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Reprint of: Breast tissue markers: Why? What's out there? How do I choose?☆

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ABSTRACT

Tissue marker placement after image-guided breast biopsy has become a routine component of clinical practice. Marker placement distinguishes multiple biopsied lesions within the same breast, prevents re-biopsy of benign lesions, enables multi-modality correlation, guides pre-operative localization and helps confirm surgical target removal. Numerous breast tissue markers are currently available, with varied shapes, composition, and associated bio-absorbable components. This review serves to familiarize the breast interventionalist with the tissue markers most widely available in the United States today and to provide guidance regarding selection of appropriate markers for various clinical settings.

1. Introduction

Image detection of non-palpable breast lesions has fueled the development of image-guided biopsy and localization. Minimally invasive image-guided breast core biopsy allows for a reliable pathologic diagnosis and, in clinical practice, has nearly replaced surgical excision for initial tissue evaluation [1]. Because > 60% of core breast biopsies yield a benign diagnosis, this change in practice has spared the vast majority of patients with indeterminate breast lesions the need for surgery, thereby reducing complication rates and decreasing cost while providing a comparable sensitivity and specificity to surgical excisional biopsy [2–4]. Moreover, in addition to yielding a quality specimen with maintenance of tissue architecture, biologic features of malignancies, such as receptor status, may also be obtained from a core biopsy specimen.

As clinical practices have shifted toward image-guided biopsy, tissue marker placement to identify the biopsy site has become a vital component of the procedure. Initially, tissue marker placement was reserved for cases where the target was no longer visible following biopsy [5]. Its widespread use today has stemmed from our improved ability to reliably sample smaller lesions in combination with the development of larger gauge biopsy devices which may obscure or entirely remove the visible component of the target. Furthermore, tissue marker placement has proven extremely useful in assessing extent of disease when more than one site is biopsied, allowing for correlation between modalities, preventing repeat biopsies of benign lesions, and allowing for accurate localization following neoadjuvant chemotherapy [6, 7]. Because they are easily identified on specimen radiographs, tissue markers allow for rapid confirmation of correct target excision at the time of surgery and can guide pathologists to the area of interest within a mastectomy specimen [8].

With numerous tissue markers currently available, choosing a marker can be a confusing task. Markers vary in their intrinsic composition, their shape, and their associated bio-absorbable components. Furthermore, the visibility of tissue markers on different imaging modalities may significantly influence marker selection. By understanding the unique characteristics of tissue markers, the radiologist will be better equipped to select an appropriate marker for a given patient and clinical scenario.

This manuscript will discuss the purpose of clip placement, present unique features of biopsy clips with specific attention to the most common commercially available tissue markers, and describe modality-specific visibility. This paper will also explore issues related to patient consent, clip migration, and clips in the axilla. Finally, a summary of the factors one ought to consider when selecting a specific marker will be presented. In this manuscript the words “biopsy clip” and “tissue marker” will be used interchangeably.

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2. The purpose of clip placement

2.1. Surgical localization

Tissue marker placement allows for reliable re-identification and accurate localization of biopsied lesions [9, 10]. Before the use of clips, if results from a needle biopsy warranted surgical excision, the targeted lesion was localized by identifying residual disease on imaging, localizing a post-biopsy hematoma, or by using surrounding landmarks in the breast tissue. This method led to the excision of larger surgical specimens in order to increase the likelihood of successfully excising the target. Despite these larger specimens, this approach resulted in a higher rate of positive margins than that found with minimally invasive breast biopsy combined with clip placement [11].

2.2. Inter-modality correlation

The biopsy clip serves a critical role in correlating findings between imaging modalities. It is common for abnormalities detected on mammography or MRI to undergo further workup with targeted ultrasound. Ultrasound guided breast biopsy is the preferred approach for lesion sampling, as it is more comfortable for the patient, a quicker procedure for the physician, performed with real-time imaging and is more cost effective than stereotactic, MRI or molecular imaging guided biopsies [12]. However, whenever a suspicious lesion is identified with one modality and another modality is used for biopsy, there is a possibility that the sampled lesion does not correspond to the originally identified suspicious target. Therefore, placement of a biopsy clip with post-biopsy imaging is essential for accurate correlation between modalities and to confirm that the initial finding was indeed sampled. Further evaluation or additional biopsy may be necessary if the findings do not correspond with the original area of suspicion.

Fig. 1(a–d) illustrates the importance of a biopsy clip to confirm multi-modality correlation. A developing asymmetry detected on screening mammography at the interface of the glandular tissue and retroglandular fat was worked up with diagnostic mammogram and ultrasound. A probable sonographic correlate was identified and targeted for biopsy. The post-biopsy mammogram demonstrated the clip within glandular tissue inferior and anterior to the developing asymmetry, which prompted repeat imaging. A second ultrasound demonstrated a suspicious mass which was thought to correspond to the developing asymmetry. This was biopsied and yielded invasive ductal carcinoma. Tissue marker location on the post-biopsy mammogram confirmed that the second mass did in fact correspond to the mammographic asymmetry.

Clip placement is particularly important for inter-modality correlation when a second look ultrasound for a suspicious MRI-detected lesion results in ultrasound-guided biopsy of a presumed sonographic correlate [13]. Meissnitzer et al. found that on follow-up MRI imaging, of 80 MRI detected lesions biopsied under ultrasound guidance and found to be benign, 10 (12.5%) of the ultrasound lesions did not correspond to the original MRI finding [14]. A limited sequence non-contrast MRI can be performed following biopsy to ensure correlation and obviate a potential delay in diagnosis should a discrepancy be identified between tissue marker location and the MRI finding.

Fig. 2(a–c) demonstrates an oval enhancing mass located approximately 1 cm posterior and superior to a known 3 cm malignancy, thought to represent a satellite lesion versus a metastatic lymph node. On second-look ultrasound, an oval hypoechoic mass was found at the 11:00 axis and thought to correlate with the MRI finding. Ultrasound guided core biopsy was performed with biopsy clip placement. Subsequent MRI demonstrates a focus of metallic susceptibility artifact at the edge of the index tumor and not within the questioned satellite lesion, indicating that the ultrasound finding was not the correct correlate.

2.3. Extent of disease assessment

When multiple lesions are found in a single breast in a patient with a known cancer, placement of uniquely shaped tissue markers at each site allows for assessment of extent of disease and differentiation between benign and malignant sites. This facilitates surgical planning and treatment decisions. Furthermore, when MRI is performed in patients with newly diagnosed breast cancer, the location of signal void from the tissue marker can help in evaluation of extent of disease and guide further workup.

Fig. 3(a–b) demonstrates suspicious calcifications spanning 3 cm in the lateral right breast targeted for stereotactic biopsy and found to be DCIS. On MRI, there is 7 cm of suspicious non-mass enhancement compatible with non-calcified DCIS. The focus of susceptibility artifact from the clip is located at the posterior aspect of the disease, important information for surgical planning. This prompted MRI-guided biopsy of the anterior most portion of enhancement to demonstrate extent of disease.

2.4. Neoadjuvant chemotherapy

In the setting of neoadjuvant chemotherapy, tumors may significantly decrease in size and may become occult on imaging. In patients who opt for breast conservation therapy, the clip placed at time of initial biopsy may serve as the only reliable landmark for pre-operative localization [15, 16].

Fig. 4is an example of a palpable invasive ductal carcinoma in the upper outer quadrant metastatic to the axilla. The patient underwent neoadjuvant chemotherapy with a complete imaging response. No residual mass was visible on mammography or ultrasound. The clip however was readily visible under both modalities and was targeted for pre-operative localization under ultrasound guidance.

2.5. Obviate repeat benign biopsies

After benign biopsies, the presence of a clip on follow up imaging can obviate unnecessary evaluation and biopsy. This is particularly useful in patients who transfer care between different facilities without transferring all of their relevant records.

3. Tissue markers: what is available?

Tissue markers are categorized by their intrinsic composition, shape, material associated with the radiopaque portion of the clip, and their compatibility with biopsy devices. Desired features include long-term visibility on ultrasound, reliable visibility on MRI, easy deployment and resistance to displacement. The number of commercially available markers is a reflection that there is no perfect clip; rather, there are often several equally appropriate options for a given patient and clinical scenario. For the purpose of this review, we have focused our discussion on the FDA-approved markers in the United States distributed by Hologic®, Mammotome®, Bard® (Becton, Dickinson and Company) and Mermaid Medical®. Please note that this review is not meant to serve as a substitute for manufacturer recommendations and device specifications.

3.1. Names and shapes

Tissue markers are available in a variety of shapes, each uniquely named by the manufacturer and distributor. The shape names can be found on the distributor's website but are not always clearly listed on the packaging of the individual clip. Examples of clip names include *top hat*, *ribbon*, *and butterfly*. Fig. 5 depicts the various clips distributed by Hologic, Mammotome, Bard and Mermaid Medical and their designated names. Using the official names of tissue markers is important for uniform reporting and to avoid confusion when correlating a clip with

