Systematic Review and Meta-Analysis

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Comparison of breast-conserving surgery with mastectomy in locally advanced breast cancer after good response to neoadjuvant chemotherapy

A PRISMA-compliant systematic review and meta-analysis

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Abstract

Background: The application of breast-conserving surgery (BCS) on patients with locally advanced breast cancer (LABC) with good response to neoadjuvant chemotherapy (NACT) still remains controversial. The objective in this study is to analyze the safety of BCS in the management of LABC in patients with good response to NACT.

Methods: We searched the electronic databases of Medline (Pubmed) and Cochrane Library for reports on local recurrence (LR), regional recurrence (RR), distant recurrence (DR), 5-year disease-free survival (DFS) or 5-year overall survival (OS) in patients with LABC receiving BCS or mastectomy (MT) and with good response to NACT. Based on the research results, we conducted a meta-analysis using Review Manager 5.3.

Results: Our study showed that 16 studies with a combined total of 3531 patients, of whom 1465 patients underwent BCS, whereas 2066 patients underwent MT. There was no significant heterogeneity among these studies (Q statistic: $P = .88$; $I^2 = 0\%$). Patients with good response to NACT showed no significant difference in LR and RR [odd ratio (OR) = 0.83; 95% confidence interval (CI): 0.60–1.15; $P = .26$; OR = 0.56; 95% CI: 0.33–0.93; $P = .03$], while we figured out a lower DR (OR = 0.51; 95% CI: 0.42–0.63; $P < .01$), a higher DFS (OR = 2.35; 95% CI: 1.84 to 3.01, $P < .01$) and a higher OS (OR = 2.12; 95% CI: 1.51 to 2.98, $P < .01$) in BCS compared with MT.

Conclusion: This meta-analysis concluded that BCS was a safe surgery for patients with LABC and had good response to NACT.

Abbreviations: ACT = adjuvant chemotherapy, BCS = breast-conserving surgery, BT = biotherapy, CI = confidence interval, CT = chemotherapy, DCIS = ductal carcinoma in situ, DFS = disease-free survival, DR = distant recurrence, ER = estrogen receptor, ET = endocrine therapy, ILC = infiltrating lobular carcinoma, LABC = locally advanced breast cancer, LR = local recurrence, MT = mastectomy, NACT = neoadjuvant chemotherapy, NOS = Newcastle-Ottawa Scale, OR = odd ratio, OS = overall survival, PR = progesterone receptor, RR = regional recurrence, RT = radiotherapy.

Keywords: breast-conserving surgery, locally advanced breast cancer, neoadjuvant chemotherapy

1. Introduction

Breast cancer is one of the most common diseases in the world, and leads cancer-related death among females in the world.[1] The development of surgery, chemotherapy (CT), radiotherapy (RT), endocrine therapy (ET), biotherapy (BT), and targeted therapy has improved treatment efficacy of breast cancer drastically. The effect of breast-conserving surgery (BCS) plus RT has been

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proved to be equivalent to that of mastectomy (MT).[2] In 1991, National Institutes of Health recommended BCS as the preferred treatment of early-stage breast cancer.[3] Many randomized trials with long-term follow-up time provided sufficient evidences that disease-free survival (DFS), overall survival (OS), and local recurrence (LR) in BCS were even higher than MT in early-stage breast cancer.[4–8] Despite the wide application of BCS in early-stage breast cancer, the use of BCS in locally advanced breast cancer (LABC) still remains controversial.

LABC refers to loco-regionally advanced tumor without distanced metastasis.[9] It is a heterogeneous group of tumors usually >5 cm, involves the skin or the underlying pectoral muscles, infiltrates axillary, supraclavicular and/or infraclavicular lymph nodes, and inflammatory carcinomas.[10] They are also represented by stage IIIA (T0N2M0; T1/2N2M0; T3N1/2M0), stage IIIB (T4N0–2M0), and stage IIIC (T0–4N3M0).[9] According to Surveillance of the Epidemiology and End Results database in 2013, the median survival for stage III is only 4.9 years.[11,12] Historically, the surgical management of LABC was limited to radical surgery with/without radiation,[13] yet the use of adjuvant chemotherapy increased the survival rate and reduced the distant recurrence (DR) and LR.[14] In 1988, the National Surgical Adjuvant Breast and Bowel Project B-18 trial reported that preoperative CT augmented the rate of BCS, especially in patients with tumors >5 cm.[15] However, there was no significant difference in OS and DFS between patients with/without postoperative CT.[16] So far, neoadjuvant chemotherapy (NACT) has been considered as a standard of treatment for patients with LABC.[17] NACT refers to CT given before surgery to downstage the advanced stage tumor and shrink the tumor size, and[18,19] therefore expanding surgical options, increasing the rate of breast conservation, and making the inoperable breast cancer operable.[20,21]

Since NACT plays an important role in pre-surgical treatment of LABC, BCS after good response to NACT has become feasible for selected patients with LABC who would have undergone MT. However, the real effect and role of BCS in LABC is still controversial. In this study, we attempted to evaluate the safety of BCS in patients with LABC who had good response to NACT.

2. Methods

2.1. Search strategy

The Medline (Pubmed) and Cochrane Library were searched using the following search term: "breast cancer," "advanced breast cancer," "neoadjuvant chemotherapy," "breast conserving surgery," "breast conservation," "mastectomy." This search was performed independently by 2 reviewers. Region and language were not limited.

