Study Protocol

Official Title: Screening Contrast-Enhanced Mammography as an Alternative to MRI (SCEMAM)

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Scientific Background

The overarching goal of our research program is to improve cancer detection on screening, particularly in women with dense breasts. Magnetic resonance imaging (MRI) depicts more cancers than other screening methods, including ultrasound. MRI is proven to both improve cancer detection and reduce clinically detected cancers ("interval cancers") after a negative screening mammogram in women with dense breasts. PA Senate Bill 595, signed into law June 30, 2020, requires insurance carriers to provide coverage for supplemental screening with MRI or ultrasound for a variety of indications. Relative to the number of women who may benefit from screening MRI, there is a shortage of equipment/capacity. Further, nearly half of women cannot have an MRI for medical or other reasons such as claustrophobia, implanted devices, body habitus, or cost (deductible and copay apply even with the new legislation). Contrast-enhanced mammography (CEM) appears to have similar performance to MRI but has not been widely validated, particularly for screening. In order to lay the foundation for improved screening of women with dense breasts, we seek to offer screening CEM as an alternative to MRI for women who meet guidelines for screening MRI but are unable to have MRI.

Approximately 43% of women of mammographic age have dense breasts (1). Dense breast tissue can hide cancers on mammography and also increases risk of developing breast cancer. Mammographic sensitivity averages 81-93% in fatty breasts, 84-90% with scattered fibroglandular density, 69-81% for heterogeneously dense breasts, and only 57-71% in extremely dense breasts (2). Women with dense breasts are more likely to have cancer found because of a lump or other symptoms in the interval after a normal screening mammogram and prior to the next screen ("interval cancers"), with the rate of interval cancers 13- to 18-fold greater in women with extremely dense breasts vs. fatty breasts (3, 4). Interval cancers are more likely to be aggressive cancers and to have spread to lymph nodes, with worse prognosis. While screening mammography reduces deaths due to breast cancer by as much as 41% in women with fatty breasts, the benefit was only 13% in women with dense breasts in an analysis from The Netherlands, with a confidence interval overlapping one (indicating there may be no net benefit in women with dense breasts) (5).

To address the issues of both masking and increased cancer risk, methods to improve cancer detection beyond mammography alone have been proposed for women with dense breasts or other risk factors. MRI has been widely studied in women at high risk and is shown to reduce late-stage disease (6), interval cancers (6-8), and use of MRI is estimated to further reduce mortality (9).

Screening MRI has also been studied in women with dense breasts. In the MRI substudy of ACRIN 6666 (for which I was the Principal Investigator), we showed in incremental cancer detection rate (ICDR) of 14.7/1000 even after the combination of ultrasound and mammography (10). Kuhl et al (11) evaluated supplemental MRI in women with <15% lifetime risk for breast cancer; for the 60% (1282/2120) of women with dense breasts, ICDR was at least 26/1282 (20.3/1000) and 11/1282 (8.6/1000) for prevalence and incidence screens respectively.

The Dutch DENSE trial invited women aged 50 to 75 years with normal screening mammograms and extremely dense breasts to undergo biennial screening with MRI and

mammography versus mammography alone (12). The first screening round yielded an ICDR from MRI of 79/4783 (16.5/1000), including 64 invasive and 15 DCIS (for an invasive ICDR of 13.4/1000); 55/64 (86%) of invasive cancers were node negative (12). Use of MRI reduced interval cancer rate from 4.9/1000 to 0.8/1000. Preliminary results from the second MRI screening round demonstrated substantial reduction in both ICDR (5.9 per 1000 overall, 4.1/1000 invasive) and false positive recalls (21/1000 vs. 80/1000) (13).

