Clinical Experience Open Access

Archives Of Breast Cancer

DOI: 10.32768/abc.20229132-39

Avoidable and Unavoidable Repeat Breast Core Needle Biopsies

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ARTICLE INFO

Received:
01 September 2021
Revised:
09 December 2021
Accepted:
31 December 2021

Keywords:
breast needle biopsy,
ultrasound,
mammogram,
MRI

ABSTRACT

Background: Breast core needle biopsies are not perfect and could miss cancer. The need for a repeat breast core biopsy is not uncommon and can occur for a multitude of reasons. Radiologists should carefully correlate the pathology results with imaging features after each breast biopsy and must recognize why certain core biopsies must be repeated to avoid missed or delayed cancer diagnosis. In this review, we discuss the main reasons for repeat core biopsies via case presentation with radiological images and pathological correlation. This review will help multidisciplinary breast care team recognize when to repeat a biopsy to reduce false negatives and will also familiarize radiologists with techniques for improving initial biopsy success.

Methods: We performed literature and chart reviews of cases at our institution between January 2015 and December 2019.

Results: While some repeat biopsies are inevitable, most can be avoided with careful pre-biopsy planning, adequate sampling techniques, and proper radiological-pathological correlation.

Conclusion: Repeat breast core needle biopsies occur due to multiple avoidable and unavoidable radiological or pathological issues. It is imperative for both multidisciplinary breast care team and radiologists to recognize when to repeat a biopsy to reduce false negative or delayed cancer diagnosis via careful reviews before and after the procedure and adequate radiological and pathological correlation.

INTRODUCTION

Core needle biopsy is the standard tool for diagnosing breast cancer and is often performed by radiologists under image guidance (mostly ultrasound, mammogram, or magnetic resonance imaging [MRI]). Each year approximately 1.6 million breast needle biopsies are performed in the United States.[1] When compared to open surgical biopsy, a core needle biopsy has comparable accuracy and lower complication rates.[2] Unfortunately, core needle biopsies are not 100% accurate and carry the risk of false negatives and missed cancers.[3,4]

Radiologists play an important role in evaluating pathology results after needle biopsies. Given the risk of false negative results, some benign or atypical biopsies may require repeating for many reasons. A meta-analysis of published series has shown 10% of biopsied lesions required repeat biopsy, with 17% of these lesions proving malignant.[5] Therefore, radiologists must recognize why certain breast biopsies need repeating so a missed cancer diagnosis may be averted. Studies also showed that core needle biopsy false negative rates reduced with experience of the performing radiologists.[6,7] While some repeat biopsies

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are inevitable, most can be avoided with careful pre-biopsy planning, proper sampling techniques, and immediate post biopsy imaging. In addition to recognizing the necessity of repeat biopsies, radiologists should know how to improve biopsy planning and techniques that will decrease the need for repeat biopsies as they cause patient anxiety and increase medical costs. The goals of this review are to examine the underlying causes of repeat biopsies through case presentation with radiological and pathological correlation. This will help the multidisciplinary breast care team recognize "when and why" to repeat a breast core biopsy to reduce false negatives and will also familiarize radiologists with biopsy techniques to improve initial biopsy success.

METHODS

In our hospital, once a breast biopsy is completed and pathology results are available, the radiologist reviews all pertinent imaging and pathology for correlation. If radiologic-pathologic discordance is present, a recommendation is made for either a repeat biopsy or discussion during weekly tumor board. Based on our review, reasons for repeated biopsies are: (1) inadequate biopsy technique, (2) challenging or discordant radiologic-pathologic correlation, (3) issues with tissue specimen, (4) progression of findings on post-biopsy follow-up. Using 5 clinical cases selected from our clinic, we also illustrated how to avoid some of the repeat biopsy and when to repeat biopsy to avoid delayed or missed best cancer diagnosis.

