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Current Status of Supplemental Screening in Dense Breasts

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Currently 24 American states have laws requiring that women receive some level of notification about breast density together with their mammography results.¹ Dense breast tissue can hide cancer on mammography, especially when the cancer lacks calcifications, resulting in delayed diagnosis and worse outcomes. Moreover, dense breast tissue is an independent risk factor for developing breast cancer. Particularly in dense (heterogeneously dense or extremely dense) breasts, a negative result on mammography does not reliably exclude the presence of cancer. Advocates pushed for legislation requiring notification of the breast density together with mammography results so that women with dense breasts would be made aware of their density, and the implications, and could pursue supplemental screening beyond mammography. The most widely available supplemental screening options for women with dense breasts are ultrasound and tomosynthesis (3D mammography), but there has been a lack of information to guide the choice to have one or the other or both. Preliminary results from the ASTOUND trial, an important study of adjunct screening ultrasound and tomosynthesis (3-D mammography) in women with dense breasts, are presented in this issue.²

Even with modern treatments for breast cancer, stage at diagnosis, and especially node status, remain the most important prognostic factors.³ Across 11 randomized trials of mammography, only those that reduced the rate of advanced breast cancer (and increased detection of node-negative invasive cancer) produced breast-cancer mortality reduction.^{4,5} In women with dense breasts, invasive cancers may be masked and missed on mammography; as a result, there is an excess of late stage disease (stage II and III).⁶ In women with extremely dense breasts, cancers are nearly 18-times more likely to be found due to clinical symptoms soon after a normal screening mammogram than in women with fatty breasts.⁷ Such “interval cancers” (diagnosed before the next routine screening exam) tend to be larger, more aggressive, and have worse prognosis than those found on screening. Thus, another measure of screening effectiveness is a low interval cancer rate (typically less than 1 per 1000 women screened per year).

Results from screening ultrasound (US) have been reported in over 200,000 women. The vast majority of US studies have examined adding US to mammography for women with dense breasts, and the vast majority of cancers seen only on US prospectively are not evident on mammography even in retrospect. In a review of 335 cancers seen only on screening US, Bae et al⁸ reported that 263 (78%) were obscured by dense tissue on mammography, 63 (19%) were interpretive errors on mammography, and 9 (3%) were not included mammographically due to difficult location/positioning. When performed by physicians, US

produces consistent increased detection of an average of 4 cancers per 1000 women screened.⁹⁻¹⁵ Over 85% of cancers detected only on screening US are invasive and node negative.¹⁶

Technologists can also be trained to perform whole breast handheld screening ultrasound. In results from training courses in Japan, 415 technologists showed significantly better performance than did 422 physicians in lesion detection on video review (85.9% vs 84.0%, respectively, $P = .037$) and higher specificity on still images (86.6% vs 85.1%, respectively; $P = .026$) with indistinguishable performance on other tasks.¹⁷ In recently published results from the Japan Strategic Anti-Cancer Randomized Trial (J-START), there was a reduction in interval cancers (0.05% vs. 0.10%, $p=0.034$) among 32,105 women receiving supplemental ultrasound compared to 32,812 women in the control group receiving only mammography; notably, only 57.7% of women in J-START had dense breasts, though results by breast density were not detailed.¹⁸ Compared to results from physician-performed US, results from technologist-performed screening US show slightly lower added cancer detection, averaging 2.5 per 1000 women in the first year.¹⁹

Several different approaches to automated whole breast ultrasound have been studied. One method uses an automated arm with standard hand-held equipment and, in multicenter experience, showed detection of another 3.6 cancers per 1000 women screened after mammography.²⁰ Another approach uses a wide footprint transducer (typically 15 cm) and produced a supplemental yield of 1.9 per 1000 women in a prospective multicenter experience, though 13% of women required recall for additional targeted US to complete initial screening.²¹ Results are expected to improve with incidence screening.

