

Research Article

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Boni Ding[#], Hongyan Zhang[#], Xiaorong Li, Liyuan Qian, Xuedong Chen, Wei Wu, Yanguang Wen, Yujun Zhao^{*}

Mastoscopic sentinel lymph node biopsy in breast cancer

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Abstract: Background: Previous studies have demonstrated that mastoscopic sentinel lymph node biopsy (MSLNB) has good identification rate (IR) and low false negative rate (FNR). However, few studies have directly compared the surgical performance and peri- and post-operative factors of MSLNB with conventional sentinel lymph node biopsy (SLNB).

Methodology: Sixty patients diagnosed with breast cancer were recruited and randomly assigned to one of the three groups: MSLNB, SLNB and SLNB with lipolysis injection. Peri- and post-operative parameters were compared using general linear models. To examine the effect of age on these parameters, we performed separate analysis stratified by age (≤ 50 years old vs. > 50 years old).

Results: Patients in the MSLNB group experienced longer surgery and suffered higher surgical cost than patients who underwent conventional SLNB or SLNB with lipolysis injection ($p < 0.0001$). Despite this, they had significantly less blood loss than those who underwent conventional SLNB (22.0 ± 7.0 ml vs. 73.5 ± 39.6 ml; $p < 0.0001$). Analysis by age group indicates a similar pattern of difference among the three groups. MSLNB and conventional SLNB have similar IR and FNR.

Conclusion: As a minimally invasive technique, MSLNB can significantly reduce blood loss while providing similar

IR and FNR, indicating that it can be a promising alternative to conventional SLNB.

Conclusion: Variations in popliteal artery terminal branching pattern occurred in 7.4% to 17.6% of patients. Pre-surgical detection of these variations with MD CTA may help to reduce the risk of iatrogenic arterial injury by enabling a better surgical treatment plan.

Keywords: Breast cancer, sentinel lymph node, mastoscopy

1 Introduction

Axillary lymph node dissection (ALND) has been routinely used for patients with breast cancer and metastasis to the lymph node. However, ALND can cause a variety of complications, such as lymphedema, shoulder dysfunction and nerve injury [1, 2], which can compromise the quality of life of patients. The sentinel lymph node (SLN) is the first lymph node that receives lymphatic flow from a primary tumor site. In recent years, sentinel lymph node biopsy (SLNB) has been widely used for staging the axillary situation in early-stage breast cancer for patients who show clinically negative axillary nodes, as an alternative to ALND [3]. Previous studies have demonstrated similar or better survival of patients receiving SLNB to that of ALND, with less local and regional recurrence [4-6]. SLNB has now become standard surgery in cases of negative sentinel lymph node as it obviates the need for ALND, and consequently reduces post-operative complications and greatly enhances patients' post-operative quality of life [7].

However, breast tumor staging using SLNB can be affected by many factors, such as size and location of the tumors, age of the patient, history of axillary surgery and the number of sentinel lymph nodes [8]. All of these factors influence two key parameters of SLNB: identification rate (IR) and false-negative rate (FNR). SLNB therefore can

***Corresponding author: Yujun Zhao**, Department of Transplantation Surgery, The Third Xiangya Hospital, Central South University, 138 Tongzipo Rd, Hexiyuelu Dist., Changsha, Hunan 410013, China, Tel: 86-731-88618235, Fax: 86-731-8618470, Email: zyjdac@aliyun.com

Boni Ding, Hongyan Zhang, Xiaorong Li, Liyuan Qian, Xuedong Chen, Wei Wu, Yanguang Wen, Department of General Surgery, The Third Xiangya Hospital, Central South University, Changsha, Hunan, 410013, China

[#] These authors contributed equally to this paper

influence an accurate assessment of the axillary stage. The false-negative rate of SLNB operated by the best surgical team can be as high as 5-10% [3].

Endoscopic techniques have been explored in ALND. Recent studies have demonstrated that mastoscopic sentinel lymph node biopsy (MSLNB) has similar disease-free survival and overall-survival to that of conventional ALND, but it can reduce postoperative complications and enhance aesthetic appearance of the axilla [9]. Compared to conventional approaches, surgeries in conjunction with endoscopic techniques are minimally invasive, thereby restricting scars. Moreover, they provide a better operation view and clear anatomic structures (Figure 1). Previous studies have demonstrated that MSLNB has good IR and low FNR [10, 11]. However, these studies focus on surgical assessment (e.g., IR) using data only from patients who underwent MSLNB, and therefore lack a direct comparison of surgical performance and peri- and post-operative factors of MSLNB (e.g., duration of surgery) with conventional SLNB.

