15-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 operable breast cancer were randomly assigned to two groups: MALND and CALND. 996 eligible patients were enrolled. The end points are disease free survival and overall survival.

Results: The final cohort of 996 patients was followed for an average of 184 months. The distribution of all events was fairly similar between two groups of patients. The incidence of local in-breast events did not differ in a significant manner between two cohorts. Similarly, the rate of distant metastases was not significantly different with 30.0% in MLND and 32.6% in CALND. And no significant difference was observed in other primary tumor between two groups ($p=0.46$). Patients who remain alive with no event comprise a total of 37.2% in MALND and 35.4% in CALND. Other primary cancers and deaths from other causes were distributed equally between two groups. The 15-year disease-free survival rates were 41.1 percent for the MALND group and 39.6 percent for the CALND group ($p=0.79$). MALND was found to be not inferior for overall survival ($P=0.54$). The 15-year overall survival rates were 49.5 percent after MALND and 51.2 percent after CALND ($p=0.86$). Probability of overall survival was not significantly different between two groups.

Conclusions: MALND does not increase unfavorable events, and also does not affect the long-term survival of patients. Therefore, MALND should be one of the preferred approaches for breast cancer surgery.

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 15 years of post-randomization follow-up.

Methods

Between January 1, 2003 through December 31, 2005, 1027 patients with operable breast cancer at 15 institutions 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 participating patients. The protocol was approved by institutional review board committees of all institutions in compliance with the Declaration of Helsinki and guidelines for good clinical practice.⁷ To be included in study, patients had to have no axillary lymph node disease on preoperative clinical examination or lymph nodes less than 1 cm by color ultrasonic inspection. Exclusion criteria included a previous history of another cancer, preexisting limb disease causing swelling, or previous surgery in the ipsilateral axilla. Of other 240 patients, 161 were deemed ineligible, 79 were not randomly assigned to a study group. Of 1027 randomized patients, 31 were not able to be evaluated.

The findings below are from the 996 eligible patients, who were enrolled in study for an average of 15 years. Detailed descriptions of patient-entry information, eligibility and ineligibility criteria, investigation plan, operative and irradiation procedures, and other aspects of the study have been presented previously.¹⁰ Each surgeon had performed at least 20 MALNDs. MALND operation was performed according to the method reported previously.^{1-3,5,7} All surgeons used the same standardized technique. Surgeons submitted a MALND video to an external monitoring committee for assessing their surgical technique, including main operative stages and the identification and dissection of critical adjacent structures.

Either type of ALND consisted of a level I to II and/or III (if the swollen node with suspected metastasis was found in level II) axillary dissection. Contemporary surgical treatment includes a modified radical mastectomy or breast-conserving treatment. In the CALND group, breast surgery and ALND were performed by traditional open method. In MALND group, the patients first underwent MALND and then breast surgery. Patients were treated with systemic therapy and radiation therapy according to the same standard institutional protocols (National Comprehensive Cancer Network Breast Cancer Practice Guideline).

Outcome Evaluation

The end points for overall treatment comparisons were disease-free survival and overall survival. Times to those end points were calculated from the date of operations. Recurrences of tumor in the chest wall and surgical scar were classified as local treatment failures. Recurrences in supraclavicular, subclavicular, in the ipsilateral axilla of patients treated with either CALND or MALND in all patients were considered to be regional treatment failures. Events considered in the determination of disease-free survival were first local, regional, or distant recurrence of tumor; contralateral breast cancer or a second primary tumor other than a tumor in breast; and death who had no evidence of cancer. Events considered in the estimation of relapse-free survival were the first local, regional, or distant recurrence or an event in contralateral breast that was judged to be a recurrence. Distant recurrences that occurred either as the first recurrence or after a local or regional recurrence, contralateral breast cancers, and other second primary cancers were considered in estimation of distant-disease-free survival. Overall survival refers to survival with or without recurrence of disease. The cumulative incidence of death was estimated after a recurrence or a diagnosis of contralateral disease and the cumulative incidence of death without a recurrence or a diagnosis of contralateral disease.

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

The final cohort of 996 patients was followed for an average of 184 months (range, 164 to 191 months) during which time. The patients' outcomes at 15 years are summarized in Table 1. The distribution of all events was fairly similar between two groups of patients. The incidence of local in-breast events, including axillary relapse, supraclavicular metastasis, recurrence in ipsilateral breast and cancer in contralateral breast did not differ in a significant manner between two cohorts and was 11.1% (55/496) in MALND and 11.6% (58/500) in CALND cohorts, respectively. Similarly, the rate of distant metastases was not significantly different with 30.0% (149/496) in MALND cohort and 32.6% (163/500) in CALND

cohort, respectively. And no significant difference was observed in other primary tumor between MALND group (0.4%, 20/496), compared with CALND (0.5%, 25/500).

