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

A meta-analysis

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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 Chi² 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=1769), 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-appearance 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 = local/regional 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
# KEY POINTS

- Breast conservative therapy and mastectomy, which are distinctly different treatment scenarios, complete a similar local/regional reappearance 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.\(^\text{[1,2]}\) 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,\(^\text{[3-5]}\) 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,\(^\text{[6]}\) thus will remaining microscopic residual lesions, if left untreated, 30% to 40% of these women are still in the detriment of disease recrudescence.\(^\text{[7]}\) 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).\(^\text{[8]}\) 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 overexpression of HER2; triple negative breast cancer (TNBC), negativity of ER, PR and HER2.\(^\text{[9-11]}\)

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.\(^\text{[12,13]}\) 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,\(^\text{[14]}\) reaffirming this conception. Inadequately, this ingenious study fails to investigate whether the surgical decisions could impact on the disease recrudescence 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

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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 Chi² 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\(^{[13-14,17-40]}\) 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 |
| themelandu   | 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 | 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 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 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 or 45 Gy plus a tumor bed boost /CMF or AC or adjuvant tamoxifen | 25 fractions | *                  | *                  |
| Millar       | 2009             | 417                   | WBI: 50Gy or 45 Gy plus tumor bed boost /CMF or doxorubicin-based | 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 | 16 fractions | 16 fractions | 6–12 months |
| Ragaz        | 1997             | 79                    | 36 patients received 37.5 Gy, 43 patients without RT /CMF | 24 patients received 50 Gy or 48 Gy, 21 patients without RT /CMF | 22–25 fractions | 28–48cycles |
| Overgaard    | 1997             | 45                    | 24 patients received 50 Gy or 48 Gy, 21 patients without RT /CMF | *                  | *                  | *                  |
| Mersin       | 2011             | 913                   | Irradiation dose and adjuvant therapy details not provided | 475 patients received 40–50 Gy RT; 229 patients without RT | 23–25 fractions | 23–25 fractions |
| Wu           | 2012             | 534                   | *                  | 475 patients received 40–50 Gy RT; 229 patients without RT | 23–25 fractions | 23–25 fractions |
| Nakamura     | 2016             | 74                    | WBI: 50Gy /AC-T or FEC-T or AC or FEC or others | 25 fractions | 25 fractions | 25 fractions |
| Moo          | 2014             | 713                   | Irradiation dose and adjuvant therapy details not provided | *                  | *                  | *                  |

AC = doxorubicin 60 mg/m² and cyclophosphamide 600 mg/m² every 3 weeks, AC-T = doxorubicin 60 mg/m² and cyclophosphamide 600 mg/m² followed by docetaxel 100 mg/m² every 3 weeks, BCT = breast conserving therapy, CMF = cyclophosphamide, methotrexate and 5-fluorouracil, DM = doxorubicin 75 mg/m² and cyclophosphamide 1,000 mg/m² 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/m² followed by gemcitabine 1200 mg/m² on days 1 and 8 every 3 weeks, LN = lymph node-positive, PBI = partial breast irradiation, RT = radiotherapy, WBI = whole breast irradiation.

* 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
3.3. Local-regional 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 superiori ty in comparison 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, 0.63; 95%CI, 0.42–0.99; P = .03; 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, 0.27–2.20; 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.

As 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 depressive disease reappearance 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.
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; (D) luminal A/B vs luminal-HER2 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,\cite{1,2} these results further consolidates them and are consistent with the study of Voduc and colleagues,\cite{3} 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 Rhemelandu 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,\cite{4,5,6} 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, \(P < 0.05\)). 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 DFS 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%; \(P = 0.04\))\cite{7}. Moreover, the optimal DFS in breast cancer women with luminal A subtype (87.4% vs luminal B of 82.6%, \(P = 0.04\); vs luminal-HER2 of 74.8%, \(P = 0.006\)) was confirmed by the study of Jia et al. who retrospective analyzed 405 breast cancer patients with luminal phenotype underwent BCT.\cite{8} 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 reformatory 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.

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