Radiology

Reducing Unnecessary Biopsy and Follow-up of Benign Cystic Breast Lesions

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One of the loudest criticisms of current breast imaging is the prevalence of false-positive findings, which result in additional testing and even biopsy of lesions that prove to be benign. This is particularly an issue for screening US, where up to 20% of masses are assessed as Breast Imaging Reporting and Data System (BI-RADS) category 3 (probably benign) and are followed-up at a short interval (usually 6 months), and only 9%–11% of masses recommended for biopsy prove to be malignant (1). The counter-concern, however, is obvious: without biopsy or close surveillance there could be a delay in diagnosis of breast cancer that would adversely affect patient outcome. This controversy is especially pertinent to cystic breast lesions, where the differential diagnosis is primarily: *(a)* benign cyst; *(b)* complicated cyst; *(c)* fibroadenoma; *(d)* phyllodes tumor; *(e)* high-grade, often estrogen-, progesterone-, human epidermal growth factor 2 receptor–negative invasive ductal carcinoma; or *(f)* metastatic lymph node.

Cysts are the most common cause of breast masses. Among 2662 unique women who underwent screening US in the American College of Radiology Imaging Network (ACRIN) 6666 trial, simple cysts were found in 1255 (47.1%) of participants over 3 years (2). Cysts were more common in premenopausal women (516 of 793 [65.1%]), but 537 of 1363 (39.4%) postmenopausal women also had simple cysts. The prevalence of cysts in postmenopausal women taking estrogen supplements (48 of 73 [66%]) was similar to that of premenopausal women. When present, cysts were bilateral in 48% of women. With appropriate technique, simple cysts are usually easily recognized as benign findings at US and only merit aspiration for patient symptoms (usually pain from a large, tense, round cyst).

Complicated cysts with debris are also very common and can be a source of diagnostic uncertainty, prompting unnecessary follow-up or biopsy. In ACRIN 6666, 376 of 2662 (14.1%) women had complicated cysts with debris, 301 (80%) of whom also had at least one simple cyst (2). Complicated cysts with debris can be dismissed as benign findings (BI-RADS category 2), with a malignancy rate of four of 1342 (0.3%) masses across seven series (2).

Clustered microcysts represent dilated acini within the terminal duct lobular unit (3), creating one overall circumscribed oval or microlobulated low-density mass when visible at mammography that has multiple small 1–7-mm cysts within it at US. Clustered microcysts are part of the spectrum of benign cystic breast change and can be lined by bland or apocrine metaplastic epithelium with or without usual hyperplasia. Uncommonly, as with larger cysts, they can be seen to communicate with a duct on US images. Individual microcysts can have debris that can mimic a solid component. Clustered microcysts are also common, seen in 104 of 2662 (3.9%) participants in the ACRIN 6666 trial (2), and are seen most often in perimenopausal women. Including the retrospective single-center study by Goldbach et al in this issue of *Radiology* (4), outcomes of 570 lesions of clustered microcysts have now been published, with nine (1.6%) proving malignant. This malignancy rate of close to 2% would seem to suggest a BI-RADS category 3 (probably benign) classification would be appropriate for clustered microcysts.

Let us, however, examine the malignancies reported among clustered microcysts. In one participant in ACRIN 6666, a node-negative 1.8-cm invasive lobular carcinoma was detected because of a suspicious change on US images at 1-year follow-up in a 43-year-old woman. A 0.5-cm cluster of cysts was the initial finding, and that did not clearly correlate with the irregular, mostly solid complex 0.5-cm mass seen 1 year later (5). The other eight malignancies were all from one series from Japan (6). These malignancies included six ductal carcinomas in situ and two invasive carcinomas. None of the three malignant lesions illustrated in that publication met the strict BI-RADS description of clustered microcysts, as all showed intervening or associated solid components; the other five malignancies were not shown. There were also four mucocele-like lesions in that series (6). If we exclude that series, the malignancy rate among clustered microcysts is one of 526 (0.2%), consistent with a BI-RADS category 2 assessment.

All types of benign cystic breast lesions can be a source of fluctuating bilateral masses seen at mammography.

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Supported by the National Institutes of Health (R01CA187593).

Conflicts of interest are listed at the end of this article

See also the article by Goldbach et al in this issue.

Radiology 2020; 295:52–53 • **https://doi.org/10.1148/radiol.2020200037** • **Content code: BR**

Multiple bilateral circumscribed masses, with at least three total masses and at least one mass in each breast, have been shown to be a benign finding at both mammography and US (7). Tomosynthesis can depict multiplicity and bilaterality of mostly circumscribed masses that might otherwise have gone unnoticed, thereby facilitating appropriate classification as a benign finding without the need for US. On US images, it is easy to recognize clustered microcysts as benign when in the company of multiple simple or complicated cysts with debris. Each mass must be carefully scrutinized, however, as cancer can coexist with multiple bilateral circumscribed masses, as was seen in two of 82 (2.4%) participants in ACRIN 6666 who also had a solitary lesion (7).

There are certain circumstances where greater caution is appropriate. Chae et al (8) reported that an otherwise probably benign finding at screening US has a higher rate of malignancy if there is a mammographic correlate: four of 184 lesions (2.2%) with a mammographic correlate were malignant compared with only four of 980 (0.4%) lesions seen only at US. All malignancies in the Tanaka et al series (6) were seen at mammography, and many (the exact number is not clear) had associated suspicious calcifications. Interestingly, all lesions in the Goldbach et al series (4) were seen at mammography. As confirmed by the absence of any malignancies among the 196 clustered microcysts in this series, mammographic depiction alone should not prompt short-interval follow-up or biopsy.

