

RESEARCH ARTICLE

Value of Sentinel Lymph Node Biopsy in Breast Cancer Surgery with Simple Pathology Facilities -An Iranian Local Experience with a Review of Potential Causes of False Negative Results

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Abstract

Introduction: Sentinel lymph node biopsy (SLNB) is a precise procedure for lymphatic staging in early breast cancer. In a valid SLNB procedure, axillary lymph node dissection (ALND) can be omitted in node-negative cases without compromising patient safety. In this study, detection rate, accuracy and false negative rate of SLNB for breast cancer was evaluated in a setting with simple modified conventional pathology facilities without any serial sectioning or immunohistochemistry. **Material and Method:** Patients with confirmed breast cancer were enrolled in the study. SLNB and ALND were performed in all cases. Lymph node metastasis was evaluated in SLN and in nodes removed by ALND to determine the false negative rate. Pathologic assessment was carried out only by modified conventional technique with only 3 sections. Detection rate was determined either by lymphoscintigraphy or during surgery. **Results:** 78 patients with 79 breast units were evaluated. SLN was detected in 75 of 79 cases (95%) in lymphoscintigraphy and 76 of 79 cases (96%) during surgery. SLN metastases was detected in 30 of 75 (40%) cases either in SLNB and ALND groups. Accuracy of SLNB method for detecting LN metastases was 92%. False negative rate was 3 of 30 of positive cases: 10%. In 7 of 10 cases with axillary lymphadenopathy, LN metastases was detected. **Conclusion:** SLNB is recommended for patients with various tumor sizes without palpable lymph nodes. In modified conventional pathologic examination of SLNs, at least macrometastases and some micrometastases could be detected similar to ALND. Consequently, ALND could be omitted in node-negative cases with removal of all palpable LNs. We conclude that SLNB, as one of the most important developments in breast cancer surgery, could be expanded even in areas without sophisticated pathology facilities.

Keywords: Breast neoplasm - lymphatic metastasis - lymph node dissection - sentinel lymph node biopsy

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Introduction

Status of axillary lymph node is an important factor in staging, prognosis and guiding treatment selection in early breast cancer. Sentinel Lymph Node Biopsy (SLNB) is a revolutionary concept in solid tumor surgery which has been introduced since 1993 in breast cancer (Krag et al., 1993). SLN is the first lymph node (LN) which drains the lymph flow from the primary tumor site. Its careful examination could accurately detect the spread of tumor cell with less aggressive surgical procedures and less morbidity (including Lymphedema, paresthesia, pain and restriction of arm motion) than axillary lymph node dissection (ALND) as the standard surgical approach to lymphatic staging (Fleissig et al., 2006; Del et al., 2008; Ashikaga et al., 2010). On the other hand, about 30% of axillary LNs are positive in early breast cancer and as a consequence, two-third of patients receive no benefit of

ALND (Lyman et al., 2005).

False negative rate is an important issue in SLNB, compromising patient safety. False negative rate of 5-10% (Veronesi et al., 2003; Goyal et al., 2006; Krag et al., 2007), 16.7% (Zavagno et al., 2008) and up to 29% (Kim et al., 2006) has been reported in different studies. Beside factors related to the patient, procedure and surgery, false negative rate usually depends on pathologic handling of the tumor. So, many extensive histopathologic examination of SLN has been designed to identify micrometastases and isolated tumor cells and even molecular changes (Lyman et al., 2005). Some studies show that detection of metastasis by SLNB technique is better than ALND and percentage of node-positive patients considerably rises at least 10% after introduction of SLNB procedure (Lyman et al., 2005; Mansel et al., 2006; van der Heiden-van der Loo et al., 2006) and is largely explained by watchful lymphatic mapping.

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This study is performed to determine accuracy and false negative rate of SLNB in breast cancer when simple modified conventional pathologic facilities are applied and to evaluate if SLNB procedure could be expanded in developing or under developing countries where more sophisticated expensive pathologic approaches are limited or absent.

Materials and Methods

Study consisted patients with histologically or cytologically confirmed breast cancer regardless of tumor size, pathology, lymphadenopathy or multicentricity. SLNB and ALND were performed in all patients to determine the predictive power of axially status using SLNB.

Radiocolloid injection and lymphoscintigraphy

SLNB practice has been followed UK Training Programme (NEW START) (Somasundaram et al., 2009). For SLN procedure, 0.2 ml radiocolloid (Antimony or phytate: IAEO, I.R. Iran) labeled with 10-30-MBq Technetium was administered by intradermal periareolar injection in the same quadrant containing the mass lesion. Injection was carried out at the same day or a day before surgery followed by preoperative lymphoscintigraphy as dynamic Imaging started immediately after injection up to 15 min. (or while SLN appeared ; usually within 30-60 minutes). Then, static imaging was performed in anterior, lateral and 30° anterior oblique views for 5 min. Finally, SLN has been marked on skin surface in 30° anterior oblique view.