RESULTS / DISCUSSION

Inadequate biopsy technique

Adequate techniques are essential for a successful breast core biopsy. Studies have shown different false negative rates for specific core needle biopsies technique. For example, the false negative rate is approximately 2% for ultrasound guided biopsy (6) and 3-4% for stereotactic biopsy.[7,8] The major important technical issues that necessitate repeat biopsies are missing the target and choosing an inappropriate image guidance method.

Poor visualization of lesion and/or needle

Ultrasound-guided biopsy is the most common breast core biopsy method. It allows real time imaging of the lesion and needle. Steps toward a successful ultra-sound-guided biopsy begin with proper lesion and needle visualization. Awareness of needle angle relative to the ultrasound probe as it is introduced into the skin towards the lesion is important. Angles too steep make visibility difficult, even with larger needles. Echogenic air introduced through the needle track may obscure visualization, especially for small and deep lesions.[8] Entry site for deeper lesions is best further away from the transducer since this gives space to maneuver the biopsy device horizontally to the chest wall and the beam of the transducer.[5] Obtaining orthogonal views helps ensure that the needle is through the lesion. Competent ultrasound-guided biopsy techniques plus the ability to troubleshoot during challenging cases will help the radiologist avoid missing a target.

Dense breast tissue and fibrosis

Dense or fibrotic tissue is difficult to for the biopsy needle to traverse through the tissue, especially during ultrasound-guided biopsy. In the dense tissue, the core needle can be very difficult to advance via single hand. In this case, a sharp or large gauge needle with introducer may be used and a biopsy track can be generated through needle firing before sampling. Coaxial method may be beneficial to confirm adequate targeting and sampling in ultrasound guided biopsy. Once a coaxial needle is in place, access to the lesion is achieved. Rotation and manipulation of the transducer and needle may be necessary to ensure sampling through different parts of the lesion.[5]

Choosing the wrong biopsy method

Although exceptions do exist, the imaging modality of choice for a biopsy should be the one that will show the suspicious finding with the most confidence. Typically, ultra-sound-guided biopsies are utilized for masses; stereotactic-guided biopsies for calcifications, architectural distortion, and asymmetries; and MRI-guided biopsies for suspicious MRI findings. However, in clinical practice, ultrasound-guided biopsy is often preferred by patients and radiologists for a few reasons: low cost, portability, minimal equipment requirement, no radiation, real time imaging, being less invasive, and the possibility of a more comfortable biopsy position for the patients. Second-look ultrasound is commonly performed for mammographic or MRI findings.[9] Before utilizing ultrasound-guided biopsies for these abnormalities, all images must be reviewed to ensure correct targeting.[10] After the biopsy, a biopsy clip should be placed in the biopsy site and post biopsy mammogram should be performed to confirm appropriate targeting.

Figure 1 illustrates how utilizing an inappropriate imaging modality for a core biopsy can result in missing the intended target and subsequently delaying diagnosis. In this case, the ultrasound correlate for the mammographically detected architectural distortion was incorrect, thus resulting in a wrong biopsy site when ultrasound-guided biopsy was attempted. Repeat stereotactic biopsy was recommended to target the architectural distortion. Mammograms after the repeat biopsy confirmed the right targeting of this lesion, which was proven to be malignant. Necessity of a post

procedure mammogram and placement of a biopsy clip is also nicely depicted in Figure 1. Post clip images allowed the radiologist to see if the intended mammographic finding was appropriately targeted. Final pathology for the initial biopsy was benign which was concordant for the ultrasound finding, but not for the intended target on mammogram. Repeat biopsy was performed after careful review of the images and the missed cancer was caught on repeat biopsy without much delay.

