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ORIGINAL ARTICLE – BREAST ONCOLOGY

Minimally Invasive Intact Excision of High-Risk Breast Lesions and Small Breast Cancers: The Intact Percutaneous Excision (IPEX) Registry

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ABSTRACT

Background. Aiming to minimize overtreatment of high-risk breast lesions (HRLs), including atypical ductal hyperplasia, and small breast cancers, including ductal carcinoma in situ (DCIS), we investigated a minimally invasive (MI) approach to definitive diagnosis and management of these conditions.

Methods. In the prospective Intact Percutaneous Excision registry study, women aged 31–86 years had removal of small invasive cancers, DCIS, or HRLs using image-guided 12–20 mm radiofrequency basket capture (MI excision). Second-pass 20 mm basket capture obtained shaved margins in cancer patients. Standard imaging (specimen, breast) and histologic criteria were applied. Patient data were registered in an Institutional Review Board approved, Health Insurance Portability and Accountability Act-compliant registry.

Results. Of 282 registered patients, 124 had DCIS (n = 52) or invasive cancer (n = 72) and 160 had HRLs. Among cancer patients, 101 (81%) had clear histologic margins [average lesion size was 11 mm for both invasive cancers (4–20 mm) and DCIS (1.5–20 mm)]; 29 patients had re-excision (six despite clear margins). Among 160 HRLs, two were upgraded to DCIS and had MI excision. Two other HRL patients had subsequent standard surgical excision (no cancer found).

Conclusion. For diminutive HRLs, DCIS, and invasive cancers, MI excision can achieve the same procedure goals as standard surgical excision. Because MI excision removes less tissue with small incisions, it may reduce the discomfort and expense associated with standard treatment.

Radiologists often refer patients for standard surgical excision with core biopsy diagnoses of atypical ductal hyperplasia (ADH), atypical lobular hyperplasia (ALH), papillary lesion (PL), radial scar (RS), or complex sclerosing lesion (CSL).

Conventional core biopsy provides a fragmented sample, potentially preventing pathologists from determining the size of a group of atypical cells or whether a sampling error under represents a more serious lesion. The presence of low-grade malignant cells in fewer than two duct profiles within an area of < 2 mm is defined as ADH; when these cells are found in more than two duct profiles within an area of > 2 mm, the lesion is defined as DCIS. Fragmentation can obscure this distinction. Evaluation of an intact specimen with standard surgical excision can be critical for distinguishing ADH, ductal carcinoma in situ (DCIS), and invasive cancer.[1–3]

Currently, underestimation rates for vacuum-assisted core biopsy (VACB) range from 15 to 30% for ADH[3,4] and 19–29% for DCIS.[5,6] Jackman et al.[7] reported that with all mammographic evidence removed, the probability of missing a cancer initially identified as ADH was 21% after VACB. These findings plus the contiguous presentation of a standard surgical specimen versus the fragmented presentation of a core, often result in referrals for surgical excision for ADH.[3,8] For most (70–85%) of these high-risk

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lesions (HRLs), surgical excision turns out to be, in retrospect, unnecessary for management of the actual pathology.[3,4]

With mammographic screening, the average size of newly diagnosed breast cancers has decreased. By 2010, 58% were < 20 mm and 23% were < 10 mm;[9] the average size in screened populations is 13–17 mm.[10–12] Small lesion size makes minimally invasive (MI) excision possible.

The Intact Breast Lesion Excision System (BLES™; Medtronic Inc., Dublin, Ireland), a vacuum- and radiofrequency-assisted breast biopsy device, was cleared by the US FDA in 2001. It allows physicians to use a 6–12 mm incision to obtain an intact specimen. A prospective study of 1170 Intact biopsies demonstrated that when standard histologic and imaging criteria are applied, intact excision can provide a definitive diagnosis in women with HRLs.[13] Presenting these findings at the American Society of Breast Surgeons Annual Meeting in April 2011, we suggested that MI excision could be explored as an alternative to standard surgical excision. Although such an application was within the scope of practice for surgeons, we believed such an experience should be documented in a registry setting and reported. In 2015, the FDA cleared an additional indication for the Intact BLES: to preserve lesion architecture in samples with diameters of 12–30 mm. The purpose of the Intact Percutaneous Excision (IPEX) registry is to document, in a variety of practice settings, results with MI excision for HRLs, small DCIS, and invasive breast cancers.

