breast conserving therapy, CMF = cyclophosphamide, methotrexate and 5-fluorouracil, DC = docetaxel 75 mg/m^2 and capecitabine 1,000 mg/m^2 orally on days 1 and 14 every 3 weeks, FEC = 5-fluorouracil, epirubicin, cyclophosphamide, FEC-T = 5-fluorouracil, epirubicin, cyclophosphamide followed by taxane, GP = paclitaxel 80 mg/m^2 followed by gemcitabine 1200 mg/m^2 on days 1 and 8 every 3 weeks, LN+ = lymph node-positive, PBI = partial breast irradiation, RT = radiotherapy, WBI = whole breast irradiation.

* Not offered in study.

† The value of radiotherapy fraction is the median.

‡ The value of radiotherapy dose is the median.

3.2. Characteristics of analyzed trials

The original nations of included studies were China (n = 3), the United States (n = 5), Denmark (n = 1), the Netherlands (n = 1), Canada (n = 4), Japan (n = 2), France (n = 2), Austria (n = 1), Australia (n = 1), Singapore (n = 1), Italy (n = 1), Turkey (n = 2), and South Korea (n = 1). The publication dates of them ranged from 2008 to 2018. The sample sizes ranged from 45 to 2202 (median: 442). In light of the assortments of disease relapse and long-dated survival, the eligible trials were stratified into 5 categories: the LRR trials (n = 16), in which concurrent focused on mastectomy and BCT (n = 4); the local recurrence (LR) trials (n = 8); the DM trials (n = 10); the DFS trials (n = 3); and the OS

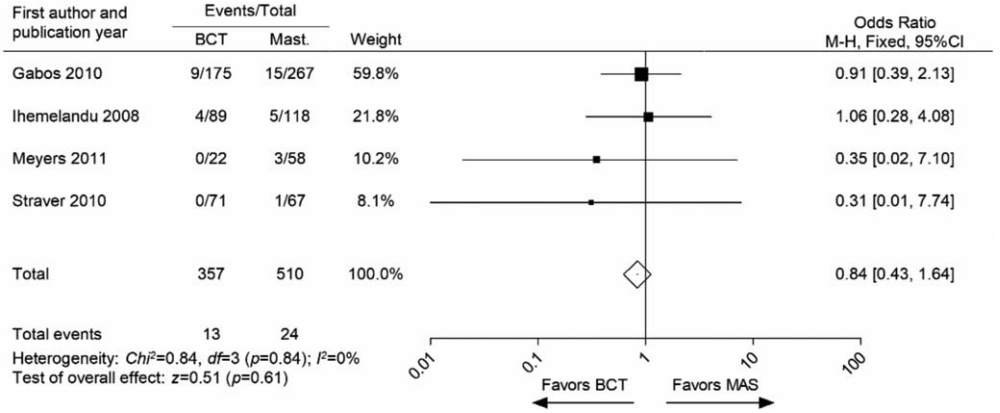


Figure 2. The comparison of LRR between BCT and mastectomy received by luminal tumors. (A) LRR in luminal cancers; (B) LRR in luminal A cancers; (C) LRR in luminal B cancers. BCT = breast conserving therapy, MAS = mastectomy.

trials (n = 5). With regard to all DFS trials, only BCT arm be could extracted the data; and for DM and OS included studies, luminal-HER2 breast cancers were solely researched in BCT strategy. Other details were provided in Supplemental Table 1 a-e, http://links.lww.com/MD/C883 (*Appendix, page 1–5*). Details on adjuvant therapy and irradiation paradigm were seen in Table 1.