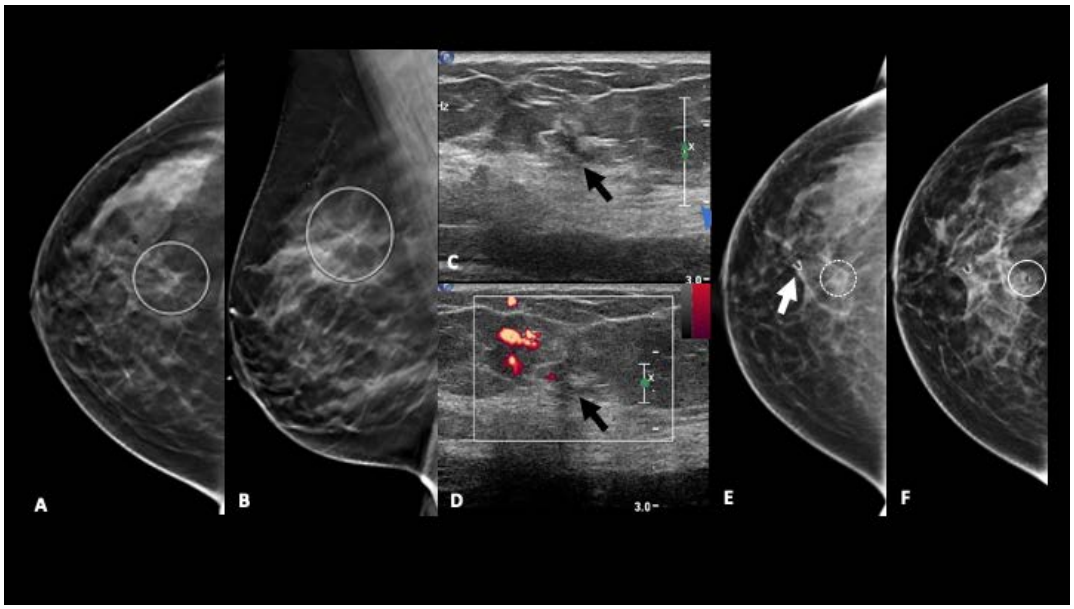

Figure 1. Missed target resulting from wrong biopsy imaging selection. A 44-year-old female with screening callback. **a.** Right craniocaudal and **b.** mediolateral oblique. views show an area of architectural distortion in the 12:00 of the right breast (white circle). **c, d.** Ultrasound images. at 12:00, 5cm from the nipple show an avascular irregular mass (black arrows) with angular margins. **e.** This likely correlates to mammographic finding post clip mammogram from initial ultrasound–guided biopsy shows U clip (white arrow) in unexpected location, anterior to architectural distortion (dashed white circle). Initial biopsy: discordant benign pathology—non-proliferative fibrocystic changes. Repeat stereotactic biopsy recommended. **f.** Post clip mammogram from repeat stereotactic biopsy shows the M clip in appropriate location (white circle). Repeat biopsy: Concordant malignant pathology—Grade 1 Invasive ductal carcinoma with ductal carcinoma in situ.

Challenging or discordant radiologic-pathologic correlation

Both radiological and pathological factors can be associated with repeat breast core biopsy. In a study conducted by Boba *et al.*, radiological failure resulted in 0.8% of biopsy false negative rates and histopathology constituted 1.5% of diagnosed cancers and atypia.[10] Despite optimal biopsy technique, failure to sample cancer may happen, possibly due to histologic heterogeneity within the lesion. Breast cancer can contain areas of normal breast tissue and fibrosis. Atypical or precancerous lesions can also coexist with the breast cancer during cancer development.[11] Figure 2 demonstrates the consequences of under sampling, likely due to histologic heterogeneity with presence of normal breast tissue or benign breast lesions.

Furthermore, histopathological interpretation is a significant cause for false-negative results, especially equivocal pathology.[10] Studies show that pathologists are particularly good at diagnosis of invasive cancer in a biopsy specimen but are less accurate at making the correct diagnosis with high risk or benign tissue.[1,10] According to one study,[1] pathologists' under-interpretation rates for ductal carcinoma in situ (DCIS) and atypia are 17% and 35%, respectively. Final pathology for the initial biopsy in Figure 3 was interpreted as a papilloma. However, the radiologist recommended surgical consultation due to concerning imaging features. Pathology from the surgical excision revealed low-grade DCIS in addition to IDP.