METHODS

Patients

The multisite, non-randomized, prospective IPEX registry enrolled 282 women aged 31–86 years who had image-guided MI intact excision of small DCIS, invasive cancers, or HRLs. Patients were enrolled from June 2014 through September 2016 and provided Health Insurance Portability and Accountability Act (HIPAA)-compliant informed consent (Sterling IRB, Atlanta, GA, USA).

Patients were registered if the imaged cancer or HRL size before MI excision was smaller than the planned 12–20 mm basket of the device. All cancer patients had a recent *diagnostic biopsy (core or Intact device; note: the Intact device is used in several centers for routine biopsy of mammographic abnormalities)* before planned MI excision and margin evaluation. Investigators were advised but not required to select residual lesions (including post-biopsy changes) with estimated imaged sizes of $\leq$ 12 mm, to allow for targeting error. Patients with DCIS or invasive cancers (recent *diagnostic biopsy* with core or Intact device) had an MI excision procedure that included a second Intact capture to provide a shaved margin. All such patients were registered. The HRL group comprised two distinct presentations: (1) previously diagnosed: all patients planned for MI excision after an HRL was demonstrated on a *diagnostic biopsy (core or Intact device; n* = 88); and (2) all patients found to have an HRL on a *diagnostic biopsy* performed with the Intact device, if imaging and histologic criteria for definitive diagnosis were met (*n* = 72)—defined as removal of all imaged evidence of the lesion with no significant lesion components at the histologic margin. The latter HRL subset had no subsequent procedures.

The registry was designed to document only the success of MI excision (imaged and histologic lesion removal) and longer-term outcomes (subsequent breast biopsies and cancer diagnosis) for patients with cancers or HRLs small enough for removal of the imaged abnormality. Sampling-type biopsies (lesions judged in advance to be too large to be removed intact) were not registered.

In our previous report of 1170 unselected patients, approximately one in three ADH lesions was removed according to imaging and histologic criteria and there were no upgrades after subsequent standard surgical excision.[13] Determining the *proportion* of all HRLs and cancers small enough for intact excision was beyond the scope of the registry. Patients were excluded if pregnant, lactating, contraindicated for surgery, or if they had subglandular implants or electronic implantable devices (Figs. 1, 2).

The endpoint for MI excision of small DCIS and invasive cancers was the proportion of patients meeting standard surgical criteria (clear histologic margin and complete removal of the imaged lesion). The primary endpoint for previously diagnosed HRL patients was the proportion of patients who did not have open excision after MI excision.

Intact Breast Lesion Excision System (BLES) Procedure

Patients had intact excision under stereotactic or ultrasound guidance in a radiology department or surgeon's office (none in an operating room). Procedures were performed by a radiologist or surgeon experienced with the technique. Patients were usually administered diazepam 10–20 mg and positioned for standard image-guided biopsy. The lesion was surrounded with 30–60 cc of dilute local anesthetic to achieve field anesthesia, and was then captured via advance of the radiofrequency cutting strut system (basket). Tissue elasticity permitted lesion removal through a 6–12 mm incision. A biopsy site marker was deployed via the biopsy track, incisions were closed with Steri-Strips™, and post-excision specimen x-rays and

