Atypical Hyperplasia at the Margin of Frozen Sections from Breast-Conserving Surgery

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Purpose: Intraoperative frozen section analysis to assess margin status during breast-conserving surgery is often performed to reduce the rate of re-excision. Whether additional resection is required if atypical cells are found at the margin during breast-conserving surgery is controversial. The aim of this study was to evaluate the accuracy of intraoperative frozen section analysis and investigate the feasibility of additional resection in cases of atypical hyperplasia on frozen sections from breast-conserving surgery.

Methods: A retrospective analysis was performed on 1,411 patients with invasive breast cancer who underwent breast-conserving surgery between July 2004 and June 2012. The microscopic margins of the intraoperative frozen sections and permanent sections were examined. Overall events (locoregional recurrence and distant metastasis) were analyzed between the negative margin group and the other margin group (including atypical hyperplasia, carcinoma in situ [CIS], and invasive carcinoma).

Results: Of the 1,411 patients, 1,201 had negative margins and 210 had other margin types in the first frozen section. 68 patients had atypical hyperplasia on frozen section analysis. This atypical hyperplasia included atypical cells, atypical ductal hyperplasia, and atypical lobular hyperplasia. Of these 68 patients, the final findings on the permanent section were negative (n=32, 47.1%), atypical cells (n=16, 23.5%), and CIS (n=20, 29.4%). The rate of overall events and distant metastases were higher in the other margin group (9.5% vs. 5.4%, p=0.021) and (5.7% vs. 3.0%, p=0.045). Of the 1,411 patients, 44 (3.1%) had false-positive findings, and 15 (1.1%) had false-negative findings in the frozen sections, with an accuracy of 95.8%.

Conclusion: The accuracy of intraoperative frozen section analysis was 95.8%, with 91.7% sensitivity and 96.4% specificity. Atypical hyperplasia on frozen section analysis requires additional resection at the time of breast-conserving surgery because of the possibility of CIS, but excessive resection may be performed in other cases. Therefore, sufficient consultation with patients is required.

Key Words: Atypical hyperplasia, Breast-conserving surgery, Frozen section analysis

INTRODUCTION

Cancer is the leading cause of death in South Korea, and breast cancer is the second most common cancer in women [1]. Many randomized control trials have shown that breast-conserving surgery has better cosmetic benefits and similar long-term survival rates to total mastectomy. Consequently, breast-conserving surgery followed by adjuvant radiation therapy has become the standard treatment for early stage invasive breast carcinoma or carcinoma in situ (CIS) [2-4]. However, since there is a possibility of local recurrence in the remnant breast tissue in the case of breast-conserving surgery, radiation therapy is required after surgery, and it is therefore important to confirm gross and microscopic clear margins during surgery [5-7]. Intraoperative frozen section analysis to assess the margin status during breast-conserving surgery reduces the rate of re-excision. Re-excision is associated with morbidity and adverse cosmetic effects. Therefore, it is important for surgeons to obtain appropriate resection margins and confirm negative margins using frozen section analysis [8,9].

When frozen section analysis is performed during surgery, various margin statuses can be reported. One of these is atypical hyperplasia, which is defined as a borderline lesion between benign ductal hyperplasia and carcinoma. However, whether additional resection is required if atypical cells are found in frozen section analysis is controversial [10].

The aim of this study was therefore to evaluate the accuracy of intraoperative frozen section analysis and to investigate the feasibility of
obtaining a negative margin at the primary resection and additional resection in cases of atypical hyperplasia on frozen sections.

METHODS

Patients and data analysis

We performed a retrospective analysis based on the medical records of 1,411 patients diagnosed with invasive carcinoma who underwent breast-conserving surgery with intraoperative frozen section analysis between July 2004 and June 2012 at Chonnam National University Hwasun Hospital. Core needle biopsy, fine needle aspiration, excisional biopsy, incisional biopsy and vacuum-assisted breast biopsy procedures were used to diagnose invasive carcinoma prior to surgery.

