Ann Surg Oncol (2011) 18:3047–3052
DOI 10.1245/s10434-011-1911-0

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – AMERICAN SOCIETY OF BREAST SURGEONS

Definitive Diagnosis for High-Risk Breast Lesions Without Open Surgical Excision: The Intact Percutaneous Excision Trial (IPET)

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ABSTRACT

Background. Open surgical excision (OSE) is generally recommended when image-guided core-needle breast biopsy demonstrates a high-risk lesion (HRL). We evaluated intact percutaneous excision (IPEX) with standard radiologic and histologic criteria for definitive diagnosis of HRL, particularly atypical ductal hyperplasia (ADH). The primary aim is to confirm criteria associated with <2% risk for upgrade to carcinoma, equivalent to risk associated with Breast Imaging Reporting and Data System (BI-RADS) 3 lesions, for which imaging surveillance is considered sufficient.

Methods. In a prospective trial, 1,170 patients recommended for breast biopsy at 25 institutions received IPEX with a vacuum- and radiofrequency-assisted device. ADH patients in whom the imaged lesion had been removed and the lesion adequately centered for definitive characterization were designated as the potential surgical avoidance population (PSAP) before OSE. Subsequent OSE specimen pathology was compared with IPEX findings.

Results. In 1,170 patients, 191 carcinomas and 83 (7%) HRL, including 32 ADH (3%), were diagnosed via IPEX. None of the 51 non-ADH HRL were upgraded to carcinoma on OSE ($n = 24$) or, if OSE was declined, on radiologic follow-up ($n = 27$). No ADH lesions meeting PSAP criteria ($n = 10$) were upgraded to carcinoma on OSE; 3 (14%) of 22 non-PSAP ADH lesions were upgraded to carcinoma on OSE. In summary, no upgrades to carcinoma were made in patients with non-ADH lesions who underwent IPEX or in ADH patients who had IPEX, met histologic and radiologic criteria, and underwent OSE or follow-up.

Conclusion. IPEX combined with straightforward histologic and radiologic criteria and imaging surveillance constitutes acceptable management of image-detected HRL, including ADH.

Open surgical excision (OSE) is generally recommended when image-guided core-needle breast biopsy (IGCNBx) demonstrates a high-risk lesion (HRL) such as atypical ductal hyperplasia (ADH), lobular neoplasia (LN, including lobular carcinoma in situ and atypical lobular hyperplasia), papilloma or radial scar (RS).[1] Unfortunately, this current practice subjects the majority of patients with HRL found on image-guided biopsy to unneeded (in retrospect), costly (healthcare expense, days out of work, discomfort, scarring) OSE.

Leading investigators from high-volume breast care programs continue to report results of well-founded strategies designed to identify a subgroup of these HRL patients with less than 2% risk of associated ductal carcinoma in situ (DCIS) or invasive cancer, permitting nonoperative management. Several of these strategies have succeeded in

This research was presented orally at the 12th annual meeting of the American Society of Breast Surgeons, Washington, DC, April 27–May 1, 2011. Abstract number 1679.

First Received: 13 April 2011

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identifying lower-risk subsets of patients.[2–8] A very recent retrospective report from Sneige and colleagues found that lesions with no cytologic atypia or necrosis and >95% removal of calcifications were upgraded in just under 3% of cases.[8] Despite these successes, the reported 3–20% rates of diagnosis upgrade from HRL on IGCNBx to DCIS or invasive cancer on OSE (designated "upgrade rate") are still too high to support surveillance without further resection, using the standard BI-RADS 3 risk of associated carcinoma. The only exception, a retrospective analysis of 300 patients with ADH, identified 17 patients with calcifications spanning ≤5 mm with no upgrades.[2] The majority of these investigations have evaluated some combination of radiologic criteria (e.g., complete lesion removal), special histologic features (≤2–3 foci of ADH), and/or increases in core sample size. Although more extensive sampling reduces the upgrade rate, the 2% target, corresponding to that associated with a BI-RADS 3 classification, has proven elusive.[9,10] All these strategies attempt to compensate for the single critical distinction between OSE and standard image-guided core biopsy: *preservation of lesion architecture with intact lesion removal* versus piecemeal (multicore) sampling or excision, which precludes evaluation of the intact lesion architecture.