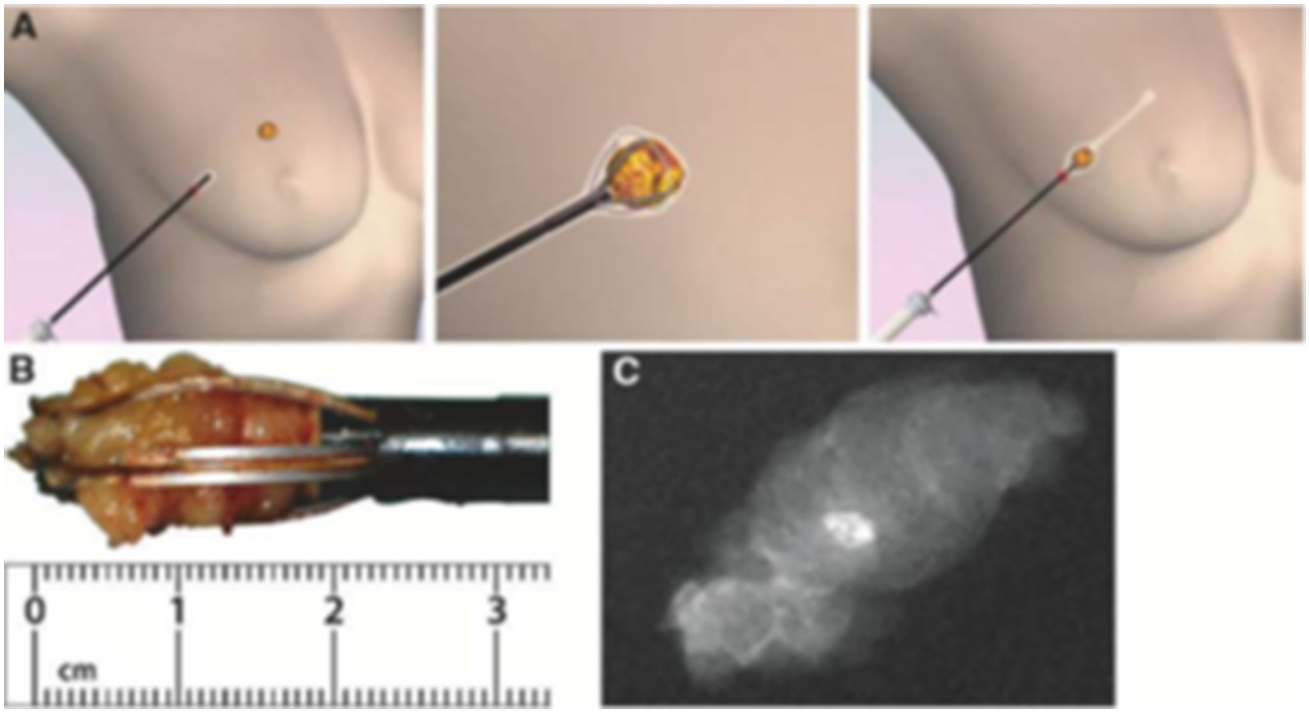

FIG. 1 **A** The flat blade of the breast lesion excision system is advanced to the target position. **B** The capture basket advances through tissue with vacuum and radiofrequency current, acquiring the specimen. **C** Target lesion is visible inside the specimen on X-ray