2.2. Inclusion and exclusion criteria

All the studies that meet the following criteria were included: female patients with LABC who were treated and responded to NACT regardless of the type of CT and the courses of the treatment; clinical trials comparing 2 different surgical managements, MT, or BCS in patients after they got NACT; the type of MT and the postoperative adjuvant treatments were not restricted and the medium follow-up was >12 months; and histological type and status of breast cancer were not restricted.

The exclusion criteria were the following: The results were published in a systematic review or as a case report; the patients were treated with RT before surgery and no comparison groups were used; the studies did not demonstrate any kinds of survival or recurrence rate.

2.3. Quality assessment and data extraction

The quality of each included study was assessed via Newcastle-Ottawa Scale (NOS). A score of 0 to 9 was allocated to each study included, and those with an NOS score >5 were assigned as high-quality studies. The GetData Graph Digitizer 2.24 software (ht*tp://getdata-graph-digitizer.com/) was used to digitize and extract the data from the Kaplan-Meier curves, in case the survival rate was only provided graphically. The following information was extracted from the eligible trials: first author's name, year of publication, number of patients enrolled, age, enrollment interval, country, medium follow-up time, NACT agent, other adjuvant therapy, status of receptor, histological type, pathological response to CT, tumor size before or after NACT, LR, regional recurrence (RR), DR, 5-year DFS, and 5-year OS.

2.4. Statistical analysis

The Cochrane Collaboration Review Manager 5.3 statistical software was used for this meta-analysis. For the LR, RR, DR, 5-year DFS, or 5-year OS in each study, the odd ratio (OR), with its variance and 95% confidence interval (CI) were estimated. The heterogeneity of ORs was evaluated by I^2 test. If I^2 value was <50%, which represents low or moderate heterogeneity, the fixed-effects model was used to calculate the pooled ORs.[22] Forest plots were used to present the outcomes of Meta-analysis. Publication bias was evaluated by the symmetry of funnel plot. To test the reliability of the results of the meta-analysis, we did sensitive analysis by excluding individual studies and analyzing the alteration of overall effects.

3. Results

After searching the databases mentioned above, 77 articles were fully reviewed. Among these studies, 61 articles were excluded for not meeting the selection criteria (Fig. 1). Overall, 16 retrospective cohort studies with 3531 LABC patients,[23–38] 1465 patients underwent BCS, and 2066 patients underwent MT were included. The choice of surgery type was made according to the tumor size after NACT, patients' clinical or pathological response to CT and doctor's decision. NACT agent that applied to the patients and the postoperative adjuvant therapy including CT, RT, ET, or BT were reported in all the trials (Table 1). Patient's average age ranged from 33 to 70. Estrogen receptor (ER), progesterone receptor, or human epidermal growth factor receptor 2 status was recorded in 12 researches. The pathological responses of patients toward NACT were shown in Table 2, as well as the menopausal status. Thirteen studies reported LR,[23–25,27–29,31–36,38] seven of them reported RR,[24,28,31–33,35,38] and seven articles recorded DR.[26,28,30,33,35,36,38] LR was defined as ipsilateral tumor or on the same side of chest wall recurrence, whereas RR included the ipsilateral axilla, infraclavicular, supraclavicular, and internal mammary lymph nodes recurrence. DR refers to the recurrence happened in a distant site. Five publications reported 5-year DFS[23,28,31–33,37] and 5 publications reported 5-year OS[23,31,33,35,37] (Table 3). The histological type of the majority of patients enrolled in these trials was infiltrating ductal carcinoma, whereas the others types were infiltrating lobular carcinoma (ILC) and ductal carcinoma in situ. Symmetric funnel

