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Tomosynthesis for breast cancer screening

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ABSTRACT

Breast tomosynthesis, a three-dimensional x-ray based breast imaging technology, has been available for clinical use in the United States since 2011. In this paper we review the literature on breast cancer screening with this new technology including where gaps in knowledge remain.

1. Introduction

Breast cancer is the second most common cause of cancer deaths among North American women [1]. It is estimated that 256,470 new cases of invasive breast cancer will be diagnosed in women in the United States and Canada with about 45,000 women dying from the disease in 2014 [1,2]. Early detection through screening has been considered an important factor in reducing mortality from this disease [3,4]. X-ray imaging techniques are currently used in early detection of breast cancer. The most commonly used imaging technique for general population breast cancer screening is digital mammography (DM). Digital mammography has been the standard of care for breast cancer screening since approximately 2005 shortly after the results of DMIST were published. That large National Cancer Institute-funded study of almost 50,000 women across 33 sites in North America showed an improvement in breast cancer detection without an increase in false positives for women with dense breasts, pre- and peri-menopausal women, and women under age 50, with no difference in accuracy for the entire population [5]. The relative risks and benefits of breast cancer screening have recently been challenged since some experts now consider the risk of detection of cancers that will never harm patients (overdiagnosis) and false positive examinations to outweigh the benefits of earlier detection of clinically important tumors that reduce breast cancer mortality [4].

The FDA approved the first tomosynthesis (TM) device for breast cancer screening in the US in 2011. TM provides images across an arc providing slices through the breast and is being rapidly adopted by breast cancer screening facilities in the US and Canada. The basis for adoption of TM in the US has rested mainly on European trials [6,7], where screening characteristics (recall rates, biopsy rates, cancer detection rates, age of patients, frequency of screening, number of readers) differ substantially from these same factors in the North American population of women and radiologists [8–10].

TM was developed to allow for the detection of lesions that had been obscured by overlapping breast tissue and, like DM, requires that the breast be compressed and immobilized during imaging. The TM units that have been approved for clinical use in the US have the ability to acquire images both as two-dimensional DMs and as three-dimensional TM slices. The most compelling clinical evidence for TM is for the use of the technology as an adjunct to two-view 2D DM. The first clinical installations of TM units in the United States occurred around 2011 with the first publications on the experiences of these early adopters appearing in the literature beginning in 2013. This paper will review the evidence to date on the use of TM for screening, will describe the relative limitations of TM versus DM, and will identify gaps in the evidence that we believe justify a large clinical trial in a US population to determine whether all US women who seek breast cancer screening should undergo TM.

2. Methods

A search was conducted for papers published between January 1, 2013, and March 28, 2015, with the search terms [breast AND tomosynthesis [ti] AND screening [ti]]. For this paper, we focus on how TM is implemented in various screening practices. A total of 29 papers were identified. We excluded two of these papers which assessed the use of TM for diagnostic workup. Two short reports with no quantitative analysis were excluded. Four citations that were comments of an original paper already counted were excluded. Two Informatics/physics based papers based on data extraction or clinical simulations were excluded. Four papers were reports of individual site results already

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included in larger multi-center published results were excluded. The three FDA Summary of Safety and Effectiveness Data reports for current FDA approved TM technologies were included in this review. A single technical paper on radiation dose data was also reviewed. This resulted in a total of 22 papers that have been included in this review.

2.1. Imaging protocols

There are currently two TM systems approved for clinical use in the United States by the US Food and Drug Administration (FDA), the Hologic Selenia Dimensions [11,12] and the GE Healthcare SenoClaire [13]. Recommendations of imaging protocols for breast screening with TM currently vary by manufacturer (Table 1), as such the FDA-approved screening protocols vary by manufacturer/machine type.

Since TM as defined by the manufacturers is quite different, henceforth in this paper, we will refer to TM (H) for Hologic's version and TM (G) for General Electric's version.

2.1.1. TM (H) – two-view TM plus two-view DM in breast cancer screening

The only TM imaging protocol for which there are published recall rates and cancer detection rates before and after the introduction of TM in clinical practice is two-view TM as an adjunct to two-view DM [14–17], or tomosynthesis as defined by Hologic. The first publications of TM(H) in screening are based on the implementation of the technology within European breast cancer screening programs in Norway (Oslo Trial) [6] and Italy (STORM) [7].

In the Oslo trial, Skaane et al. have reported results for 12,621 women who underwent screening at a single facility [7]. The ratio of false positive rates of DM and that of TM plus DM is 0.85 ($p<0.001$). An increase in cancer detection of 27% was described for TM plus DM over DM alone ($P<0.001$). This was with four independent radiologists reviewing each case with a requirement for arbitration if one or more radiologists classified a case BIRADS 2 or higher.