Table 1. Long term unfavorable Events and deaths in Two Study Groups^a

Event	CALND (n=500) no. of patients (%) ^b	MALND (n=496)	p value
Events other than death			
Axillary relapse	9(1.8)	10(2.0)	.80
Supraclavicular metastasis	12(2.4)	9(1.8)	.52
Recurrence in ipsilateral breast	17(3.4)	19(3.8)	.72
Cancer in contralateral breast	20(4.0)	17(3.4)	.63
Distant metastasis	163(32.6)	149(30.0)	.38
Other primary tumor	25(5.0)	20(4.0)	.46
Total	246(49.2)	224(45.2)	.20
Death from other causes	30(6.0)	35(7.1)	.50
Total	276(55.2)	259(52.2)	.35
Alive, event free	177(35.4)	185(37.2)	.53

^a CALND = Conventional axillary lymph node dissection; MALND = Mastoscopic axillary lymph node dissection.

^b data are presented as number (percentage) of patients unless otherwise indicated.

All patients who recurred were treated with local therapy (surgery, radiotherapy, or combination of the two) and were given systemic therapy (hormonal therapy, chemotherapy). Patients who remain alive with no event comprise a total of 185/496 (37.2%) in MALND and 177/500 (35.4%) in CALND, respectively. On the other hand, most of the treatment failures were distant metastasis (31.3%, 312/996). Other primary cancers and deaths from other causes were distributed equally between two groups (55/496, 11.1% in MALND; 55/496, 11.0% in CALND).

Disease-Free Survival The 15-year disease-free survival rates were 41.1 percent (95% CI, 76.3%–83.8%) for MALND group and 39.6 percent (95% CI, 73.5%–82.2%) for CALND group. No significant differences were observed between two groups (HR 1.10, $p=0.79$, by log rank test) (Figure 1). The hazard ratio for an event (recurrent disease or a second cancer or death without evidence of cancer) among patients underwent CALND, as compared with those underwent MALND, was 1.22 (95 percent confidence interval, 0.95 to 1.45; $P=0.67$).

Overall Survival At a median follow-up of 15 years, there were 634 deaths (311 in MALND group and 323 in CALND group). Compared with CALND, MLND was found to be not inferior for overall survival ($P = .54$, by the log-rank test). The 15-year overall survival rates were 49.5 percent (95% CI, 83.4%–90.2%) after MALND and 51.2 percent (95% CI, 81.2%–89.7%) after CALND (HR 1.00, $p= .86$, by log rank test) (Figure 2). The hazard ratio for death among the patients in MALND, as compared with those in CALND, was 1.04

(95 percent confidence interval, 0.92 to 1.31; P= .58). Probability of overall survival was not significantly different between two groups.

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.^{3,6,8,10-12} 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 ①altering 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. ②altering operation method. In MALND the axilla is aired after lipolysis, the parenchymatous axilla becomes the reticular structure just like the spider web. The dissection is easily carried out by endoscopy. This reduces operation complexity and simplifies operation process. ③altering 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 in CALND, in order to minimize 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. ④magnifying the local view of operation. The structures in axilla can be magnified to 4-7 times by the help of magnifying function of endoscopic system, which are identified clearly and preserved further. It achieves minimal invasion of operation and reduces complication and functional damage.

In China most patients with breast cancer are belonged to middle-late stages. So ALND isn't abandoned now. Since Suzanne et al first reported MALND in 1993. Several medical centers have verified its feasibility and safety using same method.¹¹⁻¹⁶ The lymph nodes number harvested, postoperative symptoms, drainage time and drainage liquid in MALND compared to those in CALND are no significantly differences. But long-term complications such as upper limb dysfunction, serious pain, edema and activity complications reduced obviously in MALND. 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.^{13, 14-20} They all stated that this technique could be a promising alternative to conventional methods.

Keshtgar et al²² (2009) made an editorial that endoscopic breast surgery was associated with minimal scarring and postoperative pain, and it appeared that wound complications were rare events. They suggested there was a need for randomized, controlled trials to provide evidence for its safety and efficacy. Leff DR et al⁴ published a long paper in Breast Cancer Res Treat 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. It showed that intraoperative blood loss, postoperative drainage, hospital stay and postoperative complications were less in MALND. There was no significant difference in operation time, lymph node numbers dissected, hospitalization costs, postoperative recurrence and metastasis rates between two groups. This study concluded that MALND can reduce trauma and postoperative complications without affecting the prognosis of patients.

Chi WM et al⁵ reviewed current literatures in 2019 on outcomes, techniques and trend of endoscopic-assisted breast surgery over a 20 years period. It was comparable in terms of oncological, surgical as well as aesthetic outcomes compared to conventional techniques. They considered that standardization of techniques, practice guidelines and objective outcome assessment methods might pave the way for better conduct and place it as one of the standards of care for breast cancer. Unfortunately, the cases enrolled in above studies were relative small, single center, and therefore lack a sufficient testimony of application value of MALND. So, a randomized multicenter trial on a larger series of patients is a burning issue.

