17-Year Follow-Up of Comparing Mastoscopic and Conventional Axillary Dissection in Breast Cancer: A Multicentres, Randomized Controlled Trial

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Abstract

Background: Longer follow-up was necessary to testify the exact value of mastoscopic axillary lymph node dissection (MALND).

Methods From January 1, 2003 to December 31, 2005, 1027 patients with breast cancer were randomly assigned to two groups: MALND and CALND (conventional axillary lymph node dissection). 996 eligible patients were enrolled.

Results The final cohort of 996 patients was followed for an average of 198 months. The events other than death differed significantly between the two cohorts ($p=0.0311$) (46.3% in MALND and 53.2% in CALND, respectively). The sum of the events other than death and deaths from other causes was much more in CALND (59.6%) than in MALND (53.4%) ($p=0.0494$). The 17-year DFS rates were 36.7 percent for MALND group and 33.6 percent for CALND group, respectively. There was a significant difference between the groups ($p=.0306$). The OS rates were 53.2 percent after MALND and 46.0 percent after CALND ($p=.0119$). The MALND patients had much less axillary pain ($p=.0000$), numbness or paresthesia ($p=.0000$), arm mobility ($p=.0000$), and arm swelling on operated side ($p=.0000$). The aesthetic appearance of axilla in MALND group was much better than that in CALND group ($p=.0000$) at an average follow-up of 17-year.

Conclusions The use of MALND in breast cancer surgery not only decreases the relapse and arm complications but also improves long-term survival of patients. Therefore, MALND should be one of the preferred approaches for breast cancer surgery when ALND is needed.

Background

Inherent shortcomings of conventional axillary lymph node dissection (CALND) for breast cancer treatment have seriously affected quality of life of patients.¹ These clinical puzzles cannot be solved with conventional surgical methods, there is an urgent need to develop new techniques to reduce trauma and improve quality of life further.

One of significant advances on clinical surgery in late 20th century is a gradual maturation of theory on minimally invasive surgery and rapid development of endoscopic operation. The prevailing applications of endoscopic techniques in various operations alleviate therapy outcome obviously. Their successful practice and maturation provide a referential theory and technology drawn lessons for breast surgery development and new thought in solving therapeutic dilemma of breast surgery. Endoscopy breast surgery has been developed in nearly all breast operations for about 30 years, which has been producing good clinical results.^{3,4} It is a typical operation model in combined minimally invasive technique with oncoplastic surgery.^{5,6}

In 2003, we initiated a multicenter randomized trial in breast cancer patients comparing mastoscopic axillary lymph node dissection (MALND) to CALND. The 5-year findings demonstrated patients underwent

MALND had less axillary pain, numbness or paresthesia and arm swelling. Aesthetic appearance of axilla was much better. There was a significant difference between two groups in distant metastasis. It also showed no significant differences in disease free survival and overall survival between two groups.⁷ We now present information through an average of 17 years of post-randomization follow-up.

Methods

Clinical Trial

Between January 1, 2003 through December 31, 2005, 1027 patients with operable breast cancer at 15 institutions by 16 credentialed surgeons were randomly assigned to 1 of 2 study groups: MALND and CALND. Patients younger than 80 years with operable breast cancer were eligible for enrollment. Randomization was allocated and controlled centrally using sealed opaque envelopes containing computer-generated random numbers. The randomized data set was recorded and maintained until all study data collection was complete. Informed consent was obtained from the participating patients. The protocol was approved by the institutional review board committees of all institutions in compliance with the Declaration of Helsinki and guidelines for good clinical practice. This trial has been carried out according to the International Standard Randomized Controlled Trial (Number ChiCTR-TRC-11001477 First registration 08/14/2011). Detailed descriptions of patient-entry information, eligibility and ineligibility criteria, randomization procedures, surgical techniques, quality control, the plan of investigation, operative and irradiation procedures, and other aspects of the study have been described previously.⁷

Of the other 240 patients, 161 were deemed ineligible, 79 were not randomly assigned to a study group. Of the 1027 randomized patients, 31 were not able to be evaluated (Figure 1). Our study adheres to CONSORT guidelines and include a completed CONSORT checklist as an additional file. The findings presented below are from the 996 eligible patients, who were enrolled in the study for an average of 17 years.