In an effort to address this costly continuing challenge, the Intact Percutaneous Excision Trial (IPET) was designed in 2006 by a group of radiologists, surgeons, and pathologists, all specializing in breast disease (see Acknowledgments). The goal was to prospectively evaluate intact percutaneous lesion excision (IPEX) with standard radiologic and histologic criteria for the definitive diagnosis of HRL in general and ADH in particular. Based in part on suggestions by Lagios and Rogers, we reasoned that it was not the tools or incision used for removal, but rather the preservation of tissue architecture and complete lesion excision, thus permitting assessment of the extent of the lesion, that were the key components in making OSE more reliable than IGCNBx for HRL.[11,12] The primary aim of IPET is to validate predefined criteria (intact lesion removal with standard radiologic and histologic confirmation) associated with less than 2% risk for upgrade to carcinoma, equivalent to that associated with BI-RADS 3 lesions. Patients with lesions meeting these criteria could thus be spared unnecessary surgery and placed in surveillance; surgical intervention and medical resources could thus be reserved for circumstances in which they are actually needed.

PATIENTS AND METHODS

From August 2006 through September 2010, 1,170 consecutive patients recommended for breast biopsy at 25 US institutions (see Acknowledgments) provided Health Insurance Portability and Accountability Act (HIPAA)-compliant informed consent and were prospectively enrolled in IPET with Institutional Review Board approval. Patients were eligible for study enrollment if they had had a mammographic lesion recommended for IGCNBx. Patients with implantable devices possibly affected by radiofrequency-assisted tissue capture (pacemakers, defibrillators, breast implants) were excluded.

In all subjects, a qualified radiologist or surgeon performed IPEX using a 15- or 20-mm vacuum- and radiofrequency-assisted device for the removal of intact specimens (Intact™; Intact Medical Corporation, Natick, MA) (Fig. 1). The Intact device was cleared by the Food and Drug Administration (FDA) for sampling biopsy in 2001 and for complete removal of imaged abnormality in 2005.

Details of the IPEX procedure, associated complications, and patient tolerance data have been reported elsewhere.[13,14] Briefly, the patient is positioned as for standard IGCNBx (stereotactic biopsy technique in >95% of patients in IPET). Complete local anesthesia is obtained by surrounding the target lesion with dilute lidocaine/epinephrine solution. Excellent local anesthetic is important for the procedure, since the entire tissue capture sequence takes place in about 10 s. The probe is advanced to the lesion, and the target tissue is captured utilizing vacuum and radiofrequency cutting. The probe, with the captured tissue in the basket (Fig. 1), is withdrawn. A biopsy site marker system is deployed manually via the residual biopsy track. Postbiopsy specimen X-ray and mammogram are then obtained. Complications and patient tolerance are similar to those with standard vacuum-assisted, multicore biopsy.[13,14]

The IPET protocol, designed to validate predefined criteria for avoiding standard OSE, included OSE for all patients with a diagnosis of HRL. Because ADH is historically the most challenging HRL, the subset of HRL patients with ADH who met standard radiologic and histologic criteria were designated as the potential surgical avoidance ADH population (PSAP) prior to OSE.

The PSAP group was defined as those patients with no residual evidence of the lesion on postexcision mammogram plus histologic removal of the lesion permitting definitive characterization on permanent pathology. To maintain fidelity with the clinical aspects of OSE for HRL, standard radiologic and histologic criteria were employed. As with wire-localized OSE, postbiopsy imaging of the specimen was used to confirm removal of the imaged abnormality, a cluster of microcalcifications in nearly all cases. Since the procedures were done in the imaging suite using stereotactic guidance, postbiopsy mammograms were also available to confirm lesion removal. Standard