3.3. Localregional recurrence

As demonstrated in Figure 2, the pooled data with respect to treatment modality of BCT compared to mastectomy for early breast cancer indicated that no statistically significant difference in luminal subtype (OR, 0.84; 95%CI, 0.43–1.64; $P = .61$; n = 867). Moreover, the pooled data of comparison across luminal tumors with different intrinsic phenotypes found some distinguishing results. Although the comparisons of luminal A vs luminal B in BCT cohort (OR, 0.74; 95%CI, 0.48–1.13; $P = .16$; n = 3732) and the combined population of luminal A and/or B (luminal A/B) vs luminal-HER2 who underwent mastectomy (OR, 0.56; 95%CI, 0.25–1.28; $P = .17$; n = 980) were not significantly different, there were an increased significant benefit favoring luminal A/B over luminal-HER2 treated with BCT (OR, 0.43; 95%CI, 0.25–0.76; $P = .004$; n = 890), and apparent superiority in luminal A compared with luminal B accepting mastectomy (OR, 0.58; 95%CI, 0.36–0.92; $P = .02$; n = 1768), as shown in Figure 3.

3.4. LR, DM, DFS, OS in single treatment modality

For patients treated with BCT, the analyses of pooled data showed that luminal A had a statistical advantage over luminal B in LR (OR, 0.61; 95%CI, 0.46–0.81; $P = .0007$; n = 5406), DM (OR, 0.53; 95%CI, 0.41–0.69; $P < .00001$; n = 4662), DFS (OR, 0.59; 95%CI, 0.36–0.96; $P = .03$; n = 776) and OS (OR, 0.65; 95%CI, 0.42–0.99; $P = .05$; n = 1149), and luminal A/B outperforming luminal-HER2 derived significantly desirable profits from DM (OR, 0.56; 95%CI, 0.35–0.90; $P = .02$; n = 1396), DFS (OR, 0.47; 95%CI, 0.27–0.83; $P = .009$; n = 532), but without LR (OR, 1.12; 95%CI, 0.57–2.20; $P = .75$; n = 3561), as seen in eFigure 1a-g, http://links.lww.com/MD/C883 (*Appendix, page 7–8*).

In mastectomy cohort, two clinical trials centered on LR and another two studies covered the disease relapse and survival situation in comparison of luminal A vs luminal B. As outlined in eFigure 2a–c, http://links.lww.com/MD/C883 (*Appendix, page 8–9*), the pooled data showed that luminal A carcinomas significantly lowered the occurrences of LR (OR,0.56; 95%CI, 0.38–0.83; $P = .004$; n = 1209) and DM (OR,0.58; 95%CI, 0.40–0.84; $P = .004$; n = 652), raised the dividend of OS (OR, 0.62; 95%CI, 0.43–0.89; $P = .009$; n = 652) when was compared with luminal B.

The fix-effect model was leveraged for all analyses owing to no heterogeneity among selected studies.

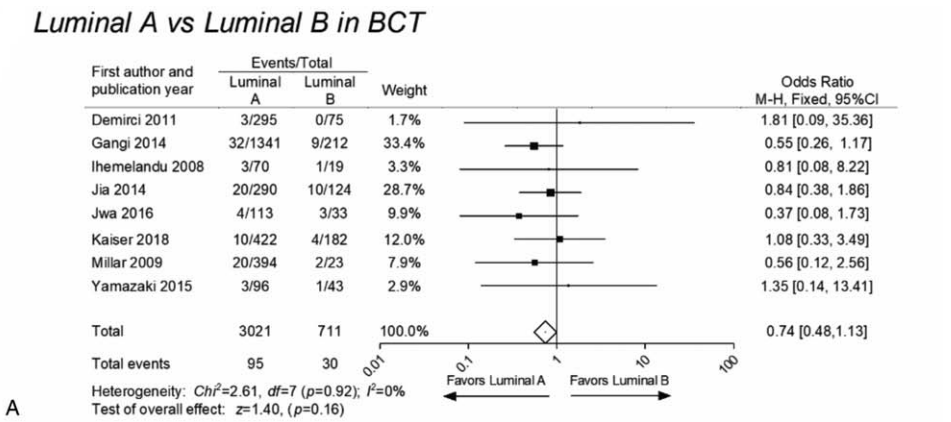
3.5. Publication bias

The funnel plots were drawn, as provided in eFigure 3a–o, http://links.lww.com/MD/C883 (*Appendix, page 9–16*), in which the analyzed data were evenly distributed at the left and right sides of the plots, indicating no advent of major asymmetry that might give rise to heterogeneity, indeed, which was not detected in each meta-analysis.