Outcome Evaluation

The primary end points of the study were disease-free survival (DFS), defined as absence of any event (specifically axillary metastases, local recurrence, ipsilateral carcinoma or distant metastasis) considered related to the primary cancer, but excluding contralateral breast cancer and any other cancer, and overall survival (OS) defined as the time from randomization until death from any cause.

The secondary end points were arm complications. The evaluation of arm complications included a subset of 100 consecutive patients from CALND group and 100 consecutive patients from MALND group. These have been reported at 6 months and 24 months after first surgery previously.⁷ These 200 patients were interviewed by physicians after surgery until death and were asked to complete a questionnaire concerning the intensity of pain, the presence or absence of numbness and paresthesia, the extent of arm mobility, and the aesthetic appearance of the axilla. The evaluation of arm swelling was according to the

circumference of the operated arm, which was measured and compared with that of the contralateral arm. The evaluation criteria of these arm complications have been presented previously.⁷ The long-term arm morbidities at an average follow-up of 17 years in these 200 patients are defined as the ones which persist to date at the last follow-up in the evaluable patients.

Statistical Analysis

Statistical analysis was performed for the parameters in end points based on an intent-to-treat population. All tests were conducted at the two-sided 5% level of significance for treatment effects. Analyses of end results were performed separately for patients in two groups.

For time to event endpoints, Kaplan-Meier plots were presented and log-rank tests were used to test the null hypothesis of no MALND effect. End points were compared between groups using two-sample t test for continuous outcome variables and chi-square test for categorical variables. The analysis was performed with missing data left missing. Estimates are provided with their standard errors. Continuous variables were summarized using mean $\pm$ SD and categorical variables were summarized using n (%). All calculations were performed using SPSS software package (version 19.0).

Results

The distribution of the patients for 996 patients finally evaluable between MALND group and CALND group according to age, histologic, tumor grade, estrogen-receptor, rate of proliferation and peritumoral vascular invasion was similar, reported previously.⁷

Unfavorable Events

The cutoff date for the present analysis was Dec 2020. The final cohort of 996 patients was followed for an average of 198 months (range, 168 to 216 months) during which time. The patients' outcomes at 17 years are summarized in Table 1. The distribution of some events was obvious different between two groups of patients. The incidence of the events in breast, including axillary relapse, supraclavicular metastasis, recurrence in ipsilateral breast and cancer in contralateral breast did not differ in a significant manner between the two cohorts and was 11.7% (58/496) in the MALND and 12.4% (62/500) in the CALND cohorts, respectively $p=0.6468$. And no significant difference was observed in other primary tumor between MALND group (4.2%, 21/496), compared with CALND (5.0%, 25/500) $p=0.5645$. And also there was no significant difference in the rate of the distant metastasis between 30.4% (151/496) in the MALND cohort and 35.8% (179/500) in the CALND cohort, respectively $p=0.0725$.

All patients who recurred were treated with local therapy (surgery, radiotherapy, or combination of the two) and were given systemic therapy (hormonal therapy, chemotherapy). Most of the treatment failures were distant metastasis (33.1%, 330/996). Other primary tumors and deaths from other causes were distributed equally between two groups (57/500, 11.4% in MALND; 56/496, 11.3% in CALND) $p=0.9563$. However, the events other than death differed significantly between the two cohorts $p=0.0311$ (46.3%

230/496 in MALND and 53.2% (266/500 in CALND, respectively). On the other hand, the sum of the events other than death and deaths from other causes was much more in CALND (59.6% (298/500) than in MALND (53.4% (265/496) ($p=0.0494$) (Table 1).

Disease-Free Survival and Overall Survival

The 17-year disease-free survival rates were 36.7 percent for MALND group and 33.6 percent for CALND group respectively. There was a significant difference between the groups [hazard ratio (HR) 1.26; 95% CI, 0.98 to 1.45; $p=.0306$, by the log rank test] (Figure 2). At a median follow-up of 17 years, there were 502 deaths (232 in MALND group and 270 in CALND group, respectively). Compared with CALND, MALND was found to be superior for overall survival. The overall survival rates were 53.2 percent after MALND and 46.0 percent after CALND (HR 1.28; 95% CI, 0.92 to 1.41; $p=.0119$, by the log rank test) (Figure 3).