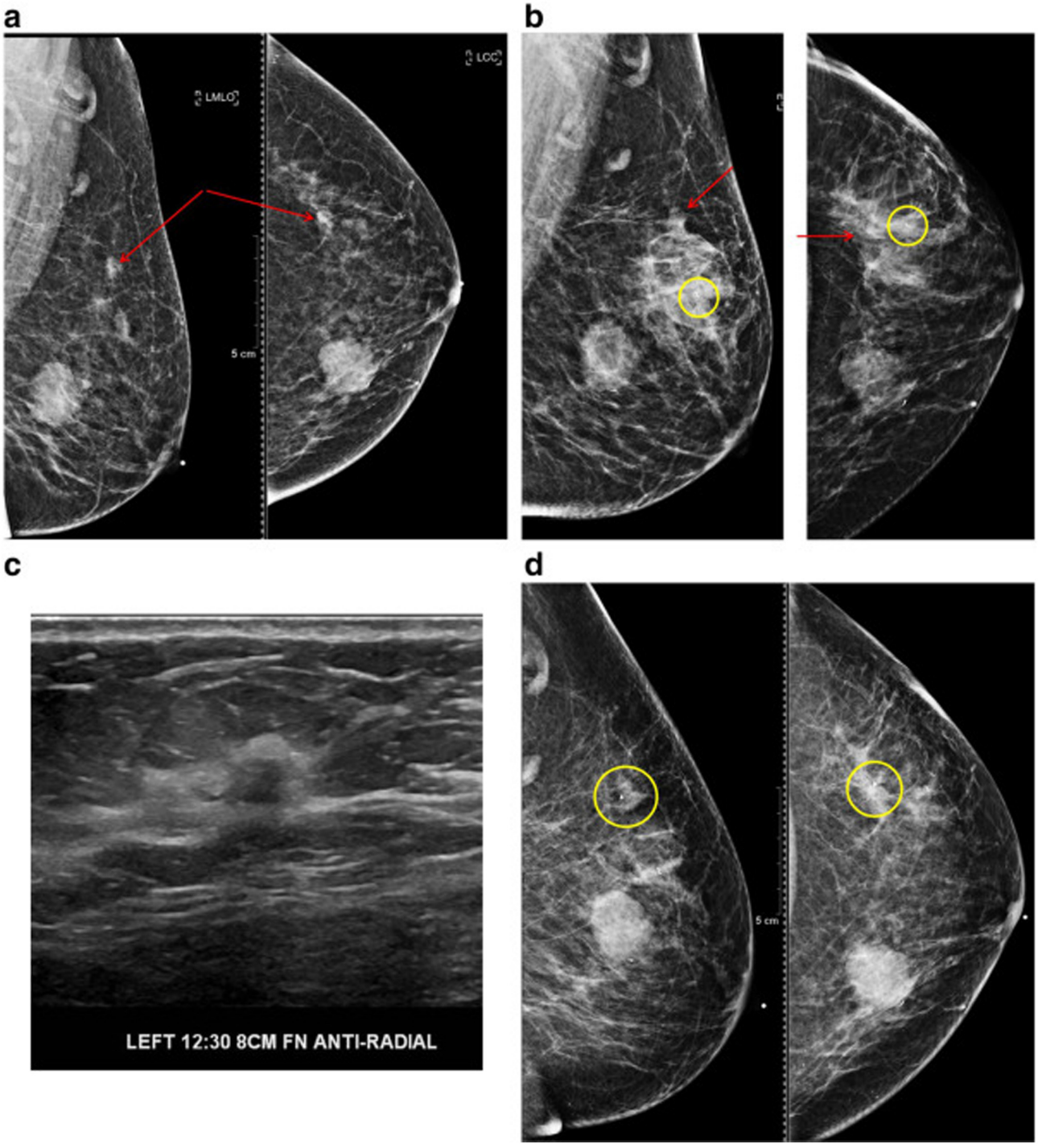

Fig. 1. a. Developing asymmetry identified on screening mammogram in the upper outer left breast at the interface between the glandular tissue and retroglandular fat.
b. Post-biopsy mammogram following biopsy of the mass thought to be the sonographic correlate. The S-shaped tissue marker (yellow circle) does not correspond to the location of the originally detected focal asymmetry (red arrow). Pathology results from this biopsy yielded fibroadenoma with microscopic foci of atypical ductal hyperplasia.
c. Second targeted ultrasound demonstrates a suspicious mass at the 12:30 axis, 8 cm from the nipple thought to be a better correlate for the mammographic finding.
d. Following biopsy of the mass at the 12:30 axis, mammogram demonstrates a top hat shaped clip within the developing asymmetry. Pathology yielded invasive ductal carcinoma with DCIS. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

its associated pathology, particularly at the time of pre-surgical localization in a breast with multiple markers.

It is important to be aware of markers with similar names and those with similar shapes. For instance, the “open coil” clip from Mammotome and “coil” clip from Bard have similar names, but distinct shapes. The “open coil” clip from Mammotome and the “spring” clip from Bard look almost identical, as do the “Q” clip from Hologic and the “ring” clip from Bard. The “mini cork” and “cork” clips from Hologic share similar names and shapes, and are primarily differentiated based on relative size: 2 mm versus 3 mm. Fig. 6 demonstrates several of these

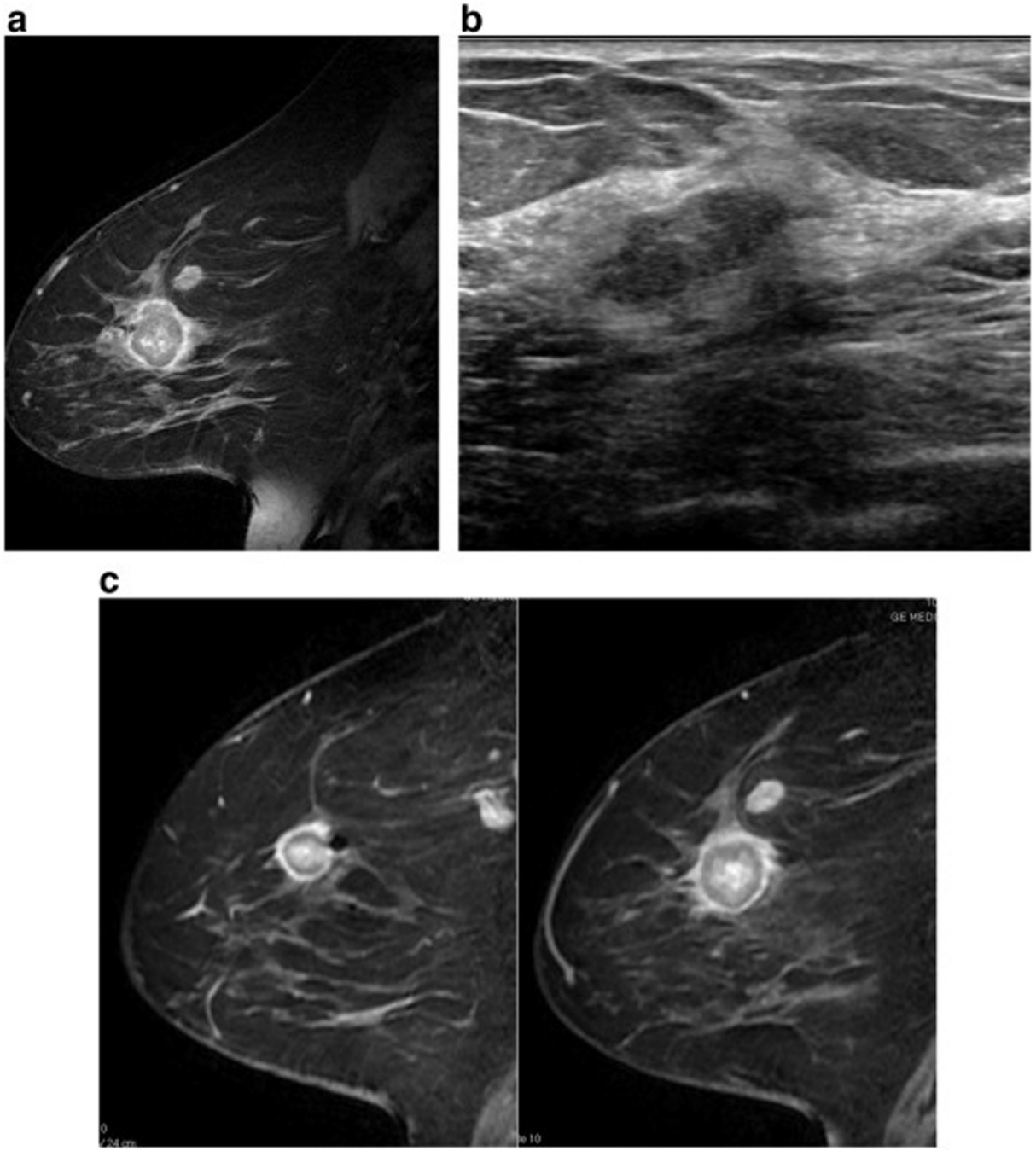

Fig. 2. a. MRI performed to evaluate for extent of disease in this patient with a known 3 cm invasive ductal carcinoma demonstrates a 1 cm oval circumscribed mass thought to represent a satellite lesion versus a metastatic intramammary lymph node.
b. A second-look ultrasound was performed to identify the mass with intent to biopsy. Ultrasound demonstrates an oval hypoechoic mass with indistinct margins felt to represent the mass.
c. An ultrasound guided biopsy was performed with placement of a biopsy clip. Sagittal images from a post-procedure MRI demonstrates the clip within the edge of the index tumor but no clip in the suspected satellite lesion confirming that the incorrect mass was sampled by ultrasound.

"look alike" and "sound alike" tissue markers. By avoiding placement of markers with similar names or similar shapes in a single breast, one can reduce the risk of incorrect localization at time of surgery.

3.2. Intrinsic composition

Another factor that differentiates the many clips is their intrinsic composition; that is, the material out of which they are made. Titanium and stainless steel are the most commonly used materials. Other clips are made of metal alloys (BioDur™ 108, Inconel™ 625, and Nitinol) and non-metal alternatives (carbon coated ceramic).

Titanium is a low density, high strength, corrosion resistant inert metal. It is extremely biocompatible, with the ability to integrate into human bone, making it the metal of choice for most orthopedic and dental procedures. Titanium is ubiquitous, present in sunscreen, cosmetics, toothpaste, and foods [17, 18]. Because titanium does not contain nickel, and since most metal allergies are attributable to nickel, it may be safely used in patients reporting multiple allergies or metal sensitivities [17]. Titanium markers include the cork, mini cork, hourglass and top hat markers from Hologic, open coil, butterfly,