There are several barriers to implementing screening ultrasound in practice. One of these has been high rates of false positives due to US. Importantly, in preliminary results from the ASTOUND trial,² false positive recalls (2.0%) and biopsies (0.7%) were acceptably low. These low rates likely reflect that most of the US screens in ASTOUND were incident screens (with prior exams available); further, recommendations for short-interval follow-up (BI-RADS 3) were not considered test positive. Results from incidence screening in years 2 and 3 in ACRIN (American College of Radiology Imaging Network) 6666 showed far fewer false positives than in the first year.⁹ In Connecticut, where reporting of the limitations of mammography in dense breasts directly to the patient has been mandated since 2009, and where supplemental screening with ultrasound or MRI is required to be covered by insurance, many practices have implemented screening US for women with dense breasts. Comparing year 5 screening US results to those in year 1 at a practice affiliated with Yale, the recall rate dropped from 25% to 6% ($p<.0001$), biopsy rate from 5% to 1% ($p<.0001$) and PPV of biopsies (PPV3) increased to 25% from 6.5% ($p<.0001$), while maintaining similar cancer detection rates of 2.4 per 1000 vs. 3.2 per 1000.²²

Another barrier to implementing screening ultrasound is manpower. For handheld ultrasound, training of investigators²³ and use of a consistent scanning protocol produced excellent results in the ACRIN 6666 trial, but it is impractical to expect radiologist physicians to perform screening ultrasound in the United States. While technologists are encouraged to use the same scanning and documentation protocol,¹⁹ standardized training is

not generally available for technologists in the United States. With automated approaches, thousands of images are generated and interpretation times averaged 9 minutes for a bilateral examination in one early study,²⁴ compared to less than 0.5 minutes for a handheld examination with standard documentation.¹⁹ For the patient, there is the additional barrier of out-of-pocket costs due to deductible and co-pays with most insurance in most states. Medicare reimbursement currently averages \$165 for whole breast ultrasound of both breasts, regardless of whether this is physician- or technologist-performed or automated.

Digital breast tomosynthesis, which is essentially 3D-mammography, is much easier to implement. Once the equipment is in place, a technologist positions the patient exactly the same as for standard mammography and simply pushes a button to obtain tomosynthesis instead of (or in combination with) a standard digital mammogram. While, compared to standard mammography, there are many more images to review (usually one for each mm of breast thickness in each view), the images are quite familiar to radiologists trained in mammographic interpretation. Compared to 2D-mammography alone, adding 3D mammography increases cancer detection across all breast densities,^{25,26} with an average added cancer yield of 1.3 per 1000 in a large retrospective analysis.²⁷ When performed together with 2D mammography, 3D mammography reduces false positive recalls as areas of overlapping normal tissue are easily recognized;^{25–27} the ASTOUND trial only considered women with negative mammograms and found a false-positive recall rate of 53/3207 (1.7%) and false-positive biopsy rate of 22/3207 (0.7%) due to 3D mammography on the prevalent (first) screening round.

When 3D mammography is added to standard digital mammography, the radiation dose is a little more than doubled. Synthetic 2D-reconstructions from the projection images obtained for tomosynthesis can replace standard 2D mammography^{28,29} so that the radiation dose for 2D plus 3D mammography is comparable to 2D alone, but radiologists have been slow to adopt this approach to date as small masses can be difficult to see on synthetic 2D images with resulting reduced diagnostic confidence. While the added cancer yield of tomosynthesis is modest, the concomitant reduction in false positives in prior studies adding 3D to 2D mammography, with net increase in accuracy, make this method attractive. Insurance coverage for tomosynthesis is highly variable at this time, though the state of Pennsylvania recently determined that “mammography is mammography” and the insurance commissioner decreed that screening 3D mammography falls under the same mandatory full coverage as 2D mammography. National screening coverage only includes 2D mammography under the Affordable Care Act at this time. Medicare reimbursement averages \$57 for tomosynthesis.