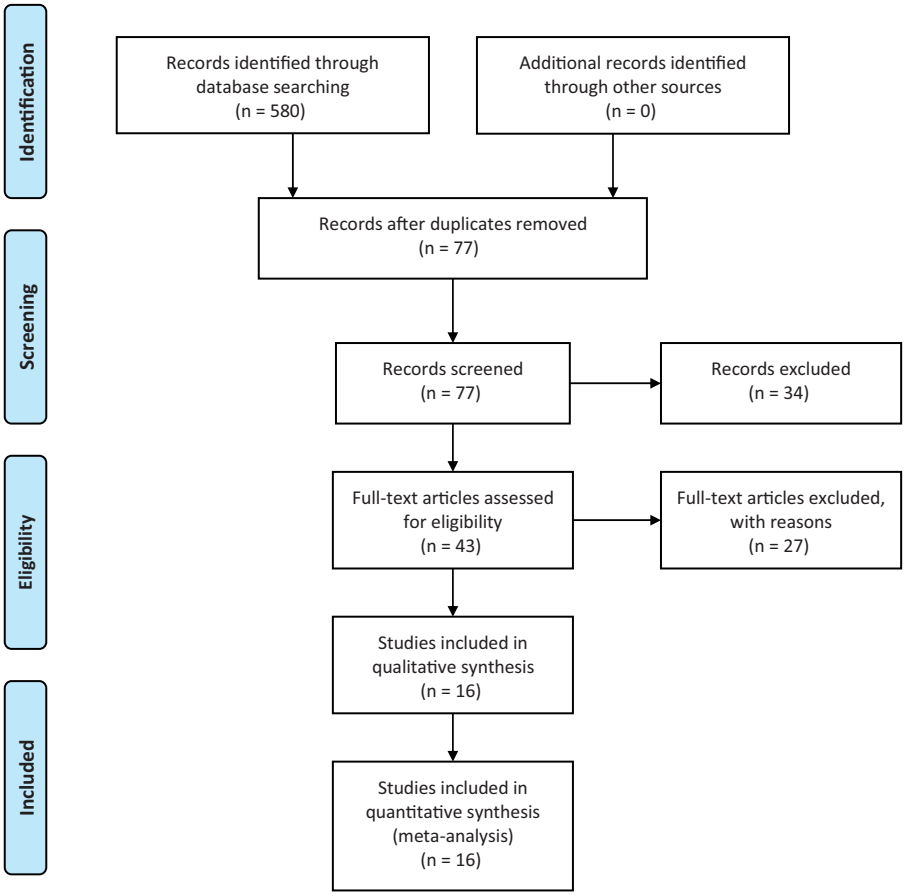

Figure 1. A flow diagram of the search progress.

plot of the 13 nonrandomized clinical trials showed no apparent publication bias (Fig. 2).

Thirteen trials reporting LR contributed to the combined calculation. There was no heterogeneity among these studies (Q statistic: $P=.88$; $I^2=0\%$). Meanwhile, results in the fixed-effect model (OR = 0.83; 95% CI: 0.60–1.15; $P=.26$) indicate no difference in LR between BCS and MT (Fig. 3).

Seven trials reporting RR were included in the calculation. No heterogeneity was found among these studies ($P=.95$; $I^2=0\%$). The pooled OR of RR was 0.56 (95% CI: 0.33–0.93; $P=.03$),

Table 1

Study information and baseline characteristic of patients.

Author Year	Country	Medium follow-up, mo	Enrollment interval, yr	Age, yr	Surgery (BCS/MT)	NACT	Adjuvant therapy	NOS
Schwartz[23] 1994	USA	46	1983–1991	55	55/103	CMF	CT, RT	7
Cance[24] 2002	USA	70	1992–1998	44	21/38	CMF	CT, RT	7
McIntosh[25] 2003	UK	62	1992–1997	51	44/115	CVAP	RT, ET	6
Rouzier[26] 2004	France	67	1987–2001	50	287/307	AVCMF/CAF/CEF	CT, RT, ET	8
Sadetzki[27] 2005	Israel	>27	1995–2001	<70	79/40	anthracycline-based	RT	7
Parmar[28] 2006	India	30	1998–2002	47.6	188/476	CAF/CEF	CT, RT, ET	8
Clouth[29] 2007	UK	33.5	2001–2005	48.2	60/40	TAC	RT, ET	5
Beadle[30] 2009	USA	91	1973–2006	33	44/56	NA	RT	7
Sweeting[31] 2011	USA	76.8	1991–2007	39	54/68	anthracycline/taxane based	RT, ET, BT	7
Meyers[32] 2011	USA	55	1991–2005	49	49/100	anthracycline/taxane based	RT, BT	7
Cho[33] 2013	Korea	45.9	1998–2010	49	124/307	anthracycline/taxane based	RT, ET	8
Shin[34] 2013	Korea	62.4	2004–2007	45.8	72/57	DA/AC/FEC	CT, RT	8
Levy[35] 2014	France	75.6	2002–2012	49	111/173	anthracycline/taxane based	RT, ET, BT	8
Cureton[36] 2014	USA	46.8	2002–2006	49.1	83/109	anthracycline/taxane based	RT	6
Barranger[37] 2015	France	41.1	2007–2012	49.6	86/33	FEC+D	RT, ET	7
Debled[38] 2015	France	38	2005–2012	49.6	108/44	FEC+D	RT, BT	7

A = doxorubicin/adriamycin, BT = biotherapy, C = cyclophosphamide, CT = chemotherapy, D = docetaxel, E = epirubicin, ET = endocrine therapy, F = 5 fluorouracil, M = methotrexate, NA = not available, NOS = Newcastle-Ottawa Scale, P = prednisolone, RT = radiotherapy, T = paclitaxel, V = vincristine.

Table 2

Study information and baseline characteristic of patients.

