

Case Report



Usefulness of 3-Dimensional-Printed Breast Surgical Guides for Undetectable Ductal Carcinoma *In Situ* on Ultrasonography: A Report of 2 Cases

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ABSTRACT

Tumor localization is challenging in the context of ductal carcinoma *in situ* (DCIS) treated with breast-conserving surgery. Conventional localization methods are generally performed under the guidance of ultrasonography or mammography and are rarely performed with magnetic resonance imaging (MRI), which is more sensitive than the aforementioned modalities in detecting DCIS. Here, we report the application of MRI-based individualized 3-dimensional (3D)-printed breast surgical guides (BSGs) for patients with breast cancer. We successfully resected indeterminate and suspicious lesions that were only detected using preoperative MRI, and the final histopathologic results confirmed DCIS with clear resection margins. MRI guidance combined with 3D-printed BSGs can be used for DCIS localization, especially for lesions easily detectable using MRI only.

Keywords: Breast neoplasms; Carcinoma, ductal; Magnetic resonance imaging; Printing, three-dimensional

INTRODUCTION

In recent decades, with the widespread use of mammography for screening, the incidence of breast ductal carcinoma *in situ* (DCIS) has dramatically increased, and DCIS currently accounts for approximately 20% of all new breast cancer diagnoses [1]. Breast-conserving surgery combined with adjuvant radiotherapy is the standard treatment for small DCIS. The goal of breast-conserving surgery is to completely remove the tumor with clear margins while preserving normal tissue as much as possible for optimal cosmesis. However, most DCIS lesions are clinically impalpable, and they frequently involve a larger area than the extent visible on preoperative imaging. These features make it difficult to accurately localize the exact tumor extent before surgery. Magnetic resonance imaging (MRI) is more sensitive than mammography or ultrasonography in detecting DCIS [2,3], and lesions are often not

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Conflict of Interest

BeomSeok Ko and Namkug Kim hold a patent for the 3D-printed breast surgical guide and are the founding members of ANYMEDI, Inc. Zhen-Yu Wu received consulting fees from ANYMEDI, Inc.

Author Contributions

Conceptualization: Wu ZY, Kim N, Ko B; Data curation: Wu ZY, Lee YJ, Shin Y, Choi S, Baek SY, Chun JW, Albinsaad LS, Choi WJ, Ko B; Formal analysis: Wu ZY, Ko B; Funding acquisition: Ko B; Investigation: Wu ZY, Lee YJ, Shin Y, Choi S, Baek SY, Chun JW, Albinsaad LS, Choi WJ, Kim N, Ko B; Methodology: Wu ZY, Kim N, Ko B; Project administration: Kim N, Ko B; Resources: Wu ZY, Kim N, Ko B; Software: Wu ZY, Ko B; Supervision: Wu ZY, Ko B; Validation: Wu ZY, Kim N, Ko B; Visualization: Kim N, Ko B; Writing - original draft: Wu ZY; Writing - review & editing: Wu ZY, Ko B

detectable using imaging modalities other than MRI. However, conventional localization methods, such as hook wire or radioactive seeding techniques, are generally performed under ultrasonographic or mammography guidance and are rarely performed with MRI guidance in current clinical practice [4,5].

Under such circumstances, an MRI-based patient-specific surgical guide for localizing the tumor extent using 3-dimensional (3D) printing technology can be an effective alternative. Here, we report the application of an MRI-based 3D-printed breast surgical guide (BSG) for breast-conserving surgery in patients with biopsy-proven invasive cancer concurrent with DCIS lesions not detected using preoperative ultrasonography.

CASE REPORT

This study was approved by the Institutional Review Board of Asan Medical Center, Seoul, Korea (No. 2016-1237, 2018-0690). Informed consent was obtained from all patients.

