Local Recurrence after Breast-Conserving Surgery and Mastectomy Following Neoadjuvant Chemotherapy for Locally Advanced Breast Cancer – a Meta-Analysis

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Keywords

Breast-conserving surgery · Mastectomy ·
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Summary

Background: Breast-conserving surgery (BCS) in patients with large tumors shrunk by neoadjuvant chemotherapy (NCT) remains controversial. We conducted a meta-analysis to evaluate the local recurrence rates in locally advanced breast cancer (LABC) patients receiving NCT comparing BCS with mastectomy. **Methods:** Pubmed, Web of Knowledge, and Ovid's database were searched for studies concerning treatment for LABC from January 2000 to June 2015. A meta-analysis was performed to compare the recurrence rates of patients receiving BCS versus mastectomy following NCT. **Results:** 8 trials with a total of 3,215 patients were analyzed. The prevalence of local recurrence was 9.2% in the BCS group versus 8.3% in the mastectomy group without significant difference (odds ratio (OR) 1.07, 95% confidence interval (CI) 0.28–1.48; $p = 0.66$). The 5-year local recurrence-free survival (LRFS) rate was lower in the mastectomy group than in the BCS group, but no significant difference was found between the 2 groups (OR 1.11, 95% CI 0.61–1.99; $p = 0.74$). **Conclusion:** BCS after NCT is safe in terms of local recurrence and LRFS in LABC women. Shrinking tumors with NCT provides the opportunity to apply BCS with no detriment to outcome.

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Introduction

Neoadjuvant chemotherapy (NCT) is regarded as the standard treatment for locally advanced breast cancer (LABC). NCT is widely accepted since it was shown that it can downstage the disease and allow for breast-conserving surgery (BCS) to be performed in LABC patients who are initially candidates for mastectomy or inoperable [1–3]. Furthermore, operable breast cancer patients treated with preoperative or postoperative chemotherapy had equivalent overall survival (OS) as well as increased rates of BCS following preoperative chemotherapy [4, 5]. Therefore, BCS with improved cosmesis and quality of life is possible, even in patients with LABC [6–8].

Some studies investigating BCS after NCT have indicated locoregional recurrence rates of less than 10% [9, 10]. Moreover, Kuerer et al. [11] reported better disease-free survival and OS in patients with LABC undergoing BCS post NCT. However, other series have reported locoregional recurrence rates for such patients of over 20% [12, 13]. Furthermore, those studies showing better survival rates in patients with LABC undergoing BCS after NCT as compared to mastectomy might have some selection bias because the BCS groups likely included patients who achieved a good response to chemotherapy.

In consideration of the current controversy regarding BCS in patients with LABC, the local recurrence rate was compared between LABC patients who underwent BCS versus mastectomy after NCT with the aim to assess the oncologic safety of NCT in LABC patients.

Xiaodong Zhou and Yujie Li are co-first authors and contributed equally to the work.

Table 1. Overview of the reviewed studies: patient demographics

Author, year [ref.]	Country	Patients, n	Patient source	Mean age, years	Tumor type, %	Mean initial tumor diameter, cm	Tumor diameter after NCT, cm	Stage, %	Lymph node involvement, %
Cho JH, 2013 [29]	Korea	431	Severance Hospital	BCS: 46.6 M: 47.65	ductal: 94.7 lobular: 1.5 other: 4.0	–	–	BCS: 0–II: 77.4 III: 22.6 M: 0–II: 67.4 III: 32.6	–
Debled M, 2015 [30]	France	152	Institut Bergonie, Bordeaux	BCS: 49 M: 51	ductal: 96.7 lobular: 3.3	BCS: 4.5 M: 7.0	–	–	–
Eugene H, 2006 [31]	USA	815	University of Texas	–	–	–	–	BCS: I: 4 II: 58 III: 38 M: II: 17 III: 83	BCS: 15 M: 31
Fitzal F, 2010 [32]	Austria	308	Medical University Vienna	–	–	–	–	–	–
Parmar V, 2006 [22]	India	664	Tata Memorial Hospital	47.6	–	7.4	BCS: 1.5 M: 4.1	–	supraclavicular lymph node presented: 15%
Rouzier R, 2006 [33]	France	594	Institut Gustave Roussy	50	ductal: 89 lobular: 11	4.9	3.1	BCS: I–II: 43.4 III: 38 M: II: 29.7 III: 70.3	BCS: 54.4 M: 56.0
Shin HC, 2013 [23]	Korea	129	Chung-Ang University College of Medicine	45.8	–	–	–	III	BCS: 75.3 M: 80.8
Sweeting RS, 2011 [24]	USA	122	University of North Carolina School of Medicine	39.5	–	BCS: 5.6 M: 6.7	BCS: 1.3 M: 3.2	BCS: I: 0 II: 42 III: 58 M: I: 3 II: 29 III: 68	–