It is essential for the radiologist to carefully correlate pathology results of the biopsy with image features of the target. When discordant benign or atypical pathology intersects suspicious imaging features, the radiologist must analyze imaging features and discuss findings with the pathologist. To adequately correlate histology with radiologic findings, radiologists must be familiar with the gamut of pathologic and benign imaging features.[5] Careful radiology-pathology correlation can help avoid the false negative result via timely repeat biopsy. At our institution, discordant radiologic-pathologic diagnoses are either re-biopsied or discussed at weekly multidisciplinary tumor boards for further management.

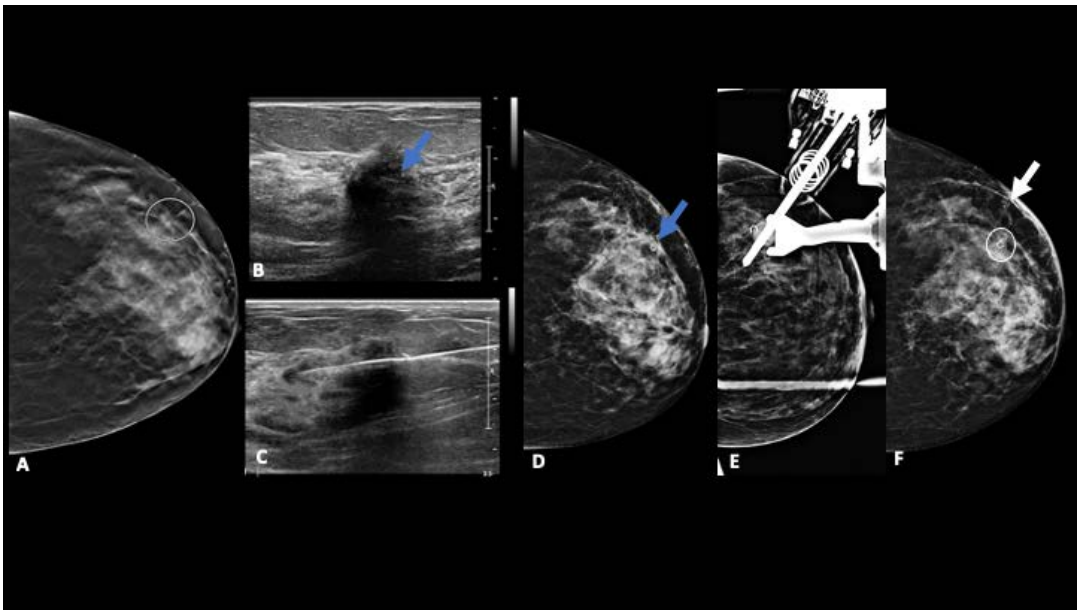

Figure 2. a–f. Radiology-pathology discordance (probably under-sampling) with timely management. A 46-year-old female presented for screening. a. Part of the left craniocaudal view shows architectural distortion at 2:00, 12cm from the nipple (white circle). b. Focused ultrasound image at 2:00, 12cm from the nipple, shows a 15mm irregular mass with spiculated margins (blue arrow), likely correlating with mammographic finding. c. Image from ultrasound-guided biopsy demonstrates sampling through the hypoechoic mass. d. Craniocaudal view from post-procedure mammogram shows U clip (blue arrow), close to area of architectural distortion (white circle). Initial biopsy: discordant benign pathology—benign breast tissue/ pseudoangiomatous stromal hyperplasia. e. Repeat stereotactic biopsy 5 days later. f. Post-biopsy mammogram craniocaudal view with ribbon clip (white arrow), which migrated laterally from biopsy site (white circle). Repeat biopsy: concordant malignant pathology—invasive well-differentiated lobular carcinoma.

