Axillary Intranodal Pressure Measurement: A Complementary Technique for Detection of Lymph Node Metastasis in Breast Cancer Patients

Abstract

Background: There is growing evidence that intranodal pressure (INP) can predict metastatic sentinel lymph nodes (SLNs). The objective of this study was to measure and utilize INP to evaluate the metastatic involvement of axillary SLNs in breast cancer patients. **Materials and Methods:** INP was measured in 73 clinically node-negative (cN0) breast cancer patients who were candidate for SLN biopsy. Clinical evaluation of the lymph node, coupled with frozen section analysis of the same excised SLN, was conducted. The level of suspicion (LOS) was used to assess the likelihood of metastases in the SLNs by the surgeons. Then, the miniature catheter tip pressure transducer was used to measure INP in the operation room. Finally, excised SLN was sent for permanent pathologic analysis as a gold standard for the evaluation of SLNs metastatic. **Results:** We identified the statistically significant increase in INP in nodes containing tumor metastasis in comparison with tumor-free SLNs (19.17 ± 13.63 vs. 8.82 ± 4.23) ($P = 0.003$). We considered the cutoff value for INP at 16 mmHg, which resulted in sensitivity of 80% and specificity of 87%. When the combination of INP above 16 mmHg and the LOS were taken into account for determining the likelihood of metastatic involvement of the LNs, the sensitivity and specificity were 87.5% and 91.7%, respectively. **Conclusion:** Our data suggest that INP measurement has the potential to help surgeons differentiate metastatic and nonmetastatic SLNs in combination with LOS. Meanwhile, it can be used along with frozen analysis to decrease false-negative rate.

Keywords: *Breast cancer, predictive value, sentinel lymph node*

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Introduction

Breast cancer is the most common malignancy in Iranian women and the peak age of this disease is younger than in western countries.[1] Due to a high incidence rate of breast cancer in Iranian women, it is essential to identify effective strategies to manage this disease and avoid unnecessary surgery procedures such as axillary lymph node dissection (ALND). Many efforts have been made to predict axillary lymph node involvement.

Sentinel lymph node biopsy (SLNB) has become the standard of care for determining the axillary lymph node status in clinically node-negative breast cancer patients.[2-4] However, after the recent unveiling of Z0011 study results, axillary dissection for a positive sentinel lymph node (SLN) has lost its importance, and it seems that the intraoperative interpretation of the SLN status is not as necessary as

before.[5-9] Conversely, especially in cases with unfavorable prognosis or need for immediate breast reconstruction with the implant, determining axillary lymph nodes status intraoperatively is very important and it helps the surgeons for best decision-making in treatment. It causes avoidance of the second admission for ALND that is not only time consuming and costly but also unpleasant for some patients.

Frozen section (FS) analysis is still the most practical method for determining the SLN metastasis intraoperatively. However, this method has own limitations, such as tissue loss, or low and different reported sensitivity.[2,4] Intraoperative palpation of axillary SLNs, sometimes, identifies suspicious nodes. SLNs that are enlarged and rubbery hard in consistency are considered suspicious for being metastatic. In some recent studies, researchers have investigated other methods, such as measurement

of intranodal pressure (INP), to recognize metastatic involvement of SLNs.[10-12] This method was considered as an alternative for qualitative assessment (stiff or hard) and transforming it into a quantitative method. There are some evidences from human studies showed breast cancer metastasis in axillary SLNs was associated with significantly higher INP compared with tumor-free lymph nodes and elevated INP significantly was correlated with SLN tumor metastasis sizes.[10] Three mechanisms were suggested for INP elevation in metastatic lymph nodes: drainage of new vessels by tumor-derived angiogenic cytokines,[13] interstitial fluid pressure following intranodal blood vessels leakage,[14-16] and cytokine-induced stiffness of the extracellular matrix and cytoskeleton.[17,18] Nathanson *et al*. in 2014, revealed that INP may be a valuable test for predicting metastasis in SLNs.[11]

This study was conducted to evaluate the predictive value of INP combined with the level of clinical suspicion in the recognition of SLN metastatic involvement in Iranian breast cancer patients using a new and more reliable device developed for this purpose.