We conducted a randomized pilot study to compare MSLNB with conventional SLNB to provide further evidence on the feasibility of MSLNB. We also examined the effect of injecting lipolysis solution during SLNB. We found that MSLNB showed similar IR and FNR, but could significantly reduce blood loss. These results indicate that MSLNB can be a promising alternative to conventional SLNB.

2 Methodology

2.1 Patients

Sixty patients diagnosed with breast cancer were recruited from March 2012 to March 2013 in the Department of Breast and Thyroid Surgery of The Third Xiangya Hospital. All patients were diagnosed by core needle biopsy or node biopsy. All of them had early stage breast cancer (International clinical staging I-II), negative clinical axillary lymph node and no history of sentinel biopsy. Women who had a cancer history, bilateral cancer, neo-adjuvant chemotherapy or distant metastasis at the time of diagnosis were excluded as well as those unwilling to participate in our study.

Participants were randomly assigned to one of the three surgery groups: MSLNB, SLNB and SLNB with lipolysis injection. Informed consent was obtained from

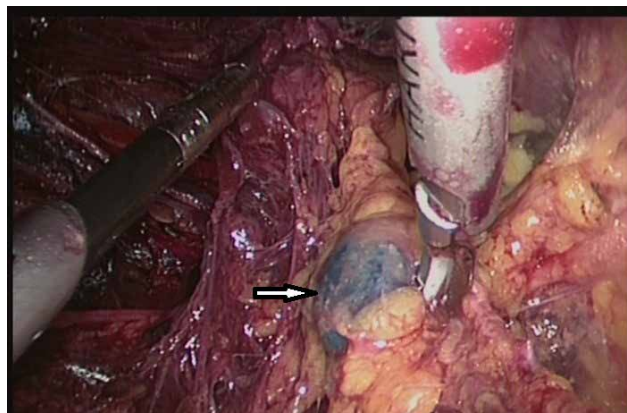


Figure 1: Blue dye sentinel lymph node hanging on the fibrous cord as seen from the screen monitor.

each participant. The trial protocol was approved by the ethical committee of the Third Xiangya Hospital, and the study was conducted in adherence to the tenets of the Declaration of Helsinki.

2.2 Surgical procedures

For each patient, conservative breast-conserving therapy (BCT), modified radical mastectomy (MRM) or radical mastectomy was considered. Due to a lack of experience in MSLNB, all of the MSLNB procedures were followed by axillary dissection. Blue dye was chosen as the localization method for SLN. Each patient received a 4 ml of blue dye injection at subcutaneous areola 5 minutes before surgery. Conventional SLNB was performed following established protocols as described previously [12]. Patients in the MSLNB group underwent surgery under endoscopy. The process was similar to mastoscopic ALND. Five minutes after blue dye injection, we injected 2000 ml of lipolysis solution into the subcutaneous fat of the axillary area. Half an hour later, we began negative pressure liposuction surgery at the point of mid-axillary line and lower edge level of the breast. Then, we inserted a mastoscope and on the mastoscope monitor screen clearly found the blue dyed SLN hanging on the fibrous cord. For the patients in the lipolysis group, prior to surgery we injected 2000mL lipolysis solution, then the surgery was performed as for the conventional SLNB group. Post-operatively, we recorded the number of SLNs for each patient. All surgeries were performed by the same surgeon (BD) who had more than 7 years' of experience in SLNB. All samples underwent routine pathological tests, and additional immunohistochemical cytokeratin antibody staining was considered if hematoxylin-eosin staining showed no metastasis.

3 Statistical analysis

Clinical and pathological characteristics of the included patients in the three groups were compared using chi-square or Fisher's exact test as appropriate for categorical variables and general linear models were used for continuous variables. The Wilson score method [13] was used to calculate confidence intervals for FNR and accurate rate of SLN for the three groups.

Intra-operative blood loss during surgery was estimated based on the blood pumped into the drainage bottle by the suction pump, and postoperative blood loss was estimated based on the blood in the drainage bottle connected with a drainage tube. Surgical costs included charges for the surgery and anesthesia. Peri- and post-operative parameters, including operation time, peri-operative blood loss, the number of SLNs and axillary lymph nodes (ALNs), postoperative drainage time and surgical costs were compared using general linear models, where multiple comparisons were adjusted from the simulated distributions of maximum or maximum absolute value of a multivariate *t* random vector [14]. To examine the effect of age on these parameters, we also performed a separate analysis stratified by age (≤ 50 years old vs. > 50 years old). A $p < 0.05$ was considered statistically significant.

All statistical analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC).

