How Can Advanced Imaging Be Used to Mitigate Potential Breast Cancer Overdiagnosis?

Habib Rahbar, MD, Elizabeth S. McDonald, MD, PhD, Janie M. Lee, MD, MSc, Savannah C. Partridge, PhD, Christoph I. Lee, MD, MSHS

Radiologists, as administrators and interpreters of screening mammography, are considered by some to be major contributors to the potential harms of screening, including overdiagnosis and overtreatment. In this article, we outline current efforts within the breast imaging community toward mitigating screening harms, including the widespread adoption of tomosynthesis and potentially adjusting screening frequency and thresholds for image-guided breast biopsy. However, the emerging field of breast radiomics may offer the greatest promise for reducing overdiagnosis by identifying imaging-based biomarkers strongly associated with tumor biology, and therefore helping prevent the harms of unnecessary treatment for indolent cancers.

Key Words: Overdiagnosis; breast cancer; breast imaging; screening risks.

INTRODUCTION

The recently revised breast cancer screening recommendations from the U.S. Preventive Services Task Force (USPSTF) and the American Cancer Society (ACS) have renewed the controversy around the potential benefits and harms of mammography among advocates and detractors of breast cancer screening (1,2). Although all authorities reiterate the mortality benefits of routine screening for the general population, they also now consider overdiagnosis and overtreatment among the potential harms of mammography. By definition, overdiagnosis is screen-detected cancer that would not have become clinically apparent during a patient's lifetime (3). Although it is now fairly widely accepted in the medical community as a legitimate potential risk of screening, it is important to note that overdiagnosis is an event that cannot be directly observed.

Accordingly, precise measurement of overdiagnosis is a challenge that requires understanding not only the effects of screening but also knowledge of alternative causes of death among women prior to development of breast cancer symptoms (3). There is no consensus on the appropriate methods for estimating overdiagnosis in breast cancer. A recent systematic review and meta-analysis of the medical literature on the harms of mammography screening that accompanied the 2016 USPSTF recommendations found that methodologies used in overdiagnosis studies are highly variable, with approaches adjusting for lead time falling in the lower range of estimates (4). Regardless of the true magnitude, both the USPSTF and ACS now acknowledge overdiagnosis from mammography screening and the eventual downstream diagnostic and treatment cascades that follow the detection of indolent cancers as potential harms that should be communicated to patients during shared decision-making (1,2).

Although some have previously pointed to the breast imaging community as a major contributor to the problem of overdiagnosis (5), detection of a malignancy at screening would have limited impact on a patient's health without subsequent intervention and treatment, sometimes referred to as overtreatment. Nevertheless, abnormal screening does launch a series of events as part of an integrated care pathway, where multiple disciplines contribute to diagnosis and treatment planning. After identifying abnormalities at screening and image-guided biopsy, pathologists assist in diagnosing breast malignancy. After the diagnosis of malignancy is made, including ductal carcinoma in situ (DCIS), treatment decisions are determined by a group of subspecialists, including surgeons, oncologists, and radiation oncologists.

As first-line physicians in a cascade of medical care that is well intentioned, many breast imagers aim to balance the known benefits with the potential harms when making a decision to recall patients from screening. The most effective approach

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From the Department of Radiology, University of Washington School of Medicine, 825 Eastlake Avenue East, G3-200, Seattle, WA 98109-1023 (H.R., J.M.L., S.C.P., C.I.L.); Department of Radiology (E.S.MD.); Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania 19104-4283 (E.S.MD.); Department of Health Services, University of Washington School of Public Health (C.I.L.); Hutchinson Institute for Cancer Outcomes Research, Seattle, Washington 98109-1023 (J.M.L., C.I.L.). Received January 28, 2016; revised February 22, 2016; accepted February 24, 2016. **Address correspondence to:** C.I.L. e-mail: stophlee@uw.edu

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by which breast imagers can mitigate overdiagnosis is, perhaps, the most exciting aspect of this controversial issue. Eliminating screening mammography is not a realistic or ethical option as it would lead to later stage breast cancer diagnoses and increased mortality, even in this era of improved therapies (6).

As members of multidisciplinary breast care teams with imaging expertise, it is imperative that radiologists engage in this issue by examining how current or emerging advanced breast imaging technologies can lessen the potential harms of overdiagnosis. In this article, we highlight recent advances and areas that warrant further investigation, with the hopes that breast imagers will take an active and leading role in a collaborative effort to decrease breast cancer overdiagnosis and overtreatment.