Intraoperative SLN detection and biopsy

After general anesthesia in operating room, the SLN detection was performed using a gamma probe to localize radioactive SLN, guided by lymphoscintigram and marked skin. All radioactive nodes were excised through axillary incision which had activity 5-10 times the background activity or 10% of SLN with highest activity. The number of excised nodes and their radioactivity and background activity were recorded. Then, ALND was performed in all patients according to immediate histopathologic examination and clinical decision, at least at level of 1 or 2.

SLN histopathologic examination

All excised SLN were assessed intraoperatively by frozen section at 3 levels: hilum, mid and distal portion of bisected LN along the major axis. Routine Hematoxyline and Eosin (H&E) staining was carried out for definite histology of SLNs as well as all nodes removed by ALND.

Statistics

Accuracy, sensitivity, specificity and false Negative rate of SLNB were determined in comparison with ALND using SPSS software. X2 test or Fisher's exact test was used to evaluate nominal data.

False negative rate of SLNB was defined as the percentage of cases with negative SLN who were found to have other metastatic nodes in the ALND specimen,

among all patients with positive nodes.

Results

Seventy-eight patients, 76 female and 2 male, with 79 breast units included in this learning phase study. Mean tumor size was 3.2 cm. (range: 1-8.5 cm.). The clinicopathologic characteristics of patients are summarized in Table 1.

Correlation of SLN visualization in lymphoscintigraphy and surgery is demonstrated in Table 2. SLN was detected in 75 cases in Lymphoscintigraphy and in 76 cases during surgery. So, detection rate was 95% in lymphoscintigraphy and 96% intraoperatively. Three non-detected SLN as well as the other one without sufficient data were excluded for later study's calculation. Two of 3 non-detected cases were neither detected in lymphoscintigraphy nor in surgery. The other one, visualized in scan but non-detected during surgery, was took place exactly at the beginning of the validation phase in a metastatic male breast cancer patient.

Table 3 shows correlation of SLNB procedure and ALND for assessment of axilla.SLN metastases was detected in 30 of 75 (40%) cases either in SLNB and ALND groups. Accuracy and sensitivity of SLNB

Table 1. Clinicopathologic Characteristics of Cases with Breast Cancer

Characteristics		
Age (years)		49(29-78)
Sex	Female	77
	Male	2
Tumor size		3.2(1.0-8.5)
	≤2 cm	2.7 (34%)
	>2≤5 cm	4.0 (51%)
Axillary Lymphadenopathy	>5 cm	1.2 (15%)
	Non -palpable	67 (85%)
	Palpable	12 (15%)
Pathologic finding	Invasive ductal ca	63 (80%)
	Invasive lobular ca	7 (9%)
	In situ carcinoma	6 (8%)
	Others	2 (3%)

Table 2. Correlation of SLN Detection in Lymphoscintigraphy and During Radio-guided Surgery

	SLN in Lymphoscintigraphy		Total
	Visualized	Non visualized	
SLN in surgery			
Detected	74	2	76
Non detected	1	2	3
Total	75	4	79

Table 3. Correlation of Axillary Metastasis in SLNB and ALND Groups

		Nodal metastasis in SLNB group		
		Positive	Negative	Total
Nodal metastasis in ALND	Positive	27	3	30
	Negative	3	42	45
	Total	30	45	75

Table 4. Correlation of Axillary Lymphadenopathy with Nodal Metastasis in SLNB and ALND Groups

	Metastatic node		
	Positive	Negative	Total
Axillary Lymphadenopathy			
Positive	42	23	65
Negative	3	7	10
Total	45	30	75

Table 5. Factors Which Could Affect FN Rate of SLNB for Lymphatic Staging of Breast Cancer

Patient-related
Age/obesity
tumor size/multicentric lesion
axillary lymphadenopathy
chemotherapy/prior breast or axillary surgery
Procedure-related
Experience (Learning phase)
Tracer: particle size / injected activity & volume
Injection: technique/ number & location/ injection-imaging or surgery interval
Lymphoscintigraphy: identification rate/ SPECT
Combination of radiocolloid and blue dye
Surgery-related
Experience (Learning phase)
Number of excised SLN
removal of palpable LN
Pathology-related
Experience (Learning phase)
Sample handling
Serial sectioning
Intraoperative analysis: imprint cytology/ frozen section/ mRNA PCR
Postoperative analysis: H&E staining/ Complementary IHC
Tumor pathology
Tumor type: inflammatory breast cancer
Tumor grade

method for detecting LN metastases was 92% and 90%, respectively. In 3 cases, metastasis was seen only in ALND group. So, False negative rate was 3 of 30 of positive cases: 10%. In 3 cases, nodal metastases was discovered only in SLNB technique, not in ALND.