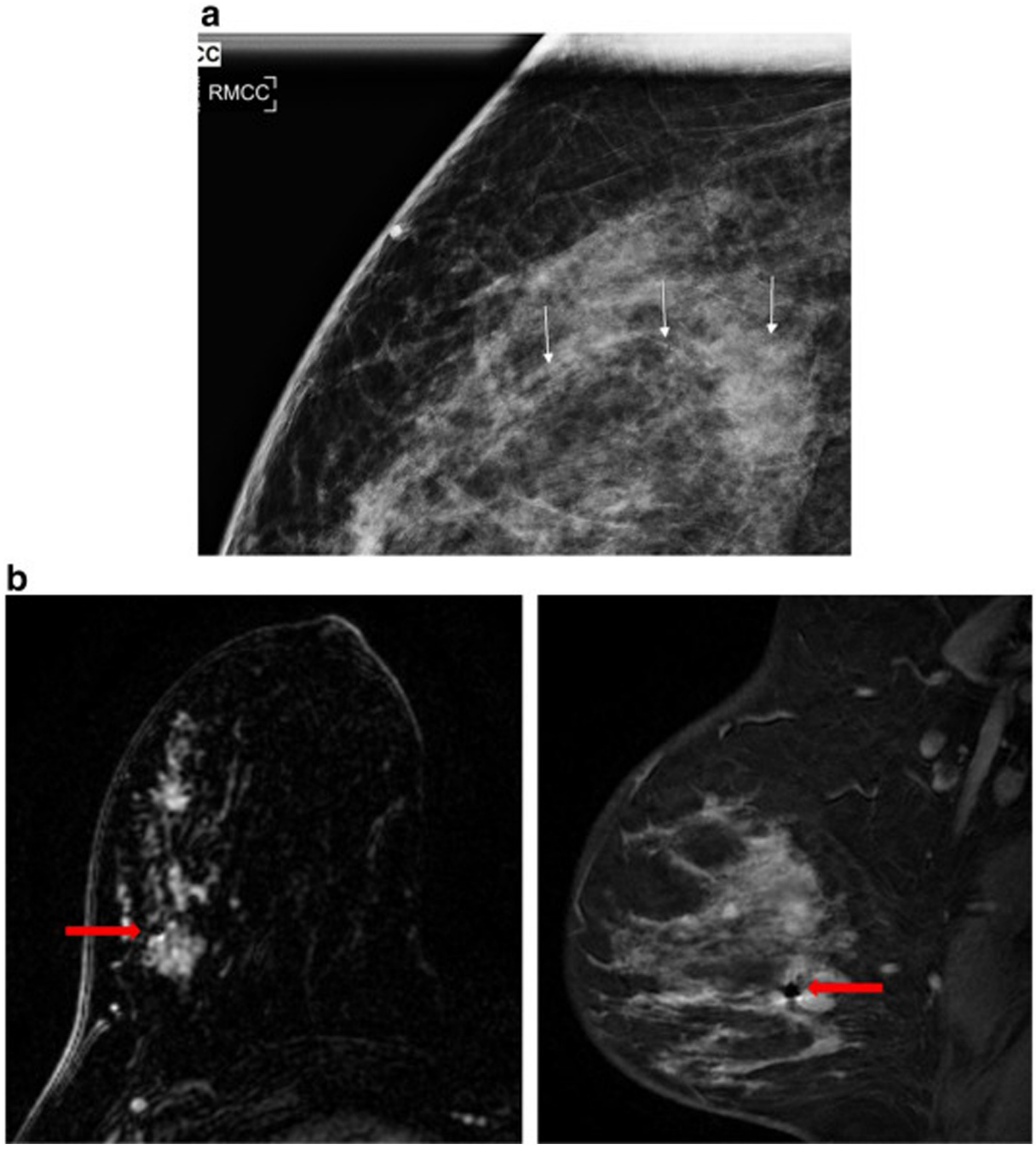

Fig. 3. a. Magnification view of the right breast demonstrates suspicious calcifications in a linear distribution spanning approximately 3 cm. Stereotactic biopsy yielded ductal carcinoma in-situ.
b. Breast MRI performed to evaluate for extent of disease demonstrates 7 cm of suspicious nonmass enhancement. The enhancement is more extensive than expected, suggesting mammographically occult disease. Susceptibility artifact from the biopsy clip at the site of stereotactic biopsy is within the posterior aspect of the nonmass enhancement (red arrow). Subsequent MRI-guided biopsy of the most anterior portion of the enhancement was performed and yielded DCIS. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

barrel, bowtie, U-shape, and triple twist clips from Mammotome, and the ribbon, heart, S, O, and X shaped clips from Bard.

Nickel containing materials (Table 1) include stainless steel, Inconel, BioDur, and Nitinol. Medical grade stainless steel (types 316 and 316 L) is a metal alloy with a nickel content ranging from 10 to 14% [19]. The stoplight, buckle, and infinity shape clips from Hologic are made of stainless steel, as are the open coil, butterfly, barrel, and anchor clips from Mammotome, and the omega, spring, V, and M shaped clips from Bard. It should be noted that the open coil, barrel, and butterfly (all part of the HydroMARK® family of clips from Mammotome) are available in both titanium and stainless steel. BioDur is a metal alloy with similar properties to stainless steel, but with almost no nickel (< 0.05%) [20]. The coil and venus shape clips from Bard are the only clips from the four manufacturers composed of BioDur. Inconel is a nickel-based metal alloy. Of the clips reviewed in this article, the wing shaped tissue marker from Bard is the only clip made from Inconel.

Nitinol is a super-elastic metal alloy composed of nickel and titanium in approximately equal proportions. Because of its super-elasticity and its biocompatibility, Nitinol has been used for vascular stents, heart

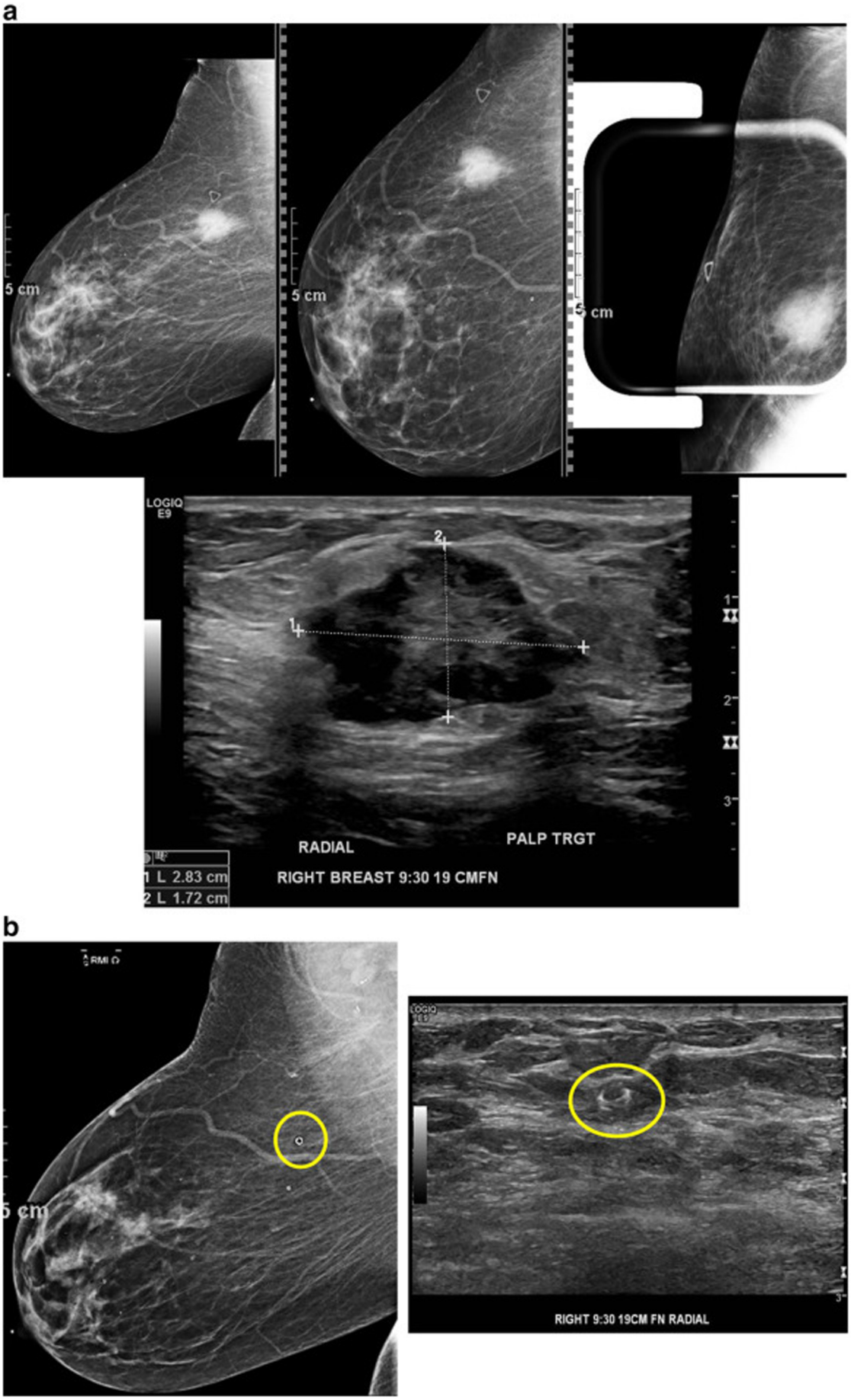

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Fig. 4. a. Palpable mass in the upper outer right breast on mammography with corresponding 2.8 cm irregular heterogeneous mass with angular margins on ultrasound. This was biopsied with ultrasound guidance and yielded invasive ductal carcinoma.
b. The patient underwent neoadjuvant chemotherapy with an excellent response. The mass was no longer visible on mammography or ultrasound. The ring shaped clip remained visible under both modalities and was targeted for pre-operative localization under ultrasound guidance.

valve devices, septal defect devices and bone anchors [21]. In the breast, Nitinol clips assume a unique shape once deployed, which is often easily visible with ultrasound. Fig. 4b demonstrates a Nitinol ring shape clip on ultrasound. The size of the available Nitinol clips tends to be larger, ranging from 3 to 7 mm versus 2–3 mm for other clips. Nitinol clips include the Tumark® Vision, X, Q, and Flex clips from Hologic and the UltraCor® Twirl® ring clip from Bard.

Mammotome's MammoSTAR® and BiomarC® clips are composed of carbon coated ceramic, a material developed as a non-metal "all natural" alternative to allay concerns some patients have about metallic or "artificial" implants. The MammoSTAR® markers are embedded in beta-glucan while the BiomarC® variety are deployed as bare clips. These clips are available in barbell and tribell shapes.

The Beacon™ and Cassi® Star tissue markers from Mermaid Medical are primarily composed of polyetherketoneketone (PEKK), a biocompatible polymer which is used in surgical implants and dental devices [22]. According to the manufacturer PEKK allows for permanent ultrasound visibility, and interspersed barium sulfate allows for mammographic visibility.

Non-metal clips result in reduced artifact on both MRI and tomosynthesis. Metal clips cause an artifact on tomosynthesis images that can obscure subtle findings in the adjacent tissue (Fig. 7a–c). Companies are working on altering the reconstruction algorithm for tomosynthesis in order to decrease the metallic artifact [23].