Comstock et al (14), in the Eastern Cooperative Oncology Group (ECOG)-ACRIN 1141 multicenter trial, compared prevalent screening Ab-MRI (including T2-weighted images) with incident DBT. Ab-MRI had superior sensitivity (96% vs. 39%) but reduced specificity (87% vs. 97%) among 1444 women with 26 cancers. Ab-MRI alone detected all 17 invasive cancers (16/17, 94% node negative) and 5/6 (83%) DCIS (missing one 7-cm high-grade DCIS seen on DBT); DBT detected 7/17 (41%) invasive cancers and 2/6 (33%) DCIS yielding an ICDR for Ab-MRI of 14/1444 (9.7/1000) and an invasive ICDR of 10/1444 (6.9/1000, p=.002). Additional imaging (recall or short-term follow-up) was 7.5% (108/1444) for Ab-MRI and 10.1% (146 women) for DBT (p=.02). Biopsy rate of Ab-MRI was nearly four-fold DBT (107 vs. 29, representing 7.4% and 2.0% of women respectively) with lower PPV3 of biopsies (19% vs. 35.5%, p=.08).

Barriers to screening MRI include claustrophobia, fear/intolerance of contrast injection, inconvenience, and fear of false positives (15, 16). In the DENSE trial, de Lange et al (16) observed a 59% acceptance rate (similar to the 58% rate in ACRIN 6666 (15)). Body habitus and implanted devices can also preclude screening with MRI. Cost remains an issue even with mandated insurance coverage as the deductible and copay still apply and can be substantial with MRI.

Contrast-enhanced mammography (CEM) is a potential alternative to MRI for screening that uses updated standard mammography equipment to obtain low- and high-energy images after intravenous injection of iodinated contrast (as used in CT scanning). Subtraction images are created, and the low-energy images are comparable to standard digital mammograms. Most reported results with CEM are from women with newly diagnosed cancer. In a meta-analysis of 13 such studies, Xiang et al (17) found overall sensitivity of CEM mirrored MRI at 97%, but specificity was higher with CEM (0.66; 95%CI 0.59, 0.71) than with MRI (0.52; 95%CI 0.46, 0.58).

Sorin et al (18) reported results from 611 women undergoing screening CEM, of whom 568 (93%) had dense breasts and 295 (48.3%) had family or personal history of breast cancer. Of 21 malignancies, 11 were seen on mammography and 19 on CEM (ICDR of CEDM 8/611; 13.1/1000; 95%CI 6.2, 21.1). Of eight malignancies seen only with CEM, seven were invasive and two of four with node staging had metastases. Sung et al (19) reported on 904 women undergoing CEM, 700 of whom had dense breasts (including the 307 women reported in (20)), with 15 (1.7%) women experiencing contrast reactions: one moderate (dyspnea, requiring diphenhydramine), the remainder mild (e.g. nausea or hives). Sixteen cancers were found; 14 (88%) on CEM and two interval cancers (2.2/1000), one seen on MRI and one on screening US 10 months later. Six of the 12 cancers in women with dense breasts were seen only on CEM (ICDR of 6/700, 8.6/1000): four invasive, with median size 0.8 cm, all node negative.

In order to address the provisions of Senate Bill 595, we at UPMC have developed an implementation strategy to expand our recommendations for screening MRI in line with national guidelines (e.g. National Comprehensive Cancer Network) and recent literature. This will require shortening the time allotted for screening breast MRI (but not quite "abbreviated" which is not billable), adding one more clinical MRI system (an increase from 3 to 4 total) and adding more evening time. Despite such changes, we know two things: 1) not all women who qualify for MRI will want to or be able to have screening MRI; 2) we will not have capacity for all women who could have MRI. As such, we would like to offer screening CEM to women who meet criteria for MRI but are not able to have it. Because our CEM systems are from Hologic and do not yet have FDA approval for screening, this funding is necessary to allow this option under a research protocol. While most suspicious findings on CEM are seen on tomosynthesis or targeted ultrasound, a few historically have required MRI for biopsy guidance in the absence of direct CEM-guided biopsy. We are just acquiring direct CEM biopsy capability which makes this appropriate timing for expanded clinical testing.

In October 2019, we started a clinical research trial sponsored by The Breast Cancer Research Foundation to compare CEM to tomosynthesis screening in women with a personal history of breast cancer. To date, we have enrolled 300 women, with 6 cancers found, including 2 seen only on CEM (and none seen only on tomosynthesis).

If we are able to confirm appropriate clinical performance of CEM screening in women who meet criteria for MRI, this will be critical information towards routine clinical implementation. Compared to MRI, the upgrades to standard mammography equipment are relatively inexpensive and the cost of iodinated contrast is low. CEM is also well tolerated compared to MRI (23), though we will also collect reasons women decline CEM. CEM alone can likely replace tomosynthesis screening has the potential to greatly improve cancer detection, particularly in women with dense breasts.