Arm Complications

The axillary pain, numbness or paresthesia, arm mobility, arm swelling and anesthetic appearance of axilla are recognized as arm complications of two cohorts at an average follow-up of 17-year. They are listed in Table 2. The patients who underwent MALND had much less axillary pain ($p=.0000$), numbness or paresthesia ($p=.0000$), arm mobility ($p=.0000$), and arm swelling on operated side ($p=.0000$). The aesthetic appearance of axilla in MALND group was much better than that in CALND group ($p=.0000$).

Discussion

With the defects of Halsted's radical mastectomy and further extensive radical surgery, we cannot but turn back to modified radical surgery and breast conserving surgery and SLNB later.^{3,6,8,9} The development of this road has burned a series of painful imprint step by step in progress to minimally invasive and functional treatment.

MALND ameliorates four key techniques below.⁹⁻¹²
① altering operation steps. No matter whether breast conserving surgery or radical mastectomy or modified radical mastectomy, axillary lymph node is first dissected and breast operation is then done. This blocks the routine of metastases via blood and lymph while breast operation. It further conforms to the operation principle of tumor surgery.¹³⁻¹⁶
② altering operation method. In MALND, the parenchymatous axilla becomes the reticular structure just like the spider web and the swollen lymph nodes hang to the "web". Thereby, the dissection is easily done by the endoscopic instruments. This reduces operation complexity and simplifies operation process.
③ altering the view angle of operation. When patients are placed supine in operation, surgeons' view is horizontal from lateral to medial. The endoscopy in MALND can reach into the narrow and irregular axillary space in any angle, which makes the dissection easier than CALND. While CALND, surgeons always take pains in minimizing the size of the axillary incision as possible, the view is small and narrow. Operators should bend waist, hunch back and skew neck to try to see the inside of axillary, and dig into step by step. Operative difficulty and risk increase.
④ magnifying the local view of operation. The endoscopy can

magnify local view by the help of the magnifying function of endoscopic system. The important blood vessels, nerves and lymphatic fatty tissues are determined clearly.

Keshtgar & Fukuma¹⁷ (2009) made an editorial that endoscopic breast surgery was associated with minimal scarring and postoperative pain. Leff et al⁴ published a long paper in 2011. Initial results had demonstrated that endoscopic breast surgery was safe and technically feasible. Twelve randomized controlled studies were finally included involving 1983 patients. This study indicated that MALND can reduce the trauma and the incidence of postoperative complications without affecting the prognosis of patients. In a meta-analysis, twelve studies including 2157 patients were selected.¹⁸ The author made a summary that MALND was reliable and feasible for breast cancer owing to the lesser incidence of intraoperative bleeding, shorter drainage duration, and lower incidence of complications compared to CALND. Chi WM⁵ reviewed current literatures in 2019 on outcomes, techniques and trend of endoscopic-assisted breast surgery over a 20 years period. They considered that standardization of techniques, practice guidelines and objective outcome assessments methods might pave the way for better conduct and place it as one of the standards of care for breast cancer.

Several medical centers have verified its feasibility and safety using same method.^{19–22} It reaches three-fold advantages of minimal invasion, and function and cosmetic. It also gains two aims in physiologically and psychologically minimal invasion. Moreover, some authors also have done a series of work on mastoscopic SLNB, single-port, 3D and robotic MALND.^{23–25} They all stated that this technique could be a promising alternative to conventional methods.

Actually, we first reported the mature experiences of MALND in 86 patients with breast cancer in 2003. We summed up a “nine-step” procedure and standardized the technique too in 315 patients in 2005.³ We also reported the experiences on a larger series of 522 patients.¹¹ We have accomplished over 20,000 cases in nearly 20 years. Over 150 hospitals have accumulated beyond 100 cases per hospital in our country. From 2003 to 2005, a large of randomized prospective study in 16 surgeons of 15 hospitals on more than 1200 patients was studied by us for comparing MALND with CALND, with an average follow-up of 63 months in 2012.⁷ The results have demonstrated a encouraged result. In a short follow-up of 6-mouth and 24-mouth after first operation, the axillary pain, numbness or paresthesia and arm swelling in MALND were much less than those in CALND. The cosmetic status of axilla in MALND was also better than that in CALND. While on the average 5-year follow-up period, the patients with MALND had similar disease-free survival and overall-survival to that with CALND.