3.3. Bare tissue markers

Tissue markers are available in two variants: the clip alone ("bare" clip) or the clip in association with bio-absorbable materials developed to enhance ultrasound visibility, improve hemostasis, and reduce migration. For small lesions and for superficial lesions, a bare clip may be preferable due to its smaller size. Table 2 lists the bare clips available from the four manufacturers. With the exception of the more recently developed Nitinol clips, the carbon coated BiomarC® clips, and the markers composed of PEKK polymers, bare clips tend to have limited visibility on ultrasound.

3.4. Associated materials

Tissue markers deployed with bio-absorbable synthetic polymers were developed to improve ultrasound visibility and reduce clip migration. Hologic's SecurMark® line of clips are embedded in a bio-absorbable suture netting which remains visible on ultrasound for at least 3–4 weeks post biopsy (Fig. 8a and 9). The netting appears as a liner echogenic structure that is approximately 1.5 cm in length with the permanent 2–3 mm metallic marker embedded in the middle of the netting. Fig. 9 demonstrates an oval hypoechoic mass that was found to be a papilloma at core needle biopsy. The patient presented for localization six weeks later at which time the liner echogenic netting was still well seen, and ultrasound guided localization was easily and accurately performed.

Bard has several lines of clips deployed with bioabsorbable pellets and pads made of polylactic acid (PLA) and polyglycolic acid (PGA). The manufacturer reports ultrasound visibility for 3–6 weeks with the pellets and pads fully resorbed by 12 weeks. One caveat when using the Bard markers deployed with pellets is to be cognizant of the number of pellets and the position of the marker relative to those pellets. For Bard markers with 10 pellets, the marker occupies the middle position. For Bard markers with 4 pellets, the marker occupies the distal position; that is, it is the first component to be deployed followed by the 4 pellets. In the case of the bioabsorbable pads, the clip is embedded in the middle position of the middle pad (Fig. 8b–c).

Bard also offers clips with interwoven polyvinyl alcohol (PVA) polymer deployed with bio-absorbable polyglycolic acid pads. According to the manufacturer, the PVA polymer interwoven into the clip is supposed to allow for permanent ultrasound visibility. In practice, however, this clip has performed poorly in studies evaluating long term sonographic visibility of breast tissue markers [24, 25].

Bard's StarchMark® and StarchMark® UltraCor® clips consist of a stainless steel clip deployed with 4–6 starch pellets (Fig. 8d), which are sonographically visible for approximately 2 weeks. Starch has been shown to enhance hemostasis [26]. The tissue marker is located in the middle position in both the 4 pellet and 6 pellet varieties.

Mammotome offers a line of titanium clips embedded in collagen, the MammoMARK® and CorMARK® clips (Fig. 8e). The collagen expands 300% within 1 min of deployment by absorbing fluid. This clip is designed to reduce migration and aid with hemostasis. The clip is easily visible with ultrasound at deployment, with decreasing visibility over time [27]. Ultrasound visibility typically lasts 3–4 weeks.

The HydroMARK® line of breast tissue markers, also manufactured by Mammotome, offers options for a titanium or stainless steel clip embedded in hydrogel (Fig. 8f). On ultrasound, at the time of deployment, the clip is visualized as a linear hyperechoic structure with posterior acoustic shadowing. Within 24 h, the hydrogel absorbs water and the clip is visualized as a nearly anechoic circumscribed mass with a central hyperechoic component corresponding to the metal clip. Ultrasound visibility has been documented at 12–15 months post deployment. Fig. 10(a–b) demonstrates a HydroMARK® clip upon deployment and on reimaging 11 months later.

Finally, Mammotome also offers the MammoSTAR® clip composed of a carbon coated ceramic clip embedded in beta-glucan (Fig. 8g). Beta glucan is a non-animal derived sugar which expands after deployment by absorbing fluid. Case reports on the manufacturer's website document ultrasound visibility at 6–7 months.

Table 3 lists these various associated materials in order of their reported duration of ultrasound visibility.

4. MRI visibility

The ability to visualize susceptibility artifact created by the tissue marker is essential in complete and accurate assessment of disease on MRI. In patients with known cancer, MRI can more accurately demonstrate extensive disease than mammography or ultrasound, and clip position within the disease is critical for surgical planning. The susceptibility artifact from the clip, seen as a signal void on MRI, should easily be seen in all planes, but the artifact should not be so large that it obscures assessment of the surrounding tissue. Visibility is influenced by three factors: mass, material and shape.

Clips made of stainless steel and BioDur 108 create the most susceptibility artifact. Titanium clips, the titanium alloys, i.e. Nitinol, and Inconel 625 result in intermediate artifact, while carbon coated ceramic clips and PEKK clips generate the least signal void artifact [28–30]. The varying degrees of susceptibility can be seen when reviewing breast MRIs in patients with multiple biopsy clips. Fig. 11 demonstrates a patient with three titanium clips and one BioDur coil clip in the upper outer quadrant. Based on the susceptibility artifact differences, the BioDur coil clip can be identified clearly and used as a point of reference.

Shape also plays an important role in MRI visibility. Our experience shows that the Hologic titanium clips (TriMark®, CeleroMark®,

a
Hologic®

Images courtesy of Hologic®

TITANIUM	STAINLESS STEEL	NITINOL
TOP HAT	BUCKLE	X
MINI CORK	INFINITY	Q
CORK	STOPLIGHT	VISION
HOURGLASS		FLEX

TriMark®/CeleroMark™ ("bare" marker): cork, hourglass
SecurMark® (in mesh basket, US visibility 3-4 weeks): top hat, mini cork, buckle, infinity, stoplight
Tumark® ("bare" marker): X, Q, Vision, Flex

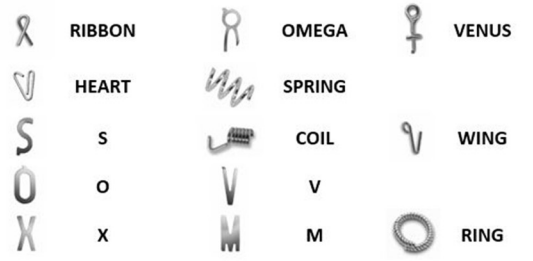
b
Mammotome®

Images courtesy of Mammotome®

TITANIUM	STAINLESS STEEL	CARBON CERAMIC
OPEN COIL§	OPEN COIL§	BARBELL
BUTTERFLY§	BUTTERFLY§	TRIBELL
BARREL§	BARREL§	
BOWTIE	ANCHOR	
U SHAPE		
TRIPLE TWIST		

HydroMARK® (embedded in hydrogel, long-term US visibility >12 months): open coil, butterfly, barrel
§These come in both titanium and stainless steel.
MammoMARK®/CorMARK® (embedded in collagen, US visibility 3-4 weeks): bowtie, U shape, triple twist
MammoSTAR® (embedded in beta glucan, US visibility 4-6 months): barbell, tribell
BiomarC® ("bare" marker): petite barbell, barbell, tribell
The petite barbell is same size as the MammoSTAR barbell, measuring 1 x 3 mm.
The BiomarC barbell measures 2 x 4 mm.
MicroMARK® ("bare" marker): anchor

c
Bard®



Images courtesy of Bard®

TITANIUM	STAINLESS STEEL	NITINOL	OTHER ALLOYS
RIBBON	OMEGA	RING	**BIODUR™108**
HEART	SPRING		COIL
S	V		VENUS
O	M		**INCONEL™625**
X			WING

ULTRACOR® (clip with 2 PEG plugs on either side): spring
ULTRACOR® TWIRL® ("bare" clip): ring
ULTRACLIP® ("bare" clip, ribbon shape with option for interwoven PVA): ribbon, wing, coil
ULTRACLIP® DUAL TRIGGER: (interwoven PVA): ribbon, wing, coil, heart, venus
GEL MARK ULTRACOR® (4 PLA/PGA pellets deployed along with clip in distal position): omega, S
GEL MARK ULTRA™ (10 PLA/PGA pellets deployed along with clip in middle position): omega, S
SENOMARK® ULTRACOR® (1 to 3 PGA pads with clip in middle, interwoven PVA): ribbon, coil, heart, venus
SENOMARK® ULTRA (3 PGA pads with clip in center of middle pad, interwoven PVA): ribbon, coil
SENOMARK® (3 PGA pads with clip in center of middle pad): omega, O, M, S, X
SENOMARK® ULTRACOR® MRI (3 PGA pads with clip in center of middle pad): M, X
STARCHMARK® ULTRACOR® (4 starch/polysaccharide pellets with clip in middle position): V
STARCHMARK® (6 starch/polysaccharide pellets with clip in middle position): V, omega

d
Mermaid Medical®

Images courtesy of Mermaid Medical®

Both of the above clips are made of polyetherketoneketone (PEKK) polymers interspersed with barium sulfate.

Fig. 5. Names and shapes of breast tissue markers as per manufacturers' websites.
a. Hologic® b. Mammotome® c. Bard® d. Mermaid Medical®.