Author Year	ER +	PR +	Her2 +	Pathological complete response (n)	Menopausal status†	Histological type
Schwartz[23] 1994	101*	76*	NA	BCS: 55 MT: 103	Pre/peri: 62; Post: 98	DCIS: 11
Cance[24] 2002	28*	NA	NA	BCS: 6 MT: 3	Pre/peri: 43; Post: 19	IBC: 13
McIntosh[25] 2003	NA	NA	NA	NA	Pre/peri: 76; Post: 90	NA
Rouzier[26] 2004	BCS: 134 MT: 184	BCS:161 MT: 203	NA	NA	NA	IDC: 527 ILC: 67
Sadetzki[27] 2005	BCS: 38 MT: 15	BCS: 30 MT: 14	BCS: 18 MT: 15	NA	NA	DCIS: 46(BCS: 19,MT: 21) IDC: 105(BCS: 71,MT: 34) ILC: 11(BCS: 8,MT: 3)
Parmar[28] 2006	BCS: 43 MT: 121	BCS: 63 MT: 146	NA	NA	Pre/peri: 305 (BCS: 83,MT: 222) Post: 359 (BCS: 105,MT: 254)	NA
Clouth[29] 2007	70	38	NA	NA	NA	IDC:70, ILC:24 Mixed:3
Beadle[30] 2009	NA	NA	NA	NA	NA	IDC
Sweeting[31] 2011	BCS: 20 MT: 32	BCS: 19 MT: 29	BCS: 9 MT: 19	BCS: 21 MT: 12	NA	IDC: 109(BCS: 45,MT: 64) ILC: 3(BCS: 2, MT: 1)
Meyers[32] 2011	NA	NA	BCS: 12 MT: 33	39	NA	NA
Cho[33] 2013	BCS: 48 MT: 190	BCS: 42 MT: 142	BCS: 39 MT: 100	BCS: 38 MT: 34	NA	IDC: 407(BCS: 115,MT: 292) ILC: 6(MT)
Shin[34] 2013	MT: 30 BCS: 35	NA	BCS: 16 MT: 20	41	NA	NA
Levy[35] 2014	NA	NA	BCS: 23 MT: 36	BCS: 28 MT: 9	Pre/peri: 158 (BCS: 60, MT: 98) Post: 126 (BCS: 51, MT: 75)	IDC: 254(BCS: 105, MT: 149) ILC: 19(BCS: 1, MT: 18)
Cureton[36] 2014	NA	NA	NA	BCS: 36 MT: 36	NA	NA
Barranger[37] 2015	NA	NA	NA	BCS: 23 MT: 4	Post: 64	IDC: 118
Debled[38] 2015	NA	NA	BCS: 108 MT: 44	NA	NA	IDC: 147(BCS: 104,MT: 43) ILC: 5(BCS: 4,MT: 1)

* Total number of patients

† Patients did not undergo surgery were also included. All IBC patients received MT surgery.

BCS = breast-conserving surgery, DCIS = ductal carcinoma in situ, IDC = infiltrating ductal carcinoma, IBC = inflammatory breast cancer, ILC = infiltrating lobular carcinoma, MT = mastectomy, NA = not available, PR = progesterone receptor, post = postmenopausal, pre/peri = premenopausal and "peri" menopausal.

Table 3

Patients' outcomes after treatment.

Author Year	Tumor size, cm		LR	RR	DR	Five-year DFS	Five-year OS
	Pre-NACT	Post-NACT					
Schwartz[23] 1994	NA	NA	BCS: 1/55 MT: 4/103	NA	NA	BCS: 42/55 MT: 58/103	BCS: 44/55 MT: 69/103
Cance[24] 2002	NA	NA	BCS: 2/21 MT: 5/38	BCS: 1/21 MT: 3/38	NA	NA	NA
McIntosh[25] 2003	NA	BCS: 1.3 MT: 3.4	BCS: 1/44 MT: 6/115	NA	NA	NA	NA
Rouzier[26]2004	4.9	3.1	NA	NA	BCS: 72/287 MT: 114/307	NA	NA
Sadetzki[27] 2005	BCS: 4.67 MT: 4.74	BCS: 1.68 MT: 3.29	BCS: 6/79 MT: 6/40	NA	NA	NA	NA
Parmar[28] 2006	BCS: 6 MT: 8.3	BCS: 1.5 MT: 4.1	BCS: 15/188 MT: 51/476	BCS: 10/188 MT: 37/476	BCS: 21/188 MT: 122/476	BCS: 117/188 MT: 176/476	NA
Clouth[29] 2007	5.2	1.45	BCS: 6/60 MT: 4/40	NA	NA	NA	NA
Beadle[30] 2009	NA	NA	NA	NA	BCS: 16/44 MT: 33/56	NA	NA
Sweeting[31] 2011	BCS: 5.6 MT: 6.7	BCS: 1.3 MT: 3.2	BCS: 6/54 MT: 11/68	BCS: 1/54 MT: 4/68	NA	BCS: 44/54 MT: 39/68	BCS: 48/54 MT: 41/68
Meyers[32] 2011	NA	NA	BCS: 2/49 MT: 8/100	BCS: 0/49 MT: 5/100	NA	NA	NA
Cho[33] 2013	NA	NA	BCS: 4/124 MT: 5/307	BCS: 3/124 MT: 14/307	BCS: 14/124 MT: 49/307	BCS: 101/124 MT: 229/307	BCS: 110/124 MT: 258/307
Shin[34] 2013	NA	<4	BCS: 5/72 MT: 3/57	NA	NA	NA	NA
Levy[35] 2014	BCS: 4 MT: 5	NA	BCS:8/111 MT: 12/173	BCS: 2/111 MT: 7/173	BCS: 19/111 MT: 50/173	NA	BCS: 100/111 MT: 131/173
Cureton[36] 2014	6	NA	BCS: 6/83 MT:8/109	NA	BCS: 14/83 MT: 26/109	NA	NA
Barranger[37] 2015	BCS: 3.4 MT: 5.5	BCS: 1.7 MT: 3.3	NA	NA	NA	BCS: 64/86 MT: 20/33	BCS: 66/86 MT: 25/33
Debled[38] 2015	BCS: 4.5 MT: 7.0	NA	BCS: 6/108 MT:0/44	BCS: 3/108 MT: 1/44	BCS: 17/108 MT: 11/44	NA	NA

BCS = breast-conserving surgery, DFS = disease-free survival, DR = distant recurrence, LR = local recurrence, MT = mastectomy, NA = not available, OS = overall survival, Post-NACT = after neoadjuvant chemotherapy treatment, Pre-NACT = before neoadjuvant chemotherapy treatment, RR = regional recurrence.