Materials and Methods

Sampling patients

This study was approved by Institutional Review Board of Tehran University of Medical Sciences. After obtaining the informed consent from patients, we recruited 73 patients with clinically negative axillary lymph nodes (cN0 BC), who were candidates for SLNB from June 2017 to May 2018. Patients who had biopsy-proven positive lymph nodes, as well as patients who had received neoadjuvant therapy, were excluded from the study. Patients who had hypertension did not enter the study, assuming that hypertension could affect the INP. The following information of all participants were recorded: demographics variables, pathological details of the breast cancer (side, histologic subtype, grade, largest diameter of the node reported by ultrasound, estrogen receptor, progesterone receptor, HER2, and breast tumor size) and the result of FS and pathologic evaluation of the SLN.

Intraoperative sentinel lymph node identification

SLN was detected by intradermal periareolar injection of both radiotracer (filtered technetium-labeled sulfur colloid) and patent blue. In measuring the INP *in vivo*, great care was taken to leave the identified SLN intact, including perinodal fat.

The level of suspicion (LOS) of a SLN to be metastatic was recorded by the surgeon. We used the LOS as a new semi-quantitative assessment of the likelihood of metastases in the SLNs that has been introduced by Nathanson *et al*.[11] SLNs were categorized clinically benign (LOS = 0), slightly suspicious (LOS = 1), or clinically obviously malignant (LOS = 2). LOS was based on four major criteria: shape, size, consistency, and presence/absence of matting of the nodes. If the node was soft, small, with the length greater than width, and was not matted, it was considered as LOS = 0. If the SLN was rounder than kidney bean shaped, larger than usual, and very firm, it was considered as LOS = 2. Any matted nodes were automatically considered as LOS = 2. Nodes that were enlarged and firm but not matted were considered LOS = 1.

Measuring intranodal pressure in lymph nodes

The miniature catheter tip pressure transducer (Gaeltec R probe, Scotland) was used for measuring INP intraoperatively [Figure 1]. This transducer device features robust metal sensing diaphragm within polished surgical steel (AISI type 304) needle (6F: 2 mm). The sensor is side mounted and the tip is sharp. The sensor has metal diaphragm with directly deposited resistive strain gauge. Gaeltec device have been used in a variety of applications, both in experimental equipment, and in clinical use for physiological measurements such as compartment pressure and intradiscal pressure. It was specifically designed and modified for measurement of INP. A bevel side needle with a 100 cm reinforced flexible silicone rubber cable transmits the pressure from lymph node to a digital pressure monitoring kit. The range of measurable pressure was between 0 and 300 mm Hg. The sensitivity of the equipment was 0.01 mm Hg pressure gradient. Prior to measurement, the needle was acclimated at room temperature (23°C), and zero pressure reading was confirmed. To measure the pressures in the nodes, the needle was inserted a few
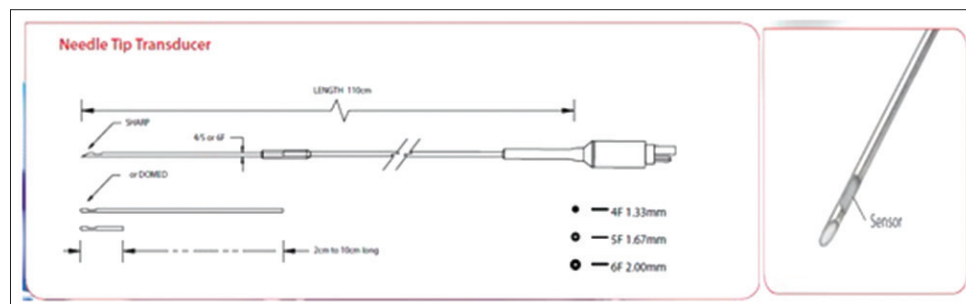

Figure 1: Gaeltec devices transducer

millimeters into the cortex of the concave surface of the SLN, while great care was taken not to damage lymphatic vessels of the node. The data were displayed on the screen of the monitoring kit. The entire procedure usually took less than 5 minutes. Once the INP was measured, the node was removed. Frozen-section analysis was done, and a complete or limited ALND was performed if the node was reported positive. The remaining of the node was embedded in paraffin for further permanent pathologic analysis.

Statistical analysis

Statistical analysis was performed using SPSS software (version 20, Chicago, IL, USA). Categorical and continuous variables are expressed as count (%), and mean ± standard deviation, respectively. The distribution of INP was not normal (Kolmogorov–Smirnov test, $P < 0.05$); it was right-skewed, and the nonparametric test was performed for comparison between groups. We tested differences in means of INP between groups by Mann–Whitney U-test and Kruskal–Wallis test. Spearman's correlation coefficients were used to evaluate the relationship between SLNs size, sonographic tumor size, and INP. All tests of statistical significance were two-sided, and $P < 0.05$ was considered statistically significant.