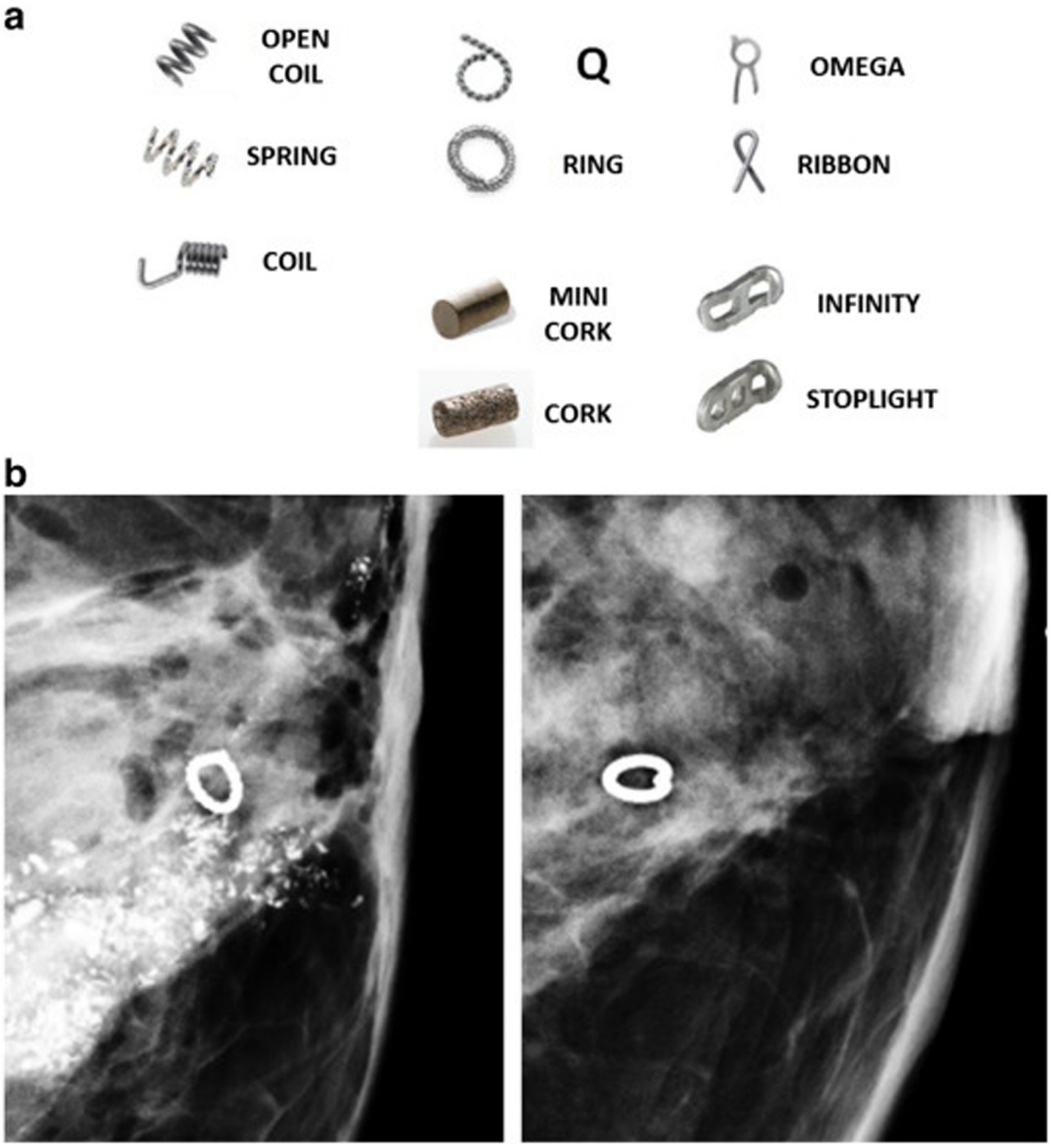


Fig. 6. a. Tissue markers with similar appearance and/or similar names.
b. Q clip on the left and ring clip on the right are nearly indistinguishable on mammography.

Table 1
Nickel containing materials.

No nickel	Yes nickel	No metal
Titanium	Stainless steel	Carbon ceramic
Carbon ceramic	BioDur™108[a]	
PEKK	Inconel™625[b]	
	Nitinol[c]	

[a] BioDur™108 is similar to stainless steel but has miniscule amounts of nickel (< 0.05% vs 10–14% in stainless steel).
[b] Inconel™625 is a nickel-based metal alloy (58% or more nickel).
[c] Nitinol is approximately 50% nickel + 50% titanium.

SecurMark® familes) are well seen on MRI while other titanium clips, such as the S-shaped clip (Bard), create a smaller artifact which may not be reliably visualized or may be visible in only one plane. This is likely attributable to the marker's shape, the amount of metal in the clip as well as clip size.

Fig. 12 demonstrates a patient with three different markers on mammogram. Sagittal post-contrast images on MRI demonstrate susceptibility from the titanium mini-cork and hourglass clips but no artifact from the titanium S-shaped clip. In Fig. 13, MRI performed for high risk surveillance demonstrates a suspicious enhancing mass in the superior left breast. Directed ultrasound demonstrated a hypoechoic mass thought to correlate with the MRI finding. Following biopsy and marker placement with an S-shaped clip, an abbreviated non-contrast MRI was performed to confirm the location of the clip. Susceptibility artifact from the S-shaped clip was not seen and therefore sonographic/

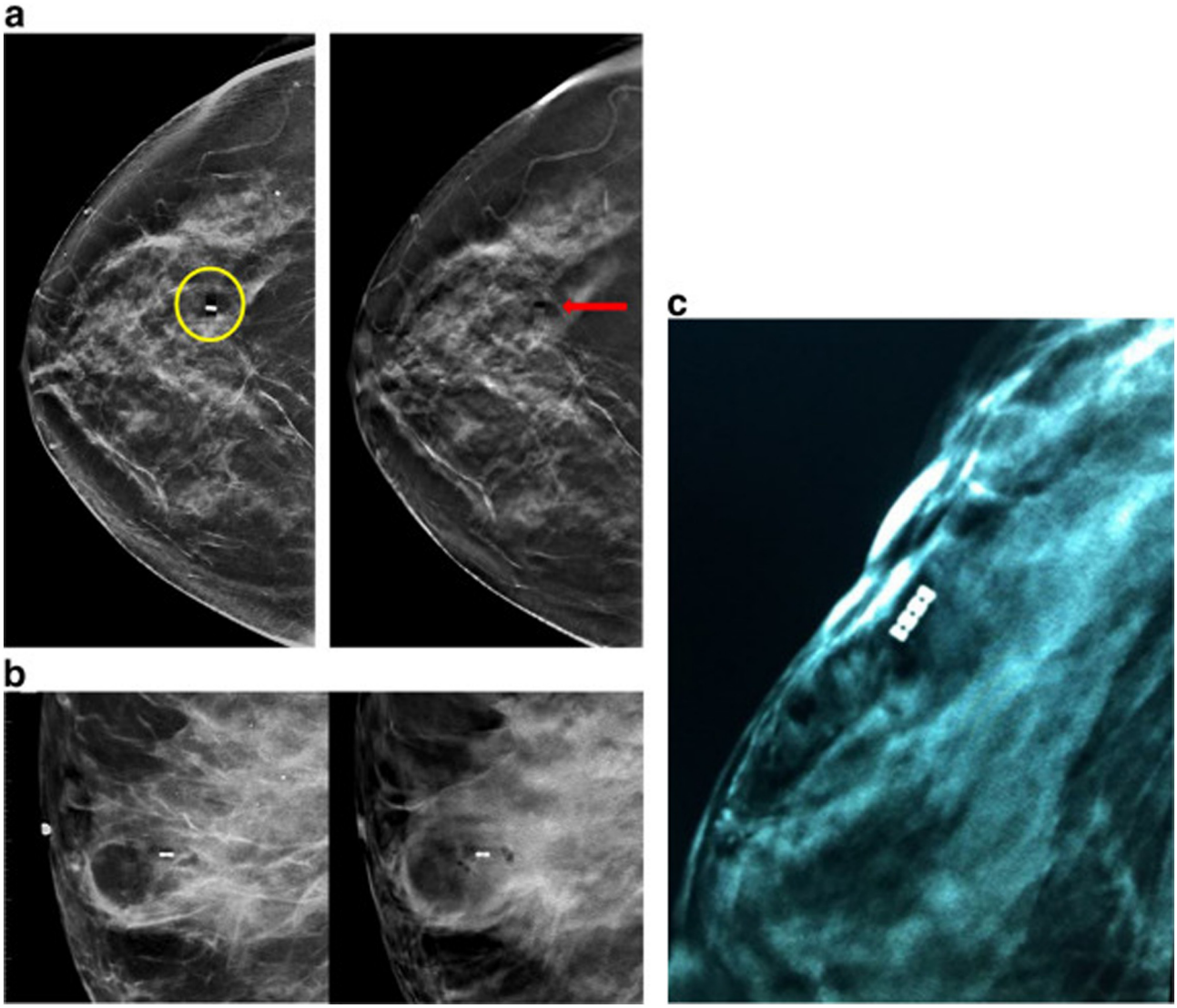


Fig. 7. a. A metallic cork shape biopsy marker demonstrates artifact on the C-view image (left, circle) as well an elongated artifact on tomosynthesis slices (right, arrow).
b. A non-metal MammoSTAR® clip demonstrates less prominent artifact on C-view (left) and tomosynthesis (right) images.
c. Tomosynthesis slice demonstrates minimal to no artifact from Cassi® Star clip made of PEKK with interspersed barium sulfate. (Image provided courtesy of Mermaid Medical.)

Table 2
Bare tissue markers.

Name	Manufacturer	Material
Anchor	Mammotome MicroMARK®	Stainless steel
Petite barbell	Mammotome BiomarC®	Carbon ceramic
Barbell	Mammotome BiomarC®	Carbon ceramic
Tribell	Mammotome BiomarC®	Carbon ceramic
Cork	Hologic TriMark®/ CeleroMark®	Titanium
Hourglass	Hologic TriMark®/ CeleroMark®	Titanium
Ribbon	Bard UltraClip®	Titanium
Ring	Bard UltraCor Twirl®	Nitinol
Q	Hologic Tumark®	Nitinol
Vision	Hologic Tumark®	Nitinol
X	Hologic Tumark®	Nitinol
Flex	Hologic Tumark®	Nitinol
Coil	Bard UltraClip®	BioDur™ 108
Wing	Bard UltraClip®	Inconel™ 625
Beacon™	Mermaid Medical	Polyetherketoneketone polymer
Cassi® Star	Mermaid Medical	Polyetherketoneketone polymer

MRI correlation could not be performed. The patient refused further sampling with MRI guided biopsy and a 6 month follow-up MRI was performed to evaluate for stability.

The titanium version of the HydroMARK® clip (Mammotome) has a unique appearance on MRI. Its susceptibility artifact is usually small and often not easily visible. However, due to its surrounding hydrogel which traps water, it is conspicuous on T2 fluid sensitive sequences and appears as an oval T2 bright oval mass with a central area of signal void from the metallic clip (Fig. 14).

5. Complications of clip placement

Although clip placement is a straightforward and safe component of image-guided biopsies, complications can arise including clip migration and extrusion, failed deployment and allergic reactions.

