RESEARCH ARTICLE

A Comparison of Diagnostic Value of Pre-operative Axillary Ultrasonography with Frozen Section Pathologic Results of Axillary Sentinel Lymph Nodes

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Abstract

Background and Objective: Although the breast cancer mortality rate has drastically decreased, it is still the second cause of cancer-induced death among women worldwide. Biopsy and surgery of sentinel lymph nodes are utilized to assess adjacent lymph nodes. However, this procedure has several side effects. Ultrasonography has been recommended as an alternative choice for distinguishing the involvement of axillary lymph nodes in breast cancer. The present study aims to investigate the diagnostic accuracy of axillary ultrasonography in patients with breast cancer to compare the results with the sentinel lymph nodes biopsy. **Method:** This is a cross-sectional study conducted on the patients diagnosed with breast cancer (n = 60), referred to Afzalipour and Bahonar Hospitals, Kerman, Iran during 2015–2016. Ultrasonography was carried out using an ultrasound device with the surface probe at 10 MHz. Those patients, whose different ultrasonography parameters such as size, thickness of cortex, and thickness of modulus related to the most accessible susceptible lymph node showed no involvement, were included in the study. Sentinel lymph nodes were studied through concurrent utilization of the isotope injection method (scintigraphy) and blue iso-sulfate injection method. All samples were subjected to pathological analyses, and the results were compared to the ultrasonography results. **Results:** Results of permanent pathology were positive in all of the 9 patients whose Frozen Section results were positive. Of the 51 patients with negative Frozen Section results, only three demonstrated positive permanent pathologic results, and 48 participants showed negative permanent pathology. Considering the validating assessments, the negative predictive value of ultrasonography is 85%, compared with the frozen section specimens of sentinel nodes. **Conclusion:** Biopsy of sentinel lymph nodes could be replaced with ultrasonography only by an expert and trained radiologist. It is recommended to use a predefined protocol in collaboration with four medical groups including radiology, nuclear medicine, surgery, and pathology groups.

Key words: Biopsy, breast cancer, sentinel lymph node, ultrasonography

INTRODUCTION

After lung cancer, breast cancer is the second cause of mortality among women worldwide.[1] The most comprehensive statistical data on the rate of incidence of this cancer was published by the center for control and prevention of diseases. These data indicate a drastic increase in the incidence of breast cancer during the past 50 years in the United States. Moreover, according to this data, an abrupt increase is seen in breast cancer incidence after 30 years of age, but an invariant rate is observed from 45 to 50 years of age.[2] The outbreak of this disease increases uniformly with the growth of age. A series of predisposing factors are involved in the outbreak of this disease, some of which include family history, diet, obesity, alcohol intake, reproductive factors, hormonal factors, and history of cancer.[3] In spite of the increase in the incidence

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of breast cancer, case fatality has dropped since 1991 due to the improved precision of diagnosis in the early stages of breast cancer and quick therapeutic interventions before the manifestation of its symptoms. Although the rate of mortality caused by breast cancer has decreased drastically, it is still the second cause of cancer-induced death among women worldwide. Deaths are mainly caused by late diagnosis, which leads to involvement of several organs in addition to the breasts. Therefore, accurate and timely diagnosis of metastasis are the key to prevent complications and reduce expenses and mortality.[4,5]

Biopsy and surgery of sentinel lymph nodes (which are the first breast cancer draining nodes) are employed to assess adjacent lymph nodes.[6] In the sentinel lymph nodes biopsy (SLNB) method, the radioisotope is infused alone or along with blue iso-sulfate into the tumor or around breast areola. Afterward, the flow path of the substances is identified until they reach the lymph nodes. These two factors are used to discover sentinel lymph nodes.[7] Various research has indicated that concurrent use of a radioisotope and blue iso-sulfate increases surgical precision and accuracy as compared to utilization of these two substances separately.[7,8] After identifying the sentinel lymph node, the node is sent for pathologic examinations, and if its metastatic involvement is proved, cancer-stroke axillary lymph nodes are explored and identified on levels 1 and 2.[9] Effectiveness of SLNB for diagnosing involvement of axillary lymph nodes has been proved so far. This surgical procedure positively affects the patient's lifestyle. Moreover, complications such as limbs inflation, motor limitation, pain, and sensory impairment in patients undergoing this surgery are significantly observed less than patients who undergo typical axillary lymph node dissection.[6] However, this method causes complications such as interference with patient monitoring devices (such as the pulse oximeter), increased sensitivity reactions, colorization of patient's excretions (such as urine), and skin problems (such as skin tattoos at the site of injection and skin necrosis).[10-13]

