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A Patient-Specific 3D-Printed Form Accurately Transfers Supine MRI-Derived Tumor Localization Information to Guide Breast-Conserving Surgery

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Abstract

Background—Wire-localized excision of nonpalpable breast cancer is imprecise, resulting in positive margins 25–30% of the time.

Methods—Patients underwent preoperative supine magnetic resonance imaging (MRI). A radiologist outlined the tumor edges on consecutive images, creating a three-dimensional (3D) view of its location. Using 3D printing, a bra-like plastic form (the Breast Cancer Locator [BCL]) was fabricated, with features that allowed a surgeon to (1) mark the edges of the tumor on the breast surface; (2) inject blue dye into the breast 1 cm from the tumor edges; and (3) place a wire in the tumor at the time of surgery.

Results—Nineteen patients with palpable cancers underwent partial mastectomy after placement of surgical cues using patient-specific BCLs. The cues were in place in <5 min and no adverse events occurred. The BCL accurately localized 18/19 cancers. In the 18 accurately localized cases, all 68 blue-dye injections were outside of the tumor edges. Median distance from the blue-dye center to the pathologic tumor edge was 1.4 cm, while distance from the blue dye to the tumor edge was <5 mm in 4% of injections, 0.5–2.0 cm in 72% of injections, and >2 cm in 24% of injections. Median distance from the tumor center to the BCL-localized wire and to the clip placed at the time of diagnosis was similar (0.49 vs. 0.73 cm) on specimen mammograms.

Conclusions—Information on breast cancer location and shape derived from a supine MRI can be transferred safely and accurately to patients in the operating room using a 3D-printed form.

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With the widespread use of screening mammography, approximately half of the women with invasive cancer and nearly all women with ductal carcinoma in situ (DCIS) have their tumors detected before they become clinically palpable.^{1,2} For nonpalpable lesions, localization of the tumor prior to breast-conserving surgery (BCS) is needed. The standard technique is wire localization, in which a wire is preoperatively placed near the tumor under mammographic, sonographic, or magnetic resonance imaging (MRI) guidance. Wire localization has several limitations. It adds another procedure prior to surgery, thereby complicating operative scheduling, and can be painful for patients. Its biggest limitation is inaccuracy; wire localization requires the surgeon to estimate the three-dimensional (3D) position of the cancer from 2-dimensional mammography images. Furthermore, wires may enter the breast skin at a substantial distance from the site of the cancer, requiring additional estimation. Prospective studies have shown that wire-localized excision results in positive margins requiring re-excisions between 22 and 34% of the time.^{3–5} Reexcision for positive margins is emotionally difficult for patients, increases the potential for complications from surgery, impairs cosmesis, and is expensive.^{6,7}

MRI of the breast has been shown to be more sensitive than mammography or ultrasound for the detection of invasive cancer and DCIS.^{8–10} Breast cancer size, as determined by histopathology, is also more accurately defined by MRI than by mammography or ultrasound.^{11–13} Despite this increased accuracy, the use of preoperative MRI obtained with patients in the prone position has not led to decreased positive margin rates.¹⁴ This outcome is not surprising; the shape of the breast during prone MRI is radically different from the supine position in the operating room (OR). In contrast, supine MRI replicates the surgical position and has the potential to increase the precision of BCS.^{15,16} Sakakibara et al. randomized patients with small foci of DCIS to wire localization or supine MRI-guided BCS and found that both the positive margin rate and resected tissue volume were lower in patients undergoing supine MRI-guided excision.¹⁵

We recently developed a method of MRI-guided BCS that incorporates preoperative supine MRI to define tumor extent and uses an intraoperative optical scan to adjust the MRI image to the breast position in the OR.¹⁷ This technique provides the surgeon with 3D views of the tumor shape and position within the breast as it appears during surgery. When combined with intraoperative tracking technology, we localized breast cancer as accurately as palpation.¹⁷ This system generates an outline of the tumor on the breast surface, but provides limited guidance for the surgeon when operating inside the breast. We now report the first clinical use of a 3D-printed device, the Breast Cancer Locator (BCL), which easily transmits both surface and intraparenchymal information on tumor position, derived from supine MRI images, to the surgeon in the OR.

METHODS

This study (Clinicaltrials.gov identifier NCT02550210) was approved by the Dartmouth Committee for the Protection of Human Subjects, which determined the BCL to be a nonsignificant risk device. Eligible patients were ≥ 18 years of age and had palpable breast cancer that enhanced on contrast-enhanced diagnostic prone MRI. Study exclusions included implanted electrical devices, gadolinium allergy, and pregnancy.