Actually, we first reported the mature experiences of MALND in 86 patients in China in 2003. The technique becomes mature and standardized gradually in ongoing exploration. We summed up a “nine-step” procedure and standardized the technique too in 315 patients in 2005.² We also reported the experiences on a larger series of 522 patients.¹¹ We have accomplished over 20,000 cases in nearly 20 years. Above 150 hospitals have accumulated beyond 100 cases per hospital in our country. From 2003 to 2005, a large of randomized prospective study in 15 hospitals in China over 1200 patients was studied for comparing MALND with CALND, with an average follow-up of 63 months in 2012.¹⁰ The results had demonstrated that bleeding was significantly fewer in MALND. The operating time, lymph node numbers harvested, drainage fluid, drainage time and axillary seroma were similar between two groups. The axillary pain, numbness or paralysis 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. On the average 5-year follow-up period, the axillary recurred totally in 11 cases, similar in two groups. There was no port-implantation in MALND. The patients with MALND had similar disease-free survival and overall-survival to that with CALND. And another important finding was significantly lower rate of distant metastases in MALND. As we know, most of death in breast cancer comes from distant-metastasis. The findings of our study raise the question of whether the significant difference on survival rates can be found in a longer-term follow-up (i.e., 10, 15 or 20 years). This is also another aim of the present study.

In our current trial of 1027 randomized patients, 31 were not able to be evaluated. The distribution of the patients for 996 patients finally evaluable between the MALND group and the CALND group was almost equal. They were followed for an average of 184 months. The findings at 15 years confirm and extend our earlier results (5-year follow-up). The incidence of local in-breast events, including axillary relapse, supraclavicular metastasis, recurrence in ipsilateral breast and cancer in contralateral breast has no significant difference between two cohorts (11.1% in MALND and 11.6% in CALND). And no significant difference was observed in other primary tumor between MALND group (0.4%) and CALND group (0.5%).

The distribution of all events was fairly similar between two groups. All patients recurred were treated with local therapy (surgery, radiotherapy, or combination of the two) and were given systemic therapy (hormonal therapy, chemotherapy). Patients alive with no event have no significant difference between two groups, 37.2% in MALND and 35.4% in CALND groups respectively. On the other hand, most of treatment failures were distant metastasis (31.3%). Other primary cancers and deaths from other causes were distributed equally between two groups (11.1% in MALND; 11.0% in CALND). These coincide with our previous results.

However, at a median follow-up of 15 years, the rate of distant metastases was not significantly different between 30.0% in MALND and 32.6% in CALND, respectively. It revises the result that distant metastases in MALND were obviously low than that in CALND ($P=.04$) at 5-year follow-up.⁷ 634 patients have died, 322 and 311 in CALND and MALND respectively ($p\geq 0.05$). No significant difference in 15-year disease-free survival rates is observed between two groups. The hazard ratio for an event among patients underwent CALND, as compared with those underwent MALND, was 1.22 ($P=0.67$). Compared with CALND, MALND was found to be not inferior for overall survival ($P = .54$). The 15-year overall survival rates were 49.5 percent after MALND and 51.2 percent after CALND ($p=0.86$). The hazard ratio for death among patients in MALND, as compared with those in CALND, was 1.04 ($P=0.58$). Probability of overall survival was not significantly different between two groups.

This finding continues to indicate that no significant difference in disease-free and overall survival among patients between two groups. Namely, the application of MALND at least has not produced any disadvantage to patients. Nevertheless, the immense benefits brought by MALND have been appearing in recent years. And the achievement of these benefits does not sacrifice any survival chance of patients.

The findings presented now can dispel previous misgivings on MALND from some specialists. 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.

Conclusion

This report provides firm evidence from a randomized controlled study of nearly 1000 patients followed for median 15 years that the use of MALND in breast cancer surgery does not increase the axillary relapse—recurrences—metastases and any other unfavorable events, and also does not affect long-term survival of patients. Therefore, MALND should be one of the preferred approaches for breast cancer surgery.

Abbreviations

- CALND = Conventional axillary lymph node dissection

- MALND = Mastoscopic axillary lymph node dissection.

Declarations

- Ethics approval and consent to participate☐Informed consent was obtained from participating patients. The protocol was approved by institutional review board committees compliance with the Declaration of Helsinki and guidelines for good clinical in practice.
- Consent for publication☐ All authors are consent for publication.
- Availability of data and material: not applicable.
- Competing interests: 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.
- Funding: This work was funded with Capital Medical development Fund.
- Authors' contributions☐

Dr Chengyu had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Figures

There was no significantly difference between two groups.

Figure 1

Disease-Free Survival during 15 Years of Follow-up after Surgery in the two study groups.

There was no significantly difference between two groups.

Figure 2

Overall Survival during 15 Years of Follow-up after Surgery in the two study groups

Supplementary Files

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