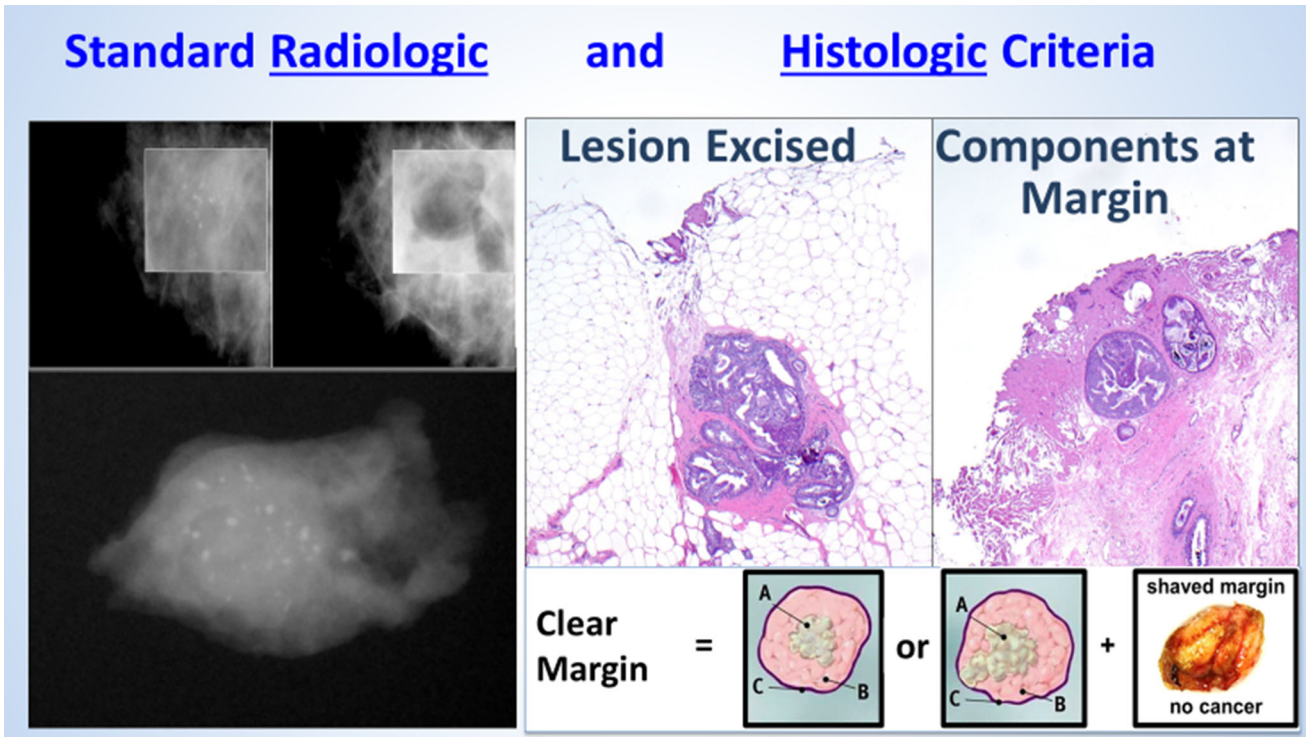

FIG. 2 Breast and specimen images confirm lesion removal (*left*), and photomicrographs demonstrate satisfactory high-risk lesion excision versus significant components at the margin (*upper right*). Schematic demonstrates clear margin criteria for ductal carcinoma in situ and invasive cancers; **A** lesion, **B** normal tissue, **C** inked margin (*lower right*)

mammograms were obtained. Procedure time (not analyzed) is similar to that for multicore devices; 30–60 cc anesthetic injection takes longer, tissue capture time (< 10 s) is less.

After removal, HRLs were classified into two groups: lesions sufficiently centered to yield a definitive diagnosis, and lesions for which a definitive diagnosis would require additional tissue. For cancers, including DCIS, a histologic clear margin was defined as 'no ink on tumor' or 'no tumor in a shaved margin' (see the "Discussion" section).[14,15]

MI excision patients are followed with mammograms for 2 (HRLs) or 5 years (cancers). Patients who did not meet radiologic and pathologic criteria for lesion removal had surgical excision or mastectomy (Tables 1, 2).

RESULTS

Among 282 patients in the registry who underwent MI excision, 124 had DCIS or invasive cancers; 160 had HRLs—two upgraded HRLs were registered again and also counted as DCIS (Fig. 3).

Of 124 cancers (52 DCIS, 72 invasive), 101 patients (81%) had clear margins on the primary specimen (n = 68) or after shaved margin capture (n = 33); average lesion size was 11 mm for both invasive cancers (4–20 mm) and DCIS (1–20 mm). Twenty-three patients did not meet imaging and/or histologic criteria; an additional six patients (who met the criteria) had re-excision based on physician or patient preference (28 breast conservation, 1 clear margin patient chose mastectomy). Among patients with positive margins, 17 had no residual lesion on re-excision; three had residual disease (three had missing data). The average pain score reported by the patient immediately after the procedure was 1.55/10 (n = 124).

Among 160 HRL patients (reported size confirmed in 150 patients), average imaged lesion size was 8 mm (1–20 mm). All patients having planned intact HRL excision after diagnostic biopsy (n = 88) were included in the registry. Removal (imaging and histology) was accomplished in all 88 patients, with two upgrades from HRL to DCIS (2.4%, n = 82; 4% of those with atypia, n = 50).

TABLE 2 Minimally invasive excision—small breast cancers—radiation and sentinel node biopsy (SNBx)

95 MI excisions	29 re-excisions
56 APBI	15 APB
15 WBRT	8 WBRT
24 no RT	6 no RT
52 invasive	20 invasive
9 SNBx	16 SNBx
43 no SNBx	4 no SNBx

MI minimally invasive, *APBI* accelerated partial breast irradiation, *WBRT* whole-breast radiation therapy, *RT* radiation therapy

Definitive diagnoses included atypia (ADH, ALH, and lobular carcinoma in situ) in 54 patients, DCIS in 2 patients, and PL, RS or CSL in 32 patients. Two HRL patients had standard surgical excision for clinical pathological concordance, with no cancer found. The remaining 72 HRL patients were only registered for long-term follow-up because their diagnostic biopsy, performed with the Intact device, met the criteria for MI excision with no subsequent procedure performed (not a planned MI excision for a known HRL). None had subsequent surgery. Among HRL patients, pain scores at the end of the procedure averaged 1/10 (n = 160).

After MI excision, 56/95 invasive or in situ carcinoma patients (59%) had accelerated partial breast irradiation (APBI), 15 (16%) had whole-breast radiation therapy (WBRT), and 24 (25%) had no RT. Among 29 re-excision patients, 15 patients had APBI, 8 had WBRT, and 6 had no RT. Reasons for omitting RT included age over 70 years (n = 13),[16] overall very low risk (n = 15), comorbidity (n = 6), and patient refusal (n = 13); most had multiple reasons reported (n = 24).