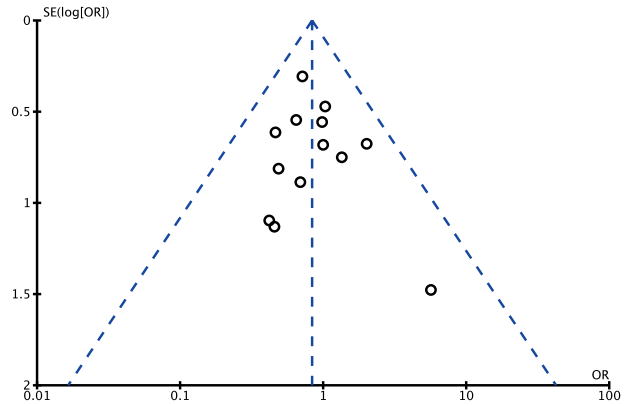

Figure 2. A funnel plot of the 13 included studies that reported local recurrence (LR).

suggesting no significant difference in RR between BCS and MT (Fig. 4).

Seven trials reported DR in the calculation. No heterogeneity was observed ($P=.73$; $I^2=0\%$). BCS was associated with lower distant relapse rate compared with patients undergone MT (OR = 0.51; 95% CI: 0.42–0.63; $P<.01$) (Fig. 5).

Five-year DFS was reported in 5 studies. No significant heterogeneity was found in these studies ($P=.31$; $I^2=16\%$). Compared with group MT, the pooled OR of DFS was 2.35 (95% CI: 1.84–3.01, $P<.01$) in BCS. This result suggests that 5-year DFS of BCS was not worse than that of MT after LABC patients' treatment with NACT (Fig. 6).

Five-year OS was demonstrated in 5 studies. The heterogeneity among these reports was not significant ($P=.12$; $I^2=46\%$). Using the fixed-effect model, the pooled OR of OS was 2.12 (95% CI: 1.51–2.98, $P<.01$) in BCS, which indicates that BCS had a slight higher 5-year OS than MT (Fig. 7).

In sensitive analysis, the results for LR, RR, DR, 5-year DFS, and 5-year OS were consistent in each single exclusion analysis (Table 4).

Based on these data, we further performed subgroup analysis on recurrences in America, Europe, and Asia. 6, 6, or 4 related studies in 3 geographic areas could be analyzed. Patients with LABC in America had no heterogeneity in recurrences (LR: $P=.95$; $I^2=0\%$, RR: $P=.57$; $I^2=0\%$, DR: $P=.81$; $I^2=0\%$) and no significant difference between BCS and MT groups (LR: $P=.22$; OR = 0.69; 95% CI: 0.37–1.26, RR: $P=.10$; OR = 0.31; 95% CI: 0.08–1.26, DR: $P=.02$; OR = 0.52; 95% CI: 0.31–0.90) (see Supplemental Contents-Fig. S1-S3, http://links.lww.com/MD/B916). In Europe, no heterogeneity was detected (LR: $P=.57$, $I^2=0\%$, RR: $P=.47$; $I^2=0\%$, DR: $P=.95$; $I^2=0\%$). The pooled ORs of LR, RR, and DR are 1.09, 0.60, and 0.55, respectively (LR: 95% CI: 0.57–2.11, RR: 95% CI: 0.17–2.05, DR: 95% CI: 0.41–0.73). There was no significant difference in term of LR and RR between BCS and MT groups (LR: $P=.79$, RR: $P=.41$). However, BCS showed lower risk in DR in comparison with MT ($P<.01$) (see Supplemental Contents-Fig. S4-S6, http://links.lww.com/MD/B916). In Asia, a higher heterogeneity was found in term of recurrences (LR: $P=.36$; $I^2=6\%$, RR: $P=.74$; $I^2=0\%$, DR: $P=.14$; $I^2=54\%$). Results indicated no difference in LR and RR, but a statistical significance in DR between 2 groups (LR: $P=.39$; OR = 0.81; 95% CI: 0.51–1.30, RR: $P=.14$; OR = 0.62; 95% CI: 0.33–1.17, DR: $P<.01$; OR = 0.45; 95% CI: 0.31–0.67) (Supplemental Contents-Fig. S7-S9, http://links.lww.com/MD/B916) (Table 5). In lack of the sufficiency of data, we were unable to analyze DFS and OS according to geographic area.

4. Discussion

This meta-analysis recruited 16 trials that matched our criteria. No difference was detected in patients' age, pre-NACT tumor size, and receptor status, such as ER, progesterone receptor (PR), and Her2. In this analysis, there was no significant difference in LR and RR but a lower DR and a higher rate of DFS and OS in BCS group compared with MT, indicating BCS was a safe way for patients with LABC who had good response to NACT. Furthermore, we performed a subgroup analysis depending on geographic area. Results also showed no difference in LR and RR between 2 groups in America, Europe, and Asia area, and BCS associated with lower DR in Europe and Asia.

