

Malignant Seeding Following Percutaneous Breast Biopsy: Documentation With Comprehensive Imaging and Clinical Implications

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■ **Abstract:** The aim of this study was to demonstrate convincing evidence that percutaneous breast biopsy may result in displacement of malignant cells that can initiate tumor growth at a separate anatomic site, other than the index lesion. Two patients with malignancy diagnosed by percutaneous breast biopsy were followed up with subsequent imaging. The observation of displaced cells initiating subsequent malignant growth was compared retrospectively with the previous year's outcomes following percutaneous breast biopsy. Two cases of displaced malignant cells resulting in malignant growth at a separate site along the biopsy needle track were demonstrated by imaging. During the preceding year, 1644 biopsies with 298 malignant results were compared with the outcomes of these two patients, resulting in a 0.7% incidence of malignant seeding. No identifiable factors could be identified to predict under what conditions this iatrogenic complication occurs. Although uncommon, percutaneous breast biopsy can result in malignant seeding, and raises issues regarding informed consent and proper subsequent treatment. ■

Key Words: breast biopsy, malignant seeding, percutaneous

With the advent of percutaneous biopsy replacing most surgical excisions for diagnostic purposes (1), the issue of epithelial displacement and, more significantly, potential recurrence of malignancy due to such displacement—sometimes referred to as “seeding”—has been raised for many years. Evidence for the implantation of tumor cells that initiate malignant growth at a site distant to the index cancer has been controversial. Histologic evaluation of displaced epithelial cells as a function of time between biopsy and surgery suggests that such seeding does not regularly initiate malignant growth, perhaps because of local growth factors required for interaction of the cells with the surrounding breast (2,3). On the other hand, reported cases of malignant recurrence, especially at the skin site of prior percutaneous biopsy entrance, have raised concern that seeding and subsequent growth of cancer cells by means of fine needle aspiration or larger needle core biopsy can be clinically observed (4,5). Although recurrence rates following

percutaneous biopsy might be a measure of this potential hazard of percutaneous biopsy, there is an absence of statistically significant differences between historic rates of recurrence from those rates in the era following the introduction of widespread percutaneous large bore needle biopsies, the analysis complicated by additional treatment interventions (6).

The significance of potential malignant seeding following percutaneous biopsy is emphasized by the current impetus to limit surgical excision to a status providing adequate tumor-free margins while maintaining desired cosmesis, as well as more limited local adjuvant radiation therapy as illustrated by data supporting the use of accelerated partial breast irradiation protocols that localize such adjuvant treatment to the tumor site. Some commentators have suggested that the phenomenon of seeding is related to certain subclassifications of breast cancer and different types of biopsy approaches. We report two cases where percutaneous core biopsy was performed and where previously unreported comprehensive imaging demonstrated malignancy developing at a site distant to the index cancer, and through which the biopsy device traversed. We analyzed the current significance of these findings in the context of previously reported data.

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REPORT OF TWO CASES

Case 1

A 64-year-old woman with a family history of breast cancer and a personal history of left breast cancer demonstrated new clustered pleomorphic calcifications in the right breast (Fig. 1a). Stereotactic biopsy using the Mammotome (Ethicon Endo-Surgery, Cincinnati, OH) 8 gauge was performed with four samples. The postbiopsy tissue marker was deployed 3 cm distal to the site of biopsy as demonstrated with pre- and postbiopsy mammography (Fig. 1b). Pathology demonstrated invasive ductal carcinoma. Given the discrepant clip placement, only the remaining calcifications were preoperatively localized with a bracket technique for excision. Due to