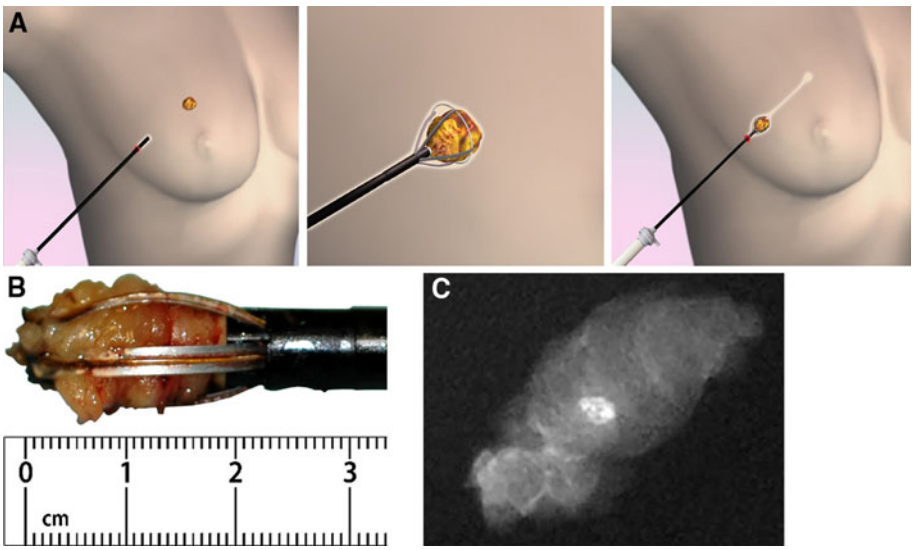

FIG. 1 The flat blade of the Intact breast lesion excision system (Intact Medical Corporation, Natick, MA) is advanced to the targeted position (**a**). Deploying the capture basket causes it to penetrate tissue with vacuum and radiofrequency current, acquiring the specimen (**b**). The target lesion is clearly visible inside the specimen on X-ray (**c**). Courtesy of Intact Medical Corporation, Natick, MA. Adapted, in part, from Whitworth PW. Image-guided percutaneous breast biopsy. In: Kuerer HM, ed. Kuerer's breast surgical oncology. New York, NY: McGraw-Hill; 2010. p 394

histologic requirements included complete removal of the pathologic lesion with no significant lesion components at the margin. As with OSE for HRL, *focal* margin contact, where the lesion was adequately centered for complete evaluation, was allowed.[15] Normal tissue separating the lesion from the specimen margin was not required. More extensive pathology at the margin or extensive/mass-forming proliferation mandated further excision (Fig. 2). Where available, central versus peripheral lesion position within the specimen, as well as the number of involved duct-lobular units, were recorded.

Because these criteria are standard for OSE, the institutional pathologists employed them routinely after establishing familiarity with IPEX specimen evaluation. All pathologists evaluating IPEX specimens completed standard on-site training provided by the vendor. This training included review of typical IPEX specimens with a full spectrum of histologic and device-specific features.

Pathologic findings in all specimens of HRL with subsequent OSE were compared with those from the initial IPEX. Pathologist recommendations and postbiopsy mammogram findings were also recorded. If a patient refused OSE after HRL diagnosis, surveillance mammograms were evaluated at 6-month intervals for a minimum of 2 years.