Case 1

A 55-year-old woman diagnosed at her local hospital with invasive ductal carcinoma in the 10–11 o'clock position of her right breast by core needle biopsy was referred to our department in December 2018 for further examination and surgical management. Physical examination revealed a well-defined palpable mass in the upper outer quadrant of the right breast. Enhanced breast MRI revealed an irregular enhancing mass in the 11 o'clock position, 6.1 cm from the nipple, with a diameter of 2.8 cm, in the right breast, which was concordant with a biopsy-confirmed malignancy (**Figure 1A**). In addition, MRI revealed an indeterminate mass in the central portion of the right breast, 3.0 cm from the nipple, with a diameter of 0.6 cm (**Figure 1B**), and another indeterminate mass at 6 o'clock of the left breast, 3.6 cm from the nipple, with a diameter of 0.6 cm (**Figure 1C**). A prominent lymph node in the right axillary level I area was observed. Magnification mammography revealed an isodense mass with calcifications measuring 2.3 cm in the upper outer quadrant of the right breast and another isodense mass measuring 0.8 cm deep in the outer portion of the right breast. No obvious abnormalities were observed in the left breast tissue. Ultrasonography did not reveal MRI-detected indeterminate masses in either breast (**Figure 2**). We proposed breast-conserving surgery using prone/supine MRI-based 3D-printed BSGs to excise the cancer and bilateral indeterminate masses not detected using ultrasonography. The patient approved of the treatment plan.

Breast imaging was performed using a 3.0-T MRI system (Ingenia; Philips Healthcare, Best, the Netherlands) with a dedicated bilateral 4-element breast coil. Additional MRI was performed with the patient in the supine position to replicate the patient's position during the surgical procedure. The patient provided written informed consent and agreed to undergo supine imaging in addition to the standard baseline MRI protocol. Data obtained from the prone/supine MRI were analyzed, and the tumors (the 2 indeterminate masses in both breasts and normal tissues) were divided using the image segmentation program Mimics Medical 17 (Materialise Inc., Leuven, Belgium) (**Figure 3**). The patient-specific hybrid-type BSGs (for each breast) containing blue dye injection columns, which can indicate the tumor extent requiring removal, were modeled at distances of 0.5 cm from the tumor boundaries to guarantee a margin of safety (**Figure 4**). The following specifications were used to model the BSGs to ensure an accurate display of the tumor resection boundaries: 1) they were made to precisely fit the breast skin surface, 2) a hole was provided to fit the nipple, and

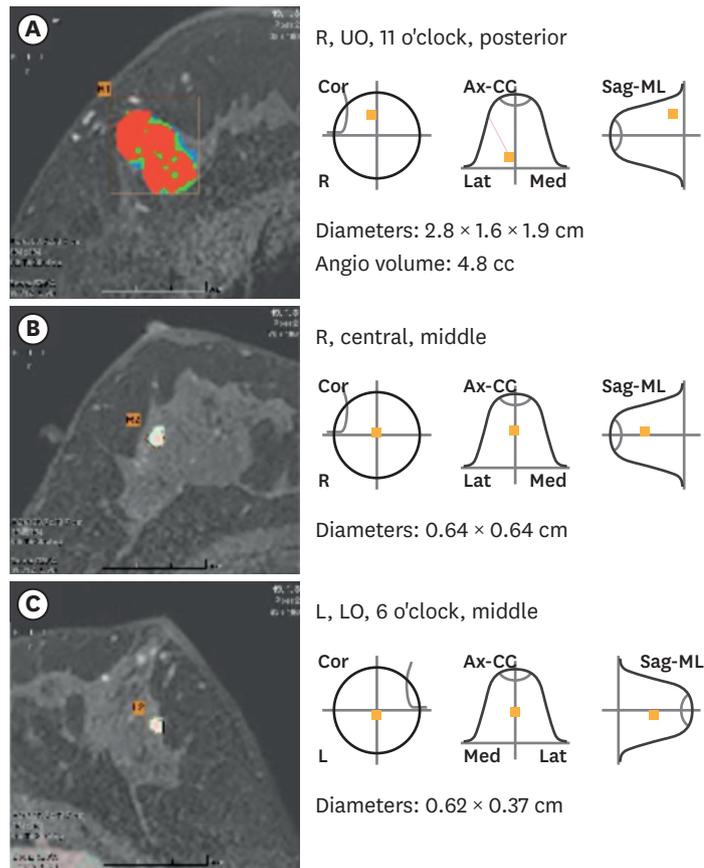


Figure 1. Enhanced breast magnetic resonance imaging (A) revealing an irregular enhancing mass in the 11 o'clock position, 6.1 cm from the nipple, with a diameter of 2.8 cm, in the right breast which was concordant with biopsy-confirmed malignancy. (B) an indeterminate mass in the central portion of the right breast, 3.0 cm from the nipple, with a diameter of 0.6 cm (C) and another indeterminate mass at 6 o'clock of the left breast, 3.6 cm from the nipple, with a diameter of 0.6 cm were detected.