It is very important for patients with LABC with good response to NACT to achieve high DFS and OS rate in BCS group.[16,39] Some studies stated that patients had good clinical response or pathological complete remission from NACT was more

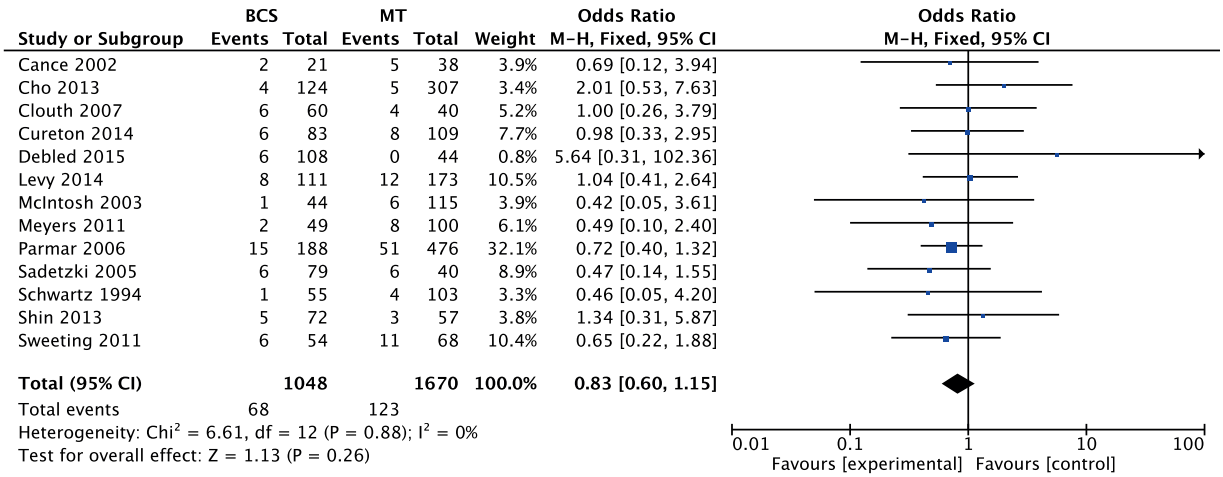

Figure 3. A Forest plot of the pooled odd ratio (OR) of local recurrence (LR) for the BCS and MT group. BCS = breast-conserving surgery, CI = confidence interval, MT = mastectomy.

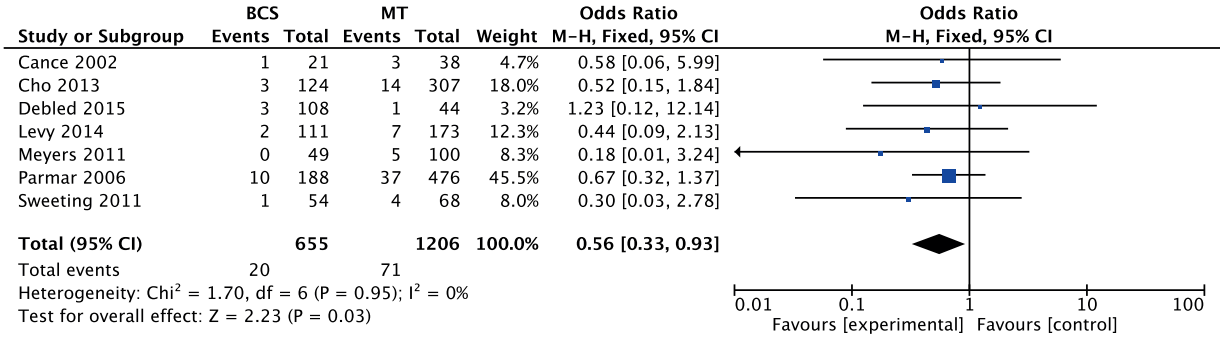

Figure 4. A Forest plot of the pooled odd ratio (OR) of regional recurrence (RR) for the BCS and MT group. BCS = breast-conserving surgery, CI = confidence interval, MT = mastectomy.

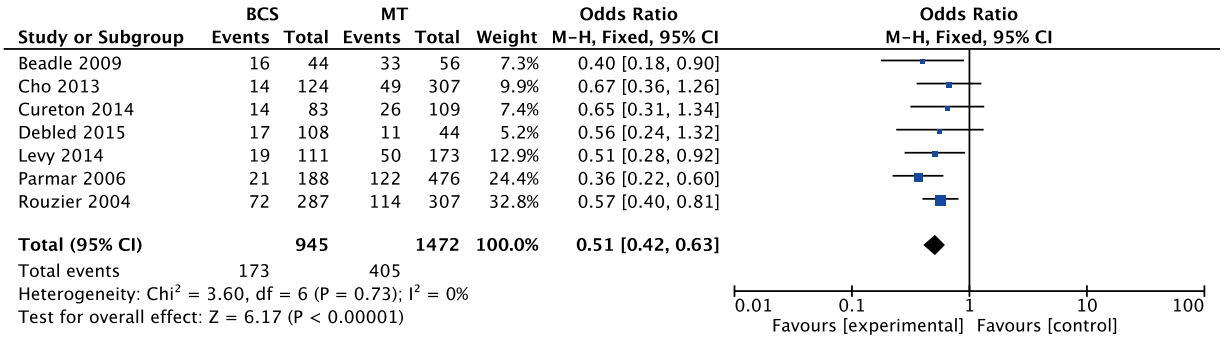

Figure 5. A Forest plot of the pooled odd ratio (OR) of distant recurrence (DR) for the BCS and MT group. BCS = breast-conserving surgery, CI = confidence interval, MT = mastectomy.