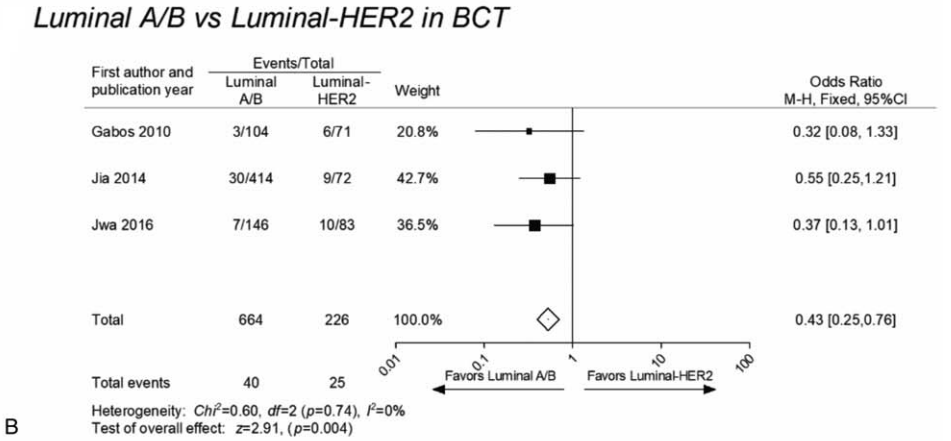
4. Discussion

As mentioned earlier that the equivalency of OS and DFS was certified in early breast tumor patient who underwent the treatment scenarios of mastectomy and BCT, our results further corroborate that the two paradigms also achieve equivalent LRR in luminal cancer. Additionally, breast cancer women with luminal A subtype are entitled to a degressive disease reappearence and reinforced survival benefit, compared to luminal B. Whilst both subtypes considered as an entirety in comparison to luminal-HER2, the latter is underway to be in disadvantageous.

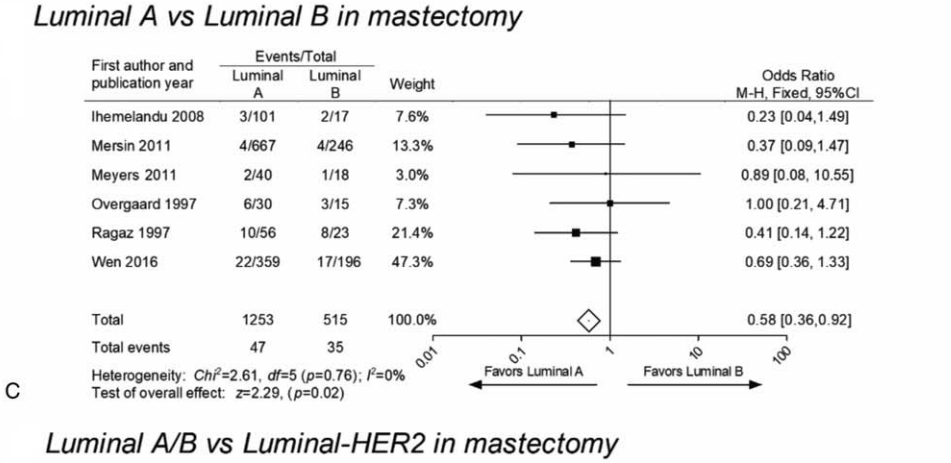
Breast cancer exhibits diversity in tumor invasiveness[10,41] and responsiveness to systematic therapy[42] on the basis of different molecular phenotypes. At present, the limited data are inefficient to validate that molecular subtype is a robust factor in predicting LRR.[43] Although some studies have sought to evaluate the result of this problem, their conclusions are still suspect in that the heterogeneity of patient populations and surgical strategies deserves to be in consideration (for instance, some only centers on patients treated with BCT, while others involve women under mastectomy).[12,24,44,45] Our results suggested that the similar LRR was captured in breast tumors with luminal phenotype regardless of the surgical strategy, and in luminal A compared to luminal B when treated with BCT.



