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Study Protocol

A Randomized Controlled Trial for Doing vs. Omitting Intraoperative Frozen Section Biopsy for Resection Margin Status in Selected Patients Undergoing Breast-Conserving Surgery (OFF-MAP Trial)

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ABSTRACT

Purpose: Intraoperative frozen section biopsy is used to reduce the margin positive rate and re-excision rate and has been reported to have high diagnostic accuracy. A majority of breast surgeons in the Republic of Korea routinely perform frozen section biopsy to assess margins intraoperatively, despite its long turnaround time and high resource requirements. This study aims to determine whether omitting frozen section biopsy for intraoperative margin

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Conflict of Interest
The authors declare that they have no competing interests.

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evaluation in selected patients is non-inferior to performing frozen section biopsy in terms of resection margin positivity rate.

Methods: This study is a phase III, randomized controlled, parallel-group, multicenter non-inferiority clinical trial. Patients meeting the inclusion criteria and providing written informed consent will be randomized to the "frozen section biopsy" or "frozen section biopsy omission" group after lumpectomy. Patients with clinical stage T1–T3 disease who are diagnosed with invasive breast cancer by core-needle biopsy and plan to undergo breast-conserving surgery will be included in this study. If a daughter nodule, non-mass enhancement, or microcalcification is identified on preoperative imaging, these features must be within 1 cm of the main mass for inclusion in the trial. The target sample size is 646 patients per arm. The primary endpoint will be the resection margin positive rate, and the secondary endpoints include the reoperation rate, operating time, residual cancer after reoperation, residual cancer after re-excision according to the frozen section biopsy result, resection volume, patient quality of life, and cost-effectiveness.

Discussion: This is the first randomized clinical trial utilizing frozen section biopsy for intraoperative margin evaluation and aims to determine the non-inferiority of omitting frozen section biopsy in selected patients compared to performing frozen section biopsy. We expect that this trial will help surgeons perform the procedure more efficiently while ensuring patient safety.

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Keywords: Breast Neoplasms; Frozen Sections; Margins of Excision; Mastectomy, Segmental

INTRODUCTION

The most important factor associated with local recurrence after breast-conserving surgery (BCS) is the presence of tumor cells on the surgical resection margin [1,2]. Successful BCS requires a clear pathological resection margin, and reoperation to re-excise the margin is required when a positive margin is identified after the initial operation. The reported re-excision rates vary widely; 10%–37.9% of women require a second surgical procedure to obtain a clear resection margin [3-5]. Among patients who undergo re-excision, more than 10% require two or more re-excisions [4]. Multiple operations to obtain adequate margins are stressful for patients and their families, increase healthcare costs, and compromise cosmetic results [6,7].

Many intraoperative margin assessment techniques have been introduced to reduce the re-excision rate, such as specimen radiography, intraoperative ultrasound, frozen section biopsy, and cytology [8]. Among these techniques, intraoperative frozen section biopsy has the highest diagnostic accuracy [8]. Its utility in reducing positive margins and reoperation rates has also been reported in several retrospective studies [9-11]. However, a slow turnaround time, disruption of the surgical workflow, interdepartmental logistical challenges, and resource requirements have led to a low uptake rate [8]. The reported rate of frozen section biopsy in North America and Europe is 0%–18%, whereas a previous survey reported that 80% of breast surgeons in the Republic of Korea routinely use frozen section biopsies to intraoperatively assess margins [8,12-15]. The high uptake rate of frozen sections in Korea is related to the relatively low cost and high accessibility of frozen section biopsy, as more than 80% of cancer surgeries are performed in high-volume centers [16]. Additionally, reluctance to return a patient to the operation room for margin clearance encouraged surgeons to use frozen sections for intraoperative margin assessment.

In a clinical situation of low re-excision rate and high frozen section biopsy uptake rate, a time- and cost-effective approach would involve selectively reducing the routine use of frozen sections without compromising the re-excision rate. Thus, we aim to investigate whether omitting frozen section biopsy for intraoperative margin evaluation in selected patients is non-inferior to performing frozen section biopsy in terms of resection margin positivity rate.

METHODS

Study goal

This study aims to demonstrate the non-inferiority of omitting intraoperative frozen sections for resection margin evaluation in selected patients compared to performing frozen section biopsy. The primary endpoint is the positive resection margin rate, defined as "ink on tumor," for ductal carcinoma in situ (DCIS) and invasive cancer. The secondary endpoints are the reoperation rates for margin re-excision, operating time, residual cancer after re-excision of the margin during reoperation, residual cancer after re-excision according to the frozen section biopsy results, resection volume, cost effectiveness, and patient quality of life. The local recurrence rate will be evaluated at the 5-year follow-up as an exploratory objective.