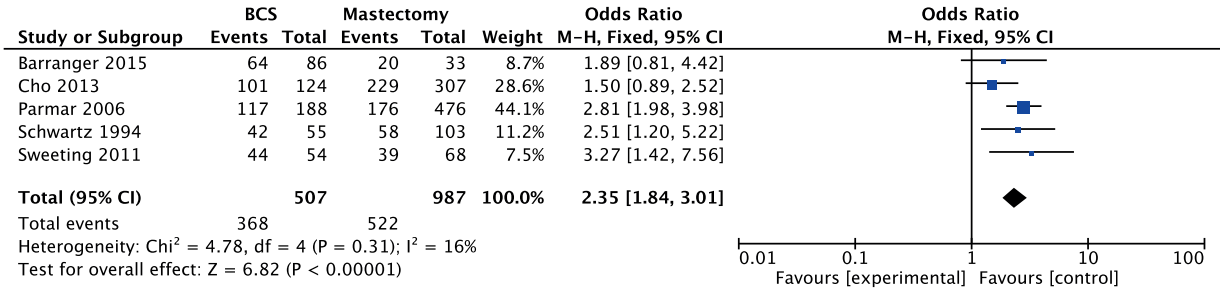

Figure 6. A Forest plot of the pooled odd ratio (OR) of disease-free survival (DFS) for the BCS and mastectomy (MT) group. BCS = breast-conserving surgery, CI = confidence interval.

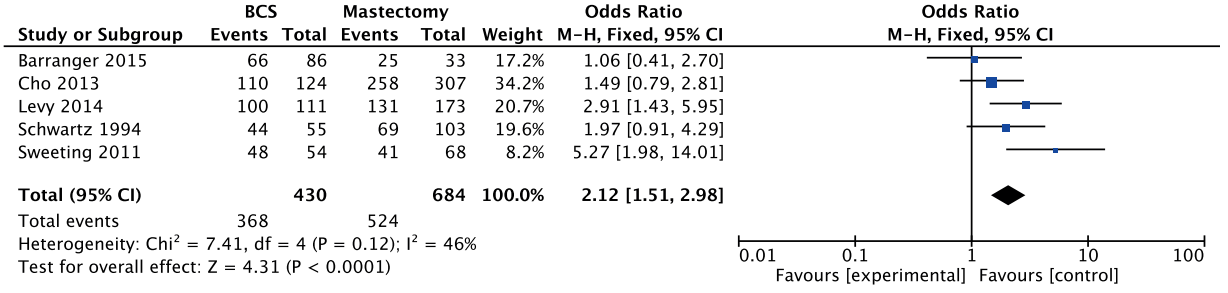

Figure 7. A Forest plot of the pooled odd ratio (OR) of overall survival (OS) for the BCS and mastectomy (MT) group. BCS = breast-conserving surgery, CI = confidence interval.

Table 4

Sensitive analysis by excluding each single study.

Results excluded study	LR OR (95%CI) and *P* value	RR OR (95%CI) and *P* value	DR OR (95%CI) and *P* value	DFS OR (95%CI) and *P* value	OS OR (95%CI) and *P* value
Schwartz[23]	.84 [.61, 1.17] *P*=.31			2.34 [1.80, 3.03] *P*<.01	2.15 [1.47, 3.15] *P*<.01
Cance[24]	.84 [.60, 1.16] *P*=.28	.55 [.33, .94] *P*=.03			
McIntosh[25]	.85 [.61, 1.17] *P*=.32				
Rouzier[26]			.49 [.37, 0.64] *P*<.01		
Sadetzki[27]	.87 [.62, 1.21] *P*=.40				
Parmar[28]	.88 [.60, 1.29] *P*=.52	.46 [.22, .97] *P*=.04	.56 [.44, 0.71] *P*<.01	2.00 [1.41, 2.82] *P*<.01	
Clouth[29]	.82 [.59, 1.14] *P*=.25				
Beadle[30]			.52 [.42, 0.65] *P*<.01		
Sweeting[31]	.85 [.61, 1.19] *P*=.35	.58 [.34, .98] *P*=.04		2.28 [1.76, 2.95] *P*<.01	1.83 [1.27, 2.65] *P*<.01
Meyers[32]	.85 [.61, 1.19] *P*=.34	.59 [.35, 1.00] *P*=.05			
Cho[33]	.79 [.57, 1.10] *P*=.16	.56 [.32, .99] *P*=.05	.50 [.40, 0.62] *P*<.01	2.70 [2.04, 3.56] *P*<.01	2.44 [1.63, 3.65] *P*<.01
Shin[34]	.81 [.58, 1.13] *P*=.21				
Levy[35]	.81 [.57, 1.14] *P*=.22	.57 [.33, .99] *P*=.05	.51 [.41, 0.65] *P*<.01		1.91 [1.29, 2.82] *P*<.01
Cureton[36]	.82 [.58, 1.15] *P*=.24		.50 [.40, 0.63] *P*<.01		
Barranger[37]				2.40 [1.85, 3.10] *P*<.01	2.34 [1.61, 3.39] *P*<.01
Debled[38]	.79 [.57, 1.10] *P*=.16	.53 [.31, .91] *P*=.02	.51 [.41, 0.64] *P*<.01		