3) guidelines were used to prevent rotation of the BSGs and indicate their placement relative to the opposite nipple and suprasternal notch. BSGs were made to fit the patient's skin surface and were manufactured as a hybrid type, with a groove for marking the breast surface and a column for precisely marking the underlying tissue.

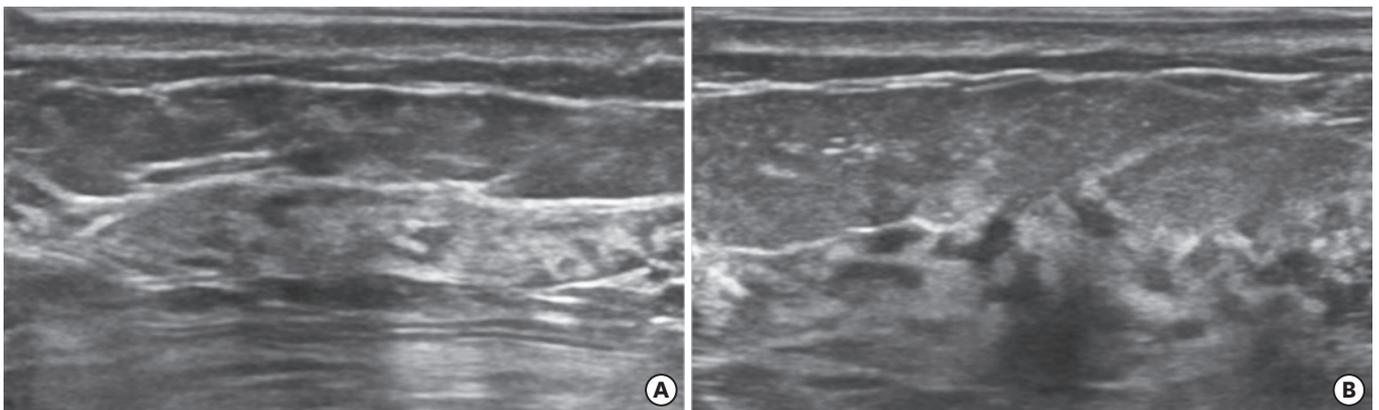


Figure 2. Preoperative ultrasonography did not reveal the magnetic resonance imaging-detected indeterminate masses (A) right 10 o'clock, (B) left 4 o'clock in either breast.