Axillary LN was palpable in 10 cases which contains metastases in 7 cases. So, 3 of 10 (30%) cases with lymphadenopathy didn't have metastasis in modified conventional pathologic examination. Correlation of metastatic nodes with lymphadenopathy is displayed in Table 4.

Discussion

Although SLNB is a relatively new procedure in breast cancer surgery, it has been recognized as a standard technique for lymphatic staging with less morbidity and better Quality of life than ALND (Fleissig et al., 2006; Del et al., 2008; Ashikaga et al., 2010). Clinical trials have been designed to answer the effect of SLNB on patients' longterm survival (Mansel et al., 2006; Zavagno et al., 2008; Gill 2009; Krag et al., 2010; Straver et al., 2010; Veronesi et al., 2010;) but predictive power of axillary status is well known. It is assessed in the validation period

of large clinical trials when SLNB is compared case by case with ALND and measured by detection rate, accuracy and FN rate. FN rate strongly indicates validity of SLNB and directly influences the patient's staging, prognosis and treatment planning. Reported FN rate in clinical trials were 5.5% (SNAC trial) (Gill, 2009), 6.7% (ALMANAC trial) (Mansel et al., 2006), 8.8% (MILAN trial) (Veronesi et al., 2003), 9.8% (NSABP-B32 trial) (Krag et al., 2007) and 16.7% (Sentinella-GIVOM) (Zavagno et al., 2008). In our experience, false negative rate of SLNB was 10% which showed a good result regarding few sections of specimen and modified conventional pathologic examination. Although, it has been stressed that FN rate to be less than 5% for omitting ALND in node-negative cases (Clarke et al., 2004; Lyman et al., 2005; Somasundaram et al., 2009) but most trials haven't achieved FN rate lower than 5% even in Milan trial with very experienced and expert pathologists and about 60 sections per node (Veronesi et al., 2003). So, threshold of 10% (Keshtgar et al., 2011) seems to be a suitable cut-off point for FN rate of SLNB.

This study showed that intraoperative assessment and routine histopathologic examination with somewhat more sections had high accuracy on the hand of expert pathologist to find macrometastases, at least equal to ALND with minimal added cost. Therefore, SLNB as a promising method in breast cancer surgery could be expanded even in areas where more precise facilities eg. serial sectioning or IHC is limited or absent. Undoubtedly, complementary methods would raise accuracy of SLNB approach for lymphatic staging but with increasing the expenses.

In this study, SLN was the only site of metastasis in 3 cases (10%) opposing to some other studies with incidence of 25-60% (Brenot-Rossi et al., 2003; Krag et al., 2007; Gill 2009; Straver et al., 2010). This could be related to advanced breast cancer with more extensive LN involvement in ALND.

Similar issue took place about percentage of node-positive cases, 40%, which is more than expected 20-30% (Krag et al., 2007; Zavagno et al., 2008; Gill 2009; Straver et al., 2010) in patients with early breast cancer. This is most probably due to enrolling symptomatic patients with large tumor lesion and palpable axillary lymphadenopathy which increases likelihood of nodal involvement (Fisher et al., 2002; Leidenius et al., 2005; Blamey et al., 2010). Accordingly, when true SLN is totally replaced by tumoral cells or lost its functional compartment, forcing drainage via a collateral, bypasses SLN to a new LN (non-sentinel LN) which necessarily doesn't contain metastases. Many studies and guidelines recommend to perform SLNB in mass lesion less than 2 cm (Veronesi et al., 2010) or 3 cm (Gill 2009; Straver et al., 2010). Without axillary lymphadenopathy to reduce false negative rate. There are limited trial results to support SLNB in lesions larger than 3 cm. Nevertheless, if large tumors and palpable LNs are included in validation phase of the study, the multidisciplinary team work would be accredited step by step in various stages of SLNB method with emphasis on surgeon and pathologist expertise.