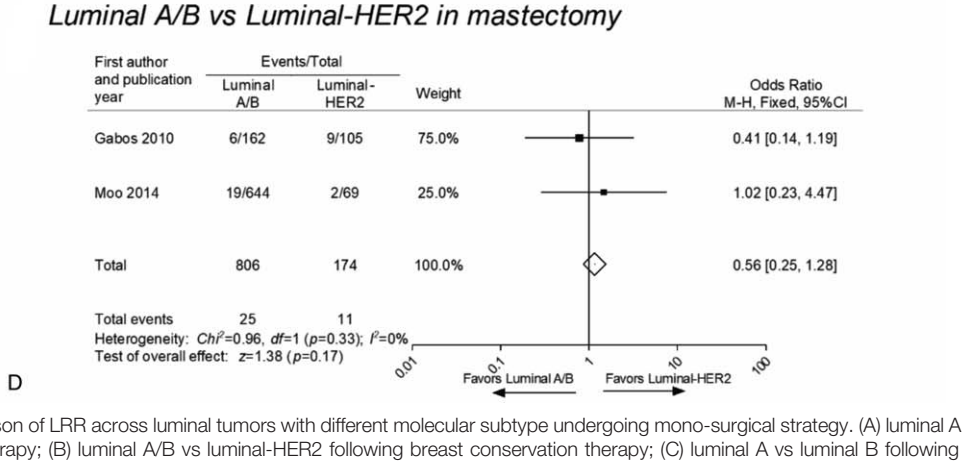
A



B



C



D

Figure 3. The comparison of LRR across luminal tumors with different molecular subtype undergoing mono-surgical strategy. (A) luminal A vs luminal B following breast conservation therapy; (B) luminal A/B vs luminal-HER2 following breast conservation therapy; (C) luminal A vs luminal B following mastectomy.

However, there was an exception of comparison between both subtypes who underwent mastectomy, representing that a significantly improved LRR benefit favored luminal A over luminal B. As the reduplicative observations that the uppermost survival dividend is experienced in luminal cancer,[9,41] these results further consolidates them and are consistent with the study of Voduc and colleagues,[13] which enrolled 2202 luminal breast cancers, suggests that luminal A tumors presents the lower LRR than luminal B in BCT cohort but not in mastectomy cohort. From the upfront descriptions, it is rational that breast cancer patient with luminal A phenotype may predict a favorable LRR outcomes when accepts BCT.

Our results elucidated that the DM incidence in luminal A cancer was significantly lower than luminal B received both surgical measures, whereas in luminal-HER2 disease was deteriorated in comparison with luminal A/B who received BCT, which is in part deviated from some previous trials. The study of Sanpaolo et al. indicated that a numerically lower rate of 5-year DM in the luminal A disease outperformed luminal B adopting BCT (11.4% vs 16.1%), albeit not significant. Nevertheless, when a subgroup analysis performed to compare patients suffered from different luminal phenotype diseases who received hormone therapy, luminal A disease derived a significantly improved 5-year DM over luminal B. For women with breast tumors in mastectomy cohort, the experiments of Ihemelandu et al and Wu et al both signified no significant difference in intrinsic subtypes between luminal A with luminal B. Notably, based on the consistent appreciation that postoperative radiotherapy can reduce the risk of tumor metastasis, disease recurrence and mortality,[46–48] Wu extracted patients who received radiotherapy after surgery for subgroup analysis and uncovered luminal A with a significantly reduced rate of DM by comparison with luminal B (26.9 vs 45.5, $P < .05$). Consequently, to sum up the aforementioned results, hormone therapy may be a crucial factor affecting the rate of DM in luminal patients accepting BCT, and postoperative radiotherapy may pave a superior way to lower DM for women affected by luminal A breast cancer in paradigm of mastectomy.

