

Investigating The Health of Resection Margins For Conducting Intra Operative Radiotherapy During Breast Conservative Surgery

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ABSTRACT

To conduct radiotherapy during operation in treating the breast cancer through breast conservative surgery method, we must ensure the healthiness of resection margins during the operation. Then, electron ray is flashed to the surrounding tissues in order to reduce the chance of the presence of any microscopic cancer cells. The present research studies the ability of Frozen in diagnosing the health or involvement of margins during the operation and seeks to compare the results of Frozen with the results of gold standard (permanent pathology) diagnostic method in patients suffering from breast cancer who have undergone breast conservative surgery and Intra-operative radiotherapy. In this observational study conducted in the form of a retrospective research, some 496 patients suffering from breast cancer who have undergone breast conservative surgery were selected through the convenience sampling method and the results of breast margin pathologies conducted through Permanent and Frozen section were compared against one another so that we may find the sensitivities and specifications of the Frozen sections in comparison with the Permanent method. In the Frozen and Permanent methods, the margins had a freedom degree of 83.1% and 98% respectively. The sensitivity and peculiarity of the Frozen section as compared to the Permanent method were 80% and 84% respectively, however the negative predictive value was 99.5%. A significant relationship was observed here based on chi square test. The level of accuracy was 84.3%, and the pseudo negative was 0.5%. The compliance level of the Permanent and Frozen diagnostic methods was 84.3%. It is therefore concluded that the Frozen section has a good degree of compliance in determining the state of margin of the removed cancerous lump in breast conservative surgeries and false negative reports have been issued for 0.5% of the cases. Thus, it is recommended to use the Frozen section before radiotherapy to determine the freedom of margins.

Key words: Breast Conservative Surgery and Intra-operative radiotherapy,
Frozen section, Permanent Method.

INTRODUCTION

The breast cancer is one of the most common types of cancer observed among the Iranian women. In 70% of the cases, this cancer is diagnosed only after it has reached the advanced

or the metastatic state. In 50% of the cases, this cancer is diagnosed only when its size has exceeded 5 cm¹⁻². Thanks to the awareness of the patients, this disease is usually diagnosed in its early stages and only 45.5% of them are diagnosed when they have reached the advanced level³. The

5-year perseverance level of this disease in Iran is 62% which is slightly more than what is observed in other countries⁴. Those afflicted with this cancer will experience deterioration of their life quality due to its physical side effects and other psycho-mental problems⁵⁻⁶. Today, various methods are used to diagnose breast cancer each one being of certain accuracy. Such methods include pre-surgery biopsy, sampling and pathologic examination during the surgery using Frozen and Permanent methods⁷⁻⁹. Examining the Permanent pathology samples taken during breast surgery is considered to be the main method. Utilizing a method with the same degree of precision during the operation for diagnosing the involvement of margins can be of great help for conducting intra operative radiotherapy during the breast conservative surgery and reduce treatment costs and side effects of re-surgery^{10, 11}. The first step will be the measurement of diagnosis precision and the compliance level of the Frozen section in comparison with the Permanent method about the margins of the breast that is under surgery. The present research has studied the compliance level of the pathology results of breast margin in Permanent and Frozen sections on those afflicted with breast cancer who have undergone breast conservative surgery.

Patient and Methods

In this research conducted as a diagnostic study, 496 patients with breast cancer in Khatam Al Anbiya Hospital who had undergone breast conservative surgery were selected through convenience sampling method. The results of breast margin pathologies through both Permanent and Frozen sections were compared against one another so that we may learn about the sensitivity and peculiarity of the Frozen section in comparison with its Permanent counterpart. SPSS version 13 was utilized to analyze the collected data. Frequency and frequency percentage were calculated for the qualitative data, while mean and standard deviation were calculated for the quantitative data. Chi square and Fisher tests were used and the significance level for the interpretation of the results was 0.05. Furthermore, the sensitivity and peculiarity of the Frozen section in comparison to its Permanent counterpart and the Positive Predictive Value (PPV) and Negative Predictive Value (NPV) for the patients were also measured.

RESULTS

The average age of the 496 participants studied was 50.4, the average number of positive lymph nodes was 2 and the average size of tumor was 21.5 mm. The following frequencies were reported for different tumors: 5.2% for DCIS, 72.8% for IDC, 11.9% for ILC, 6.9% for Mixed type and 3.2% for other types of tumors. The following grades were also reported for tumors: 1 for 10.25% of the cases, 2 for 60% of the cases, and 3 for 29.75% of the cases. Perineural invasion was observed in 21.6% of the cases. Vascular invasion of tumor was observed in 38.9% of the cases. 21.4% of the tumors had calcification. 30.8% of the tumors had necrosis. 46.4% of the involvements were observed on the right hand-side, 46.8% were observed on the left hand-side, and 0.4% was bilateral. Family history was positive in 9.5% of the cases. The estrogen receptor was positive in 69.7% of the cases. The progesterone receptor was positive in 69.9% of the cases. HER2 receptor was positive in 19.1% of the cases. In the Frozen state, the margin was free in 83.1% of the cases. However in the Permanent state, the margin was free in 98% of the cases. The sensitivity and specificity of the Frozen section as compared to the Permanent method were 80% and 84% respectively, however the negative and positive predictive values were 99.5% and 9.5% respectively. A significant relationship was observed here based on Chi square test. The level of accuracy was 84.3%, and the pseudo negative and pseudo positive were 0.5% and 90.5% respectively. The compliance level of the Permanent and Frozen diagnostic methods was 84.3%. The 2 cases (0.5%) which were pseudo-negative were finally diagnosed as ductal carcinoma insitu tumors (DCIS). The negative state of estrogen receptor was accompanied by higher levels of sensitivity and specificity. The negative state of progesterone receptor was accompanied by higher levels of sensitivity and specificity. The positive state of HER2 receptor was accompanied by higher levels of sensitivity; but it had no influence over specificity. The pathologic type of the tumor had no influence on the sensitivity and specificity of the Frozen. As the grade of tumor increases, we witnessed in rise in sensitivity and a reduction in specificity. In the cases where we had Perineural invasion, we observed higher levels of sensitivity but the