Study Objectives

We seek to validate screening CEM as an alternative to screening MRI. The primary objective is to show significantly improved cancer detection with CEM compared to standard mammography/tomosynthesis.

Study Design & Methods

This is a prospective clinical trial to see if contrast-enhanced mammography substantially improves breast cancer detection compared to mammography with tomosynthesis, with minimal

increase in false positives, in women who meet criteria for supplemental screening MRI, age 30-75, but who are unable to have MRI for medical/access/cost reasons.

Many state laws require insurance coverage for supplemental screening MRI in women at elevated risk for breast. There are women for whom screening MRI is clinically recommended but not feasible either due to patient factors (body habitus, pacemaker or other implant, claustrophobia) or access (cost, other constraints). For women whom screening MRI is clinically recommended but who cannot or will not have screening MRI, they will be offered contrast-enhanced mammography as an alternative at no cost. CEM will be performed in addition to standard-of-care tomosynthesis. We will prospectively record findings seen only on CEM and outcomes. Results from low-energy CEM images (which mimic standard mammography) will be recorded as well.

Eligibility Criteria

1. Asymptomatic women under age 75 who are recommended for annual screening MRI and mammography based on current criteria:
    a) Women known to be at high risk for breast cancer because of known or suspected pathogenic mutation, prior chest radiation therapy at least 8 years earlier and before age 30, or estimated lifetime risk of at least 20% based on family history/prior biopsy history (22), between age 30 and 75.
    b) Women with extremely dense breasts age 40-75 (about 7% of the screening population (1)) (12).
2. Women with lobular carcinoma in situ (1% of women biopsied each year; about 0.06% of our screening population) beginning the year after diagnosis.
3. Women with a personal history of breast cancer diagnosed by age 50 or with dense breasts (21), beginning the year after diagnosis (will be recruited under separate ongoing TOCEM protocol).
4. Women with heterogeneously dense breasts and any family history of breast cancer (about 36% of the screening population has dense breasts and about 20% have a family history of breast cancer) who do not meet current high-risk criteria, beginning at age 40 or ten years prior to the age of the youngest relative but not before age 30.

Participants are expected to have medical or other reasons that they are not able to have screening breast MRI.

Statistical Considerations

The primary objective is to show significantly improved cancer detection with CEM compared to standard mammography/tomosynthesis. The secondary objective is to show acceptably low false positive recall rates from CEM.

We expect that the addition of CEM to tomosynthesis (TOMO) will lead to detection of additional cancers demonstrating a similar cancer detection rate but substantially smaller false recall rate than would be expected from a supplemental MRI. We plan to detail the additionally detected cancers while statistically proving the substantially smaller rate of false recalls.

We are proposing a prospective observational study of performance of supplemental screening CEM in women eligible for supplemental MRI screening under the criteria in SB 595. From the 4800 women eligible for CEM under this protocol, we expect to be able to enroll 600 women (12.5%).

Despite the expectation that addition of CEM will substantially increase sensitivity of tomosynthesis (TOMO)-based evaluations (from 70% to 90%), due to relatively small rate of cancers, we anticipate to observe only a few additional cancers detected by CEM among 600 women. The detected cancers will be detailed with the emphasis on highlighting the possible advantages of CEM comparing to hypothetical MRI.

For the non-cancer examinations, we expect that the false recall rate for TOMO+CEM would be approximately 40% lower than what was historically reported for TOMO+MRI (e.g., 8% instead of 13%, based on Sung and Comstock studies respectively). With 600 women, we expect to estimate the false recall rate to within +/- 2.23% and have 80% statistical power for confirming that it is smaller than 11.5% (i.e., much smaller than 13% expected with MRI) using a two-sided 0.05-level test. The sample of 600 women will also allow maintaining at least 80% statistical power for estimating TOMO+CEM's false positive rates are up to 9.3% (instead of expected 8%), which cannot be excluded based on the current state of knowledge.

Based on a 25% rate of screen failures (e.g. elevated creatinine) and no-shows/cancellations, failed iv access, we expect to enroll up to 800 women to complete 600 examinations.

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