NCT = Neoadjuvant chemotherapy; BCS = breast-conserving surgery; M = mastectomy.

Materials and Methods

Search Strategy

PubMed, Web of Knowledge, and Ovid's database were searched for the period of January 2000 to June 2015 without language restrictions. The search terms used were 'neoadjuvant chemotherapy', 'locally advanced breast cancer', 'breast-conserving surgery', and 'mastectomy'. The reference lists of relevant studies were checked manually to locate any studies that may have been missed.

Study Selection

Identified studies were assessed for eligibility for inclusion in the meta-analysis by scrutinizing the titles, abstracts, and keywords of every record retrieved. Studies were restricted to those published in English and Chinese. Clinical studies concerning comparisons of recurrence between BCS and mastectomy following NCT for LABC were also included.

Data Extraction

Two coauthors (LY and ZX) independently selected studies for inclusion and exclusion and reached a consensus when they did not agree on the initial assignment. The following variables were recorded: authors, journal and year of publication, number of patients, age, and local recurrence rate. If necessary, the corresponding authors of the studies were contacted to obtain additional information.

Fig. 1. Flowchart of the results of the literature search.

Statistical Analysis

Pooled estimates of outcome were calculated using a fixed effects model, or a random effects model was used according to the degree of heterogeneity. The test of homogeneity of effects was performed using the χ^2 tests, with $p \leq 0.05$ indicating significant heterogeneity. When the hypothesis of homogeneity was not rejected, the fixed effects model was used to estimate the pooled effect of outcomes; when the reverse was true, the random effects model was also calculated. Statistical analyses were carried out using Cochrane Review Manager 5.0 software (Cochrane Collaboration, Freiburg, Germany).

Results

Study Selection

We identified 231 potentially relevant articles (fig. 1). After exclusion of duplicate references, nonrelevant literature, and studies that did not satisfy the inclusion criteria, 17 candidate articles were considered for the meta-analysis. After careful review of the full text of these articles, 8 studies were included. The study characteristics are summarized in tables 1–4.

All papers were retrospective chart reviews. Patient demographics for the 8 studies are presented in table 1. The publication dates ranged from January 2000 to June 2015. Study size ranged from 122 to 815 patients.

Fig. 2. Forest plot of the comparison of recurrence rates for BCS vs. mastectomy.

Table 2. Overview of the reviewed studies: endocrine data

Author, year [ref.]	ER-positive, %	PR-positive, %	HER2-positive, %	NCT responders CR+PR, %	Endocrine therapy received, %	Radiation received, %	Median follow-up, months
Cho JH, 2013 [29]	BCS: 38.7 M: 55.7	BCS: 33.9 M: 46.7	BCS: 31.5 M: 33.0	16.7 (CR)	BCS: 45.2 M: 59.9	–	45.9
Debled M, 2015 [30]	–	–	–	–	–	–	46.5
Eugene H, 2006 [31]	–	–	–	BCS: 45.2 M: 54.1	BCS: 39 M: 32	BCS: 100 M: 0	BCS: 60 M: 76
Fitzal F, 2010 [32]	–	–	–	–	–	–	60
Parmar V, 2006 [22]	BCS: 22.9 M: 25.4	BCS: 33.5 M: 30.7	–	BCS: 92.7 M: 67.1	–	–	30
Rouzier R, 2006 [33]	61	54	–	BCS: 74.2 M: 38.1	–	–	67
Shin HC, 2013 [23]	BCS: 48.6 M: 52.6	–	BCS: 27.8 M: 28.1	–	–	BCS: 100 M: 100	62.4
Sweeting RS, 2011 [24]	BCS: 42 M: 49	BCS: 40 M: 45	BCS: 27 M: 33	87	BCS: 33 M: 57	BCS: 98 M: 78	76.8