The preferable prognosis with reference to OS and DPS is always attached importance by people who suffer from carcinomas. Our study found that there was a more promising OS in luminal A breast cancer compared with luminal B under both treatment modality, alongside a favorable DFS in whom diagnosed with luminal A disease choosing BCT as the treatment intervention, which is in agreement with some similar studies. A longish-term clinical trial initiated by Kaiser and colleagues who took the 10-year OS as an endpoint and realized a statistically significant result that luminal B cancer women who received BCT had disadvantageous survival compared with luminal A (83.2% vs 89.1%; $P = .04$).[26] Moreover, the optimal DPS in breast cancer women with luminal A subtype (87.4% vs luminal B of 82.6%, $P = .04$; vs luminal-HER2 of 74.8%, $P = .006$) was confirmed by the study of Jia et al. who retrospective analyzed 405 breast cancer patients with luminal phenotype underwent BCT.[33] Therefore, it is reasonable to believe that an improved survival is beneficial to early-stage breast cancer patient with luminal A in any surgical strategies.

It is acknowledged that there are some limitations in this article. First, albeit no publication bias, the inclusion criteria exerted restriction on publication in English might lead to selection bias. Second, for the purpose to omit mixing diverse therapies and avert heterogeneity among included trails, only articles with similar arms were analyzed, thus causing only 2 to 4 eligible studies with small sample sizes in some meta-analyses, which might lead to result bias. Third, as reviewed above, hormone therapy and postoperative radiotherapy were essential agents that impacted on prognosis in luminal disease. However, due to finite information in the included trials, we did not conduct a subgroup analysis on them that might imply some impressive findings.

Despite of these limitations, this novel meta-analysis with a large volume of sample size amply evidences that LRR of luminal breast cancers not vary with the alternative of surgical decision-making, but with the usage of certain surgical intervention, either BCT or mastectomy, the best prognosis and the minimum rate of tumor relapse preferred luminal A tumor. In the future, the results of subgroup analysis in terms of luminal tumor whether receives hormone therapy and postoperative irradiation will be also in expectation.

5. Conclusion

For early luminal breast cancer, the similar LRR appears after implementation of BCT and mastectomy. In addition, no matter how the treatment intervention is selected, patients with luminal A subtype experience the most reformative clinical prognosis of luminal diseases; whereas in women following BCT, the luminal-HER2 cancers are injured by the poorest outcomes.

Author contributions

Data curation: Zhumin Su.
Formal analysis: Min Liu.
Funding acquisition: Shengnan Zhao, Min Liu.
Resources: Shengnan Zhao, Min Liu, Zhumin Su.
Software: Lin He.
Supervision: Yuhua Song.
Validation: Yuanzhong Ren.
Visualization: Yuanzhong Ren.
Writing – original draft: Lin He.
Writing – review & editing: Yuhua Song.
Lin He orcid: 0000-0002-7390-1702.

References

[1] Fisher B, Anderson S, Bryant J, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. N Engl J Med 2002;347:1233–41.
[2] Veronesi U, Cascinelli N, Mariani L, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. N Engl J Med 2002;347:1227–32.
[3] Fodor J, Major T, Polgár C, et al. Prognosis of patients with local recurrence after mastectomy or conservative surgery for early-stage invasive breast cancer. Breast (Edinburgh, Scotland) 2008;17:302–8.
[4] Fodor J, Polgár C, Major T, et al. The time-course of metastases from breast cancer after mastectomy and breast-conserving surgery with and without isolated local-regional recurrence. Breast (Edinburgh, Scotland) 2002;11:53–7.
[5] van Dongen JA, Voogd AC, Fentiman IS, et al. Long-term results of a randomized trial comparing breast-conserving therapy with mastectomy: European Organization for Research and Treatment of Cancer 10801 trial. J Natl Cancer Instit 2000;92:1143–50.
[6] Holland R, Veling SH, Mravunac M, et al. Histologic multifocality of Tis, T1-2 breast carcinomas. Implications for clinical trials of breast-conserving surgery. Cancer 1985;56:979–90.
[7] Clarke M, Collins R, Darby S, et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. Lancet (London, England) 2005;366:2087–106.