Enrolled patients had fiducials placed on the breast surface and underwent contrast-enhanced breast MRI in the supine position using either a Phillips 3T scanner with circular coils or a Siemens 1.5 T scanner with a rectangular flex coil. Patients were positioned in the scanner with their ipsilateral arm parallel to their body. One of two study radiologists outlined the tumor edges on contiguous slices of the MRI. A 3D virtual model of the tumor, breast surface, and chest wall was constructed. Immediately after MRI, patients 1–9 also underwent an optical scan of the breast in the supine position using the Go!Scan device (Creaform, Levus, QC, Canada). The 3D model was adjusted to fit the optical scan to create files for printing the BCL. For patients 10–19, the 3D model used to fabricate the BCL was created solely from the supine MRI images.

The BCL (Fig. 1) was manufactured for each patient using a 3D printer to create a bra-like plastic form that matches the breast surface when the patient is in the supine (surgical) position. Cut-outs for the nipple and a location 4 cm cranial to the nipple, as well as a contoured inframammary fold, were incorporated into the BCL to ensure proper placement on the breast in the OR. The BCL facilitates placement of three cues to guide surgery. (1) It has small openings to allow the surgeon to draw the outline of the projected tumor edges on the skin. (2) A cylindrical central port that projects out from the BCL surface allows the surgeon to deploy a hook wire (Ghiatas; Bard Peripheral Vascular, Inc., Tempe, AZ, USA) in the center of the MRI-defined tumor. (3) Cylindrical side ports allow the surgeon to inject columns of blue dye (medial, lateral, cranial, and caudal) 1 cm from the MRI-defined tumor edge.

Each BCL underwent quality assurance optical scanning to confirm that the fabricated product matched its 3D virtual model. BCLs were sterilized using the Sterrad plasma system and packaged for use in the OR. The virtual 3D image of the tumor in the breast, which included the tumor shape and the distance from the tumor to the skin and chest wall, was available for the surgeon to view in the OR.

Under general anesthesia, the tumor edges were delineated by palpation, intraoperative tracking, and the BCL. The optical scanner was used to image the breast. The tumor location defined by the supine MRI images was transposed into the optically scanned image and displayed for the surgeon.¹⁷ Using a tracker, the surgeon marked the middle of the tumor, as projected by the 3D model, on the breast skin. Using that perspective, the surgeon then palpated the tumor and marked the palpable medial, lateral, cranial, and caudal edges of the tumor on the breast skin. Using the optical tracker in conjunction with the 3D model, the surgeon also marked the optical tracker-defined tumor edges on the skin, as previously described.¹⁷ The patient's skin was then prepped, the BCL was placed on the breast, and a marker was placed through the small openings in the BCL to outline the tumor edges on the breast skin. Each of the four side ports were utilized to inject 0.1 ml methylene blue (Methylene Blue Injection 1%; Akorn, Inc., Lake Forest, IL, USA) in a column towards the skin surface. The central port was used to deploy the hook wire. The BCL was then removed and the distances between the BCL-derived, palpable, and optical tracker system tumor edges were measured by the surgeon. The patient was then repped.

The tumor was resected with the goal of removing 1 cm of normal-feeling tissue around the palpable tumor (Fig. 2a). Knowing the distance from the skin to the tumor, from the virtual 3D model, the surgeon dissected along the wire until they were 1 cm from the tumor, then created flaps parallel to the skin until the blue columns were identified. The surgeon then used the columns as a guide to resect deeper into the breast. The depth of the resection was determined by the distance from the deep tumor edge to the chest wall, as determined by the virtual 3D model. The surgeon tried to resect tissue 1 cm past the deep end of the tumor, unless the tumor was <1 cm from the chest wall, in which case the dissection included the fascia of the underlying muscle in the specimen. The specimen volume was determined by water displacement and optical specimen scanning. The locations of the blue dye in the specimen were identified by the surgeon with sutures, and the specimen surfaces were inked by the surgeon with six different colors for orientation.¹⁸ Specimen mammograms were obtained and were used by the study radiologist (TR) to measure distances from the center of the tumor to the wire, and to the clip placed at the time of the initial core biopsy (Fig. 2b).

In pathology, the specimen was cut along the horizontal plane defined by the sutures placed at the blue spots (Fig. 2c), and the pathologist placed black-inked pins through the middle of the blue-dye spots. When tissue sections were cut, the black ink from the pins appeared in the sections, allowing the study pathologist (WW) to measure distances from the blue-dye injection sites to the tumor. The study pathologist measured the distance from the center of the blue dye to the nearest focus of neoplasia, be it invasive cancer or DCIS. Distances from the tumor to the nearest specimen margins were also measured. Margins for invasive cancers and DCIS were considered positive if cancer cells were present at ink or >1 mm from the edge, respectively.