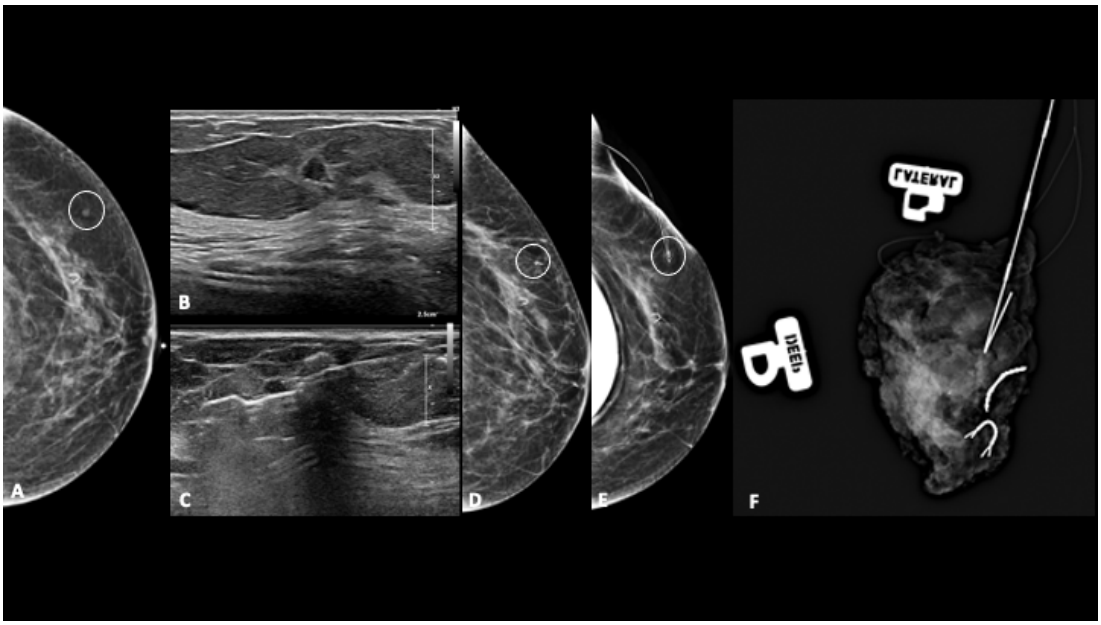

Figure 3. a–f. Challenging pathology (equivocal lesion) upgraded with surgical excision. A 68-year-old female screening callback. a. Craniocaudal implant displaced view shows a 3mm mass in the lateral left breast (white circle) 5cm from the nipple. The U clip shown is from prior benign biopsy. b. Ultrasound image shows an irregular mass with indistinct margins that may correlate with the mammographic finding. c. Image from ultrasound-guided biopsy shows proper targeting. d. Post-biopsy mammogram craniocaudal view shows eye clip in appropriate location (white circle). Initial biopsy: concordant benign pathology—papilloma with atypical ductal hyperplasia. Surgical excision recommended. e. Craniocaudal view following wire localization for surgical excision and f. post-lumpectomy surgical specimen radiography show adequate excisional biopsy. Repeat biopsy: concordant malignant pathology—ductal carcinoma in situ and intraductal papilloma (IDP).

All high-risk lesions (atypia, lobular carcinoma in situ, radial scar/complex sclerosing lesion, papillary lesions, fibroepithelial lesions) are also discussed at the tumor boards. Management often includes repeat biopsy, surgical excision, or 6-month image follow-up.