Of 72 patients with invasive cancer, 25 had sentinel lymph node biopsies (all negative). Reasons for omission of nodal staging included age older than 70 years (n = 26),[17,18] overall very low risk (n = 40), comorbidities (n = 12), patient refusal (n = 11), or positive node would not change treatment (n = 14); most had multiple reasons reported (n = 29).

TABLE 1 Histologic status of 124 cancers (invasive or DCIS)

Margin status	No. of patients	Percentage of total (%)
Clear	101	81
Positive	23	19
Open re-excision	29[a]	23
Re-excision: no residual lesion	23[b]	88
Re-excision: residual lesion	3	12

DCIS ductal carcinoma in situ

[a]Six due to physician or patient choice

[b]Three re-excision patients missing histology

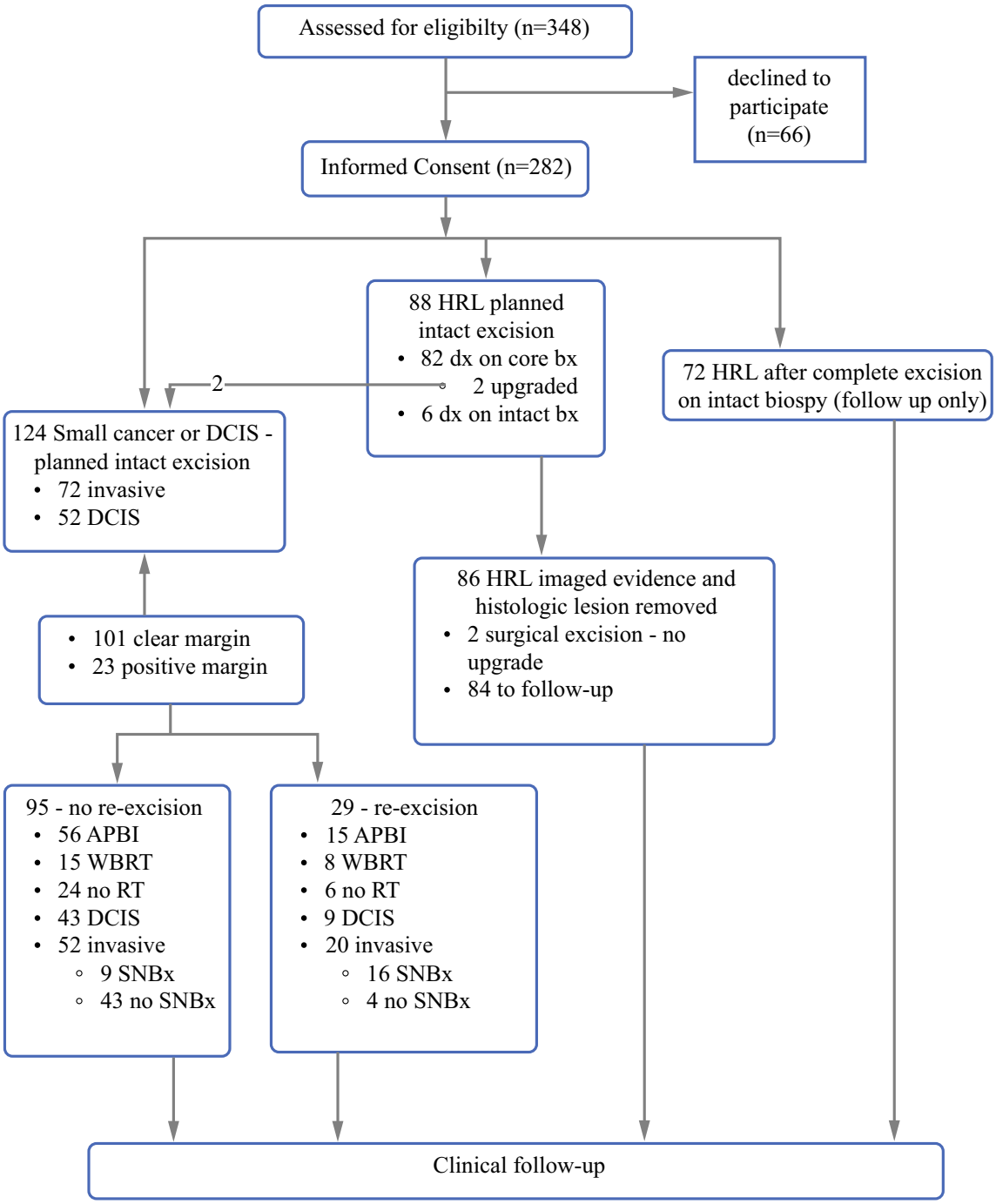

FIG. 3 Consort diagram; 282 patients provided informed consent. All patients taken for planned MI excision of an HRL, DCIS, or invasive cancer were included in the results. Seventy-two additional patients were included for long term follow-up since the diagnosis of HRL was not known prior to MI excision (diagnostic biopsy was performed using the Intact device and met all imaging and histologic criteria for definitive removal, therefore no subsequent procedure was performed). *MI* minimally invasive, *HRL* high-risk lesion, *DCIS* ductal carcinoma in situ, *APBI* accelerated partial breast irradiation, *WBRT* whole-breast radiation therapy, *RT* radiation therapy, *SNBx* sentinel node biopsy, *dx* diagnostic, *bx* biopsy

Institutional Review Board (IRB) approval required reporting of adverse events. One patient had a large, self-limited hematoma after MI excision, while another complained of severe pain despite the administration of additional local anesthetic (the procedure was aborted). No infections were reported.

Overall, 75 of 124 cancer patients had at least 1 year of follow-up, of whom 46 had an additional year of follow-up. Three patients required subsequent biopsy in the same breast with benign findings. Twenty-one of 156 HRL patients had 1-year follow-up data, 12 of whom had an additional year. One HRL patient had diagnosis of contralateral invasive cancer at 1 year. Formal evaluation of subsequent events (biopsies, cancers) is planned—HRL's at 2 years and cancers at 5 years.

DISCUSSION

Despite advances in technology characterizing breast cancer biology, indolent breast cancers (tumors detected during screening that would not become clinically relevant) cannot be reliably identified.[19–21] Many patients with HRLs undergo standard surgical excision to confirm benignity. Avoidable surgery is costly in terms of healthcare dollars, missed work, and physical discomfort. This registry study suggests MI excision can meet the same procedure goals, including imaging and histologic objectives, as standard surgical excision for selected small cancers and HRLs. Positive margin and re-excision rates with MI excision for invasive or in situ carcinoma are comparable with those for conventional lumpectomy.[22,23] MI excision can be performed in an office or imaging suite, potentially reducing morbidity, discomfort, time, and expense.[24–26]