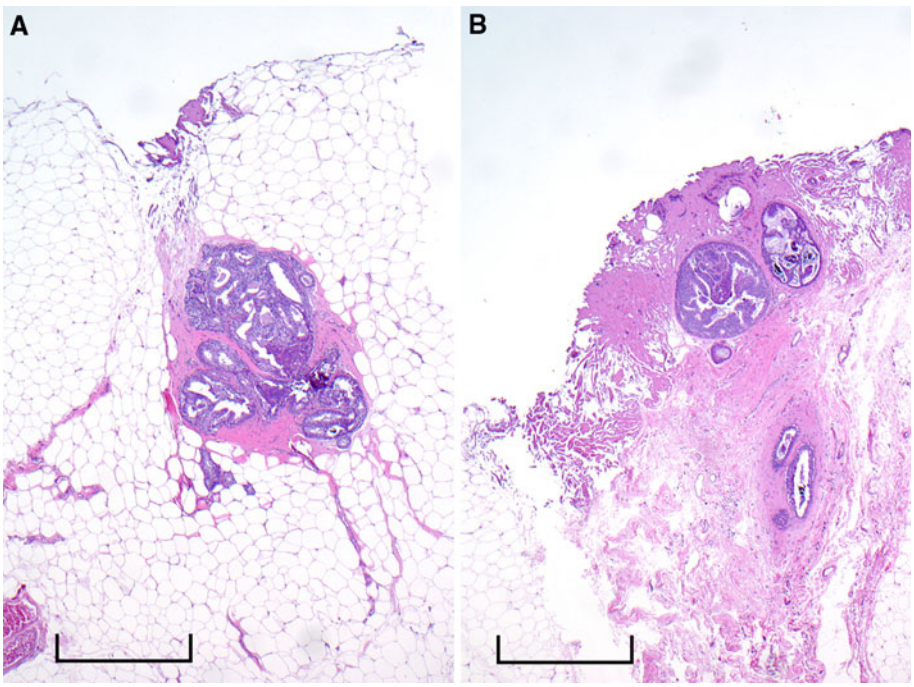

FIG. 2 Intact excisional breast biopsy samples [hematoxylin and eosin (H&E) stain, ×80 magnification, *scale bar* 0.5 mm]. **a** Atypical ductal hyperplasia (ADH) with focal margin proximity, but no significant lesion components at the margin; lesion is adequately centered for complete evaluation and other critical features removed. Because patient risk is less than that of BI-RADS 3, surveillance management is acceptable. **b** In another patient, significant ADH is seen at the cauterized margin, mandating further excision. Courtesy of Jean F. Simpson, MD. BI-RADS, Breast Imaging Reporting and Data System

RESULTS

Among the 1,170 patients enrolled in the study, 191 carcinomas and 83 HRL (32 ADH, 20 LN, 24 papillomas, 7 RS) were diagnosed by means of IPEX (Table 1). Using standard histologic and radiologic criteria, 10 of the 32 ADH patients were categorized as PSAP patients. No ADH lesions that met PSAP criteria were upgraded to carcinoma on OSE ($n = 7$) or imaging follow-up ($n = 3$, minimum 24 months); 3 (14%) of the 22 ADH lesions that did not meet these standard criteria were upgraded to carcinoma on OSE (2 DCIS, 1 invasive cancer), none on imaging follow-up at 24 months (3 of 22 refused OSE).

Two of the 22 non-PSAP cases were designated non-PSAP because of inadequate excision on postbiopsy mammogram. The remainder failed to meet the histologic requirement that the lesion be adequately excised for definitive evaluation. The single reason for non-PSAP designation in the other 20 non-PSAP cases was that the lesion had more than focal contact with the specimen margin or with artifact at the margin. Central versus peripheral lesion position within the specimen was recorded for 18 non-PSAP cases (11 peripheral) and 9 PSAP excisions (1 peripheral). None of the 51 non-ADH HRL were upgraded to carcinoma on OSE ($n = 24$) or on radiologic follow-up if OSE was declined ($n = 27$).

In summary, 7% (83/1,170) of patients in this prospective validation trial of primary diagnostic IPEX had HRL. Overall, lesions with ADH were found in 3% (32/1,170) of patients; among these, 22 failed to meet prespecified histologic and radiologic criteria (the non-PSAP group), and the diagnosis for 14% (3/22) of these non-PSAP ADH patients was upgraded to carcinoma on OSE. No upgrade to a diagnosis of carcinoma occurred in ADH patients who met standard histologic and radiologic criteria (the PSAP group) or in patients with non-ADH HRL on IPEX.