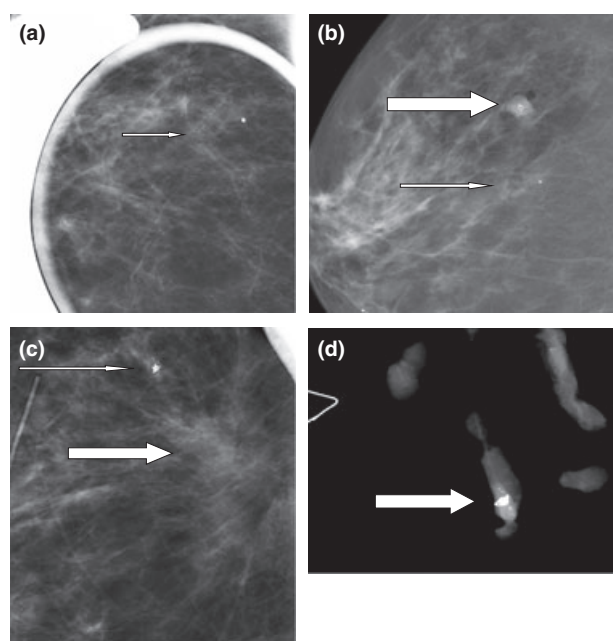


Figure 1. Percutaneous biopsy of clustered microcalcifications associated with subsequent malignancy at site of displaced postbiopsy marker. (a) Right breast spot compression magnification (1.5×) CC view demonstrating suspicious clustered microcalcifications (arrow). (Note macrocalcification particle posterior to clustered microcalcifications). (b) Right CC view. Status postremoval of microcalcifications, site marked by thin arrow (Note again macrocalcification particle posteriorly located with respect to initial anatomic position of initial cluster seen in [a]). Postbiopsy marker (wide arrow) located 3 cm lateral to site of initial cluster of microcalcifications and associated with small mass representing hematoma. (c) Right CC view: New suspicious microcalcifications at the site of the postbiopsy marker (thin arrow). Lumpectomy site scar noted by wide arrow. (d) Specimen radiograph from right breast stereotactic biopsy, containing the postbiopsy marker and malignant calcifications (arrow).

the distance of the clip from the index malignant anatomic site, the clip was not localized and remained in the breast following surgery. Subsequent pathology corroborated the initial core needle biopsy (CNB) diagnosis of invasive ductal carcinoma and solid and comedo ductal carcinoma in situ (DCIS), the residual invasive cancer measuring 6 mm and DCIS measuring 3 mm. Greater than 5 mm disease free margins were identified and there was no evidence of axillary lymph node metastatic disease.

Follow-up mammography 15 months later demonstrated a cluster of microcalcifications at the site of the remaining tissue marker, with no additional calcifications seen at the lumpectomy site or elsewhere in the breast (Fig. 1c). A subsequent stereotactic biopsy (again, Mammotome, 8G needle, four samples) was performed with recovery of the tissue marker and intimately associated calcifications (Fig. 1d), with pathology showing DCIS.

Case 2

A 54-year-old woman with no family history presented with a lump at the right 12 o'clock position. Mammography showed a mass with associated microcalcifications and ultrasound demonstrated a 11-mm hypoechoic mass with irregular margins (Fig. 2a). Ultrasound guided core biopsy was performed using a Suros 12G needle (ATEC; Hologic, Danbury, CT). A tissue marker was placed at the site of the mass and the pathology demonstrated invasive papillary carcinoma. Subsequent breast magnetic resonance imaging demonstrated the 12 o'clock cancer, which measured approximately 3.3 cm in greatest diameter (Fig. 2c). Enhancement at the skin puncture site 1.7 cm lateral to the cancer was noted, with an ill-defined subdermal mass (Fig. 2d). As the skin enhancement at the biopsy device entrance site was larger and of greater signal intensity than usually seen following percutaneous biopsy, the possibility of epithelial displacement and possible tumor seeding were considered and the surgeon was asked to include this area in the definitive excisional surgery. Due to authorization and scheduling delays, MRI localization was performed 2 months later. At this time, MRI performed prior to MR-guided needle localization suggested an increased size of the subdermal mass to 1 cm (allowing for mild compression employed during the procedure) (Fig. 2e). Final pathology showed a 5 cm invasive papillary carcinoma as the index cancer and also a separate 1 cm papillary carcinoma abutting the skin and associated with aggregates