Issues with tissue specimen

Obtaining specimen radiographs is important for confirming retrieval of calcifications during stereotactic or ultrasound-guided biopsies. If calcifications are not present, timely and appropriate trouble shooting should be performed. Depending on the underlying causes, additional samples, retargeting, or switching biopsy methods should be considered if calcifications are not present on specimen radiographs due to inadequate tissue sampling. However, 6% specimens that did not show calcifications in radiology were described as calcified in final biopsy results by pathologists.[12] Calcifications that are not detected in the specimen radiograph can be aspirated into the debris stuck in biopsy equipment tubing and collecting basket or canister during the stereotactic vacuum-assisted biopsy.[13] One type of calcification – oxalate crystals – while often seen in the specimen radiography, are not detected by the routine pathology section and requires more comprehensive histologic examination, such as polarizing lenses.

Although the sampling of calcifications is mostly conducted with stereotactic guidance, ultrasound guidance can be performed in special situations where the stereotactic biopsy is not feasible. Biopsy of calcifications under ultrasound-guidance can be tricky, but certain techniques (i.e., open-trough method) may help minimize failure. Figure 4 demonstrates the importance of a specimen radio-graph. Upon completion of the initial ultrasound-guided biopsy, a specimen radiograph was not performed, and the clip was just anterior to the calcifications on the post-procedure mammogram. A repeat ultrasound-guided biopsy was performed followed by a specimen radiograph confirming retrieval of calcifications. Final pathology was malignant. If calcifications cannot be confidently sampled with ultrasound-guidance, a stereotactic-guided biopsy, when possible, should be utilized.