5.1. Clip migration/displacement

Clip migration is most commonly observed in biopsies performed under stereotactic guidance with displacement of the clip along the

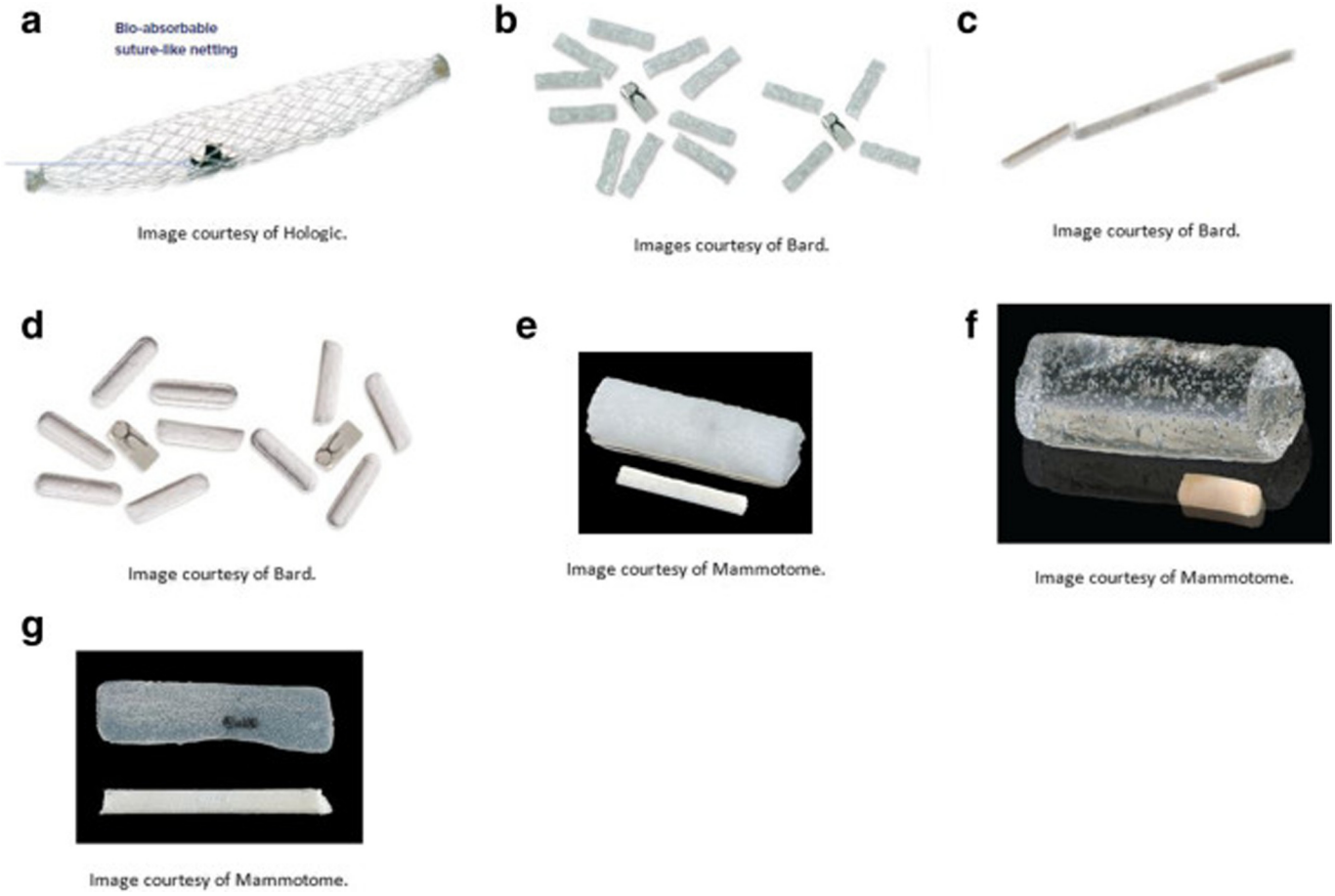


Fig. 8. Associated materials.
a. Hologic SecurMark® basket.
b. Bard PLA/PGA pellets (Gel Mark®). Note that the marker is located in the middle for the 10 pellet variety but is located distal in the 4 pellet variety.
c. Bard PGA pads (SenoMark®).
d. Bard polysaccharide pellets (StarchMark®). Marker located in the middle position for both the 6 pellet and 4 pellet versions.
e. Mammotome MammoMARK®/CorMARK® collagen.
f. Mammotome HydroMARK® hydrogel.
g. Mammotome MammoSTAR® beta glucan.

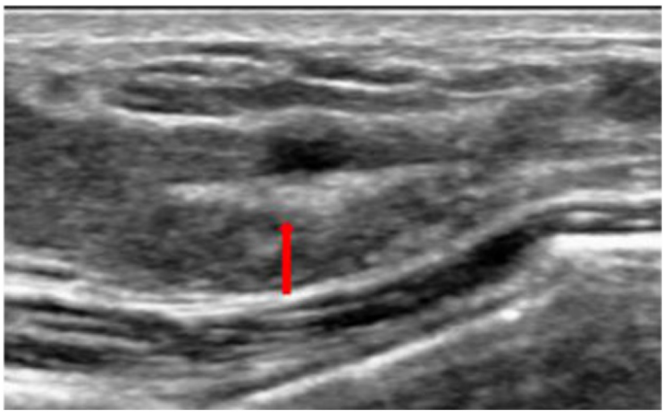


Fig. 9. A Hologic SecurMark® clip was placed at the time of biopsy of a hypoechoic mass which yielded papilloma. Six weeks later (arrow) the linear echogenic clip was still seen and the lesion was easily localized under ultrasound guidance.

biopsy tract in the "z" or compression axis. This is most often attributed to the "accordion effect," in which the clip moves as the breast is removed from compression [10, 31]. Since the clip does not immediately adhere to the biopsy cavity, it has the potential to move as the breast is decompressed, and this is more likely to occur when larger gauge needles are employed and multiple samples are obtained [6]. Careful comparison of pre and post biopsy mammograms is necessary to identify the direction and degree of migration so that a residual target and/or appropriate anatomic landmarks can be used to accurately localize the biopsy site in the setting of clip migration. The amount and direction of migration should be documented in the biopsy report to facilitate subsequent pre-operative needle localization, should the lesion require excision. In the event of clip migration, localization should target the lesion of interest and not the clip.

In addition to immediate clip migration along the biopsy tract, delayed clip migration has been reported weeks to months following biopsy [32, 33]. Migration may occur along the biopsy tract or through the fatty tissue of the breast. At our institution, a patient presented with pain, redness and a "bump" at the skin entrance site 2 weeks after a stereotactic biopsy. Targeted ultrasound of this location was performed and demonstrated skin thickening with an echogenic focus thought to represent the clip within the dermis. Local surgical resection of this area was performed due to the patient's symptoms and confirmed the presence of the clip which had migrated 3 cm from its position at the time of post-biopsy mammogram. A similar case was reported in the literature in 2004 [34].

A displaced clip can also occur due to hematoma formation or

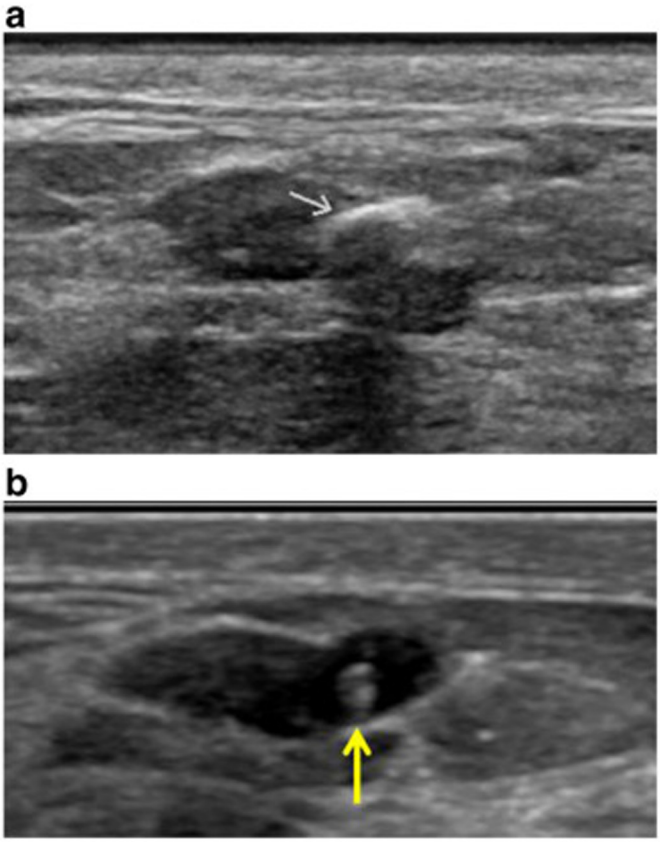


Fig. 10. a. Ultrasound of a HydroMARK® clip at time of deployment visualized as a linear echogenic structure.
b. Ultrasound of HydroMARK® clip 11 months after deployment visualized as a nearly anechoic oval mass (hydrogel) with the echogenic marker within it.

Table 3
Length of visibility of associated bio-absorbable materials.

Material	Time visible
Polysaccharide (StarchMark®)	2 weeks
Bioabsorbable suture netting (SecurMark®)	3–6 weeks
Bioplastics (Gel Mark®, SenoMark®)	
Collagen (MammoMARK®/CorMARK®)	
Beta Glucan (MammoSTAR®)	7 months
Hydrogel (HydroMARK®)	12–15 months

excess air at the biopsy site. This is most common with stereotactic and MRI-guided procedures which tend to use larger gauge needles. When a hematoma forms immediately after samples are obtained, the clip can float freely within the biopsy cavity. Application of vacuum suction prior to clip placement collapses the biopsy cavity, reducing the amount of air and blood, and decreases the chance of clip migration [35]. It is important to note that apparent clip displacement on post-biopsy mammogram can significantly improve as blood and air are reabsorbed. If this is suspected, a mammogram prior to localization should be performed to reassess the position of the clip in relation to the biopsy site.

Non-visualization of the clip on post-biopsy mammogram is another potential complication and may be due to failed deployment or extrusion of the clip out of the breast. Extrusion of the clip usually occurs when the biopsy site is located superficially and/or when there is excessive bleeding, particularly when manual compression is applied for hemostasis. At our institutions, when the clip is not seen on post-biopsy mammogram, the patient is transferred to the ultrasound suite for ultrasound guided placement of a clip into the biopsy cavity identified by air and blood, followed by repeat mammographic imaging, as this is a reliable and accurate method for re-marking the biopsy site.