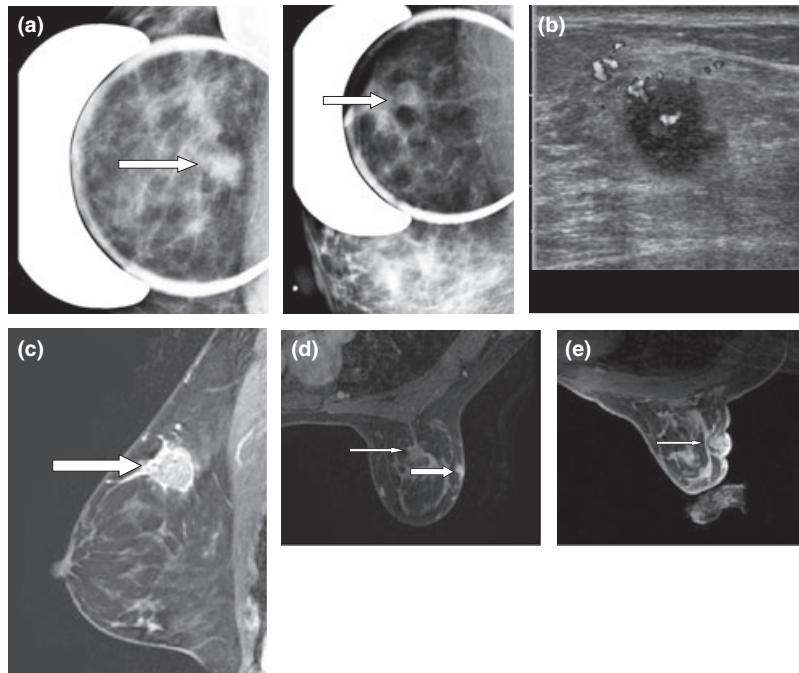


Figure 2. Percutaneous biopsy of malignant mass associated with subsequent development of malignancy at skin entrance site. (a) Right CC and ML spot compression magnification (1.5 $\times$) views to suspicious mammographic mass (arrow). (b) Ultrasound image of mammographic mass demonstrating shows suspicious hypoechoic mass with irregular margins and increased vascularity. (c) Postcontrast sagittal breast MRI (2 minutes image after injection) demonstrates same mass as shown by mammography and ultrasound with suspicious heterogeneous and increased rim enhancement. No other lesions were identified at MRI study. (d) Postcontrast axial breast MRI demonstrates a small irregular mass with enhancement at the skin, corresponding to the prior biopsy entrance site (wide arrow). The caudal margin of the index cancer is seen on the image (thin arrow). (e) Postcontrast axial breast MRI performed 2 months after the study shown in 2D. The subdermal mass has increased in size and demonstrates suspicious irregular margins and heterogeneous enhancement (arrow). (f) Postcontrast axial breast MRI study on different patient following percutaneous biopsy of malignant lesion. Arrow demonstrates dermal and minimal subadjacent enhancement at biopsy entrance site that is commonly seen following percutaneous core needle biopsy [see Reference (13)].

of histiocytes and multinucleated giant cells indicative of biopsy site changes. Regional axillary lymph nodes were negative for metastatic involvement.

RESULTS

Of 1644 percutaneous biopsies performed during a 1-year period, 298 malignancies were diagnosed. Two of these cases (0.7%) were associated with malignant seeding of cells to an anatomic site not originally involved along the track of the CNB. No specific parameters regarding needle size, type of lesion, or histology were found to be predictive of malignant seeding.

DISCUSSION

The cases presented here prompt clinical concern beyond simple epithelial displacement that may sometimes complicate pathologic diagnosis of invasive versus in situ carcinoma. They illustrate the more pernicious

condition whereby malignant growth is initiated at a separate anatomic site consequent to such displacement or “seeding” by iatrogenic means; namely, the use of percutaneous biopsy instruments. That epithelial displacement can occur has been observed in both clinical and studied circumstances. Washings from 18G core biopsy needles (notch unexposed) have demonstrated a 65% incidence of malignant cellular material on the external biopsy instrument, more common in DCIS and invasive ductal carcinoma than in invasive lobular carcinoma (7). Youngson reported soon after the introduction of stereotactic large needle biopsy procedures that 12 of 43 consecutive patients who had undergone 14G biopsy demonstrated detached carcinoma fragments in the excised specimen (8). On the other hand, Brown confirmed work done decades ago that circulating tumor cells following surgical preparation of an operative breast site can be found, with no direct clinical implications (9).