4 Results

Table 1 shows the clinical and pathological parameters of the 60 patients. Overall, the mean age of the patients was 48.2 ± 11.6 . The majority of patients had T1 or T2 stage of tumor (83.1%). Histological examination revealed that the majority of tumors were ductal-related (83.3%), and most patients underwent modified radical mastectomy (93.3%). We did not find statistically significant differences in all clinical and pathological characteristics among the three groups except for estrogen receptor/progesterone receptor (ER/PR) positive rate. This showed bottom-line significant difference: patients in the lipolysis group had a higher ER/PR positive rate (85.0%) than that of the other two groups ($p = 0.04$). As ER/PR is the result of post-operative pathological examination, and is mainly considered in selecting post-operative treatments, this difference in ER/PR rate should not be a big concern for our analysis.

We observed statistically significant differences among the three groups regarding surgery time, peri-operative blood loss, and surgical cost (all p 's $< .0001$; Table

2). Specifically, patients in the MSLNB group experienced longer surgery (184.9 ± 39.8 mins) than those in the conventional SLNB group (119.6 ± 28.6 mins; $p < .0001$) and those in the SLNB with lipolysis injection group (139.2 ± 34.9 mins; $p = .0002$). Meanwhile, they suffered significantly higher surgical cost (4261.4 ± 419.7 RMB; RMB=currency unit of China) than those in the conventional SLNB group (3007.7 ± 331.6 RMB; $p < .0001$) and those in the SLNB with lipolysis group (2881.9 ± 370.3 RMB, $p < .0001$; Table 2). Despite this, they had significantly less blood loss (22.0 ± 7.0 ml) than those who underwent conventional SLNB (73.5 ± 39.6 ml; $p < .0001$). The post-operative rehabilitation time was 6.7, 7.3 and 7.2 days, for patients in the MSLNB, the conventional SLNB and the SLNB with lipolysis injection group, respectively, showing no significant differences among the groups ($p = .65$; Table 2).

Analysis by age group indicated a similar pattern of difference among the three groups (Table 2). An exception was that among those aged > 50 years; there was no statistically significant difference in duration of surgery between MSLNB (190.2 ± 55.4 mins) and SLNB with lipolysis injection (142.4 ± 31.3 mins; $p = 0.11$), probably due to reduced sample size. Altogether, these results imply that there was no dramatic age influence on the peri- and post-operative parameters that we have examined.

We observed no statistical difference in the average number of SLNs or ALNs among the three groups (Table 3). All the negative SLNs were stained using cytokeratin antibody to test their possibility of being positive. There were three positive cases in the MSLNB group, four in the conventional SLNB group and five in the SLNB with lipolysis injection group (Table 3). MSLNB and conventional SLNB had similar FNR and IR, and there was a trend of higher FNR (80%, 95% CI: 34%-100%) and lower IR (60%, 95% CI: 39%-78%) in the SLNB with lipolysis injection group, but the difference was not statistically significant (Table 3).

5 Discussion

In this paper, we randomly assigned 60 patients with breast cancer to three SLNB surgery groups: MSLNB, conventional SLNB and SLNB with lipolysis injection. We compared the peri- and post-operative parameters of these three surgery approaches. Although MSLNB took more surgical time to complete and consequently, incurred more surgical costs, it can dramatically reduce blood loss during surgery. It also exhibited similar FNR and IR to that of conventional SLNB.

Table 1: Clinical and pathologic characteristics of the 60 patients undergoing sentinel node biopsy.

	Overall	MSLNB	SLNB	SLBN+L	P-value
Age (mean±SD)	48.2±11.6	47.1±9.1	45.8±11.0	51.6±13.8	0.25
Menopausal status (n, %)					0.72
Premenopausal	34 (56.7)	11 (55.0)	13 (65.0)	10 (50.0)	
Postmenopausal	26 (43.3)	9 (45.0)	7 (35.0)	10 (50.0)	
Tumor stage (n, %)					0.57
Tis	5 (8.5)	3 (15.8)	1 (5.0)	1 (5.0)	
T1	22 (37.3)	6 (31.6)	9 (45.0)	7 (35.0)	
T2	27 (45.8)	9 (47.4)	8 (40.0)	10 (50.0)	
T3	2 (3.4)	0 (0)	2 (10.0)	0 (0)	
T4	3 (5.1)	1 (5.3)	0 (0)	2 (0)	
Histology (n, %)					0.54
Ductal	50 (83.3)	16 (80.0)	18 (90.0)	16 (80.0)	
Lobular	1 (1.7)	0 (0)	1 (5.0)	0 (0)	
Ductal+lobular	5 (8.3)	2 (10.0)	1 (5.0)	2 (10.0)	
Paget's disease	1 (1.7)	1 (5.0)	0 (0)	0 (0)	
Ductal+Paget's disease	1 (1.7)	1 (5.0)	0 (0)	0 (0)	
Mucinous carcinoma	2 (3.3)	0 (0)	0 (0)	2 (10.0)	
ER/PR (n, %)					0.04
Positive	38 (63.3)	12 (60.0)	9 (45.0)	17 (85.0)	
Negative	22 (36.7)	8 (40.0)	11 (55.0)	13 (15.0)	
Lymph node (n, %)					
Sentinel					
Axillary					
Type of surgery (n, %)					0.77
Breast-conserving surgery	3 (5.0)	2 (10.0)	0 (0)	1 (5.0)	
Modified radical mastectomy	56 (93.3)	18 (90.0)	19 (95.0)	19 (95.0)	
Radical mastectomy	1 (1.7)	0 (0)	1 (5.0)	0 (0)	