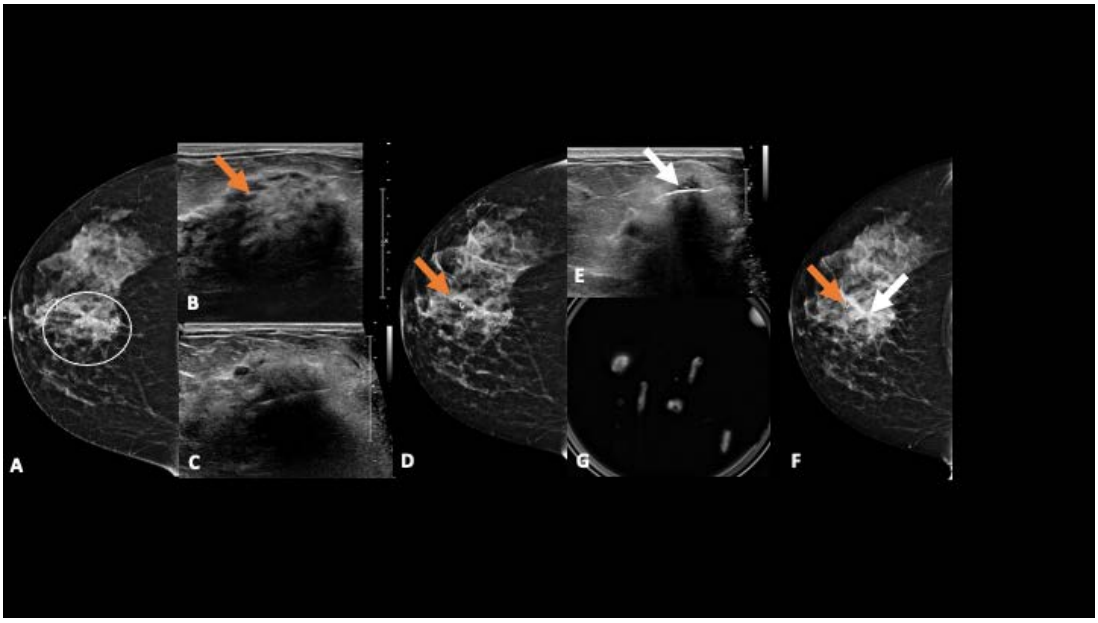

Figure 4. a–g. Importance of specimen radiograph. A 49-year-old female presented with a palpable concern. a. Right mediolateral oblique view shows focal asymmetry with fine linear-branching calcifications (white circle). b. Ultrasound image shows a mass with possible calcifications (orange arrow). c. Ultrasound-guided biopsy image shows sampling through hypoechoic mass. d. Post clip mammogram with U clip (orange arrow) anterior to the calcifications. No specimen radiograph was obtained. Initial biopsy: discordant benign pathology—stromal fibrosis and fibrocystic changes without calcifications. Repeat biopsy was performed. e. Repeat ultrasound-guided biopsy sampling through hypoechoic mass and calcifications (white arrow). f. Post clip mammogram shows eye clip (white arrow) in appropriate location within the calcifications. g. Specimen radiograph obtained after 5 core specimens show calcifications in all 5 specimens. Repeat biopsy: concordant malignant pathology—high grade ductal carcinoma in situ.

Progression and localization of MRI findings on post-biopsy follow-up

To avoid the delayed cancer diagnosis from false negatives of the core needle breast biopsies, some radiologists have found post-biopsy follow-up to be helpful, even for concordant benign diagnoses. False

negative biopsy rate is often higher in the MRI guided biopsy than in the ultrasound guided biopsy due to uncertain lesion localization and lack of real time image guidance. Second look ultrasound is typically used to find a sonographic correlate for suspicious MRI findings to allow for an ultrasound-guided core needle biopsy.[14,15] However, it does not come without challenges. It is important to know how various lesions may present on both MRI and US and to also use the largest number of anatomical landmarks or other findings such as cysts when correlating between the two modalities. Furthermore, it is important to take into consideration the differences in positioning between MRI and US as in US, the patient is either in a supine or supine oblique position and for MRI the patient is prone. A US correlate is more likely to be found for larger masses or if it is an invasive cancer as opposed to smaller lesions or non-mass enhancement.[15] Clip confirmation is also important following a US-guided biopsy as clips can be displaced or end up in a completely wrong position because a wrong lesion has been targeted. Standard practice is to obtain a post biopsy mammogram to confirm clip placement. A T1-wieghted gradient echo sequence could also be obtained to confirm the biopsy clip location. If the MRI lesion of interest is a large area of enhancement but the sonographic correlate is much smaller, that needs to be taken into consideration if needle localization will be performed for lumpectomy.

It will be important to localize the clip in relationship to the entire extent of disease involvement. Recent studies,[16,17] have showed that there is up to 4% false negative rate for benign MRI biopsy with concordant radiology-pathology correlation. Thus, patients with benign biopsy may be recommended for imaging follow-up to confirm the stability of biopsied imaging findings. Patient compliance with follow-up is essential to minimize further delay,[5] especially in patients who are at high risk for developing breast cancer and require close monitoring for the biopsy proven benign lesions. Figure 5 shows the importance of close, short-term surveillance following a benign MRI biopsy in a high-risk patient. In this case, a cancer was missed on the initial biopsy and the cancer had progressed significantly when the patient missed the follow-up.