Study design

This study is a phase III, randomized controlled, parallel-group, multicenter, non-inferiority clinical trial. Seventeen centers belonging to the Korean Breast Cancer Society Study Group are participating in this study (KBCSG-17). The study protocol has been approved by the Institutional Review Board (IRB) of Samsung Medical Center (IRB No. SMC 2020-02-142-009) and is subject to ongoing evaluation by each center's IRB. Informed consent will be obtained by the co-investigators authorized by each center's IRB. An electronic case report form will be used to collect data that will be blinded to the patients' personal information.

The trial is registered at clinicaltrials.gov (NCT03975179; date of registration, June 5, 2019) and the Clinical Research Information Service (KCT0004606; date of registration, December 23, 2019).

Eligibility criteria

A literature review was conducted to identify clinicopathological factors related to a positive resection margin [3,10,17-21] (**Table 1**). The inclusion and exclusion criteria for this clinical trial were determined using these data to select patients who were at minimal risk of positive resection margins after BCS.

The inclusion criteria are:

1. Women aged ≥ 19 and ≤ 70 years
2. Breast cancer pathologically confirmed by core needle biopsy and clinical stage T1–3 according to the American Joint Committee on Cancer (AJCC) 8th edition
3. Candidate for BCS
4. Daughter nodule within ≤ 1 cm of the main mass on breast magnetic resonance imaging (MRI) or ultrasonography when preoperative MRI was not performed
5. Non-mass enhancement within ≤ 1 cm of the main mass on breast MRI
6. Microcalcification within ≤ 1 cm distance of the main mass
7. Written informed consent provided for participation in the trial

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Table 1. Literature review of clinicopathological factors related to a positive resection margin

Study	Number of patients	Included tumor type	Factors related to positive margin or reoperation rate
Shin et al. [17]	1,034	Invasive In situ	Positive margin: microcalcifications, Gr 4 density, > 0.5 cm difference in tumor size between MRI and sono, DCIS on CNB, lobular
Jorns et al. [10]	Frozen: 181 Control: 188	Invasive In situ Neoadjuvant	Reoperation: lobular, multifocality, larger tumor size (> 2 cm) Frozen biopsy false negative: multifocality, larger tumor size, lobular, both mass and microca+ on MMG
Jung et al. [3]	711	Invasive In situ	Positive margin: younger, non-palpable, multifocality, DCIS component
Jeevan et al. [18]	55,297	Primary surgery	Reoperation: carcinoma in situ
Kikuyama et al. [19]	1,835, all frozen	Invasive In situ Neoadjuvant	Residual tumor in frozen positive specimens: lobular, younger, extensive intraductal component, pT3
Tóth et al. [20]	214	Nonpalpable	Positive margin: younger, larger tumor size, larger proportion of tumor volume/specimen volume, DCIS, multifocality, learning curve
Rosenberger et al. [21]	1,205	Primary Invasive, In situ	Reoperation: extensive intraductal component, multifocality, positive/close DCIS margin, positive/close invasive margin, before guidelines published

MRI = magnetic resonance imaging; DCIS = ductal carcinoma in situ; CNB = core needle biopsy.

The exclusion criteria are:

1. Clinical T4 tumor according to the AJCC 8th edition
2. Cancer diagnosis confirmed by vacuum-assisted biopsy or surgical biopsy
3. Initial operation plan was total mastectomy
4. Personal history of ipsilateral breast cancer
5. Preoperative diagnosis of DCIS or invasive carcinoma with an extensive DCIS component
6. Preoperative diagnosis of lobular carcinoma (invasive or in situ)
7. Neoadjuvant chemotherapy
8. Lesion with diffuse microcalcifications
9. Multicentric tumor; however, a daughter nodule within ≤ 1 cm of the main mass is acceptable
10. Non-mass enhancement extent > 1 cm from the main mass on breast MRI

Sample size calculation

The rate of margin positivity varies widely among countries. The positive margin rate when frozen section biopsy is performed is approximately 10% in the Republic of Korea, but is normally higher when a frozen section biopsy is not performed [3,22,23]. Thus, the positive margin rate was 10% in both groups. The non-inferior margin was determined to be 5% using the 50% rule for the statistical calculation. The sample size was estimated at 581 patients per group, for at least 80% power to demonstrate the non-inferiority of omitting frozen section biopsy with a one-sided significance level of 2.5% and non-inferior margin of 5%. A planned sample size of 646 patients per treatment arm (1,292 patients in total) was calculated assuming a dropout rate of 10%. The PASS 13 program was used for the analysis of non-inferior tests of two independent proportions using a score test (Farrington and Manning) to calculate the sample size [24].