ER = Estrogen receptor; PR = progesterone receptor; HER2 = human epidermal growth factor; NCT = neoadjuvant chemotherapy; CR = complete response; PR = partial response; BCS = breast-conserving surgery; M = mastectomy.

Table 3. Overview of the reviewed studies: inclusion and exclusion criteria

Author, year [ref.]	Inclusion criteria	Exclusion criteria
Cho JH, 2013 [29]	–	stage IV disease at diagnosis, bilateral breast cancers, data on type of surgery or radiotherapy unavailable, pathologic tumor size > 3 cm, and nonepithelial origin or special type tumors
Debled M, 2015 [30]	HER2-positive, T2–T4 breast cancer	distant metastasis
Eugene H, 2006 [31]	–	distant metastasis
Fitzal F, 2010 [32]	–	metastatic breast cancer, inflammatory breast cancer, infiltration of the thoracic wall, ECOG > 2, bilateral breast cancer, any previous malignancy treated with curative intent and no freedom from disease for 5 years, any recurrent cancer disease, pregnant or lactating women
Parmar V, 2006 [22]	all patients underwent an initial incision biopsy for tissue diagnosis, receptor study, and quadrant localization	distant metastasis
Rouzier R, 2006 [33]	–	inflammatory, bilateral, T4, and metastatic tumors
Shin HC, 2013 [23]	clinical stage III breast cancer patients	inflammatory breast cancer
Sweeting RS, 2011 [24]	–	stage IV disease, inflammatory breast cancer

Fig. 3. Forest plot of the comparison of 5-year local recurrence-free survival rates for BCS vs. mastectomy.

Fig. 4. Forest plot of the comparison of 5-year overall survival rates for BCS vs. mastectomy.

Outcome Measures

A total of 1,361 patients who underwent BCS and 1,854 patients who underwent mastectomy were analyzed. All patients in the included studies underwent NCT following the diagnosis of cancer.

Five included studies assessed patients for local recurrence. The prevalence of local recurrence was 9.2% in the BCS group versus 8.3% in the mastectomy group without significant difference (odds

ratio (OR) 1.07, 95% confidence interval (CI) 0.28–1.48; $p = 0.66$) (fig. 2). The 5-year local recurrence-free survival rate (LRFS) was lower in the mastectomy group than in the BCS group, but no significant difference was found between the 2 groups (OR 1.11, 95% CI 0.61–1.99; $p = 0.74$) (fig. 3). 5-year OS was generally better for the BCS group compared with the mastectomy group (OR 0.32, 95% CI 0.14–0.72; $p = 0.006$) (fig. 4).