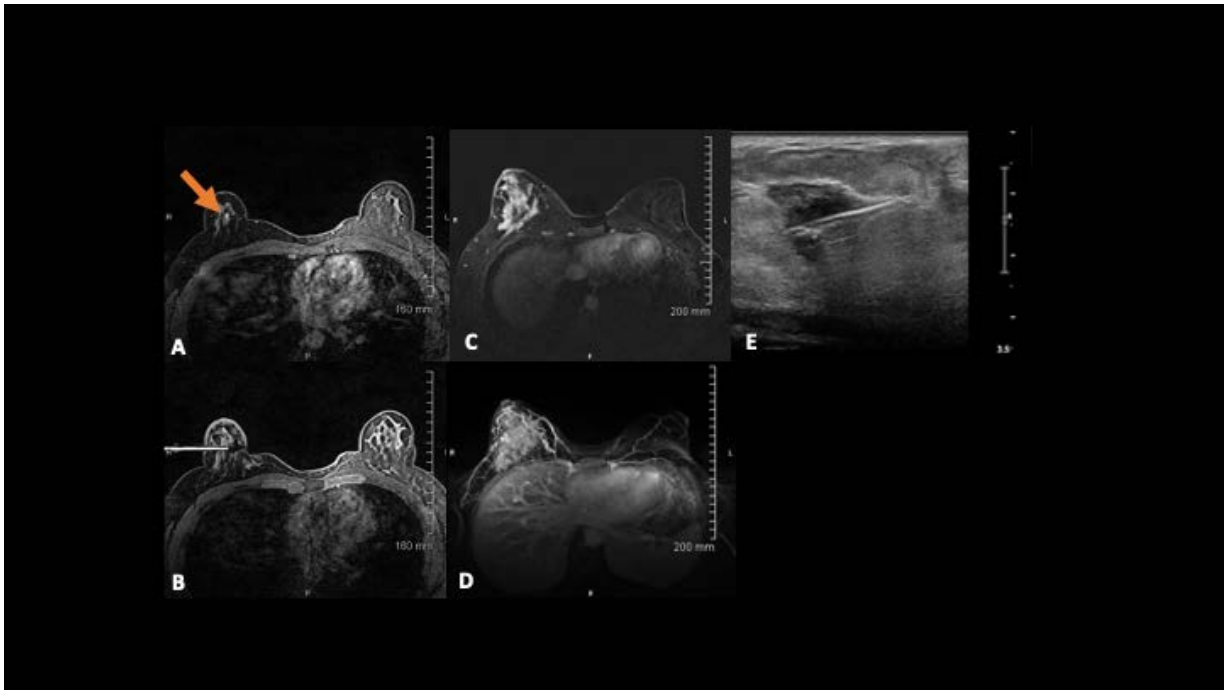

Figure 5. a–e. Delayed cancer diagnosis due to failure in follow-up of a false negative MRI biopsy. A 35-year-old female with positive breast cancer gene (BRCA1). **a.** Screening MRI axial post contrast subtraction imaging shows a 9mm irregular mass with delayed washout curve at 12:00 of right breast, 3cm from the nipple. **b.** MRI biopsy was performed. Initial biopsy: concordant benign pathology—non-proliferative fibrocystic changes with dense fibrosis. Follow-up MRI 14 months later (patient had difficulty scheduling MRI due to insurance issues). **c, d.** Axial post contrast subtraction and maximum intensity projection images show large volume diffuse non-mass enhancement measuring 69mm, occupying the entire right breast. **e.** Ultrasound biopsy was performed. Repeat biopsy: concordant malignant pathology—Infiltrating poorly differentiated grade 3 ductal carcinoma.

CONCLUSION

Repeat breast core needle biopsies occur due to multiple radiological or pathological issues. While some repeat biopsies are inevitable, most can be avoided by careful pre-procedure planning, improvement of biopsy techniques, post procedure imaging, and adequate radiology-pathology correlation. It is imperative for multidisciplinary breast care team to recognize reasons for the need for a repeat breast biopsy to avoid false negative or delayed diagnosis of breast cancer. The performing radiologist's experience and knowledge are very important in increasing initial biopsy success rate by providing appropriate planning and optimized biopsy techniques. With multidisciplinary approach and careful review of the repeated breast core needle biopsy, we can not only improve to the chances of having an accurate diagnosis in a timely fashion, but also help reduce patient's anxiety and the unnecessary cost of a potentially avoidable additional biopsy or medical procedure.

ACKNOWLEDGEMENTS

None.

CONFLICT OF INTEREST

None.

FUNDING

This work did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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How to Cite This Article

Wang X, Shikoh F, Clark A, Hanaoka M. Avoidable and Unavoidable Repeat Breast Core Needle Biopsies. Arch Breast Cancer. 2022; 9(1):32-39.
Available from: https://www.archbreastcancer.com/index.php/abc/article/view/458