To compare events according to the first margin status, we divided patients into a negative margin group and an other margin group (including atypical hyperplasia, CIS, and invasive carcinoma). Event analysis included local recurrence in the ipsilateral skin, breast, and chest wall and regional recurrence in the axillary lymph nodes and internal mammary lymph nodes, and distant metastasis in the bone, liver, brain, lung, pleura, distant lymph nodes, and others. Overall, events included all of these events and death. The first margin atypia group and the CIS and invasive carcinoma margin groups were also analyzed. The difference between the frozen section and permanent biopsy was investigated in the atypia, carcinoma in situ, and invasive carcinoma groups. In addition, false-positive and false-negative rates were analyzed to test the accuracy of the frozen section analysis. This study was approved by the Institutional Review Board at Chonnam National University Hwasun Hospital, with the reference number HTMP-2021-020. Informed consent was waived owing to the retrospective nature of the study.

Surgical procedure and frozen section analysis

Preoperative mammography-guided wire localization or ultrasonography-guided staining was performed in cases of nonpalpable microcalcification or small-sized lesions. During the surgery, we aimed to achieve a safe margin of 1 cm grossly at the first excision. When microcalcification was present, the surgeon performed specimen mammography to confirm precise excision. Sentinel lymph node biopsy was performed using indigo carmine blue dye for axillary lymph node staging. After the first lumpectomy specimen resection, the upper, lower, inner, and outer margins were excised from the breast tissue and sent to the pathology department for frozen section analysis. The surgical defect was repaired with a glandular interposition. If tumor or atypical cells were observed in the frozen section analysis, additional resection was performed to obtain a negative margin.

Statistical analysis

The Student’s t-test was used to compare continuous variables, and the chi-squared or Fisher’s exact test were used to compare categorical variables. All data analyses were performed using SPSS version 25.0 (SPSS Inc., Chicago, IL, USA). Two-sided p-values of < 0.050 were considered statistically significant.

RESULTS

Baseline characteristics

We divided patients into the negative margin group and the other margin group based on the frozen margin status. There were 1,201 patients in the negative group and 210 patients in the other margin group. The median follow-up duration was 60 months. Table 1 lists the baseline characteristics of the patients. The proportion of pathologic T1 stage was slightly higher in the negative group than in the other margin group (72.0% vs. 70.9%, p = 0.049), and the proportion of progesterone receptor-positive samples was higher in the other margin group (76.2% vs. 68.9%, p = 0.034). There were no significant differences in other variables between the two groups. In both groups, core needle biopsy was the most commonly used diagnostic method, and the upper-outer quadrant was the most common tumor location. Pathologic T1 and N0 stages were the most common.

Events according to margin status on the first frozen section

Table 2 shows the difference in events between the negative group and the other margin group (including atypical hyperplasia, CIS, and invasive carcinoma) in the frozen sections. Local and regional recurrences were not significantly different between the two groups, but the rate of distant metastasis was higher in the other group (5.7% vs. 3.0%, p = 0.045), and the overall events were higher in the other group than in the negative group (9.5% vs. 5.4%, p = 0.021). When events were compared by subdividing the other group into the atypical hyperplasia
There was no significant difference in locoregional recurrence, distant metastasis, or overall events between the two groups (Table 3). 

Correlation between frozen section and permanent biopsy for margin assessment

Figure 1 shows the difference between the frozen section analysis and the permanent section in each group. In the group with atypical hyperplasia on frozen sections, 32 (47.1%) were negative, 16 (23.5%) were found to have atypical cells, and 20 (29.4%) margins were CIS in the permanent section.
To assess the accuracy of frozen section analysis, we excluded atypical hyperplasia groups that had borderline and undetermined features. Of the 1,201 patients with negative margins on the frozen section, 15 patients had positive margins in the permanent section and were defined as false-negative cases (1.1%). Of the 142 patients with CIS or carcinoma in the margin of the frozen section, 12 patients were found to have negative margins in the final permanent section and were defined as false-positive cases (3.1%). The accuracy of the frozen section analysis was 95.8%, with 91.7% sensitivity and 96.4% specificity (Table 4).