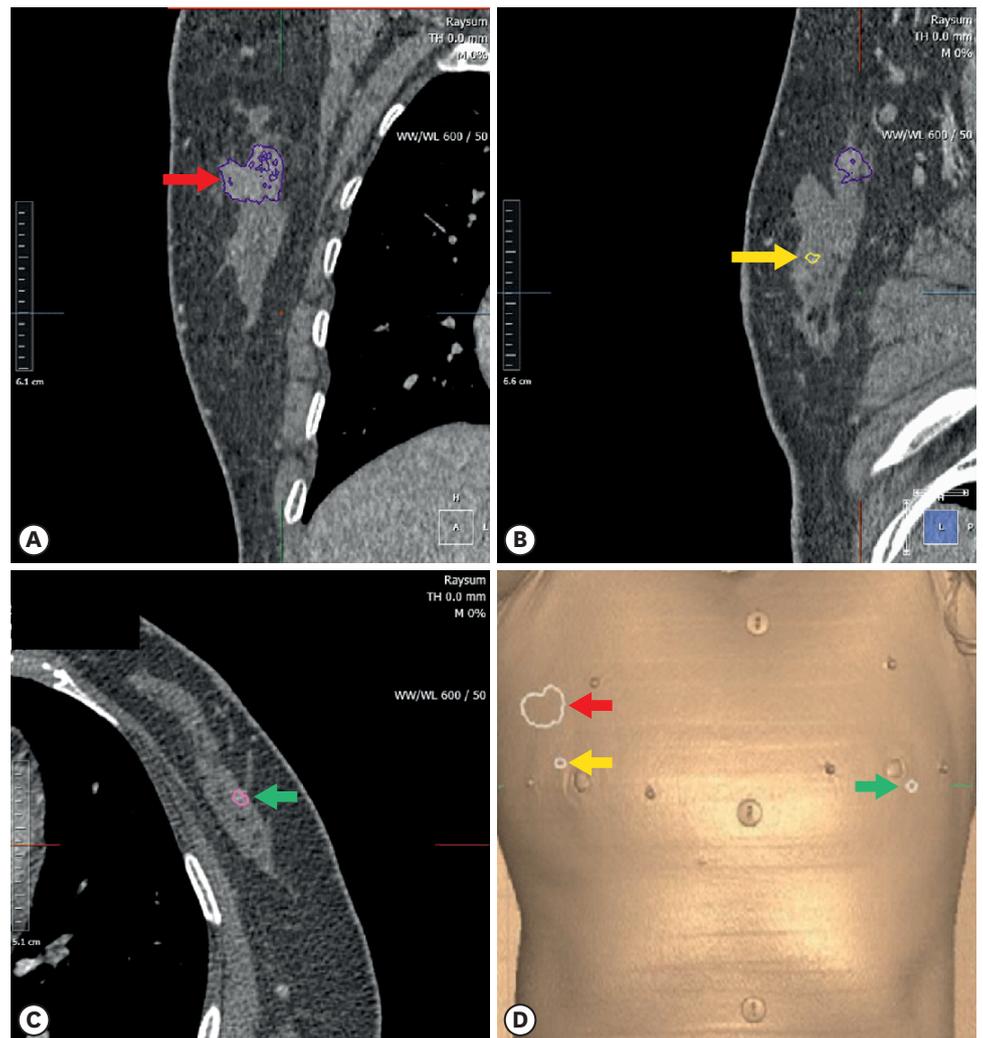


Figure 3. Data obtained from supine magnetic resonance imaging were analyzed, and the tumors, including the right breast biopsy-confirmed cancer (A, D: red arrow) and the indeterminate tumors in the right breast (B, D: yellow arrow), left breast (C, D: green arrow), and normal tissues, were divided. The final histopathologic diagnosis of the 11 o'clock specimen from the right breast was invasive ductal carcinoma. Furthermore, the tumor in the central portion of the right breast was a DCIS, and the tumor in the left breast was a DCIS with lobular carcinoma *in situ*. DCIS = ductal carcinoma *in situ*.

Surgery was performed in January 2019. BSGs were then printed and sterilized preoperatively. The tumor resection boundaries were drawn on the breast skin surface along the lines designed to match the tumor shapes. Blue dye was injected through the columns to indicate the extent that needs to be removed around the tumors. Tumors in the 11 o'clock position and central portion of the right breast and those at the 6 o'clock position of the left breast were separately removed using the blue borders as excision boundaries. A sentinel lymph node biopsy sample was obtained from the right axilla, and frozen biopsy was negative for malignancy (0/4). No sentinel lymph node biopsy sample was obtained from the left axilla. The intraoperative resection margin frozen biopsy yielded negative results (3, 6, 9, and 12 o'clock margins of the right breast biopsy-confirmed cancer). The operation was completed in 82 min.