CI = confidence interval, DFS = disease-free survival, DR = distant recurrence, LR = local recurrence, OR = odd ratio, OS = overall survival, RR = regional recurrence.

favorable to accept BCS ($P<.001$).[26,33,35] Tumor stage was one of early phase factors to decide whether patients can accept BCS or not. Normally, early-staged breast cancer patients were more suitable to BCS. Meyers et al[32] suggested that post-NACT staging was more prognostic than pretreatment assessment, whereas the latter had no association with LR. As a matter of fact, post-NACT pathologic stage III indicated a poor prognosis predictor in BCS. In addition, based on the data we analyzed, there was no difference in pre-NACT tumor size, but a significant difference in post-NACT tumor size was found between BCS and MT group ($P<.01$). This result suggested that patients with LABC who received BCS had a better response to NACT. Because of data limitations, we cannot get more results from that (Table 3).

The effectiveness of NACT in patients with LABC is decided by many factors. Rouzier et al[26] indicated that lobular breast cancer associated with ineligibility for BCS. Some trials showed patients receiving MT had more ILC.[33,35] Receptor status also associated with the choice of surgery type.[26] As is known to all, ER- and PR-positive status breast cancer correlated with a good prognosis, whereas Her2 positive status breast cancer leaded a poor prognosis.[40] Her2-positive breast cancer often occurred in young patients and its clinical feature was usually aggressive.[41,42] Moreover, LR ratio was extremely higher in triple negative breast cancer and Her2-positive breast cancer.[43,44] In our study, tamoxifen treatment was added for menopausal women or those with positive ER or PR. Trastuzumab was also used for Her2-positive patients. In addition to tumor molecular signature, chemotherapeutic agents that used in NACT also impact on BCS rate.[45,46] In our study, chemotherapeutic agents changed upon years from anthracycline-based CT in early treatment strategy[23–30] to anthracycline and taxane-based therapy[31–37] in recent managements. Overall, we confirmed that chemotherapeutic agents influences the rate of BCS in LABC, but more data and subgroup analyzed should be finished in the future for further results.

There are some limitations in this study. The funnel plot excludes the possibility that the publication bias may significantly affect the ultimate results. However, none of these trials were randomized and the assignment of patients was influenced by many factors including pathologic stage of tumor, clinical and pathological responses, receptor status, and the application of adjuvant therapy. Data extraction such as converting percentage of each rate to real number of patients could also introduce bias. Some studies only focused on one specific subgroup of breast cancer. DFS and OS were only mentioned in some articles, and thus might cause the high heterogeneity that negatively affects the results of our study.

Chawla et al[47] reported patients with LABC undergoing BCS had higher LR for NACT might diminish the primarily tumor to

Table 5

Subgroup analysis.

Geographic area	Factor	Articles (n)	I^2 (%)	*P*	OR (95% CI)
America	LR	5	0.0	.22	0.69 [0.37, 1.26]
	RR	3	0.0	.10	0.31 [0.08, 1.26]
	DR	2	0.0	.02	0.52 [0.31, 0.90]
Europe	LR	4	0.0	.79	1.09 [0.57, 2.11]
	RR	2	0.0	.41	0.60 [0.17, 2.05]
	DR	3	0.0	<.01	0.55 [0.41, 0.73]
Asia	LR	4	6.0	.39	0.81 [0.51, 1.30]
	RR	2	0.0	.14	0.62 [0.33, 1.17]
	DR	2	54.0	<.01	0.45 [0.31, 0.67]

CI = confidence interval, DR = distant recurrence, LR = local recurrence, OR = odd ratio, RR = regional recurrence.

multicentric fragments, but our study showed the good effect of BCS with LABC with good response to NACT. However, all patients in BCS group in this research received RT following surgery, whereas some patients in MT group without postsurgical RT were also included. Moreover, all patients were treated with other adjuvant therapies after their surgeries, including BT and ET, which maybe affect the outcomes of analysis. Furthermore, most of the trials controlled for age, which was an important predicting factor of survival. Brandt et al[48] showed that patients who were younger than 40 years or older than 80 years had a significantly higher 10-year mortality rate. Unfortunately, there is no further applicable data for us to analyze in this research.

Briefly, this analysis mainly focused on patients received NACT with locally advanced staged breast cancer, whose tumors were larger than 3 cm without DR and with good response to NACT, which was different from those articles that included both early-staged and later-staged breast cancer or those did not take NACT. We further subanalyzed these data based on geographic area and showed no difference among these areas. However, all results showed patients with LABC who had a good response to NACT are suitable and safe to accepted BCS. In this situation, BCS can be a rational choice to improve patients' long-term life quality.

5. Conclusion

We analyzed LR, RR, DR, DFS, and OS in patients with LABC received BCS or MT after good response to NACT. Our study suggested that there was no significant difference in LR and RR between BCS and MT. Moreover, BCS was associated with better DFS, OS, and lower DR in these patients. Thus we concluded that BCS was a safe option for the patients with initially advanced stages tumor but good response to NACT after taking their post-treatment staging and other controllable factors into consideration. However, well-designed larger RCTs with long follow-up time are needed to support our conclusions in the future.

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