While reported upgrade rates that guide current practices are significant,[3–6] we found only two upgrades from HRL to cancer and none from DCIS to invasive cancer. We speculate that the relatively low upgrade rate in this series is at least partly explained by the requirement limiting MI excision to small lesions expected to be removed completely. Reference series included all lesion sizes with no requirement for excision.

For both invasive cancers and DCIS, a clear margin was defined as 'no ink on tumor' or 'no tumor in a shaved margin', in keeping with the recent multidisciplinary DCIS margins panel guideline,[14] which states "negative margins less than 2 mm alone are not an indication for mastectomy, and factors known to impact rates of ipsilateral breast tumor recurrence should be considered in determining the need for re-excision".[14] (While stating 2 mm margins are ideal, the guideline identifies positive 'ink on tumor' margins as the actionable cut-off for reoperation for DCIS, as for invasive cancers.[15]) The panel emphasized that although a negative margin of 2 mm may yield a statistically lower local recurrence risk, it is not an indication for mastectomy or re-excision unless other factors, e.g. multiple close margins or young patient age, are judged to contribute an unacceptably high local recurrence risk.

Two adverse events were reported in this study of 282 patients. Killebrew and Oneson[27] reported no significant complications in a series of 800 patients, and comfort during the procedure (1.9/10) was superior to that reported using the stereotactic table alone (4.1/10, $n = 500$). Additionally, Sie et al.[28] reported one adverse event (an infection that resolved with antibiotics) in a consecutive series of 742 patients.

This study has limitations. The ideal evaluation of MI excision would be a large randomized trial. However, such an approach is impractical because of the necessary infrastructure and competition for limited resources from federal funding agencies. Industry funding for such an undertaking for an FDA-cleared indication (complete removal of an imaged lesion) was unavailable.

We relied on pathology findings from each institution. While this may be considered a reflection of the broad spectrum of practice, it lacks the uniformity obtained with central review. We did not assess the learning curve. Therefore, our results represent use of MI excision in experienced hands. Finally, although margin assessment and definitive diagnosis were the endpoints for this study (as in daily practice), a future report on long-term outcomes, including the need for subsequent diagnostic procedures and interventions, is desirable to supplement cost–benefit analysis.

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