MSLNB, mastoscopic sentinel lymph node biopsy; SLNB, sentinel lymph node biopsy; SLBN+L, sentinel lymph node biopsy with lipolysis injection; ER, estrogen receptor; PR, progesterone receptor; SD, standard deviation

Although patients receiving SLNB with lipolysis injection experienced similar reduced duration of surgery and surgical cost as conventional SLNB, this procedure seems to be associated with higher FNR and lower IR. To the best of our knowledge, this is the first study to directly assess these three surgical approaches in performing SLNB.

Little work has been done to examine the performance of MSLNB. A study of 30 patients with negative axilla who underwent MSLNB showed minimal operative bleeding and a high sentinel node IR of 93.3% [10], consistent with the findings in our study. Another study found that MSLNB could keep better operative visual fields, was less invasive and had high IR (94.3%) [11]. These studies

provide valuable information on the feasibility of MSLNB. However, they fail to show whether MSLNB has any advantage over classical SLNB in important peri- and post-operative parameters, whereas our randomized study indicates that compared to conventional SLNB, MSLNB had significantly less blood loss during surgery (Table 2) while showing similar FNR and IR (Table 3).

Previous studies found that a combination of blue dye and radiolabeled colloid was superior to using blue dye or radiolabeled colloid alone, leading to higher IR [15, 16]. For simplicity and consistency, in this study we used only blue dye for all surgeries, and SLN was detected in all patients. A recent study reported higher IR using

a combination rather than using blue dye only (98.4% vs. 90.9%, $p=0.043$) [11]. Therefore, we could anticipate a higher IR for all the three groups when a combination approach is used. However, the comparative advantage

of MSLNB in relation to the other two surgery approaches warrants further examination when both blue dye and radiolabeled colloid are used in the surgery.

Table 2: Comparison of peri- and post-operative parameters among the three surgery groups.

Overall				
	MSLNB	SLNB	SLBN+L	P
Duration of surgery (minutes)	184.9±39.8 ^{a, b}	119.6±28.6 ^{a, b}	139.2±34.9 ^{a, b}	<0.0001
Blood loss (ml)	22.0±7.0 ^{a, c}	73.5±39.6 ^{a, c}	25.0±8.9 ^{a, c}	<0.0001
Number of ALNs	12.2±4.1	10.2±4.2	11.9±3.7	0.248
Number of SLNs	4.2±2.3	3.8±0.8	3.4±1.5	0.362
Drainage time (days)	6.7±1.3	7.3±2.8	7.2±1.5	0.65
Surgical cost (RMB)	4261.4±419.7 ^{a, b}	3007.7±331.6 ^{a, b}	2881.9±370.3 ^{a, b}	<0.0001
ages≤50 years				
Duration of surgery (minutes)	182.6±33.4 ^{a, b}	118.6±26.6 ^{a, b}	137.1±38.3 ^{a, b}	<0.0001
Blood loss (ml)	20.7±7.3 ^{a, c}	62.1±26.1 ^{a, c}	25.0±10.0 ^{a, c}	<0.0001
Number of ALNs	12.0±4.6	9.1±3.6	12.6±3.6	0.061
Number of SLNs	4.3±2.6	3.9±0.9	3.3±1.2	0.380
Drainage time (days)	6.6±1.4	7.4±3.1	7.1±1.7	0.649
Surgical cost (RMB)	4260.4±467.3	2976.2±283.5	2855.9±468.9	<0.0001
age>50 years				
Duration of surgery (minutes)	190.2±55.4 ^a	121.8±35.3 ^a	142.4±31.3 ^a	0.028
Blood loss (ml)	25.0±5.5 ^{a, c}	100.0±54.8 ^{a, c}	25.0±7.6 ^{a, c}	0.0004
Number of ALNs	12.7±2.9	12.8±4.7	10.8±3.7	0.534
Number of SLNs	3.8±1.8	3.5±0.5	3.5±1.9	0.915
Drainage time (days)	6.8±1.2	6.8±1.9	7.3±1.3	0.828
Surgical cost (RMB)	4263.6±318.6 ^{a, b}	3081.1±446.8 ^{a, b}	2920.8±154.2 ^{a, b}	<0.0001