**DISCUSSION**

Many randomized control trials have shown that breast-conserving surgery has better cosmetic benefits and a similar long-term survival rates to total mastectomy [2–4]. For this reason, breast-conserving surgery for breast cancer treatment has increased worldwide. Likewise, in Korea, breast-conserving surgery accounted for 65% of surgeries for newly diagnosed breast carcinoma, which is significantly higher than the total mastectomy rate (34%) [11]. Many studies have reported that intraoperative frozen section analysis during breast-conserving surgery reduces the rate of re-excision [8,12,13]. Whether frozen section analysis reduces local recurrence is controversial, but it is important to confirm negative margins for local control after breast-conserving surgery [7,14]. There is also controversy over the local recurrence rate when additional resection is performed. In two previous studies, patients with resection margins noted as positive on the final diagnosis after surgery, required re-excision to obtain negative margins after surgery and were comparable to those who had a negative margin at the time of primary surgery with no significant difference in the local recurrence rates [15,16]. In contrast, other studies have reported higher local recurrence rates in re-excision cases [17,18]. However, it is feasible to confirm negative resection margins by performing frozen section analysis during breast-conserving surgery, since re-excision has a costly mental and physical burden on the patient. For this reason, many surgeons employ frozen section analysis during breast-conserving surgery to confirm a clean resection margin status [8,19].

To compare the baseline characteristics and overall events including locoregional recurrence and distant metastasis, we divided the patients into two groups, the negative group and the other group, based

![Image](https://www.jbd.or.kr)
on the frozen section. Overall events and distant metastases were significantly higher in the other margin groups.

The need for additional resection is controversial when atypical hyperplasia is reported in frozen sections, but it is feasible for several reasons. First, atypical hyperplasia has a relatively high risk of developing cancer [20-23]. Second, atypical cells are difficult to identify because they are at the morphological boundary between benign lesions and CIS. Therefore, it is possible to downstage diagnosis [24,25]. In addition, the margin could be insufficient for diagnosis. In our study, of the 68 patients who had atypical hyperplasia on the first frozen section, 20 (29.4%) patients were diagnosed with ductal carcinoma in situ and 16 (23.5%) patients were diagnosed with atypical cells in the permanent section. If additional resection was not performed during the surgery, 20 patients would have required reoperation. Because CIS is a premalignant lesion, it has a high risk of invasive breast cancer [26,27]. In a comparison of the overall events, the frozen atypical hyperplasia and carcinoma groups showed no difference in locoregional recurrence or distant metastasis. In addition, in a previous study, because atypical cells found at the margin are associated with a high rate of residual atypical ductal hyperplasia and carcinoma, re-excision was recommended [10]. In contrast, Li et al. [28] reported that there is a lack of evidence for re-excision because there was no significant difference in the ipsilateral recurrence rate and distant metastasis-free 5-year survival rate between the group with atypical hyperplasia and the non-atypical hyperplasia group. However, since 29.4% of patients who noted atypical hyperplasia on frozen section were diagnosed with CIS in the permanent section, it is important to confirm a negative margin through additional resection during surgery.

In our study, we found frozen section analysis to have an accuracy of 95.8%. The sensitivity and specificity were 91.7% and 96.4%, respectively. In other studies, the false-negative rate reached up to 18.6%, but in this study, it was as low as 1.1% [8,9,19,29]. Despite the effectiveness of this method in reducing re-excision, frozen section analysis is controversial among many pathologists because it can sometime lead to unnecessary resection due to false positives. However, in our study of a large number of cases, it had important implications with high accuracy (95.8%) and a low false-positive rate (3.1%).

Our study has some limitations. First, this was a retrospective study. Since only patients who underwent breast-conserving surgery for invasive carcinoma were included, the margins of other types of surgery were not evaluated. Second, because all of the atypical hyperplasia margin groups underwent an additional resection, comparison with the non-resected case was not possible. Third, it was not possible to compare how radiotherapy or medical treatment affected progression after breast-conserving surgery.

In conclusion, the accuracy of intraoperative frozen section analysis was 95.8%, with 91.7% sensitivity and 96.4% specificity. Intraoperative frozen section analysis with a negative margin can decrease the rate of overall events and distant metastases. For atypical hyperplasia on frozen section analysis, additional resection is required at the time of breast-conserving surgery because of possibility of CIS, but excessive resection may be performed in other cases. Therefore, sufficient consultation with patients is required.

**CONFLICT OF INTEREST**

The authors declare that they have no competing interests.

**REFERENCES**

6. Obedian E, Haffty BG. Negative margin status improves local con-

https://doi.org/10.14449/jbd.2021.9.2.71