The multi-center STORM trial, reported by Ciatto et al. [6], consisted of the more traditional two independent parallel mammography interpretations, which is common practice in Europe, of DM versus TM plus DM There were a total of 7292 participants in this study. Overall the cancer detection rate was 8.1 per 1000 women screened for two-view TM plus two-view DM and 5.3 per 1000 for two-view DM alone. This difference of 2.7 per 1000 was significant ($P<.0001$).

In the US, Friedewald et al. [14] have reported retrospective performance comparisons between TM plus DM vs. DM alone for 454,850 screening examinations (281,187 DM, and 173,663 TM plus DM) acquired from 13 academic and non-academic breast imaging facilities in the US that introduced TM into their clinical practices. Two centers performed full TM conversion and the others had one or more TM systems with some DM remaining units. Across all sites, there was a significant reduction in the recall rate of 16.1 ($P<.001$) per 1000 for TM plus DM versus DM alone. However, 2 of the 13 sites reported an increase in recall rates for TM plus DM over DM alone. The authors attribute that difference in those two sites to the short length of time TM had been used at those facilities and the relative lack of experience with TM of the radiologists at those practices [14]. In other words, the authors believe that the benefits of TM plus DM in clinical practice are not realized until after some period of use of the new technology. Radiologist training and experience over time with TM is an important factor in achieving performance improvements seen over DM alone [18]. Friedewald also demonstrated a significantly higher cancer detection rate (0.12% [95% CI 0.08%, 0.16%]) and a nonsignificant increase in biopsy rate (0.13%, $P=.004$), for TM plus DM versus DM.

Lourenco 2014 [19] and Destounis 2014 [15], both in retrospective single site studies of the Hologic TM system which compared TM plus DM to DM, showed significant reductions in recall rates (2.9% for Lourenco and 7.25% for Destounis) for TM plus DM versus DM alone. Neither of these two studies showed significant changes in cancer detection rates between TM plus DM versus DM alone.

2.1.2. Two-view TM plus synthetic two-dimensional (2D) mammography (sDM)

At present, the clinical data on two-view TM with synthetic 2D mammography for screening is limited. There are data from a single European study by Skaane [20] comparing two different versions of Hologic software for creation of sDM and from the Hologic FDA application for their version of sDM, C View. In the Skaane study, algorithms to create synthetic 2D mammograms were applied to a total of 24,901 TM scans, 12,631 cases with the first version of the algorithm and 12,270 cases with the second. With the synthetic 2D mammograms (sDM) created by algorithm 1, the cancer detection rates were 8.0 per 1000 for TM plus DM and 7.4 per 1000 for TM plus sDM, a reduction that was not statistically significant ($P=.62$). When algorithm 2 for creation of sDM was applied to TM, the cancer detection rate was 7.8 per 1000 for TM plus DM and 7.7 per 1000 for TM plus sDM, again a difference that was not statistically significant ($P=.89$) [20].

Hologic's FDA application for approval of sDM [12] showed that TM plus sDM was not inferior in diagnostic performance compared with DM alone, with ROC analysis showing that the Areas under the curve (AUC) were within 0.05 of each other, demonstrating statistically no difference in diagnostic performance overall. The false positive rate for TM plus sDM was 13.9% (95% CI=3.8–25%) lower than for DM alone. Since the confidence interval measurement of recall rate difference fell within the pre-defined rate difference of less than 0.05, TM plus sDM was deemed non-inferior to DM by the FDA, so that TM plus sDM was approved for use in place of TM plus DM for breast cancer screening. It is important to note that TM plus sDM was not compared directly to TM plus DM in this FDA trial (Table 2).

2.1.3. TM (G)-one-view TM (MLO) plus one-view DM (CC)

At present there is no published report of the clinical implementation of this acquisition method besides the FDA Summary of Safety and Effectiveness Data (SSED) reported when General Electric received FDA approval [13]. As the SenoClaire systems have not been available for clinical use until the fall 2014, the first clinical reports will be available in the fall of 2015 at the earliest. The FDA SSED for the SenoClaire, which is approved for screening using this one-view 3D TM MLO plus one-view 2D DM CC acquisition protocol, demonstrates a reduction in

Table 1
Manufacturer specific acquisition protocols for breast cancer screening that have been approved by the US FDA

Manufacturer	3D Acquisition protocol FDA approved
Hologic	2-view TM plus 2-view DM (approved Feb 2011) 2-view TM plus synthesized 2-view DM (approved May 2013)
GE Healthcare	1-view TM (MLO) plus 1-view DM (CC) (approved Aug 2014)

Table 2
AUC comparison of two-view of TM plus synthetic 2D (sDM) versus DM alone test of non-inferiority submitted as part of Hologic FDA supplement for FDA approval of clinical use of synthetic 2D software

	FDA summary of safety and effectiveness data Selenia dimensions 3D system – P080003/S001	
	(TM+sDM) – (DM) *All breast densities*	(TM+sDM) – (DM) *Dense breasts only*
AUC	0.040	0.045
p-value	0.005*	0.027*