Table 4. Overview of the reviewed studies: applied treatments

Author, Year [ref.]	Kind and duration of NCT	Kind and duration of adjuvant chemotherapy	Radiation to breast and/or regional lymph nodes	Endocrine treatment	5-year overall survival
Cho JH, 2013 [29]	NCT groups received 3–8 cycles of neo-adjuvant anthracycline and/or taxane	–	adjuvant radiotherapy with a median boost dose of 10 Gy covering the whole breast with or without regional nodal area	using selective estrogen receptor modulators (SERMs) or aromatase inhibitors (AIs)	BCS: 89.1% M: 84.2%
Debled M, 2015 [30]	trastuzumab-based NCT	no patient received adjuvant chemotherapy	–	no patient received endocrine treatment	–
Eugene H, 2006 [31]	patients received 1 of the following combinations of chemotherapy: 5-FU, doxorubicin, cyclophosphamide (FAC); vincristine, doxorubicin, cyclophosphamide, prednisone (VACP); or doxorubicin and docetaxel (AT)	adjuvant chemotherapy was given after surgery and before radiation in 254 (77%) of the BCS patients and 460 (95%) of the mastectomy patients	50 Gy delivered in 25 fractions to the breast or chest wall tangential fields, followed by a 10-Gy boost to the tumor bed or chest wall scar using an appositional electron field	tamoxifen was used by 129 (39%) of the BCS patients and 154 (32%) of the mastectomy patients	BCS: 86% M: 59%
Fitzal F, 2010 [32]	ABCSG; trials ABCSG-7, ABCSG-14 and ABCSG-24	–	–	–	BCS: 81% M: 58%
Parmar V, 2006 [22]	cyclophosphamide 500 mg/m ² , anthracycline (adriamycin 50 mg/m ² or epirubicin 90 mg/m ²), and 5-FU 500 mg/m ² (2–6 cycles) until maximum clinical response	completion of remaining chemotherapy (if any)	sequential radiotherapy (chest wall and supraclavicular fossa)	tamoxifen 20 mg/day after chemotherapy if the tumor was ER- and/or PR-positive	–
Rouzier R, 2006 [33]	206 (35%) patients received AVCMF (doxorubicin 50 mg/m ² , vincristine 1 mg/m ² , cyclophosphamide 600 mg/m ² , methotrexate 30 mg/m ² , and 5-FU 900 mg/m ²); 22 (4%) and 170 (28%) patients received FAC 50/FEC 50–60 (doxorubicin 50 mg/m ² , epirubicin 50/60 mg/m ² , cyclophosphamide 600 mg/m ² , and 5-FU 900 mg/m ²), respectively; and 196 (33%) patients received FEC 100 (epirubicin 100 mg/m ² , cyclophosphamide 1,000 mg/m ² , and 5-FU 1000 mg/m ²). 3 or 4 cycles of NCT	2 or 3 cycles of FAC 50 or FEC 50/60/100	postoperative radiotherapy to the breast (45 Gy)	tamoxifen 20 mg per day was prescribed for all postmenopausal patients and for premenopausal patients with ER-positive tumors	–
Shin HC, 2013 [23]	158 patients received intravenous adriamycin 50 mg/m ² infused over 30 min, followed by docetaxel 75 mg/m ² over 1 h every 3 weeks for 3 cycles; 6 patients received intravenous adriamycin 60 mg/m ² over 30 min and cyclophosphamide 600 mg/m ² over 30 min (AC) every 3 weeks for 3 or 4 cycles; 2 patients received intravenous 5-FU 500 mg/m ² , epirubicin 100 mg/m ² , and cyclophosphamide 500 mg/m ² (FEC) every 3 weeks for 3 cycles	given to patients who received 3 cycles of neoadjuvant docetaxel in the NCT group; 3 additional cycles of DA offered after surgery 168 patients in the surgery group: adriamycin 60 mg/m ² and cyclophosphamide 600 mg/m ² infused over 30 min every 3 weeks for 4 cycles followed by docetaxel 75 mg/m ² over 1 h every 3 weeks for 4 cycles after surgery; the remaining 25 patients in the surgery group received adriamycin +cyclophosphamide +methotrexate +5-FU, or 5-FU +adriamycin +cyclophosphamide	all patients received radiation therapy to the entire breast (50.4 Gy in 28 sessions over a 5–6 week period) with additional boost radiation (9–10 Gy) to the tumor bed axillary and supraclavicular radiation (50.4 Gy) was performed on patients with clinical N2 stage or higher regardless of the pathologic N stage in the NCT group	–	–
Sweeting RS, 2011 [24]	97% of patients underwent a regimen that included an anthracycline and 69% of patients underwent a regimen that included a taxane	–	majority of patients received adjuvant radiation (87%)	of the 25 patients who were HER2-positive, 40% received trastuzumab; 57 (47%) patients received endocrine therapy	BCS: 83.0% M: 68.0%

NCT = Neoadjuvant chemotherapy; BCS = breast-conserving surgery; M = mastectomy; 5-FU = 5-fluorouracil; FAC = 5-FU+doxorubicin+cyclophosphamide; FEC = 5-FU+epirubicin+cyclophosphamide; ER = estrogen receptor; PR = progesterone receptor.