In our current trial, the findings at 17 years support and extend our earlier results (5-year follow-up).⁷ Other primary tumors and deaths from other causes were distributed equally between two groups. However, the events other than death differed significantly between the two cohorts, respectively. On the other hand, the sum of the events other than death and deaths from other causes was much more in CALND than in MALND. The risks for relapse and death in MALND patients reduce greatly. DFS and OS differed significantly between groups at an average follow-up of 17-years. The MALND patients had significantly

longer DFS, which corresponds to an absolute DFS benefit of 3.1%. The MALND patients also survived significantly longer than CALND patients, corresponding to an absolute survival benefit of 7.2%. In all, 996 eligible patients were randomized and with a median 17-year follow-up, the patients do benefit from MALND in terms of local control, DFS, or OS over CALND.

With a limited follow-up of 6–24 months reported by us,⁷ the question about arm complications is not sufficiently answered, as many breast cancer survivors may experience long-term consequences years and even decades after their first operations. The treatment still renders significant side effects and morbidity to survivors. Thus, elaborating on the issue of long-term complications is crucial and may aid both medical practitioners and the patients alike in improving management of patients. Our study presents a long-term data and 17 year follow-up rates of arm complications which patients may experience after MALND or CALND. Both cohorts had similar for age, histological type, tumor grade, estrogen-receptor status, rate of proliferation, peritumoral vascular invasion and systemic therapy. Arm complications as determined at a 17-year follow-up is related to the following five complications: axillary pain, numbness or paresthesia, arm mobility, arm swelling and aesthetic appearance of axilla (Table 2).

As previously reported at the 6-month and 24-month follow-up by us,⁷ the axillary pain, numbness or paresthesia, arm swelling and anesthetic appearance of axilla was much better for the MALND group than the CALND group at a 17-year follow-up, and the differences are even greater (all of p values = 0.0000). Similarly, the arm mobility in MALND group is significantly superior than that in CALND (p = 0.0000), but it couldn't be found any significant difference in 6-month (p = .14) and 24-month (p > .99) follow-up in two groups previously. These findings indicate that the arm complications of the patients with the CALND are getting worse as time goes on. On the contrary, MALND significantly improve these aspects obviously.

Conclusions

this report provides firm evidence from a randomized controlled study of nearly 1000 patients followed for median 17 years that the use of MALND in breast cancer surgery not only decreases the relapse and arm complications but also improves long-term survival of patients. MALND has provided great benefits to patients. And most importantly, the achievement of these benefits does not sacrifice any survival chance of patients. The current findings presented now can also dispel previous misgivings on MALND. For example, whether the liposuction affects pathologic characteristics of lymph node and interferes with pathoanatomic study of the lymph node, whether it increases the risk of exfoliation and implantation of tumor cells from the lymph node with metastasis, and whether it raises the risk of hematogenous dissemination or metastasis.

Therefore, MALND should be one of the preferred approaches for breast cancer surgery when ALND is needed.

Abbreviations

CALND = Conventional axillary lymph node dissection; MALND = Mastoscopic axillary lymph node dissection ; DFS = disease-free survival; OS= overall survival .

Declarations

Trial registration information The comparison of long-term outcomes of mastoscopic and conventional axillary lymph node dissection in breast cancer: a multicenter randomized control trial. ChiCTR-TRC-11001477 ChiCTR. First registration 08/14/2011.

Ethics approval and consent to participate: Written informed consent was obtained from the participating patients. The protocol was approved by the institutional review board committees of all institutions in compliance with the Declaration of Helsinki and guidelines for good clinical practice Ethics committee of Fuxing Hospital of Capital Medical University (No 4, 2002).

Consent for publication Not applicable.

Availability of data and material All data generated or analyzed during this study are included in this published article.

Competing interest: There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported, and no any financial or other potential conflict of interest.

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Tables

Due to technical limitations, tables are only available as a download in the Supplemental Files section.

Figures

Figure 1 Consort Diagram

Figure 1

See image above for figure legend

Figure 2

Disease-Free Survival during 17 Years of Follow-up after Surgery in the two study groups. There was a significantly difference between two groups ($p=0.0306$).

Figure 3

Overall Survival during 17 Years of Follow-up after Surgery in the two study groups. There was a significantly difference between two groups ($p=0.0119$).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Table1.LongtermunfavorableEventsanddeathsinTwoGroups.doc](#)
- [Table2.ArmComplicationsintheTwoStudyGroups.doc](#)