Ishizuna et al. described observing at ultrasound a hypoechoic band extending from the targeted tumor

toward the skin following a negative core biopsy and subsequent positive fine-needle aspiration biopsy (5), which they reported as more likely with mucinous lesions. However, no other report has validated this observation.

It remains unclear whether the type of lesion, size of needle, or method of biopsy influences the potential for malignant seeding. Nagi reported a retrospective review of 53 cases showing epithelial displacement that was most often associated with papillary lesions (10). Thursfell et al. speculated seeding in describing three cases of recurrent invasive cancers in patients whose surgery was not followed up by adjuvant radiotherapy with histologic subtypes of mucinous, tubuloductal, and adenoid cystic carcinoma (11).

The only common variable in the two cases reported here is that both lesion involved calcifications, one case with a demonstrable mass, which was underestimated in size based on subsequent MRI findings. The significance of this observation is indeterminate, and may be coincidental, given the limited number of studied patients and the lack of recognizing malignant seeding in the large majority of calcifications associated with a malignant process that are biopsied without such sequelae. Two different biopsy devices were used (ATEC; Suros Surgical, Indianapolis, IN and Mammotome; Ethicon Endo-Surgery) and two different gauge needles were employed (8G and 12G), both with four samples obtained. One of the two currently described cases involved a papillary lesion, which has been suggested as a more likely source for seeding (4), but one did not. Our limited data combined with prior reports do not support the proposition that needle size, type, or histologic subtype is predictive of which malignancies are more prone to result in malignant seeding following percutaneous biopsy.

Many patients undergo preoperative evaluation for extent of malignancy, once a known cancer has been diagnosed; in fact, this is likely the most common current indication for breast MRI (12). Like others (13), we have observed minimal enhancement of the skin at the biopsy site entrance for MRI cases performed within a few weeks of initial biopsy (Fig. 3), the enhancement of the skin and subdermal mass on case 2 was both more prominent than usual and with increased skin thickening. Of greater concern were the observations of a subcutaneous mass that, in combination with the skin changes, suggested malignant seeding. We have observed similar masses with smooth

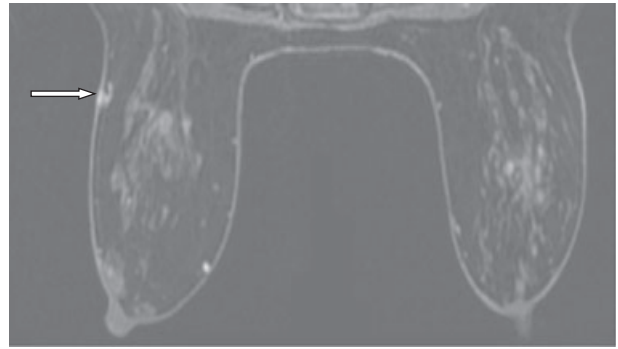


Figure 3. Breast MRI following percutaneous biopsy one week previously, on patient different than those reported here. Small enhancing focus a skin often seen following such procedures (see Reference 13).

margins and homogeneous enhancement that are shown by biopsy to represent fat necrosis. The current mass was distinguished by its suspicious heterogeneous enhancement and irregular margins. Whether or not isolated skin enhancement to any extent is predictive of seeding is not known and cannot be reconciled on the basis of this report.

In the first case, we did not seek to recover the postbiopsy marker, which was placed more than 2 cm from the anatomic site of the calcifications. A larger retrospective review of marker placement noted that more than 28% of markers are placed >1 cm away (14). Methods have been described whereby such clips can be percutaneously removed (15), but given the clear margins of the excision, this maneuver was not considered indicated at the time.