Randomization

Participants will be randomly assigned to either treatment arm at a 1:1 allocation ratio. Stratified randomization will be performed by participating centers. The assignment list will be generated by a computer program and notified by the electronic case report from the website. The surgeon will be notified intraoperatively of the randomization results after the initial wide excision specimen is removed.

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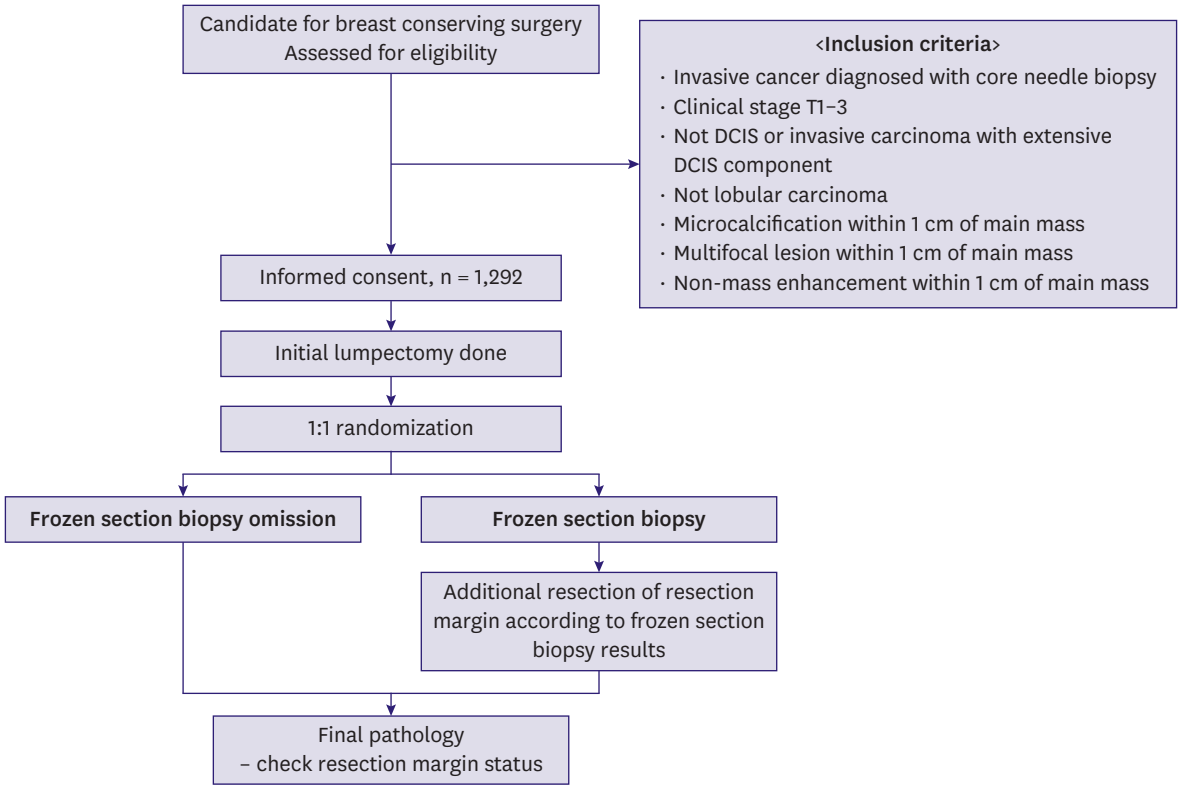

Figure 1. Scheme for the OFF-MAP trial. Patients meeting the inclusion criteria will be 1:1 randomized to the "frozen section biopsy omission" or "frozen section biopsy" group. Randomization will be performed after the initial lumpectomy has been completed.
DCIS = ductal carcinoma in situ.

Clinical trial plan

Patients will be randomly assigned to either the "frozen section biopsy omission" or "frozen section biopsy" group for intraoperative resection margin evaluation (**Figure 1**). An initial wide excision will be performed as usual, followed by randomization. No further procedures will be needed for breast surgery in the frozen section biopsy omission group. Frozen section biopsy of the resection margin will be performed in the frozen section biopsy group. The method used to obtain tissue for frozen section biopsy will be at the surgeon's discretion, but a breast parenchymal tissue specimen with a minimum size of 1 × 0.5 cm in four directions of the specimen or cavity with a thickness of approximately 0.1 cm will be recommended. The superficial and deep margins will not be included as resection margins. The patient will be blinded to the group at the time of operation but can be acknowledged by the randomization group postoperatively. When patients are not subjected to a randomized treatment modality, data will be analyzed on an "intention-to-treat" basis.