[8] Buchholz TA, Wazer DE. Molecular biology and genetics of breast cancer development: a clinical perspective. Semin Radiat Oncol 2002;12:285–95.
[9] van't Veer LJ, Dai Hongyue , van de Vijver Marc J, et al. Gene expression profiling predicts clinical outcome of breast cancer. Nature 2002;415: 530–6.
[10] Sorlie T, Tibshirani R, Parker J, et al. Repeated observation of breast tumor subtypes in independent gene expression data sets. Proc Natl Acad Sci USA 2003;100:8418–23.
[11] Tang P, Skinner KA, Hicks DG. Molecular classification of breast carcinomas by immunohistochemical analysis: are we ready? Diagn Mol Pathol 2009;18:125–32.
[12] Nguyen PL, Taghian Alphonse G, Katz Matthew S, et al. Breast cancer subtype approximated by estrogen receptor, progesterone receptor, and HER-2 is associated with local and distant recurrence after breast-conserving therapy. J Clin Oncol 2008;26:2373–8.
[13] Voduc KD, Cheang MC, Tyldesley S, et al. Breast cancer subtypes and the risk of local and regional relapse. J Clin Oncol 2010;28:1684–91.
[14] Lowery AJ, Kell MR, Glynn RW, et al. Locoregional recurrence after breast cancer surgery: a systematic review by receptor phenotype. Breast Cancer Res Treat 2012;133:831–41.
[15] Sutton AJ, Abrams KR, Jones DR. Methods for Meta-analysis in Medical Research. Wiley Series in Probability and Statistics—Applied Probability and Statistics Section Hoboken, NJ: Wiley; 2000.
[16] Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Controll Clin Trials 1996;17:1–2.
[17] Bane AL, Whelan TJ, Pond GR, et al. Tumor factors predictive of response to hypofractionated radiotherapy in a randomized trial following breast conserving therapy. Ann Oncol 2014;25:992–8.
[18] Braunstein LZ, Taghian AG, Niemierko A, et al. Breast-cancer subtype, age, and lymph node status as predictors of local recurrence following breast-conserving therapy. Breast Cancer Res Treat 2017;161:173–9.
[19] Braunstein LZ, Niemierko A, Shenouda Mina N, et al. Outcome following local-regional recurrence in women with early-stage breast cancer: impact of biologic subtype. Breast J 2015;21:161–7.
[20] Jwa E, Shin KH, Kim JY, et al. Locoregional recurrence by tumor biology in breast cancer patients after preoperative chemotherapy and breast conservation treatment. Cancer Res Treat 2016;48:1363–72.
[21] Demirci S, Broadwater G, Marks LB, et al. Breast conservation therapy: the influence of molecular subtype and margins. Int J Radiat Oncol Biol Phys 2012;83:814–20.
[22] Gabos Z, Thoms J, Ghosh S, et al. The association between biological subtype and locoregional recurrence in newly diagnosed breast cancer. Breast Cancer Res Treat 2010;124:187–94.
[23] Gangi A, et al. Breast-conserving therapy for triple-negative breast cancer. JAMA Surg 2014;149:252–8.
[24] Ihemelandu CU, Naab TJ, Mezghebe HM, et al. Treatment and survival outcome for molecular breast cancer subtypes in black women. Ann Surg 2008;247:463–9.
[25] Wen G, Zhang JS, Zhang YJ, et al. Predictive value of molecular subtyping for locoregional recurrence in early-stage breast cancer with N1 without postmastectomy radiotherapy. J Breast Cancer 2016;19: 176–84.
[26] Kaiser J, Kronberger C, Moder A, et al. Intraoperative tumor bed boost with electrons in breast cancer of clinical stages I through III: updated 10-year results. Int J Radiat Oncol Biol Phys 2018;102:92–101.
[27] Ragaz J, Jackson SM, Le N, et al. Adjuvant radiotherapy and chemotherapy in node-positive premenopausal women with breast cancer. N Engl J Med 1997;337:956–62.
[28] Overgaard M, Hansen PS, Overgaard J, et al. Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. Danish Breast Cancer Cooperative Group 82b Trial. N Engl J Med 1997;337:949–55.
[29] Mazouni C, Rimareix F, Mathieu MC, et al. Outcome in breast molecular subtypes according to nodal status and surgical procedures. Am J Surg 2013;205:662–7.