Diaz et al. (2) reviewed their experience with surgical excisions following percutaneous biopsy, observing that the longer the period of time between the diagnostic interventional procedure and definitive surgery, the less viable the displaced cells appeared at microscopy. On the other hand, Stoller et al. deliberately removed the skin and subcutaneous fat from the site of core needle insertion in 89 consecutive patients undergoing stereotactic biopsy and 58 undergoing ultrasound guided biopsy and observed one patient with recurrence at the skin biopsy site at 34 months, and two others with nests of cancer cells in the dermis of patients who had undergone multiple insertion biopsy procedures (16). Our cases both involved single insertion devices where tissue is transferred internally to a collection chamber. However, as was pointed out (5), cells may attached to the needle bevel and be displaced to other parts of the breast during withdrawal of even a single insertion device. Uriburu reported a

local recurrence in a patient undergoing skin-sparing mastectomy following CNB at the site of insertion (4). The absence of more definitive imaging in these reports, in contrast to the current report, as was performed in our cases, raises the possibility that coexistent (multifocal, multicentric) malignancy was already present prior to the initial biopsy and subsequent therapy. Thus, our study provides validated evidence of no pre-existing malignancy at the site where malignant seeding was subsequently demonstrated.

The clinical significance of this displacement of cells from the initial malignant anatomic site has been generally discounted in the past, in part due to the limited imaging and subsequent speculation discussed above. In addition, outcomes have not supported malignant seeding. Chen et al., reported a recurrence-free rate at a mean follow-up of 4.9 years (range 2.0–8.9) to be less for patients undergoing percutaneous CNB than non-image guided biopsy (5). This conclusion was supported by a retrospective review of 719 patients where 189 had and 530 did not have percutaneous biopsy procedure. At a median follow-up of 78 and 71 months respectively, local recurrence rates were not significantly influenced (16). However, most conservation therapy approaches that provide adjuvant radiotherapy have included whole breast radiation that presumably targets such small clusters of displaced cells in a cell-killing manner. As a consequence, a recent review of 15 published studies concluded no increased morbidity due to this phenomenon (16).

We report two cases where imaging examinations were sufficiently separate in time to virtually exclude multifocal or multicentric primary malignant sites and demonstrate interval change that supports the concept of malignant seeding and growth. During the calendar year that we observed these changes, we performed 1644 percutaneous biopsies (image guided with ultrasound, stereotaxis, or MRI) with needle sizes ranging from 22G (fine needle aspiration biopsy) in <3% of cases and 11G or larger in the remaining cases, resulting in malignant diagnoses in 298 cases, all but one diagnosed with CNB of 14 Gauge or greater. Thus, two of 298 cases or 0.7% demonstrated malignant seeding. It is difficult to reconcile why this number is not higher or lower.

It is tempting to postulate reasons for the low but finite incidence of malignant seeding as now demonstrated in this report. As noted, cells from the biopsy site are displaced through the breast (7), but rarely result in distant-initiated malignant growth. There are

thought to be certain so-called tumor-initiating cells (stem cells), progenitors required for growth that have been found with hematopoietic malignancies and have been implicated in solid organ and breast cancer (17–24). Whether or not this theory accounts for the tracking of certain cells that would initiate a malignant process along the track of the percutaneous biopsy in ours and other cases could be validated in clinical trials that specifically analyze and distinguish the gene signature of such deposited cells from other cells of the index cancer site. Such signatures have already been suggested (24,25).

While our incidence of malignant seeding is small, it raises four important issues. First, should such adverse consequences be included in the informed consent process for percutaneous biopsy? Second, should MRI be routinely performed at an interval following initial diagnosis by percutaneous biopsy so that the issue of malignant seeding is excluded? Third, should definitive surgery and choices for adjuvant radiotherapy be based on the unlikely but finite possibility that malignant seeding occurs? Finally, should all remaining clips that are not included with the excised specimen during surgery be subsequently removed?

While our observed incidence of malignant seeding is small, and probably reflects the low likelihood of the procedure in general, based on the prior discussion, it does occur and we have used sequential imaging to demonstrate the phenomenon. Whether or not surgery should be modified to include the biopsy track in all cases, or accelerated partial breast irradiation needs to be predicated on an imaging demonstration of lack of seeding, are additional issues that will need to be addressed in the future as clinicians accumulate more empiric data regarding this unusual phenomenon.

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