TABLE 1 Cancer and HRL diagnoses by intact percutaneous lesion excision at enrollment ($N = 1,170$)

IPEX biopsies	1,170
Carcinoma	191 (16%)
HRL	83 (7%)
ADH	32 (3%)
LN	20 (2%)
Papilloma	24 (2%)
RS	7 (1%)

ADH atypical ductal hyperplasia, *HRL* high-risk lesion, *IPEX* intact percutaneous excision, *LN* lobular neoplasia, *P* papilloma, *RS* radial scar

DISCUSSION

This prospective, multi-institutional clinical trial supports IPEX, when combined with standard histologic and radiologic criteria, as definitive management of image-detected HRL in general and of ADH in particular (risk below the 2% threshold for BI-RADS 3 lesions). These findings are important since until now patients with HRL, especially those with ADH, have proceeded to OSE for definitive diagnosis subsequent to IGCNBx. By eliminating OSE for properly selected patients with ADH and other HRL, clinicians using IPEX can safely and substantially reduce patient distress, discomfort, and healthcare costs.

These findings in 1,170 patients with 83 HRL uniformly suggest IPEX integrated with standard histologic and radiologic criteria may be preferable to routine OSE; nevertheless, this study suffers the limitations of all prospective studies of HRL diagnosis. The number of affected patients is too small to yield statistically definitive conclusions. However, these results represent a step forward as the first positive prospective evaluation of an improved diagnostic strategy, substituting IPEX for OSE in the management of HRL.

In contrast to standard sampling or excisional multicore biopsy, IPEX with standard histologic and radiologic criteria can replace OSE for HRL because it accomplishes the same thing. The targeted tissue is removed in one piece to be evaluated by the pathologist. Since one criterion for distinguishing low-grade DCIS from ADH is the extent of involvement (the other criteria being a uniform population of cells and rigid architectural configurations), the intact nature of the specimen allows this important assessment to be made. Contiguous tissues and lesion architecture are preserved by intact removal. For small lesions, IPEX amounts to more precisely targeted removal than can be accomplished by standard OSE. OSE has served as definitive management for HRL because it removes the intact lesion for pathologic evaluation. Intact removal, not the distinction between open and percutaneous access, is the critical feature.

Based on these findings, we have altered our management of ADH lesions diagnosed with image-guided biopsy. If a lesion harboring ADH is diagnosed by primary IPEX with standard histologic and radiologic criteria, we place that patient in surveillance identical to that for patients with BI-RADS 3 lesions (diagnostic mammogram every 6 months times two, then a final surveillance mammogram 12 months later). If a patient presents with ADH diagnosed on IGCNBx, we proceed with IPEX using a 15-, 20- or 30-mm device (the 30-mm size became available after the trial was completed), provided the imaged biopsy cavity dimensions are suitable. If IPEX with standard histologic and radiologic criteria requirements are met (standard

histologic and radiologic removal), the patient is managed as above (for BI-RADS 3 level risk). Standard histologic and radiologic criteria are critical. A large retrospective evaluation of stereotactic sampling biopsies using the same device and *not* employing standard radiologic and histologic criteria demonstrated an ADH upgrade rate of 9.4%, similar to the non-PSAP group and to rates reported with stereotactic, multicore, vacuum-assisted, image-guided biopsy.[14]

In addition, successful implementation of this approach requires technical modifications by the physician performing the biopsy, since the radiofrequency tissue acquisition takes place in a single 8- to 10-s capture.[15] Patient comfort depends on careful application of local anesthetic. Finally, pathologists evaluating specimens obtained with the radiofrequency cutting basket report improved satisfaction compared with that with multicore specimens *after* gaining familiarity with the expected 0.2- to 0.5-mm radiofrequency artifact.[15]

To monitor outcomes with this change in practice, we have asked the manufacturer of the Intact percutaneous excision device to support a voluntary IPEX for HRL Registry, supervised by the American Society of Breast Surgeons that will be available to any qualified physician using IPEX. The registry will be accessible for Internet-based patient accrual. Patients and the general public who fund healthcare can benefit from careful implementation of this change in practice for HRL.