ASTOUND is the first published prospective trial to directly compare US and tomosynthesis for adjunct screening after standard mammography in women with dense breasts. The added cancer detection yield of 7.1/1000 (95%CI 4.2–10) for US was significantly higher than that from tomosynthesis at 4.0/1000 (95%CI 1.8–6.2, $P=0.006$) with only one cancer seen only on tomosynthesis. The difference in yields in favor of ultrasound is consistent with results of prior trials of each modality separately though the absolute yields are higher than in prior studies. Preliminary results from the University of Pennsylvania suggest that the cancer detection benefit from tomosynthesis is maintained each year,³⁰ though further study is

needed; this has been shown for ultrasound.⁹ The low interval cancer rate of 0.82/1000 in the first year of the multicenter Italian trial of tomosynthesis³¹ is encouraging, though this was across all breast densities and further evaluation is warranted and is a proposed endpoint of the Tomosynthesis-Mammography Imaging Screening Trial (T-MIST).

Since the primary goal of screening is detection of early breast cancer, ultrasound would seem the clear choice compared to tomosynthesis. Given comparable false positive rates in ASTOUND, the estimated cost per cancer detected would be similar for US and tomosynthesis. US equipment is becoming much less expensive, requires no ionizing radiation, and it is very easy to guide needle biopsy of lesions seen only on ultrasound. While a recent analysis from ACRIN 6666 showed comparable cancer detection for US alone as for mammography alone, with more of the cancers seen on US being invasive and node negative,³² US was complementary to mammography⁹ and should be seen as a supplement to mammography where both are available. Based on results from ASTOUND, tomosynthesis still misses a substantial number of invasive cancers in women with dense breasts and supplemental US after tomosynthesis would still be reasonable, though further study is warranted.

For high-risk women³³ of any breast density, supplemental screening with annual MRI has been proven to reduce late stage disease³⁴ and to produce increased metastasis-free survival.³⁵ In 2016, the American Cancer Society plans to update their guideline for screening women at high risk, and will include breast density and other risk factors in their systematic evidence review; their recent guideline for average-risk women³⁶ recommends women start screening at least by age 45, and by age 40 if the woman is willing to accept the risk of false positives. Preliminary results in average-risk women indicate that MRI has a much higher cancer detection rate of over 22 per 1000 in year one and 7.5 per 1000 in subsequent years, even after digital mammography and physician-performed screening US, with 93% of cancers seen on MRI node negative, across all breast densities.³⁷ Insurance reimbursement for screening MRI typically exceeds \$1000, which has prompted interest in a lower-cost alternative using an abbreviated protocol. In a pioneering study of “fast MRI” from Kuhl and colleagues,³⁸ all 11 cancers were detected by both fast and standard MRI and the false positive rate was substantial but insignificantly higher than for standard MRI among 595 women without cancer (87, 14.6%, vs. 70, 11.8%, $p=0.17$) if short-interval follow-up (BI-RADS 3) cases were included among false positives. An ACRIN-ECOG multicenter trial that will prospectively evaluate abbreviated MRI is eagerly awaited.

In summary, preliminary results from ASTOUND are extremely important in helping inform personalized screening choices for women with dense breasts. Guidelines on these issues are planned but often limit recommendations to those based on evidence from randomized trials with mortality as an endpoint. Our knowledge of the natural history of breast cancer and results from randomized trials of mammography should inform guidelines for supplemental screening. Methods that improve detection of node-negative invasive cancer should benefit women; a reduction in interval cancers has been shown for screening US, and a reduction in late-stage disease and improved metastasis-free survival has been shown for MRI. For tomosynthesis, the benefits are likely more modest. For women with dense breasts given the choice of ultrasound or tomosynthesis, ultrasound shows more cancers. Further validation of

these results is critically needed, as is longer-term follow-up to compare incidence screening results for tomosynthesis and US.

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