The final histopathologic diagnosis of the right 11 o'clock mass was invasive ductal carcinoma: Grade 2, T2 (2.7 cm) N0 (0/4) M0, Stage IIA, estrogen receptor (+), progesterone

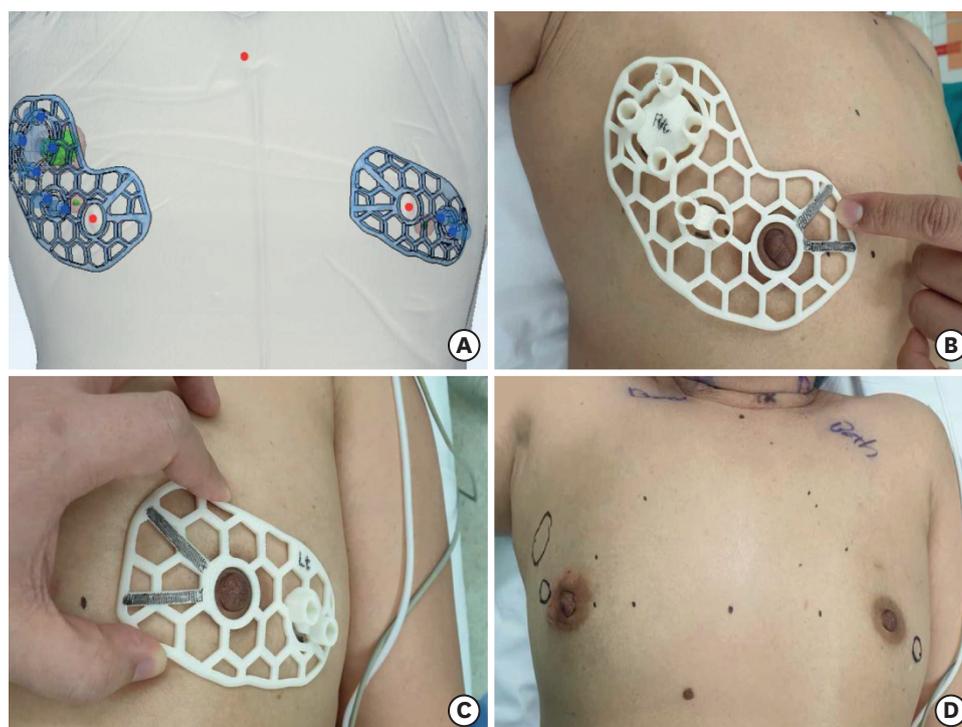


Figure 4. Patient-specific hybrid-type breast surgical guides (BSGs) containing the blue dye injection columns, which can indicate the tumor extent requiring removal, are modeled (A). The following specifications were used for modeling the BSGs to ensure an accurate display of the tumor resection boundaries: 1) they were made to precisely fit the breast skin surface, 2) a hole was provided to fit the nipple, and 3) guidelines to prevent rotation of the BSGs and indicate their placement relative to the opposite nipple and the suprasternal notch were included (B, C). The tumor resection boundaries were drawn onto the breast skin surface designed to match tumor shape (D).
BSG = breast surgical guide.

receptor (+), HER2 (-), and Ki67 index of 70%–80%. Moreover, the tumor in the central portion of the right breast was a multifocal DCIS measuring 0.3 cm. The tumors in the 6 o'clock position of the left breast were DCIS measuring 0.9 cm and multifocal lobular carcinoma *in situ* measuring 0.4 cm. All resection margins were free of tumor. The patient received adjuvant chemotherapy, radiotherapy, and hormonal therapy. At the last follow-up, before the composition of this report, the patient remained disease free for 18 months.

Case 2

A 61-year-old woman diagnosed with invasive ductal carcinoma in the 1 o'clock position of her right breast by core needle biopsy at her local hospital was referred to our center in January 2019 for surgical treatment. Physical examination showed a palpable mass in the upper inner quadrant of the right breast. Enhanced breast MRI revealed an irregular enhancing mass at 2 o'clock, 7 cm from the nipple, with a diameter of 2.0 cm, in the right breast, concordant with biopsy-confirmed malignancy. Furthermore, MRI revealed another suspicious mass in the 12 o'clock position of the right breast, 6.5 cm from the nipple, with a diameter of 0.7 cm. Magnification mammography revealed an irregular mass measuring 2.3 cm in the upper inner quadrant of the right breast. Ultrasonography did not reveal the corresponding suspicious mass in the 12 o'clock position of the right breast that was detected using MRI. After careful evaluation, we suggested breast-conserving surgery using an MRI-based 3D-printed BSG to excise the biopsy-confirmed cancer and suspicious mass in the right breast after obtaining patient's approval.