ADJUSTING IMAGING FREQUENCY AND THRESHOLDS

Some experts have argued that revised imaging interpretation strategies can be used to curb diagnosis by raising the threshold for defining disease (7,8). Current standards of practice as defined by the American College of Radiology Breast Imaging-Reporting and Data System (BI-RADS) guidelines state that any findings identified with ≥2% of malignancy require tissue diagnosis to exclude breast cancer (9). As a result, microcalcifications that may represent low-grade DCIS are biopsied rather than followed with serial noninvasive imaging. Currently, such findings are designated as BI-RADS category 4, which indicates a 2%–95% likelihood of malignancy (9). This extremely broad range of suspicion and resulting low threshold for intervention, particularly in cases of calcifications, may contribute to overdiagnosis. This raises the question of whether breast imagers could safely follow low-risk lesions (ie, BI-RADS category 4A) with serial imaging rather than proceeding to image-guided biopsy. Such adjustments could include different biopsy thresholds based on individualized risk, aided by imaging features. For example, biopsy thresholds for equivocal calcifications may be lower for women with a high lifetime risk of developing breast cancer than for women with an average lifetime risk of breast cancer.

Others have suggested that less frequent screening could mitigate potential harms, including overdiagnosis, at the population level. Both the 2015 ACS and 2016 USPSTF recommendations suggest that starting routine screening at an older age (45 or 50 years rather than 40 years) and undergoing biennial rather than annual screening may lead to reductions in screening harms, including overdiagnosis, based on projections from simulation models (1,2). However, the actual reduction in overdiagnosis from less frequent screening has not been rigorously assessed in prospective studies. Whereas some indolent cancers may go undetected with less screening, other more aggressive cancers may be detected at later stages and lead to greater morbidity and mortality. Overdiagnosis likely increases with age, attributable primarily to increasing competing mortality; 14%–36% of screen-detected cancers at age 80 have been projected to represent overdiagnosis (10).

Although worthy pursuits, it is important to note that adjusting both the threshold for biopsy based on imaging features and the frequency of screening mammography does not directly address the issue of overdiagnosis. The major limitations with these two approaches remain the reliance on standard imaging features for identifying breast cancer, as well as the standard of care dictating a rigid treatment cascade once malignancy is confirmed after image-guided breast biopsy.

NEW IMAGE-BASED SCREENING TECHNOLOGIES

There is a great deal of excitement around digital breast tomosynthesis (DBT) and its ability to decrease screening-related harms, especially false-positive findings. A recent review suggests that adding DBT to digital mammography screening can decrease the frequency of false-positive results by 15%–30% (11). In addition, DBT may improve cancer detection. Friedewald et al found that adding DBT to standard digital mammography screening increased the overall cancer detection rate by 29% (from 4.2 to 5.4 per 1000 screens). Moreover, there was a 41% increase in invasive cancer detection and no significant change in DCIS detection (12). Although detection of a greater number of early invasive cancers without increasing the number of preinvasive malignancies may very well lead to greater lives saved, ongoing clinical trials will require many additional years of follow-up to definitively establish this long-term outcome benefit. Thus, it remains uncertain what DBT's effect will be on overdiagnosis.

Further studies are needed to determine if the additional cancers detected by DBT over routine mammography are aggressive, more lethal cancers, or less aggressive indolent cancers, based on tumor biology (2,13–16). Initial data from cancer rates in a population undergoing repeated DBT screening suggest a decrease in interval cancers (17). If this trend continues, it may indicate that DBT screening is detecting more clinically significant cancers. Currently, more longitudinal and multi-institutional data are needed to substantiate these results. Even if DBT is identifying clinically significant cancers, it is still unlikely to mitigate overdiagnosis in and of itself because DBT is based on digital mammography technology and is limited to identifying morphologic features rather than providing more biological or physiological insights regarding tumors.

Supplemental screening ultrasound has also been shown to increase cancer detection among women with dense breasts and other additional risk factors (18). These cancers tend to be small, invasive, and node-negative. However, similar to DBT, screening ultrasound evaluation is heavily reliant on morphology of masses without providing additional biological or functional information. The low positive predictive value of ultrasound screen-detected masses (less than 10%) continues to be a concern, as supplemental screening leads to a relatively high number of benign biopsies (19). Recently, abbreviated breast magnetic resonance imaging (MRI), with an acquisition time of 3 minutes and expert radiologist