specificity remained unaffected. Higher levels of sensitivity were recorded in the cases of vascular invasion, but no difference was observed for specificity. Higher levels of sensitivity were recorded in the cases of calcification, but lower levels of specificity were observed. Higher levels of sensitivity were recorded in the cases of necrosis, but lower levels of specificity were observed. Family history had no impact on specificity and sensitivity.

DISCUSSION

In the Frozen and Permanent methods, the margins had a freedom degree of 83.1% and 98% respectively. This means that 16.9% of the margins were positive during the first surgery and if intra operative radiotherapy is conducted without checking the margin, this percentage of the patients would not benefit from anything. The sensitivity and specificity of the Frozen section as compared to the Permanent method were 80% and 84% respectively, however the negative and positive predictive values were 99.5% and 9.5%. A significant correlation was observed here based on Chi square test. This means that Frozen was wrong only among 0.5% of the patients and this error has probably been due to the engagement between Margin and DCIS centers. No need for a new surgery after the removal of the margin was reported and the percentage of a successful surgery reached zero.

Another study conducted by Nafissi *et al.* in Iran whose results were published in 2012, 237 people were studied and based on the study of Frozen, margin was positive in 25% of the cases all of whom underwent Re-Excision in the very same session. As for Permanent, margin was positive in 2.9% of them which shows using Frozen prevented re-surgery in 23% of the patients. In this study, the sensitivity of Frozen in diagnosing the malignant cases in breast margin was 100%, while its specificity was 99.2%¹². In another study conducted by Tan *et al.* in Singapore whose results were published in 2014, 161 patients who had undergone breast surgery were studied. The results showed non-compliance in terms of Frozen and Permanent results among 4 patients (pseudo positive) and no case of pseudo negative which needed re-operation was recorded. There was non-

compliance between the results of Frozen and Permanent in 98.4% of the cases¹³. In another study conducted by Jorns *et al.* in U.S.A whose results were published in 2012, 181 patients were studied. They were compared with 188 people who had undergone the Permanent method without Frozen. The results showed that conducting Frozen has resulted in decreased need for Re-excision in 34% of the patients, while this level in our study was only 9.5% (real positive Frozen) which is well below the level reported in this research¹⁴. In another study conducted by Dener *et al.* in Turkey whose results were published in 2009, 186 patients were studied using Frozen Section method. The results indicated the need for Re-excision in 16% of the cases and only 2.1% of the patients experienced local recurrence¹⁵. In another study conducted by Weber *et al.* in Switzerland whose results were published in 2008, 80 patients were studied using the Frozen section and it was announced that the diagnosis precision and sensitivity and specificity of this method were 83.8%, 80% and 87.5% respectively¹⁶. In another study conducted by Olsen *et al.* in the US whose results were published in 2009, 290 patients were studied using Frozen Section method and the results showed that 2.7% of the patients required Re-excision¹⁷. In the study conducted by Weber *et al.* in the US whose results were published in 1997, 169 patients were studied using Frozen Section method and the results showed that 15% of the patients required Re-excision and the sensitivity and specificity levels of the Frozen section were 91% and 100% respectively¹⁸. In another study conducted by Noguchi *et al.* (1995) in Japan, 95 patients were studied using Frozen section and the diagnostic precision of this method in comparison with the Permanent method was recorded to be 87%, while its sensitivity and specificity were 96% and 84% respectively¹⁹.

Isaacs *et al.* studied 89448 patients with breast cancer who had undergone breast conservative surgery from 2003 to 2013 in USA. As the results indicate during the early years of the research (2003 & 2004), 39.5% of the patients required Re-operation but this percentage decreased significantly in the final years (2011 to 2013) to 23%. This can be attributed to the doctors' gaining more experience in breast conservative surgery²⁰. In our study, 16.9% of the margins were

positive during the first surgery and according the result of frozen section the involved margin was resected in same session.

CONCLUSION

Based on all evidences presented in this research, we may conclude that Frozen section

exhibits a good level of compliance in determining the state of the margin of the tumor removed in breast conservative surgery before conducting intra-operative radiotherapy. Thus, utilizing the Frozen section is recommended.

Finally, multi-center studies with larger samples are recommended so that more generalizable results may be achieved.

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