Ultrasonography has been recommended as an alternative approach for distinguishing of the involvement of axillary nodes in breast cancer. According to results of some studies, ultrasonography has a diagnostic power of 88% for positive sentinel lymph nodes, and it yields 11% false negative results.[14] In addition, pre-operative ultrasonography can diagnose N2 and N3 ductal carcinoma metastases by 96%, but its sensitivity is much lower in diagnosing lobular metastasis.[15]

The side effects of SLNB, low popularity of this procedure, and some clinical contraindications[16] are among the reasons for the use of less invasive paraclinical procedures such as ultrasonography. However, selection of diagnostic methods (especially in the case of diseases such as cancer) calls for complete investigation of the diagnostic power and sensitivity of the method as compared to its utility. Since the SLNB procedure is almost new to Kerman University of Medical Sciences, Iran, and since so far no study has been carried out on this procedure, it seems necessary to determine the predictive value and precision of axillary ultrasonography in patients of this academic center before increasing the use of this method and determining the targets for this technique, who are mainly identified through pre-operative axillary ultrasonography. The objective of this research was to compare the results of SLNB in patients with breast cancer to typical axillary ultrasonography results.

MATERIALS AND METHODS

This was a cross-sectional study conducted on the breast cancer patients from 2015 to 2016 referred to the Afzalipour and Bahonar Hospitals of Kerman City, Iran, during 2015–2016. The same size was estimated 60 based on the similar studies and a statistical formula.

The inclusion criteria included the presence of early breast cancer (diagnosis by pathological assessment), lack of palpable surface axillary lymph node, being a candidate for sentinel lymph node biopsy (i.e. no SLNB prohibition), and negative ultrasonography results caused by susceptible or clear axillary lymph node malignancy. The exclusion criteria were the patients who were candidates for other diagnostic methods and not candidates for SLNB.

First, ultrasonography was carried out on patients by a radiologist, who was unaware of patients' conditions and preliminary diagnoses, using an ultrasonography device and 10MHz surface probe. Results of different ultrasonography parameters including size, cortex thickness, and thickness of modulus related to the most accessible susceptible lymph node showed no involvement and the patient was finally included in the research.

To examine the sentinel lymph nodes, the isotope injection (scintigraphy) and blue iso-sulfate injection methods were used jointly. To this end, half mCi of sulfur colloid labeled with 99m technetium was injected into the tumor in the morning of the operation day. Next, 3–5 ml of a colored substance (blue iso-sulfate) was injected into the subareolar region before the operation in the operating room. A radioisotope counter was used to identify sentinel lymph nodes. After identifying the sentinel lymph node, the nodes were removed and were sent for the frozen section procedure and permanent pathology. All specimens were pathologically examined, and results were compared to ultrasonography results. The decisive measure for assessing involvement or non-involvement of lymph nodes was the permanent pathology result. The results were finally recorded and subjected to statistical analysis.

According to the study of reference 6 the specificity of axillary ultrasonography is 82% in the diagnosis of the involvement of lymph nodes. The sample size was calculated according to the 6% prevalence breast cancer in Kerman, w=0.05, confidence interval of 5% and statistical power of 80%.

RESULTS

The present study conducted on 60 women with breast cancer who underwent typical ultrasonography. The average age of patients was 52.4.4.2 years old with the age range of 26–61 years old.

For the 60 patients studied in this study, the frozen section samples obtained from sentinel lymph nodes during surgery were examined. The results were positive for 9 patients and negative for the remaining 51 patients. Therefore, 15% and 85% of the studied samples demonstrated positive and negative frozen section values, respectively.

The samples obtained from all of the participants (n = 60) were sent to a specialized laboratory for permanent pathology analyses. All of the 9 patients with positive frozen values section had positive permanent pathology values. Of the 51 samples with the negative frozen section values, only three had positive permanent pathology values, while 48 had negative permanent pathology values.

Table 1 presents the results of tumor pathology for the two evaluation methods.

The results showed that the negative predictive value of ultrasonography is 85% compared to the frozen section values.

The statistical analyses showed no statistically significant difference between the results of sentinel lymph node biopsy and typical axillary ultrasonography, demographic variables, and cancer pathologic type ($P > 0.05$).