MSLNB, mastoscopic sentinel lymph node biopsy; SLNB, sentinel lymph node biopsy; SLBN+L, sentinel lymph node biopsy with lipolysis injection; SLN, sentinel lymph node; ALN, auxiliary lymph node; RMB, the currency unit in China; a: significant difference between MSLNB and conventional SLNB; b, significant difference between MSLNB and SLNB with lipolysis injection; c, significant difference between conventional SLNB and SLNB with lipolysis injection

Table 3: Diagnosis accuracy of SLN among the three surgery groups.

	MSLNB		SLNB		SLNB+L	
SLN	+	-	+	-	+	-
Yes	2	1	3	1	1	4
No	2	15	1	15	4	11
Diagnosis						
False negative (95% CI)	0.33 (0-1)		0.25 (0-0.80)		0.80 (0.34-1)	
Identification (95% CI)	0.85 (0.64-0.95)		0.9 (0.70-0.97)		0.6 (0.39-0.78)	

MSLNB, mastoscopic sentinel lymph node biopsy; SLNB, sentinel lymph node biopsy; SLBN+L, sentinel lymph node biopsy with lipolysis injection; +, Patients were found to be positive using axillary lymph node (ALN); -, patients were found to be negative using ALN; SLN, sentinel lymph node; ALN: auxiliary lymph node

Although the surgical cost for MSLNB is significantly higher than the other two surgical approaches, we think the difference is affordable to most patients in China (mean difference in cost is ~1350 RMB, and average income is 29,547 RMB per capita among urban residents in 2013 in China) [17]. Moreover, patients had less blood loss and given that MSLNB is minimally invasive, we have reasons to believe that it will result in reduced scars. Taken together, our results indicate that MSLNB is a promising alternative to conventional sentinel lymph node biopsy.

Post-operative quality of life of patients is an important concern in selecting surgery techniques. A prospective study compared the impact on quality of life of SLNB vs. ALND, and found that although there was no statistically significant difference in general well-being, SLNB is beneficial compared to ALND in that patients experienced less upper arm impairment [7]. However, another prospective study found that SLNB did not demonstrate advantage in patient's quality of life two years post SLNB surgery, compared to ALND [18]. There have been no studies comparing the post-operative quality of life between MSLNB and conventional SLNB. Such longitudinal studies are certainly needed to thoroughly evaluate the feasibility and safety of MSLNB.

It is interesting to note that SLNB with lipolysis injection significantly reduced the duration of surgery, consistent with previous studies [19]. However, it seemed to have decreased IR and increased FNR in our study. Epinephrine in the lipolysis solution has vasoconstrictive effect, which probably accounts for the reduced congestion and blood loss of the tissues [20]. The vasoconstrictive effect can potentially provide a better view during surgery. Moreover, lipolysis solution can also increase gap transparency of subcutaneous soft tissues such that the surgeons can clearly identify the anatomical structure and intercostobrachial nerves, thereby reducing the possibility of causing damage to these nerves. We have not examined the reasons underlying the relatively high, albeit not statistically significant, FNR and low IR. Small sample size might be an important factor that affects an accurate estimation of these rates. Further studies with larger sample size are needed to provide more conclusive evidence regarding the FNR and IR of this surgery approach.

Our study has limitations. First, the sample size is limited. Although we were able to detect significant differences in some peri- and post-operative parameters, we may lack statistical power in testing the difference in FNR and IR, especially the difference between SLNB and SLNB with lipolysis injection. Second, the cross-sectional nature of the study prevents us from exploring other important factors in evaluating MSLNB, such as post-operative

complications and quality of life, as mentioned above. Third, our study was conducted in a single medical care institution and the results represent the performance of surgeons in our department, which may limit the generalizability of the findings to other institutions.

In summary, we found that MSLNB can significantly reduce blood loss during surgery while producing similar FNR and IR to conventional SLNB, and therefore is a promising alternative to conventional SLNB. Future studies investigating its post-operative complications, the quality of life of patients undergoing MSLNB, or MSLNB with the assistance using other techniques, such as three-dimensional computed tomography (3D-CT) [21], are needed to provide further evidence on the feasibility and safety of this surgery technique.

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