As mentioned above, axillary lymphadenopathy is a potential cause for FN study. Nevertheless, some cases

with lymphadenopathy are node-negative and potentially suitable for lymphatic staging by SLNB approach. In the present study, 3 of 10 (30%) cases with palpable axillary LN didn't contain metastasis. This has been reported in 20-30% of patients with clinically axillary lymphadenopathy and it could be due to reactive process (Specht et al., 2005). Subsequently, it is advised to perform preoperative US-guided FNA or core biopsy to detect metastatic LNs (Hinson et al., 2008). In node-negative cases, SLNB could be performed with harvesting of all palpable LNs during surgery regardless of its activity to reduce FN rate (Krag et al., 2007; Somasundaram et al., 2009).

Alternatively, surgeon's experience in perioperative and intraoperative assessment of lymph node could influence FN rate (Carmon et al., 2006).

Lymphoscintigraphic pattern is a predictor of FN study since failure to visualize a SLN in lymphoscintigraphy predicts a higher risk of axillary involvement (Abdollahi et al., 2010; Goyal et al., 2006). In Rossi study, 28.5% of cases with visualized SLN had nodal involvement versus 63% of cases with nonvisualized node in lymphoscintigraphy (Brenot-Rossi et al., 2003). In our study, extensive involved LN was reported in ALND in one of 2 cases not visualized in both lymphoscintigraphy and probe-guided surgery as well as in 2 other cases not identified in lymphoscintigraphy but detected during surgery. This could be due to heavily infiltrating SLN which leads to non-visualized or faintly visualized true SLN in lymphoscintigraphy and/ or surgery.

Tissue attenuation and shine through effect of injection site are causes other than tumoral infiltration which lead to non-visualized SLN in lymphoscintigraphy but detected by intraoperative gamma probe (Krynycky et al., 2004). Delayed migration has the same finding specially in obese or old patients with reduced tracer migration from injection site to SLN (Krynycky et al., 2004; Goyal et al., 2006; Soran et al., 2007). This could be due to increased fatty tissue with impeding the flow of the tracer through the lymphatics or fatty degeneration of LNs reducing their capacity to concentrate the tracer.

Delayed migration could be seen in patients with prior surgery whose lymphatic pathways has been excised.

Slow or no migration to SLN may technically occur with large-sized radiocolloids and insufficient time between injection and scan/ surgery as well as in deep injection with inherent slow migration (Krynycky et al., 2004; Soran et al., 2007).

In some studies, SPECT or SPECT/CT study is advised specially when SLN is not visualized in conventional imaging to find SLN near injection site and in obese or old patients (HusarikSteinert 2007; van der Ploeg et al., 2008; 2009).

Other factors which could results to a FN study are summarized in Table 5. FN rate is affected by surgeon's experience in SLNB technique (Goyal et al., 2006; Abdollahi et al., 2010). In 2 trials that required surgeons to be trained (Veronesi et al., 2003; Clarke et al., 2004), FN rate has been less than 10% and lower than the GIVOM trial without such a formal experience and with FN rate of 16.7% (Zavagno et al., 2008). It is advised to perform 20-40 completed procedures and meet required set criteria

(FN rate less than 5-10% and identification Rate more than 90%) (Clarke et al., 2004; Straver et al., 2010). In addition, FN rate is reduced when surgeon is expert enough to remove as more hot SLNs as possible (Goyal et al., 2006; Krag et al., 2007; 2009). Lymphoscintigraphy is a guide for the minimum SLNs (not exact number of SLNs) which a surgeon should attempt to resect.

One important factor directly affecting false negative rate of SLNB is pathologic examination of sample. Strength of SLNB technique over ALND is its careful and precise evaluation of few specimen by intensive methods as serial sectioning and ImmunoHistoChemistry (IHC) to detect more micrometastasis as well as isolated tumor cells (Lyman et al., 2005). Although detection of node-positive patients considerably rises at least 10% after introduction of SLNB procedure (van der Heiden-van der Loo et al., 2006), however, importance of these cells and probable effect on outcome and treatment planning is a controversial issue (Cox et al., 2008; Langer et al., 2009; TruongLesperance, 2010)and requires to be answered in ongoing clinical trials as ACOSOG -Z0010 and IBCSG-23-01 (Giuliano et al., 2011; Galimberti, 2006).

In conclusion, SLNB is standard technique for lymphatic staging in breast cancer. SLNB with modified conventional pathologic examination accurately detects at least macrometastases and some micrometastases and it could be safely expanded in areas without sophisticated expensive facilities. We recommend it in breast cancer with various tumor size but with clinically node-negative status and removal of all LNs during surgery regardless of their activity to reduce false negative rate. We recommend to perform lymphoscintigraphy as a "road map" for surgeon to confirm SLNB success and predict possible FN study. When SLN is not detected at surgery, adding blue dye injection or ALND approach is advisable.

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