DISCUSSION

Breast cancer is the most common women-specific cancer, and thus its diagnosis and prevent are of high importance. Breast cancer staging needs clinical, paraclinical, and also intraoperative evaluations. In breast cancer staging, it is particularly important to determine the involvement of lymph nodes. In patients who do not demonstrate the clinical involvement of axillary lymph nodes and who are in the first and second stages of breast cancer, SLNB improves the staging precision and may prevent unnecessary dissection of axillary lymph nodes and its subsequent side effects. However, due to the side effects of SLNB (such as development of seroma and wound infection) imaging techniques such as ultrasonography has attracted attention for screening purposes.[17,18]

Our research revealed that the negative predictive value of ultrasonography is 85% in biopsy of sentinel lymph nodes, which is acceptable considering the ease and availability of this paraclinical method that causes no complication. In addition, for all of the 9 patients whose frozen section results were positive results of permanent pathology were also positive. Of the 51 patients whose frozen section results were negative, only three had positive permanent pathology results while the remaining 48 patients had negative pathology results. Moreover, results of tumor pathologic analyses indicated that 68%, 20%, and 12% of patients under study were suffering from invasive ductal carcinoma, ductal carcinoma *in situ*, and lobular carcinoma, respectively. Statistical analyses showed no statistically significant difference between results of sentinel lymph node biopsy in patients with breast cancer and results of typical axillary ultrasonography, demographic variables, and cancer pathologic type ($P > 0.05$) [Figure 1].

The negative results of SLNB in our research were approximately 6%. Different negative SLNB results were reported by different studies, and it varies between 0% and 2.22% reportedly.[19,20] The high precision of SLNB in assessing the conditions of breast cancer draining lymph nodes has been proved in various studies. Since results of SLNB are used in making decisions on supplementary treatments, the false negative value should be as close to zero as possible.[19] In our study, the false negative value was in the mentioned range. Although success of SLNB increases with the surgeon's experience, false negative cases will still exist.[20] Hence, the frozen section procedure is a suitable way of studying the metastatic involvement of sentinel lymph nodes, and this method often requires <10 min.[21] In the present research, after identifying and removing sentinel lymph nodes, the frozen section procedure was carried out on all patients. The study of Halwitt *et al*. showed that the predictive value of SLNB can be 100% for tumors <2 cm. They also reported that there was no relationship between number of early breast cancer lesions and precision of SLNB.[22] The presence of early tumors in primitive tumors in the lower and internal quadrants of the breast has negative effects on the success and accuracy of SLNB.[23,24]

The negative predictive value of ultrasonography in this study was calculated 85%. Few studies have also compared ultrasonography with SLNB in patients with breast cancer. For instance, Taylor *et a*l. reported a negative predictive value of 100% for ultrasonography, which is higher than our finding.[25] However, other studies have reported a lower negative predictive value. Ying *et a*l. reported a negative

Table 1: The results of tumor pathology for the two evaluation methods

Frequency	Quantity (%)	Permanent pathology result	
		Positive (%)	Negative (%)
Frozen section result	Positive	9 (15)	0 (0)
	Negative	3 (5)	48 (80)

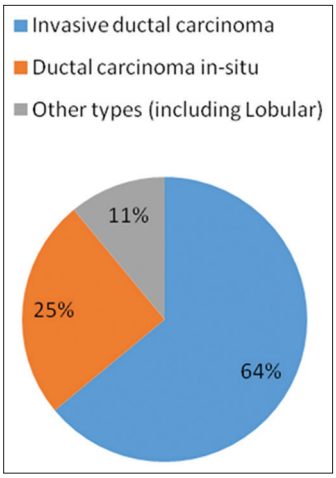

Figure 1: The percentages of the different types of cancer pathology

predictive value of 76%.[26] In a more recent study, carried out by Kilic *et al.* they compared the accuracy of ultrasonography against the SLNB assessments in 30 patients. They reported a negative predictive value ranging from 57 to –95 by analyzing different ultrasonography parameters.[27] Choi *et al*. examined 60 patients and reported a negative predictive value between 58 and 79% by examining various ultrasonography parameters.[28] Although results of this research are very similar to the results of other studies; there are differences in some cases. One of the reasons for this difference could be the limited experience of the project's executive team. Another factor could be the effect of tumor size on the outcomes where SLNB in patients with smaller tumors is more accurate accompanied by a lower false negative value.

CONCLUSION

This study investigated the predictive value of considering our findings, ultrasonography can be replaced with SLNB only by a skilled, trained radiologist, and under-experienced radiologists shall not leave the SLNB method until an acceptable result (which is determined by identification of sentinel lymph nodes and the related false negative value) is obtained.

It is recommended to use a defined protocol in collaboration with a team composed of the medical, radiology, nuclear medicine, surgery, and pathology groups. The precision of ultrasonography and sentinel lymph node biopsy depends on the performance of these four experts, which form a group. Hence, this procedure shall be carried out in hospitals, which have the required equipment for this procedure.

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