RESULTS

Nineteen patients with palpable breast cancer underwent supine MRI, formation of a BCL, and surgery. Mean patient age was 62 years (Table 1). The tumor was located in the upper outer (47%), upper inner (26%), lower inner (21%), and lower outer (6%) quadrants. Mean tumor volume as calculated from the 3D image generated from the supine MRI was 22.7 (± 35) cm³, mean optimal resection volume (calculated from the 3D model with 1 cm of normal tissue surrounding the cancer) was 103 (± 86) cm³, and the mean actual resection volume was 116 (± 73) cm³. The actual resection volume was larger than the optimal volume in 12 cases [the mean increase in volume resected was 38 (± 16) cm³], and smaller than the optimal volume in 7 cases [the mean decrease in volume resected was 30 (± 20) cm³]. The mean pathologic tumor diameter was 3.2 (± 1.4) cm; median diameter was 2.8 cm, with a range of 1–7 cm. Fifteen of the tumors (79%) were infiltrating ductal, three were infiltrating lobular, and 1 was mucinous. Thirteen of the 19 patients (69%) had both invasive cancer and a component of DCIS in the tumor, and in three of these patients the intraductal component was considered extensive.

All patients had a margin negative resection. The mean nearest margin distance was 0.48 cm; median was 0.4 cm, with range of 0.1–1 cm. The nearest margin was the deep margin in 12 patients, superficial margin in 1 patient, and one of the four horizontal margins in 6 patients. In 11 of the 12 patients whose closest margin was the deep margin, the surgeon

knew from the 3D model that the tumor was close to the chest wall, and hence documented in the operative report that the fascia of the underlying muscle was included with the specimen.

Accuracy of the Breast Cancer Locator (BCL)-Derived Surgical Cues

The main outcome measure was the histologically measured distance from the center of the blue dye to the tumor edge. Our objective was to inject blue dye 1 cm from four MRI-defined tumor edges in each patient. Seventy-two injections were performed in 19 patients; the BCL was formed with three ports in four patients due to geometric considerations. In 18/19 cases, the blue-dye injections surrounded the tumor and all blue injections were outside of the tumor; these cases were considered to be accurately localized. In one case, the four blue-dye injections were outside of the tumor, but the tumor was eccentrically located between two blue-dye injection sites, 2 cm lateral to the center of the blue-dye injections. Although no blue dye was injected into the tumor, this case was considered to be inaccurately localized. For the 68 blue-dye injections in the 18 accurately localized cancers, the median histologically measured distance from the blue-dye center to the tumor edge was 1.4 cm (mean 1.7 cm) [Table 2]. Four percent of the distances from the blue dye to the tumor edge were <0.5 cm, 72% were 0.5–2 cm, and 24% were >2 cm.

Eighteen patients had a total of 72 tumor edge measurements made on the skin surface (Table 2). The median distance from the palpated edge to the BCL-defined edge was 0.50 cm (mean 0.62 cm), and the median distance from the optical scan/tracker system-defined edge to the BCL-defined edge was 0.20 cm (mean 0.33 cm).

To determine the accuracy of the wire placement, measurements were made on specimen mammogram images. Median distance from the tumor center to the BCL-directed wire was 0.49 cm [mean 0.81 (± 0.68) cm], and median distance from the tumor center to the preoperatively placed clip was 0.73 cm [mean 0.79 (± 0.56)] cm; $p =$ nonsignificant (Fig. 3).

BCL Safety and Ease of Use

BCL cue placements (tumor edge markings, blue-dye injections, and wire placement) were completed in <5 min for all patients, and no adverse events occurred.

DISCUSSION

Safety and ease-of-use of a device specifically designed to impart supine MRI imaging information to the surgeon in the OR was tested. Results show the BCL is safe and its MRI-derived cues can be transferred quickly and easily. All general surgeons have the skills to inject blue dye and place a hook wire. BCL provides a localization cue (the hook wire) with which surgeons are familiar, yet improves current practice because the wire placement does not require a separate procedure on the day of surgery, which can complicate surgical scheduling and cause patients pain.

The accuracy of the cues that the BCL delivers was also tested. The first cue—outlining the tumor edges on the skin surface—was compared with the standard palpated tumor edges and was found to be within 6 mm of these markings. However, this standard may not be optimal;

feeling the edges of an irregularly shaped cancer, or the location of a small satellite cancer near the primary tumor is difficult. In prospective trials, lumpectomy of palpable cancers is imprecise, with positive margins 28–29% of the time.^{19,20} The data also suggest that our two methods of transmitting supine MRI-defined tumor edge information (through the intraoperative tracker and the BCL) are essentially concordant (within 2 mm).