It should be noted that the challenges attending HRL diagnosis may not apply equally to the special case of intentional ultrasound-guided, vacuum-assisted, multicore excision of masses containing ADH.[16,17] This possible exception might be partially due to the higher sensitivity of image-guided biopsy for masses as opposed to microcalcifications.[16,18,19] In the largest such series (29 ADH lesions) analyzing ADH underestimation, Grady et al. reported no ADH upgrades when ultrasound-guided percutaneous multicore mass excision was the intended procedure.[17] In a subsequent evaluation of the worldwide literature on the topic, Grady identified a total of 43 ADH lesions diagnosed among 1,191 intended ultrasound-guided percutaneous multicore excisions.[17,20–27] There were no ADH upgrades on OSE in these nine published series.

For future studies the advantages of combining standard radiologic and histologic criteria with intact lesion removal (percutaneous instead of open) make IPEX an attractive approach for minimally invasive management of breast cancers. In a pilot study from the Royal Marsden Hospital, clear margins were obtained in 7 of 15 subcentimeter cancers.[28] We are currently evaluating IPEX for management of selected small carcinomas in the Excision Margin Assessment Trial.

ACKNOWLEDGMENT Funded by an unrestricted grant from Intact Medical Corporation, Natick, MA. The Intact Percutaneous Excision Trial (IPET) Design Advisory Group convened in Newport Beach, CA, on January 28, 2006. Members: Thomas B. Julian, MD; Larry Killebrew, MD; Michael D. Lagios, MD; Elsie Levin, MD; William R. Poller, MD; Elizabeth A. Rafferty, MD; Lowell W. Rogers, MD; Melvin J. Silverstein, MD; Jean F. Simpson, MD; Laszlo Tabar, MD; Pat W. Whitworth, MD; Shauna C. Willey, MD; Victor J. Zannis, MD. Participating institutions and investigators of the Intact Percutaneous Excision Trial: N. Craig Brackett III, MD, Costal Carolina Breast Center, Murrells Inlet, NC; William L. Diehl, MD, Morristown Memorial Hospital, Morristown, NJ; Michael J. Farrell, MD, Wilson Hospital Breast Center, Johnson City, NY; Robert A. Gardner, MD, Center for Breast Care HCA, West Palm Beach, FL; Linsey P. Gold, DO, Genesys Regional Medical Center, Grand Blanc, MI; Leopoldo B. Gonzalez, MD, Flagler Hospital, St. Augustine, FL; Rhonda S. Henry-Tillman, MD, Arkansas Cancer Research Center, Little Rock, AR; Elizabeth Jett, MD, Oklahoma University Breast Institute, Oklahoma City, OK; Joel M. Johnson, MD, Tift Regional Medical Center, Tifton, GA; Kevin M. Kelly, MD, Hill Breast Center, Pasadena, CA; Marla R. Lander, MD, The Breast Health Center, Indio, CA; Bettina Lowe, MD, Shawnee Mission Medical Center, Shawnee Mission, KS; Samuel Dwight Lyons, MD, Maui Medical Group, Wailuku, HI; Mary C. Mahoney, MD, University Radiology Associates of Cincinnati, Inc., Cincinnati, OH; Rogsbert F. Phillips, MD, Metro Surgical Associates, Inc., Decatur, GA; William R. Poller, MD, Allegheny General Hospital, Pittsburgh, PA; Steven Schonholz, MD, Mercy Medical Center, Springfield, MA; Michael J. Schultz, MD, St. Joseph Medical Center, Towson, MD; John W. Shook, MD, Saint Luke's Cancer Institute, Kansas City, MO; John F. Turner, MD, Evangelical Community Hospital, Lewisburg, PA; Dariush Vaziri, MD, Lourdes Hospital Breast Center, Binghamton, NY; Keith M. Warner, MD, Elyria Memorial Hospital, Elyria, OH; Elizabeth A. Weaver, MD, Jewish Hospital Breast Center, Cincinnati, OH; Pat W. Whitworth, MD, Nashville Breast Center, Nashville, TN; Ronald B.Workman, MD, Decatur Hospital, Decatur, AL. The authors thank Marcia Ringel for editorial support.

CONFLICT OF INTEREST P.W.W. and J.F.S. have served as scientific consultants to Intact Medical Corporation.

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