[30] Mersin H, Gülben K, Berberölu U, et al. Prognostic factors affecting postmastectomy locoregional recurrence in patients with early breast cancer: are intrinsic subtypes effective? World J Surg 2011;35:2196–202.
[31] Meyers MO, Klauber-Demore N, Ollila David W, et al. Impact of breast cancer molecular subtypes on locoregional recurrence in patients treated with neoadjuvant chemotherapy for locally advanced breast cancer. Ann Surg Oncol 2011;18:2851–7.
[32] Moo TA, McMillan R, Lee M, et al. Impact of molecular subtype on locoregional recurrence in mastectomy patients with T1-T2 breast cance r and 1-3 positive lymph nodes. Ann Surg Oncol 2014;21:1569–74.
[33] Jia WJ, Jia HX, Feng HY, et al. HER2-enriched tumors have the highest risk of local recurrence in Chinese patients treated with breast conservation therapy. Asian Pac J Cancer Prev 2014;15:315–20.
[34] Millar EK, Graham PH, O'Toole SA, et al. Prediction of local recurrence, distant metastases, and death after breast-conserving therapy in early-stage invasive breast cancer using a five-biomarker panel. J Clin Oncol 2009;27:4701–8.
[35] Sanpaolo P, Barbieri V, Genovesi D. Prognostic value of breast cancer subtypes on breast cancer specific survival, distant metastases and local relapse rates in conservatively managed early stage breast cancer: a retrospective clinical study. Eur J Surg Oncol 2011;37:876–82.
[36] Straver ME, Rutgers EJ, Rodenhuis S, et al. The relevance of breast cancer subtypes in the outcome of neoadjuvant chemotherapy. Ann Surg Oncol 2010;17:2411–8.
[37] Wong FY, Chin FK, Lee KA, et al. Hormone receptors and HER-2 status as surrogates for breast cancer molecular subtypes prognosticate f or disease control in node negative Asian patients treated with breast conservation therapy. Ann Acad Med Singapore 2011;40:90–6.
[38] Yamazaki N, Wada N, Yamauchi C, et al. High expression of post-treatment Ki-67 status is a risk factor for locoregional recurrence following breast-conserving surgery after neoadjuvant chemotherapy. Eur J Surg Oncol 2015;41:617–24.
[39] Wu SG, He ZY, Li Q, et al. Predictive value of breast cancer molecular subtypes in Chinese patients with four or more positive nodes after postmastectomy radiotherapy. Breast (Edinburgh, Scotland) 2012;21: 657–61.
[40] Nakamura N, Arahira S, Zenda S, et al. Post-mastectomy radiation therapy without usage of a bolus may be a reasonable option. J Radiat Res 2017;58:66–70.
[41] Sorlie T, Perou CM, Tibshirani R, et al. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proc Natl Acad Sci U S A 2001;98:10869–74.
[42] Rouzier R, Perou CM, Symmans WF, et al. Breast cancer molecular subtypes respond differently to preoperative chemotherapy. Clin Cancer Res 2005;11:5678–85.
[43] Parker JS, Mullins M, Cheang MC, et al. Supervised risk predictor of breast cancer based on intrinsic subtypes. J Clin Oncol 2009;27:1160–7.
[44] Haffty BG, Yang Q, Reiss M, et al. Locoregional relapse and distant metastasis in conservatively managed triple negative early-stage breast cancer. J Clin Oncol 2006;24:5652–7.
[45] Dent R, Trudeau M, Pritchard KI, et al. Triple-negative breast cancer: clinical features and patterns of recurrence. Clin Cancer Res 2007; 13:4429–34.
[46] Overgaard M, Jensen MB, Overgaard J, et al. Postoperative radiotherapy in high-risk postmenopausal breast-cancer patients given adjuvant tamoxifen: Danish Breast Cancer Cooperative Group DBCG 82c randomised trial. Lancet (London, England) 1999;353:1641–8.
[47] Ragaz J, Olivotto IA, Spinelli JJ, et al. Locoregional radiation therapy in patients with high-risk breast cancer receiving adjuvant chemotherapy: 20-year results of the British Columbia randomized trial. J Natl Cancer Inst 2005;97:116–26.