Risk of malignancy generally increases with increasing age. With so few malignancies reported, it is not possible to advise distinct management of clustered microcysts at any particular age, but strict criteria must be applied—especially to any new mass seen at mammography in a postmenopausal woman. Indistinct or angular margins, associated suspicious calcifications, or a definite solid component should prompt biopsy. When clustered microcysts are very small, deep (eg, >3 cm from the skin at US), or both, there can be diagnostic uncertainty. A BI-RADS category 3 (probably benign) assessment with 6-month follow-up is reasonable in this circumstance. Greater caution is also appropriate for lesions ipsilateral to newly diagnosed malignancy, particularly if there is associated enhancement on MRI.

It is interesting that Doppler US was used for every lesion in the study by Goldbach et al (4), though the details of Doppler findings are not specified. Internal vascularity typically implies a solid lesion and can help in the recognition of a metastatic node or triple receptor–negative invasive breast cancer otherwise mimicking a simple cyst. With current highly sensitive equipment, minimal vascularity can be seen along the thin (<0.5 mm) septations separating microcysts. Such subtle vascularity alone does not necessitate biopsy.

Harmonic imaging can help distinguish (and remove) artifactual internal echoes in cystic lesions and can be especially helpful in depicting clustered microcysts and excluding a solid mass. Elastography may or may not be helpful in recognizing the very few malignancies that might otherwise be mistaken for clustered microcysts. Ductal carcinoma in situ can appear relatively soft, as can mucinous carcinoma (9). Elastography does appear to help distinguish circumscribed high-grade invasive ductal carcinomas, which typically show a rim of surrounding stiffness, from fibroadenomas and complicated cysts, which are generally soft (9). Elastography can facilitate appropriate downgrading of soft circumscribed low-suspicion BI-RADS category 4A masses that would otherwise undergo biopsy to a BI-RADS category 3 assessment with surveillance at 6 months. It is not specified if elastography was used by Goldbach et al (4). Lack of enhancement on contrast material–enhanced mammography is another approach to reducing biopsy of benign low-suspicion (BI-RADS category 4A) or even moderate-suspicion (BI-RADS category 4B) breast masses (10).

In summary, it is time that we reduce unnecessary follow-up or biopsy of many benign cystic breast masses. With this additional study on the outcomes of clustered microcysts, we now have sufficient data to support a BI-RADS category 2 (benign) assessment for the vast majority of such findings, with the caveat that there is one published series with conflicting results, as discussed. Some clustered microcysts still merit biopsy. Biopsy should be performed if there are indistinct or angular margins, associated suspicious calcifications, or a suspicious change at subsequent imaging. Overall, 24 of 196 (12%) of clustered microcysts in the study by Goldbach et al (4) were given a BI-RADS category 4 assessment, and 38 (20%) were biopsied. The biopsy rate is higher than that in the prospective multicenter ACRIN 6666 trial, where only five of 123 (4.1%) such lesions were biopsied. The latter lesions were nearly exclusively seen at screening US, where the risk of malignancy appears to be even lower than when masses are first seen at mammography. As with any guidance in breast imaging, it is important to audit one's own practice to verify appropriate outcomes.

Disclosures of Conflicts of Interest: W.A.B. Activities related to the present article: disclosed no relevant relationships. Activities not related to the present article: institution received grants and equipment support from GE Healthcare and Hologic and software support and a pending grant from Koios Medical. Other relationships: disclosed no relevant relationships.

References

1. Berg WA, Vourtsis A. Screening breast ultrasound using handheld or automated technique in women with dense breasts. J Breast Imaging 2019;1(4):283–296.
2. Berg WA, Sechtin AG, Marques H, Zhang Z. Cystic breast masses and the ACRIN 6666 experience. Radiol Clin North Am 2010;48(5):931–987.
3. Warner JK, Kumar D, Berg WA. Apocrine metaplasia: mammographic and sonographic appearances. AJR Am J Roentgenol 1998;170(5):1375–1379.
4. Goldbach AR, Tuite CM, Ross E. Clustered microcysts at breast US: outcomes and updates for appropriate management recommendations. Radiology 2020;295:44–51.
5. Barr RG, Zhang Z, Cormack JB, Mendelson EB, Berg WA. Probably benign lesions at screening breast US in a population with elevated risk: prevalence and rate of malignancy in the ACRIN 6666 trial. Radiology 2013;269(3):701–712.
6. Tanaka A, Imai A, Goto M, Konishi E, Shinkura N. Which patients require or can skip biopsy for breast clustered microcysts? Predictive findings of breast cancer and mucocele-like tumor. Breast Cancer 2016;23(4):590–596.
7. Berg WA, Zhang Z, Cormack JB, Mendelson EB. Multiple bilateral circumscribed masses at screening breast US: consider annual follow-up. Radiology 2013;268(3):673–683.
8. Chae EY, Cha JH, Shin HJ, Choi WJ, Kim HH. Reassessment and Follow-Up Results of BI-RADS Category 3 Lesions Detected on Screening Breast Ultrasound. AJR Am J Roentgenol 2016;206(3):666–672https://doi.org/10.2214/AJR.15.14785.
9. Berg WA, Mendelson EB, Cosgrove DO, et al. Quantitative Maximum Shear-Wave Stiffness of Breast Masses as a Predictor of Histopathologic Severity. AJR Am J Roentgenol 2015;205(2):448–455.
10. Zuley ML, Bandos AI, Abrams GS, et al. Contrast Enhanced Digital Mammography (CEDM) Helps to Safely Reduce Benign Breast Biopsies for Low to Moderately Suspicious Soft Tissue Lesions. Acad Radiol 2019S1076-6332(19)30369-1.