Discussion

It is well known that NCT can efficaciously downstage the primary tumor. For patients with large tumors warranting mastectomy at the initial diagnosis, the use of NCT has been shown to downsize the primary tumor and make BCS possible [14, 15]. In 2006, Rouzier et al. [16] developed a nomogram for breast cancer patients who receive NCT to predict residual tumor size and whether the patients could become eligible for BCS following anthracycline-based or paclitaxel-based chemotherapy.

In our study, we investigated local recurrence rates after BCS compared with mastectomy in LABC patients having received NCT. The main challenge for patients with LABC treated with BCS after NCT is to show an acceptable local recurrence rate compared to those treated with mastectomy. There are concerns that advanced primary tumors treated with BCS may have higher local recurrence rates than those treated with mastectomy after NCT because tumors treated with NCT may dwindle into multicentric fragments such as honeycombs. This response is the main barrier to applying routine BCS in patients receiving NCT due to the difficulty of assessing surgical margins accurately [17]. The oncologic safety of BCS after NCT in patients with an initial diagnosis of LABC has been investigated in previous studies. The NSABP-B18 trial demonstrated higher LRFS in the NCT-BCS group compared with the NCT-mastectomy group [4]. However, after adjusting for patient age and clinical tumor size, that difference was no longer significant [18]. Another study also failed to show a significant difference in LRFS between NCT-BCS and NCT-mastectomy patients [19]. The study by Ishitobi et al. [2] also found no significant difference in LRFS according to type of surgery after NCT in patients with a planned mastectomy at the initial exam. This is in concordance with our finding that BCS after NCT does not significantly increase the risk of LRFS compared to mastectomy (fig. 3). Hence, the current study suggests that BCS after NCT in LABC patients is a safe alternative to mastectomy.

Previous studies [20, 21] demonstrated that OS rates were not statistically different between the BCS group and the mastectomy group. However, our meta-analysis indicated that 5-year OS rates were improved for women who were able to undergo BCS after NCT as compared with those who underwent mastectomy, suggesting that being a candidate for BCS after NCT may be a proxy for tumor biology.

Three studies [22–24] supported the concept that BCS after NCT in patients with large primary breast tumors could be a reasonable treatment option if the tumor size decreased to ≤ 4 cm

after NCT, regardless of the initial tumor size. However, patients who showed no response to NCT undergoing BCS had a significantly increased local relapse rate compared with mastectomy patients. However, because of significant differences in nodal status, grading, and tumor size between the 2 groups, the results have to be viewed with caution.

Several studies [25–27] showed that the local recurrence rate for patients with advanced breast cancer was significantly reduced by radiation therapy, and the use of radiation therapy was also associated with improved OS [25]. Investigators concluded that radiation therapy provides a significant clinical benefit for breast cancer patients who present with advanced disease and achieve a pathologic complete response after NCT [28]. However, our included studies did not show much information about the efficacy of radiation therapy. The benefit of adjuvant radiotherapy should be further investigated in prospective studies.

In summary, our meta-analysis reviewed much of the relevant literature published to date, and demonstrated that BCS after NCT is a reasonable option for women who respond to NCT. However, this study has several limitations. First, it was a retrospective study and there may be bias in the analysis of the data. Second, the local recurrence rate was low and the follow-up of some studies [22, 29] was very short. This may have been a reason why these studies failed to reveal a difference in local recurrence rates between groups. Further research must be performed with adequate reporting of recurrence based on stage and 5-year OS, which would then allow clinicians to better counsel patients about BCS-NCT for LABC.

Conclusion

Breast conservation can safely be offered to women with LABC who respond to NCT. Surgery remains an essential part of treatment even in good responders. Responders automatically form a subgroup with better clinical outcome. BCS after NCT is safe in terms of local recurrence and LRFS in women with LABC. Shrinking tumors with NCT provides the opportunity to apply BCS with no detriment to outcome.

Disclosure Statement

No sponsorship or funding arrangements relating to our research and no conflicts of interest exist.

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