5.2. Extrusion or displacement of clip during surgical excision

Movement of a breast biopsy clip at the time of surgical excision is not uncommon and has been reported in the literature [36]. Clips may get extruded from the surgical specimen, be displaced as the surgeon dissects through breast tissue or may accidently be removed during suctioning. In these cases, the specimen radiograph fails to demonstrate a biopsy clip and it is unclear if the clip was displaced or if the clip is still in the breast. A mammogram following surgery is advised to evaluate for the presence of the clip. Decision to remove a residual clip can be based on its position in the breast relative to the original biopsy site and the pathology of the surgical specimen. Of note, there have been several instances where a patient desired a clip removed, either because it remained in the breast following surgery, or following a benign percutaneous biopsy, but adamantly did not want surgery. In this clinical situation it is possible to use a stereotactic vacuum assisted percutaneous procedure to remove the clip. However, the patient must be cautioned prior to the procedure that the entirety of the clip may not be removed.

In our experience, the Mammotome HydroMARK® clips are particularly susceptible to displacement and extrusion during surgery. Some surgeons report that the surrounding hydrogel material makes the clip "slippery" causing it to move or be easily suctioned. In a small study by Klein et al., there were intra-operative difficulties in 16 of 31 lesions marked with HydroMARK® clips - most due to extrusion of the clip as the biopsy tract was transected by the surgeon [37].

5.3. Allergic reaction to biopsy clips

Allergic reactions to biopsy markers are exceedingly rare. There are no cases of allergic reactions to breast biopsy markers reported in the medical literature although some have been reported in the lay literature and in online patient forums. Since allergy/sensitivity to nickel is not uncommon, the greatest theoretical risk is to nickel-containing markers. There have also been reports of allergic reactions to titanium based dental and orthopedic implants, however these devices are larger in size compared to biopsy markers and are in direct contact with bone and mucosa [38–40]. In review of the literature there have been two reported allergic reactions to titanium based breast surgical clips, also larger in size than biopsy markers [41, 42]. In patients who have a known nickel allergy, avoid nickel containing breast clips and use titanium only markers or alternatively a non-metal marker.

6. Clips in the axilla

There has been growing interest in reliably re-identifying metastatic lymph nodes identified with minimally invasive biopsy in patients post treatment with neoadjuvant chemotherapy. Patients treated with neoadjuvant chemotherapy have been shown to have complete pathologic resolution of all nodal metastasis in 41.1% of cases, with rates of 49.4% and 64.7% reported in the subsets of cases with triple-negative and HER-2 positive disease, respectively [43]. This has prompted interest in use of sentinel lymph node surgery after neoadjuvant chemotherapy for post-treatment staging.

In the American College of Surgeons Oncology Group Z1071 trial, the false negative rate for sentinel lymph node surgery after neoadjuvant chemotherapy was 12.6% in women with node-positive breast cancer [44]. In cases where a clip was placed in the biopsied positive axillary lymph node and the clipped node was included in the sentinel lymph node specimen, false negative rate dropped to 6.8% [44].

A study from MD Anderson compared outcomes of sentinel lymph node evaluation alone to targeted axillary dissection directed to clipped biopsy proven nodal metastases [45]. In this study, as compared to

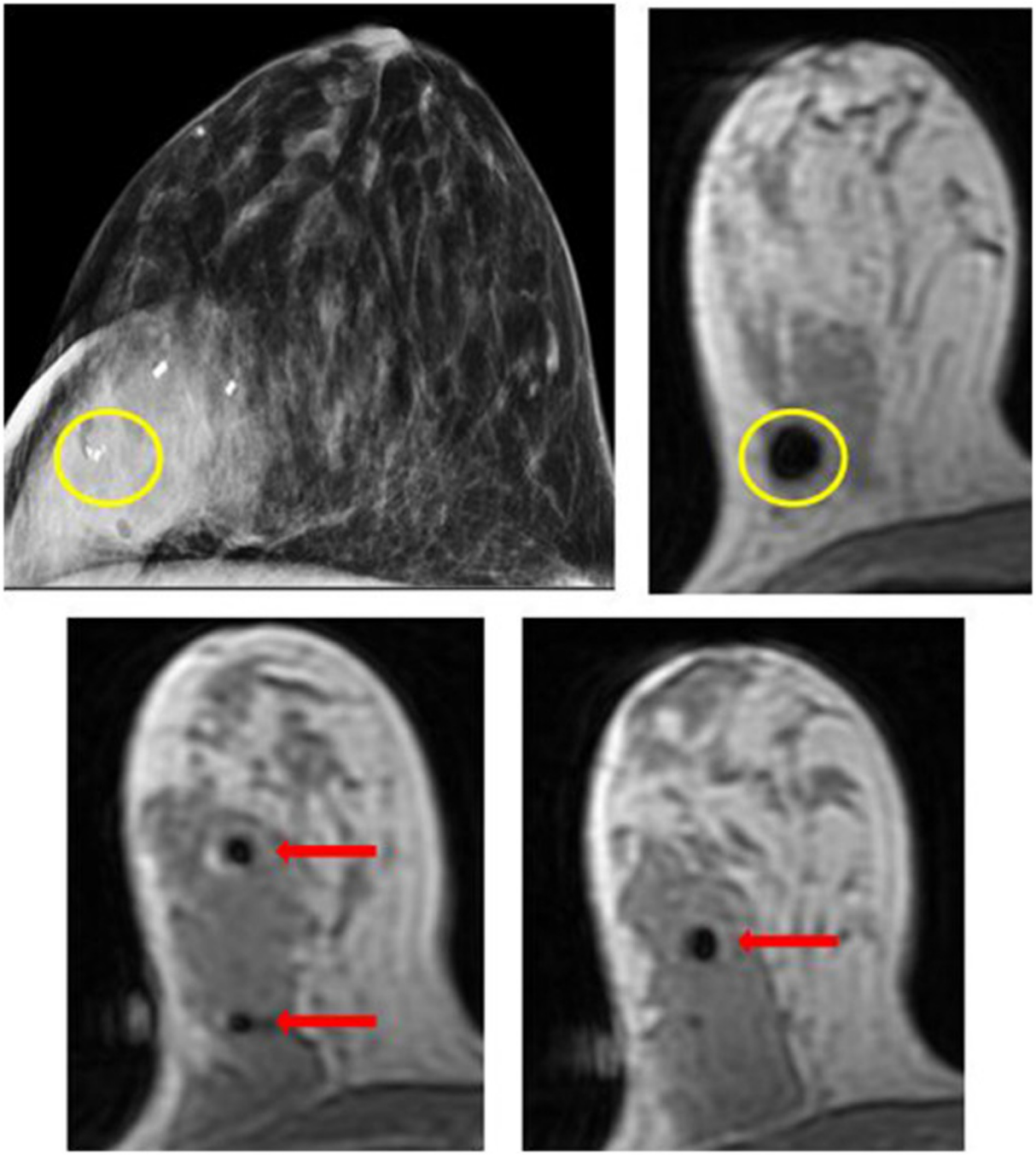


Fig. 11. Patient with multiple clips in the outer right breast (mammogram flipped to match the orientation of the MRI). BioDur 108 coil clip (yellow circle) corresponds to the known invasive ductal carcinoma. Remaining clips (top hat, hourglass, cork) are all made of titanium. BioDur creates a larger artifact on MRI (yellow circle) than titanium (red arrows) allowing for easy identification of the BioDur coil clip for orientation of the patient's MRI findings. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

complete axillary lymphadenectomy, sentinel lymph node biopsy yielded a false negative rate of 10.1%, while assessment of the clipped node alone yielded a false negative rate of 4.2%. The combination of sentinel lymph node biopsy with targeted axillary dissection directed to the clipped biopsy proven lymph node dropped the false negative rate to 1.4%.

These studies highlight the importance of deploying clips in axillary lymph nodes at the time of biopsy in breast cancer patients who may undergo subsequent neo-adjuvant chemotherapy. Selection of a clip with long-term ultrasound visibility is critical to allow for pre-operative localization.

7. Clip selection: how do I choose?

Having reviewed the many features that differentiate the various clips, it is prudent to now consider practical clinical factors that may influence selection of a specific clip.

7.1. Lesion location

If one is sampling a lesion under ultrasound guidance that would be difficult to localize mammographically due to its far posterior location, selection of a clip with long-term sonographic visibility should be

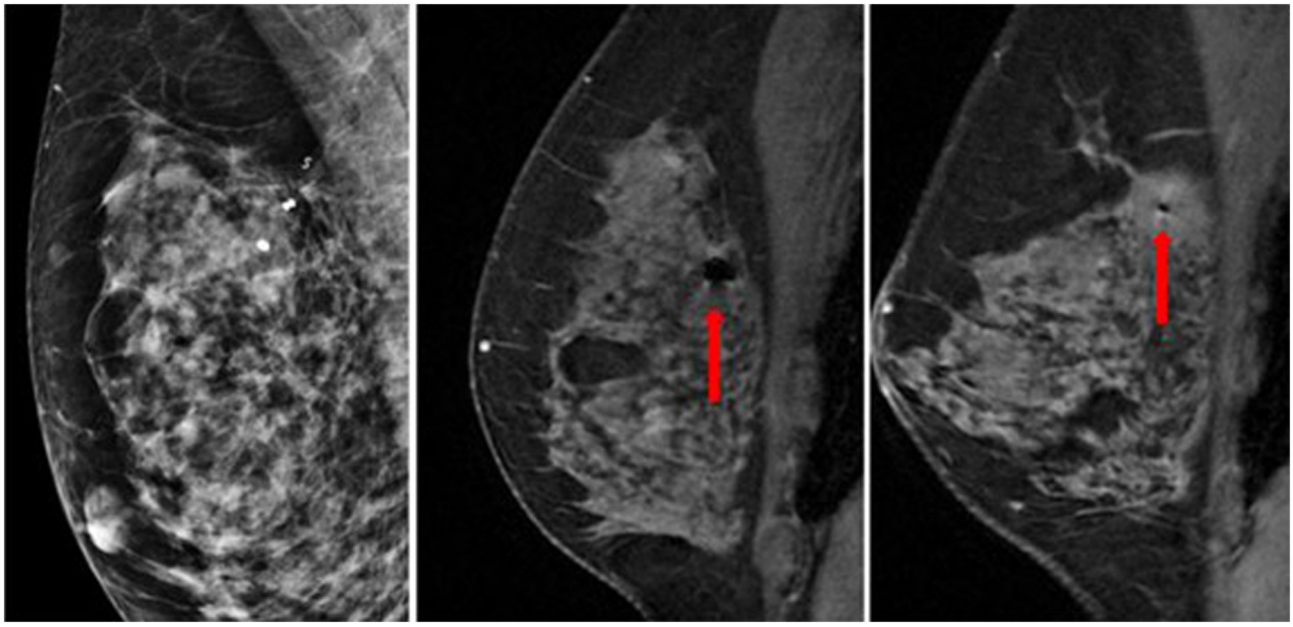


Fig. 12. Three different titanium clips are seen on the MLO projection of the right breast. On sagittal MRI images, artifact is only visualized for the mini cork and hourglass shaped clips (red arrows). The S-shaped clip could not be seen on this patient's MRI. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

considered, such as the HydroMARK®, MammoSTAR®, Nitinol, or PEKK clips.