Results

The final analysis was conducted in 73 patients. Tables 1 and 2 show continues and categorical characteristics of the study population. In eleven patients, INP measurement was made on 2 SLNs. FS was not performed in six patients, due to high level of suspicious to be metastatic or unavailable FS. Identified SLNs in four cases were not metastatic and further suspicious non-SLNs were identified and INP was measured. High INP beside high LOS in these LNs was accompanied by a positive FS result for metastasis.

Table 3 shows the comparison of INP between pathologic results, LOS, frozen-section, and subtype of breast cancer (hormone receptors and HER2). Our results manifested the significant differences between INP by final pathologic results, frozen, and LOS ($P < 0.001$). Patients who had HER2-positive tumors had significantly higher INP compared with HER2 negatives. There was not any relationship between INP and either clinical SLN size, or sonographic tumor size ($r = 0.06$ and $r = 0.04$, respectively; $P > 0.05$). There was statistically significant ($P = 0.003$) higher INP in SLNs with tumoral involvement compared with non tumoral SLNs (19.17 ± 13.63, range 1.03–49.80 vs. 8.82 ± 4.23, range 1.47–24.00 mmHg, respectively).

The sensitivity, the specificity, the positive predictive value, and negative predictive value (NPV) for detecting metastasis in axillary lymph nodes are summarized in Table 4. We considered the cutoff value for INP at 16 mmHg, which resulted in sensitivity of 80% and specificity of 87%. When the combination of INP above 16 mmHg and the LOS

Table 1: Continuous clinical and pathological variables

Variables	Mean±SD
Age	50.47±12.01
Sonographic size of the tumor (mm)	22.18±11.80
Pathologic size of the tumor (mm)	25.16±14.19
Number of lymph nodes dissected	6.22±5.40
Number of metastatic lymph nodes	1.25±2.34
Size of SLN#1 (cm)	1.60±0.85
Size of SLN#2 (cm)	1.28±0.56

SLN: Sentinel lymph node, SD: Standard deviation

Table 2: Categorical variables: Percentage

Variables	Percentage
Side	
Right	52.1
Left	47.9
Histology	
IDC	47.9
IDC and DCIS	25.4
ILC	15.5
Others	11.3
Grade	
1	22.1
2	63.2
3	14.7
ER	
Positive	78.3
Negative	21.7
PR	
Positive	73.3
Negative	26.7
Her2	
Positive	22
Negative	78
LOS	
0	61.2
1	25.4
2	13.4
Frozen analysis of SLN	
Involved	23.9
Free	76.1
Permanent pathologic analysis of SLN	
Involved	26
Free	69.9
Microscopically involved	4.1
INP group (SLN) (mmHg)	
<16	76.7
Above 16	23.3

SLN: Sentinel lymph node, INP: Intranodal pressure, IDC: Invasive ductal carcinoma, ILC: Invasive lobular carcinoma, DCIS: Ductal carcinoma insitu, LOS: Level of suspicion, ER: Estrogen receptor, PR: Progesterone receptor

were taken into account for determining the likelihood of metastatic involvement of the LNs, the sensitivity and specificity were 87.5% and 91.7%, respectively.

Discussion

The results of the present study illustrated the intraoperative FS of the SLN(s) was the most accurate method in detecting axillary metastasis. Meanwhile, intraoperative INP was the second most accurate method, especially when it was combined with LOS. Our finding shows the INP was more precise than preoperative ultrasonic evaluation of the axillary lymph nodes and the surgeon's level of suspicious according to the physical examination and intraoperative findings.

INP measurement as a new, simple, and quick test has been introduced by Nathanson *et al.*[10,11] However, the method of their measurement was based on a simple device, which was connected to the anesthetic computer monitoring system. In this study, we improved the method of measuring INP by utilizing precise equipment specifically designed for this purpose. We evaluated metastatic involvement of SLN in axilla based on the firm consistency of metastatic nodes by measuring the INP. This study result illustrated that INP was significantly elevated (more than twice as high) in SLNs with metastases, compared with free SLNs. There were significant differences between INP in LOS categories, as well [Table 3].