Additional resection according to the frozen section biopsy results will be performed at the surgeon's discretion. After reviewing the final pathology report, a second operation for re-excision will be decided at the surgeon's discretion. Re-excision in cases with only a positive margin (tumor on the inked margin) will be recommended but will not be mandatory. For instance, if the tumor is located at the end of the breast parenchyma with a positive resection margin in that direction, re-excision may not be necessary.

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	Before surgery	Doing surgery	After surgery	5-yr follow-up
Enrollment:				
Eligibility screen				
History taking and physical examination	✗			
Core needle biopsy	✗			
Mammography	✗			
Breast ultrasound	✗			
Breast MRI	✗*			
Informed consent	✗			
Interventions:				
Surgery – Frozen biopsy omission		✗		
Surgery – Frozen biopsy		✗		
Assessments:				
Operation time		✗		
Pathology result			✗	
Survey for quality of life	✗*		✗*	
Cost-effectiveness analysis			✗	
Local recurrence				✗†
History taking and physical examination				✗†
Mammography				✗†
Breast ultrasound				✗†

Figure 2. Clinical trial schedule.
*Not mandatory; †Exploratory outcome.

Quality-of-life assessment will also be performed in selected centers to analyze patients' stress and surgical satisfaction related to reoperation. The Korean version of the BREAST-Q™ survey for breast-conserving therapy will be used [25].

The schedule of this trial is shown in **Figure 2**.

Data collection, management, and monitoring

The investigators at each participating hospital will collect the medical information required to ensure accuracy. Data will be stored as online electronic case report forms, with private information replaced with an identification number. Each investigator will have access to the website and a private account, and the data will only be accessible by the principal investigator and sub-investigator. No interim analyses will be performed.

Data safety monitoring will be performed after 100 patients are enrolled and annually thereafter until the clinical trial is completed by the KBCSG. Monitoring may also be performed when the trial is identified as proceeding incorrectly. Trial results, protocol modifications, and authorship will be discussed and decided by all principal investigators via email or online/offline meetings.

Statistical analysis

The primary outcome will be analyzed in intention-to-treat and per-protocol populations, and the non-inferiority of omitting the frozen section biopsy will be confirmed only if both analyses demonstrate this. Statistically, non-inferiority will be demonstrated by the difference in the higher boundary of the one-sided 97.5% confidence interval for the positive resection margin

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rate being less than 5%. Pre-specified subgroup analysis will be performed according to the use of preoperative MRI, frozen section biopsy method, and participating hospital.

DISCUSSION

This clinical trial will aim to determine whether omitting frozen section biopsy of the resection margin is non-inferior to performing frozen section biopsy in selected patients with BCS. The inclusion and exclusion criteria were carefully selected after a literature review and panel discussion, to ensure the inclusion of patients for whom omitting a frozen section biopsy would not increase their risk of re-excision.

Although the superiority of frozen section biopsy for evaluating resection margins and obtaining negative margins has not been demonstrated in a prospective trial, the high accuracy and reliability of frozen section biopsy have been determined in meta-analyses [8,26]. A recent meta-analysis reported an average reoperation rate of 5.9% when frozen section biopsy was performed, which is considerably lower than the reoperation rates previously reported by nationwide and registry-based studies (11.6%–14.0%) [4,9,27]. Performing frozen section biopsy to assess the margins and reduce the reoperation rate is not contentious in terms of accuracy or efficacy, but rather in terms of cost-effectiveness and resource requirements. Considering the high rate of frozen section biopsy in the Republic of Korea and the previously demonstrated accuracy of this method, this non-inferiority trial aims to reduce the rate of frozen section biopsy without compromising the positive margin rate.

From the perspective of the patient, reduction of frozen section biopsy in this study will lead to reduced surgical time and medical cost, along with a decreased risk of false-positive frozen section biopsy, avoiding unnecessary additional resection. However, patients who participate in this clinical trial also risk the possibility of increased margin positive rate after omitting frozen section biopsy, which leads to more re-excision. To minimize this risk, inclusion criteria were determined to select patients who have minimal risk for a positive margin after BCS.

This study aims to promote more efficient application of frozen section biopsy by reducing its use without increasing the re-excision rate. This is also the first prospective randomized trial of frozen section biopsy to assess BCS margins. We expect that this trial will help surgeons perform the procedure more efficiently while ensuring patient safety.

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