Breast-conserving surgery guided by a 3D-printed BSG was performed in January 2019 in the same manner as in case 1. A right sentinel lymph node biopsy was performed, and frozen biopsy revealed metastatic carcinoma in 2 of three lymph nodes. An axillary lymph node sampling was also performed. Intraoperative resection margin frozen biopsy yielded negative results. The operation was completed in 73 minutes.

The final histopathologic diagnosis of the right 2 o'clock specimen was invasive ductal carcinoma: Grade 2, T1 (2 cm) N1a (2/4) M0, stage IIA, estrogen receptor (+), progesterone receptor (+), HER2 (+), and Ki67 index of 20%–30%. In addition, the tumor in the 12 o'clock position of the right breast was a multifocal DCIS measuring 0.3 cm. All resection margins were tumor free. The patient received chemotherapy and radiotherapy along with trastuzumab and hormonal therapy as adjuvant treatments. At the last follow-up, the patient remained disease free for 18 months.

DISCUSSION

We used MRI-based 3D-printed BSGs for patients with DCIS who underwent breast-conserving surgery, and this allowed us to successfully resect DCIS lesions with clear resection margins only detected using preoperative MRI.

An appropriate preoperative tumor localization strategy is critical for achieving clear resection margins and optimal cosmetic results after breast-conserving surgery for DCIS. However, as the vast majority of DCIS lesions are clinically undetectable or frequently have a diffuse growth pattern, accurate DCIS localization becomes extremely challenging. There are two generally used localization methods for DCIS: wire-guided and radioactive seeding localization. Although previous studies have reported the utility of these localization methods [4,5], the mean rate of re-excision associated with positive resection margins is 30% [6], and re-excision may lead to potential complications, as well as stress and additional costs, for patients. The sensitivity of MRI in detecting DCIS is higher than that of mammography or ultrasonography [2,3], and MRI is often performed for patients with DCIS. However, it is difficult to directly mark the tumor region on MRI using conventional localization methods. Moreover, patients screened using mammography or ultrasonography may not undergo biopsy or excision if they have undetected lesions. Lesions that were not identified using ultrasonography could be identified and confirmed via MRI-guided biopsy. However, MRI-guided biopsy is time consuming and complicated, possibly leading to long waiting times for patients scheduled for breast cancer surgery.

In the cases reported herein, DCIS lesions were not detected on ultrasonography, but they were observed as indeterminate or suspicious tumors only using MRI. Thus, preoperative biopsies were not performed for these tumors. We used individualized MRI-based 3D-printed BSGs to excise these indeterminate or suspicious tumors, and the tumors were histopathologically confirmed as DCIS. If we had used conventional ultrasonography-guided localization for managing these patients instead of MRI-based BSG, these lesions would have likely been missed and not removed, leading to subsequent recurrence(s). In addition, the removal of suspicious lesions and histopathologically confirmed tumors may improve the efficacy of planned operations.

Three-dimensional printing is a versatile technology with expanding applications in various medical fields [7,8]. In a prospective pilot study conducted at our institution, Ko et al. [9]

employed MRI-based 3D-printed BSGs for breast-conserving surgery in patients receiving neoadjuvant chemotherapy. The authors found that this technique was useful for accurately marking the tumor region based on pretreatment MRI data, and they successfully used 3D-printed BSGs for patients with DCIS using a similar technique [9]. A patient-specific 3D-printed BSG can use MRI data to directly mark the tumor extent on the affected breast skin. Through the columns that are modeled in three dimensions, the blue dye injection into the breast tissue can provide additional quantitative representation of the extent of tumor requiring removal. Besides potentially improving patient care and surgical outcomes, this technique is less invasive than conventional localization methods (hook wire-guided or radioactive seeding localizations) and has advantages such as the absence of pain and radiation exposure, as well as a shorter procedure duration.

In conclusion, MRI guidance combined with 3D-printed BSGs can be useful for DCIS localization, especially for lesions that can only be detected on MRI but cannot be easily visualized using other imaging modalities. Large-scale prospective studies are required to establish the safety and effectiveness of this technique in patients with DCIS.

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