For superficial lesions biopsied under any modality, it may be wise to select a bare clip without associated materials that could protrude through the skin. A bare clip may also be considered in small lesions to allow for more precise marking of the biopsy site.

The petite versions of the HydroMARK® and MammoSTAR® clips may also be considered for small superficial lesions if enhanced visibility with ultrasound is desired. The petite versions of the tissue markers are composed of a smaller amount of embedding material, but the size of the radiopaque portion of the clip is unchanged relative to the standard versions. One should be cognizant of the fact that duration of visibility under ultrasound is also reduced compared to the standard size clips due to the decreased amount of embedding material.

When sampling lymph nodes in the axilla, leaving a clip with long-term visibility may be desirable if pre-operative localization of biopsy proven metastatic lymph nodes after treatment with neoadjuvant chemotherapy is planned. In our experience, the HydroMARK® clip has performed superior to the MammoSTAR® clips for this purpose. Standard size clips are preferred over the petite clips due to the longer term visibility of their embedding material in this scenario. Nitinol clips and PEKK may also be considered.

7.2. Patient allergy

In patient's reporting allergy or sensitivity to metals, selection of a non-nickel containing titanium or carbon-ceramic clip is optimal. If long-term ultrasound visibility is not necessary, a bare clip may be preferable in order to reduce the amount of foreign material introduced to mark the biopsy site.

7.3. Prior biopsies

Before selecting a tissue marker, it is important to review the patient's mammogram in order to determine what clips, if any, are present from prior biopsies. By selecting a unique marker shape for the current biopsy, one can obviate potential errors at time of localization if surgical excision is subsequently required.

7.4. Bleeding diathesis

In a patient with a bleeding diathesis, it may be wise to consider a clip that absorbs fluid upon deployment, such as the clips embedded in collagen, hydrogel, or beta-glucan. Alternatively, a clip deployed with starch pellets could be considered.

7.5. MRI visibility

Selection of a marker which is more apparent on MRI, such as a stainless steel clip or a titanium clip with sufficient mass, should be strongly considered if biopsy is being performed under MRI guidance or if an MRI finding is biopsied under second look ultrasound. This facilitates inter-modality correlation and follow up.

8. Informed consent

A brief discussion regarding placement of a tissue marker is imperative during consent. Patients must understand that a small foreign body will be left in the breast at the conclusion of the exam, as patients may be upset if this information is not shared prior to the procedure. Discussing the tissue marker while obtaining consent also provides an opportunity to specifically inquire about metal allergies, as patient's may fail to report this allergy when initially questioned. A discussion of the benefits of marker placement, specifically that a more accurate surgical specimen can be obtained if surgical excision is required, may serve to convince patients who may be reluctant to accept marker placement. Moreover, surgical excisional biopsy may be offered as an alternative in those patients who continue to refuse marker placement. It is useful to include the actual size of the clip in the discussion and to show the patient a sample clip, if available. If utilizing a metal based clip, patients should know that it is MRI compatible and that it will not set off a metal detector due to its small size. Lastly, it is helpful to tell patients about the post-procedure mammogram during consent. Some institutions require patients to initial a portion of the consent form in which they agree specifically to clip placement.

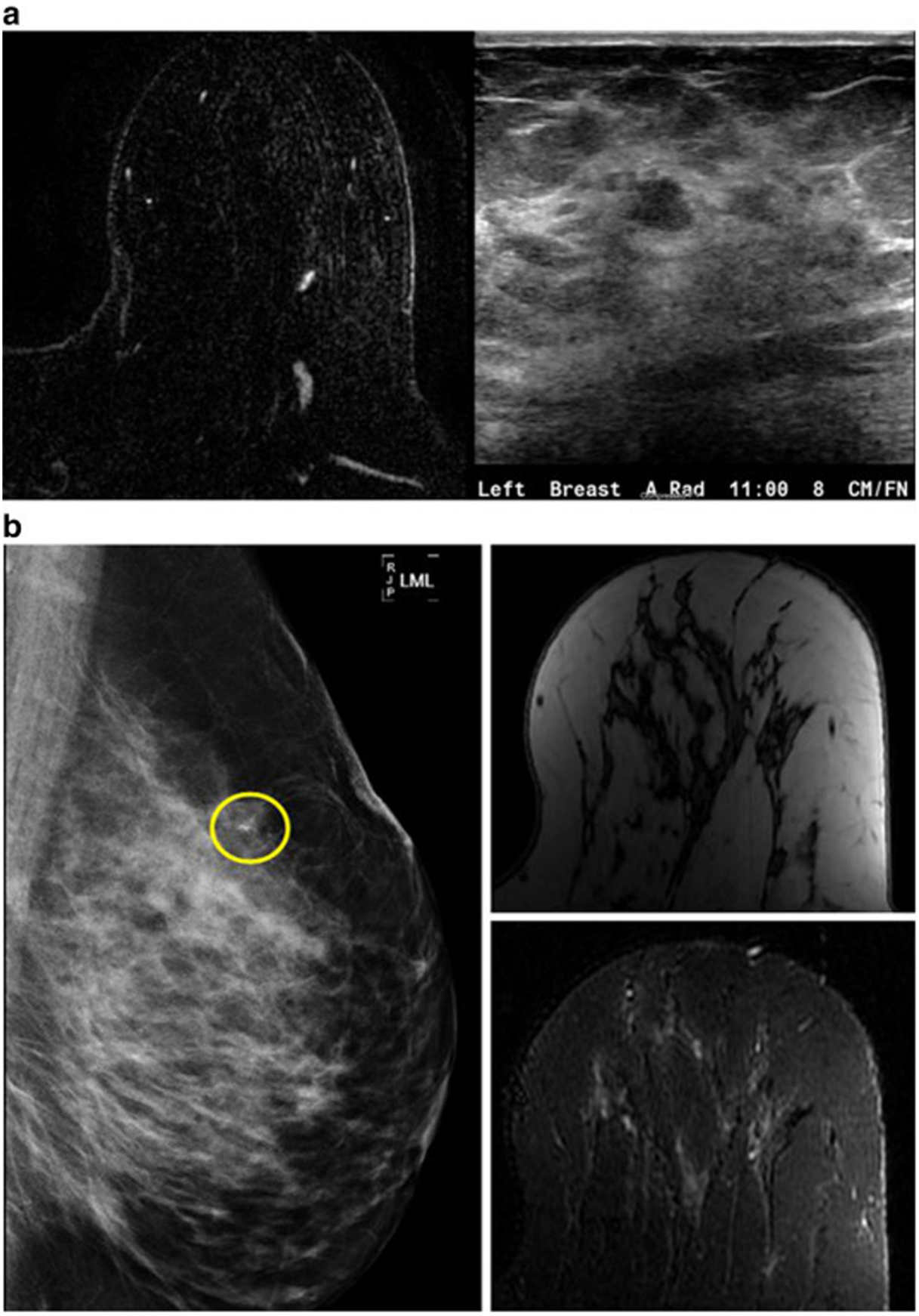


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Fig. 13. a. MRI performed for screening in this high-risk patient demonstrated a new enhancing mass in the superior left breast. Second-look ultrasound demonstrated an irregularly shaped mass at the 11:00 axis thought to correlate with the MRI finding and ultrasound-guided core biopsy was performed followed by clip placement.
b. Post-biopsy mammogram demonstrated the S-shaped clip placed at the time of biopsy. A post-procedure non-contrast MRI was performed to evaluate for MRI/ultrasound correlation. The S-shaped clip could not be visualized on the MRI and thus no correlation could be made.

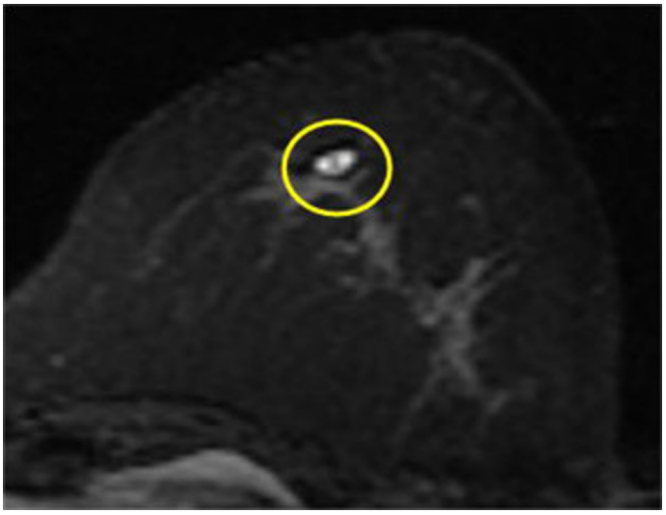

Fig. 14. T2-weighted axial sequence demonstrates a HydroMARK® clip in the left breast 3 months after placement. The hydrogel is a T2 hyperintense oval mass containing signal void from the titanium marker.

9. Conclusion

Breast tissue markers have become an integral component of the percutaneous breast biopsy procedure. With the myriad of commercially available tissue markers, this review aims to highlight various features specific to each marker and serve as a reference so that the radiologist can make an informed choice, selecting a clip most appropriate for a given patient and clinical scenario. When selecting a clip, one should assess for patient metal hypersensitivity and bleeding diathesis. Determining whether long-term ultrasound visibility or conspicuity with MRI will be necessary can also influence clip selection. Finally, it is critical to ensure that uniquely different shapes are used for multiple biopsy sites within a single breast in order to obviate confusion during pre-surgical localization and at follow up imaging.

Declarations of interest

None.

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