3-marker technique for the localisation and delineation of residual tumour bed following neoadjuvant chemotherapy in patients within the I-SPY 2 trial

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Aims and objectives

Breast biopsy clips allow for the precise localization of biopsy-proven neoplastic breast lesions, minimizing the volume of breast tissue needed to be excised during the surgical removal of the tumor.\(^1\) Already, clips have been shown to be useful in the delineation of the tumoral bed, with negative margins reportedly to be as high as 90% with the use of clips.\(^2\) Furthermore, biopsy clips are known to be extremely safe, with allergic reactions reported only in exceptionally rare cases.\(^1,3\)

Our institution treats patients participating in the I-SPY 2 trial, an ongoing clinical study that tests the efficacy of a combination of standard and investigational neoadjuvant chemotherapy agents for breast cancer. Patients within the trial are often noted to have near or complete pathologic response to the neoadjuvant chemotherapy. This has caused increased technical difficulty in the ultrasound delineation and/or detection of residual tumor during preoperative guidewire placement.

To address this, we developed a novel technique in which 3 breast markers rather than a single breast marker are placed within a tumor, allowing for improved post-neoadjuvant chemotherapy guidewire placement into the tumor bed and eventual surgical excision. The 3 markers are placed at specific sites within the tumor: a BiomarC (Carbon Medical Technologies, Minneapolis, MN) marker is placed centrally, and 2 VizMark (Mermaid Medical, Copenhagen, Denmark) markers are placed peripherally at the edges of the tumor's longest diameter. The purpose of this study is to both describe this technique and to demonstrate its capability to aid in the detection of residual tumor and the delineation of tumoral margins following neoadjuvant chemotherapy.
Methods and materials

Patient Selection and Imaging

Institutional review board approval was obtained for this study. An early trial of the use of multiple markers was completed on a patient who presented to our center with a suspicious lesion that was found to be an intraductal papilloma on tissue biopsy. Subsequently, the 3-marker technique was performed on patients that were participants of the I-SPY 2 trial, a multicenter clinical study that is currently in progress. Per the requirements of the I-SPY 2 trial, all patients underwent 4 MRIs, 4 ultrasound examinations, and 3 digital mammograms during their 4-month trial of neoadjuvant chemotherapy.

Pathology and follow-up

Pathology specimens were obtained during the initial biopsy and at the time of definitive surgical excision following neoadjuvant chemotherapy. Operative notes were utilized to assess the accuracy of guidewire placement within the tumoral bed. The presence of positive or negative margins during surgical excision was recorded based on final pathology reports. Tumors were tested for the presence or absence of estrogen receptor (ER+/ER-), progesterone receptor (PR+/−), and human epidermal growth factor receptor (HER2 +/-).
Results

Patient 1

Prior to the use of the 3-marker technique in patients within the I-SPY 2 trial, 2 markers were placed in the breast lesion of a patient found to have intraductal papilloma on final pathology. The 50-year-old patient initially presented for a screening mammogram, which showed a 0.4 cm nodular opacity in the 6:00 position of the right breast, 4.5 cm from the nipple. Corresponding ultrasound images noted a 0.5 x 0.5 x 0.4 cm oval hypoechoic lesion in the same area. Ultrasound-guided core needle biopsy was completed, with markers placed both within and at the periphery of the lesion (Figure 1). Final pathology noted a detached fragment of intraductal papilloma and fibrocystic changes.

Patient 2

Patient 2 is a 66-year-old patient who presented for diagnostic mammography after noting a palpable mass in her left breast. Mammography demonstrated a large area of architectural distortion in the left breast with 2 ill-defined spiculated masses at the 4:30 position and at the 2:00 position. A subsequent ultrasound examination showed corresponding hypoechoic masses at the 4:00 position 5 cm from the nipple and at the 2:00 position 4 cm from the nipple. US-guided biopsy of both lesions revealed 2 invasive lobular carcinoma, ER+, PR-, and HER2-. 3 breast markers were placed at the time of biopsy, which were demonstrated on both follow-up mammography (Figure 2); clips were also present on follow up MRI but were less well visualized (Figure 3).
Fig. 1: Image 1: Early use of multiple markers within a benign breast lesion. 50-year-old female found to have a 0.4 cm nodular opacity in the right breast on screening mammogram (A) (CC view shown, red arrow). Corresponding ultrasound images (B) demonstrated a hypoechoic lesion within the same area of the breast (between white arrows). Subsequent mammogram images (C and D) noted the presence of the BiomarC (blue arrows) and VizMark (yellow arrows) markers.

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Fig. 2: 66-year-old patient who presented for a mammogram after noting a palpable lesion within her left breast. Initial mammogram images (A) 2 ill-defined spiculated lesions (larger image marked by red arrow). Follow-up ultrasound (B) noted irregular hypoechoic lesions in the aforementioned areas, which corresponded with a lobulated mass on maximum projection intensity (MIP) images on MRI (C). Follow-up mammogram images (C and D) demonstrated the central BiomarC (blue arrow) marker and peripheral VizMark (yellow arrows) markers.

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**Fig. 3:** Image 3: Patient #2 follow up MRI. One of the 3 markers is present (white arrow), although all three are better visualized on mammography.

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Conclusion

Because patients in the I-SPY 2 trial are frequently observed to have a complete pathologic response to neoadjuvant chemotherapy, a single breast marker was considered inadequate for guidewire localization of residual tumor burden. In this study, we developed and demonstrated a 3-marker technique in which a single marker was inserted into the center of the lesion and 2 breast markers were placed at the periphery. In doing so, the tumor location and margins were better delineated for guidewire placement and subsequent surgical removal of the tumor.

Future directions

To date, the 3-marker technique has only been employed in patients that are participants in the I-SPY 2 trial; the applicability of the technique in a broader patient population would require further investigation. Additionally, the performance of the 3-marker technique has not yet been compared to the standard placement of 1 breast marker. Future studies are needed to assess the efficacy of the 3-marker method to the current standard of care in terms of 1) ultrasound identification of residual tumor bed, 2) accuracy of guidewire placement, 3) positive or negative margins during surgical excision, and 4) patient outcome.
Personal information

Dr. Nelson and Dr. Bolan hold licenses and patents on the VizMark breast marker