The second cue is wire placement. The standard for this measurement is localization of the mammographically-defined tumor in the specimen mammogram. Although not the optimal standard for determination of the accuracy of a BCL-directed wire placement (because the wire is being directed by the BCL to the center of the MRI-defined tumor volume, not the mammographically-defined tumor center), the wire was placed very close to the mammographically-defined tumor center (median of <5 mm from the center). In fact, the wire was placed as close to the tumor center as the clip left at the time of preoperative biopsy.

The third cue was the intraparenchymal blue-dye injections. Since our goal was to minimize positive margin rates, avoidance of any blue-dye injections into the tumor was critical. No blue-dye injections were made into the tumor, and only 4% were within 5 mm of the tumor edge. The majority of the injections (72%) were 0.5–2 cm from the pathologic tumor edge, while a small percentage were >2 cm from the pathologic tumor edge. In several cases, this was because the blue dye was targeted 1 cm past the farthest extent of the tumor, and the central plane through which irregularly-shaped tumors were sectioned was not the farthest extent (see Fig. 2d). Oversensitivity of MRI and/or inclusion of areas of borderline enhancement in the segmented tumor volume could also lead to distances >2 cm. However, it is quite unusual for MRI to overestimate tumor size; the MRI-determined tumor size was more than 1 cm greater than the histologic size in only 2 of 60 patients in the study by Boetes et al.¹² and in 2 of 76 patients studied by KristoffersenWiberg et al.¹¹

The one inaccurate localization was in a patient (#6) with a tumor deep in the upper outer quadrant of a large breast. The breast was deformed by the circular coils placed on the breast during MRI. The BCL for this patient was constructed from the nondeformed breast surface defined by the optical scan obtained after the patient was removed from the scanner. Thus, the BCL did not account for the breast deformation caused by the coil. Construction of BCLs directly from the MRI-defined breast surface solved this problem; any indentation from a coil was printed into the BCL, which reproduced the same indentation in the breast when used in the OR. No inaccurate localizations occurred in the 10 patients treated after this modification.

CONCLUSION

We have described the first clinical use of a new device that imparts supine MRI imaging information to the surgeon in the OR. It is safe, quick and easy to use, and accurately localizes breast cancers.

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FIG. 1.

Breast cancer locator. The alignment holes are for the nipple and a mark 4 cm medial to the nipple. Small holes in the breast cancer locator allow the surgeon to mark the tumor edges on the skin. Several ports enable blue dye to be injected to define the tumor edges, while a central port enables the surgeon to deploy a hook wire in the tumor

FIG. 2.

a A lumpectomy specimen resected using the breast cancer locator. Note the centrally placed wire and the blue-dye markings at the periphery. b Mammogram of the specimen shown in Fig. 2a. c A transverse cut through a lumpectomy specimen, demonstrating the distance from the blue-dye injections, marked with black-inked pins, to the tumor edges. d Example of an irregularly shaped tumor leading to a blue-dye to tumor edge distance of >2 cm

FIG. 3.

Distance from the center of the tumor on the specimen mammogram to the clip placed at the time of diagnostic core biopsy or the breast cancer locator-directed wire. SD standard deviation, IQR interquartile range

TABLE 1

Clinical characteristics

Age, mean (years)	62
Tumor quadrant location	
Upper outer	47%
Upper inner	26%
Lower inner	21%
Lower outer	6%
Tumor volume on supine MRI, mean, cm ³ (SD)	22.7 (35)
Optimal resection volume, mean, cm ³ (SD)	103 (86)
Volume of resected specimen	
Water displacement, mean, cm ³ (SD)	116 (73)
Optical scanning (mean, cm ³ (SD)	107 (77)
Cases resected volume > optimal	12
Mean increase in volume resected, cm ³ (SD)	38 (16)
Cases resected volume < optimal	7
Mean decrease in volume resected	30 (20)
Tumor diameter (cm)	
Mean (SD)	3.0 (1.4)
Median (range)	2.8 (1–7)
Tumor histology	
Infiltrating ductal	79%
Infiltrating lobular	16%
Mucinous	5%
Node positive	26%
Marging negative resection rate	100%
Nearest margin (cm)	
Mean (SD)	0.48 (0.28)
Median (range)	0.4 (0.1–1.0)

TABLE 2**Accuracy of BCL directed surgical cues**

Blue dye injections (<i>N</i> = 68)	
Distance from blue dye center to tumor edge (cm)	
Median	1.4
Mean (SD)	1.7 (1.2)
Distance from blue dye center to tumor edge	% within distance ranges
<0.5 cm	4%
0.5–2.0 cm	72%
>2.0 cm	24%
Skin surface tumor edge markings (<i>N</i> = 72)	
Distance from palpated edge to BCL defined edge (cm)	
Median	0.5
Mean (SD)	0.62 (0.37)
Distance from optical scan/tracker edge to BCL edge (cm)	
Median	0.2
Mean (SD)	0.33 (0.32)