Our results are consistent with previous studies in human and animals that reported the breast cancer metastasis in axillary SLNs was associated with significantly higher INP than in normal lymph nodes.[10-12] However, we could not find any statistically significant correlation between LNs size in clinical and sonographic examinations and INP. The animal study by Miura *et al.* supported our results which showed the increasing of INP in lymph node when metastasis was detected, while the axillary lymph node volume had not increased significantly.[12]

Our results show the statistically significant differences in INP in HER2-positive patients, compared with HER2 negative. A recent study in 2016 revealed HER2 expression is an independent predictor of ALN involvement in breast cancer.[18] Therefore, we expect these patients are at increased risk of lymph node metastasis and increasing INP.

In practice, FS analysis is the most commonly used technique in the evaluation of SLN status intraoperatively. However, this method is expensive and requires a well-trained pathologist. Meanwhile, it is associated with false-negative results, tissue loss, and consequently missing micrometastatic disease in the process of frozen analysis.[19]

Although INP measurement does not replace the need for frozen sectioning of the SLN, it can be used along with frozen analysis to decrease false negative rate of recognition of metastatic SLNs. The Z0011 study has persuaded many surgeons to avoid complete ALND (CALND) when a positive SLN is identified in a patient undergoing a lumpectomy.[20] Because false-negative rates of FS in SLNs range from 13% to 60%, patients may require a CALND at another time, especially when total mastectomy was done before. If there is a way to improve the intraoperative diagnosis of metastasis, a second operation could be avoided.[21,22] In our study, three patients had a high INP with a negative node on FS, which

Table 3: Comparison of intranodal pressure in sentinel lymph node 1 and sentinel lymph node 2 in different categories

INP (mmHg)	n	Mean INP±SD	P
Pathologic results			
Not involved	63	8.8±4.2	0.003
Involved	21	19.1±13.6	
LOS			
0	48	8.2±0.58	<0.001
1	20	14.7±2.03	
2	9	24.0±5.0	
Missing	7		
Frozen results			
Negative	59	9.0±0.7	<0.001
Positive	19	17.6±3.1	
Missing	6		
ER			
Positive	54	11.6±8.5	0.71
Negative	14	10.7±6.7	
Missing	16		
Her2			
Positive	51	15.8±9.9	0.01
Negative	16	10.1±7.2	
Missing	17		

INP: Intranodal pressure, SD: Standard deviation, LOS: Level of suspicion, ER: Estrogen receptor

Table 4: Specificity, sensitivity, positive predictive value, and negative predictive value for recognizing axillary lymph node metastasis

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Physical exam of the axilla	20.8	73.3	23.8	69.8
Ultrasound	28.6	75.5	31.6	72.2
Level of suspicious	55.6	79.4	26.3	93.1
INP of the SLN	80	87	57.1	95.2
Frozen analysis of the SLN	89.5	96.6	89.5	96.6
INP and LOS combined	87.5	91.7	80	95.7

PPV: Positive predictive value, NPV: Negative predictive value, LN: Lymph node, INP: Intra-nodal pressure, SLN: Sentinel lymph node, LOS: Level of suspicion

prompted the surgeon to perform a CALND. More than two dissected LNs in these patients were metastatic. Although this is clearly a rare experience, decreasing false-negative rate of FS of SLNs by our technique might be worth consideration. Meanwhile, there were four patients without metastatic SLNs, but their adjacent lymph nodes (non-SLNs) were hard and neither "hot" nor "blue." On observing very high INPs in these nodes they were removed and FS revealed metastasis in the hard nodes.

Our results manifested if the surgeon LOS is low and intranodal pressure is lower than 16 mmHg, the probability that SLNs is truly diagnosed negative is 95% and the combination of these two tests (INP and LOS) gets a higher NPV than LOS or FS alone. It is worth to mention that LOS evaluation along with INP measurement is a simple technique that can be available, do not require a well-trained pathologist, and are not time and money consuming.

The advantage of this study was improving the method of measuring INP by utilizing precise equipment. Our limitation was the possibility that the needle passes completely through the nodes especially in smaller nodes or inserted into the perinodal tissue and it gives a false reading, as it was previously described by Nathanson *et al*.[11] In conclusion, our results suggest that INP measurement has the potential to aid the differentiation of metastatic and nonmetastatic SLNs in combination with LOS by a surgeon. However, it is not a powerful test for the definite diagnosis and cannot be applied alone for all patients due to high false-negative results. Further evaluation with more sample size and measurement of the INP by the ultrasound guidance of the tip of the needle might provide higher accuracy.

Financial support and sponsorship

Conflicts of interest

There are no conflicts of interest.

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