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Benefits of 3D Breat Tinisynthesis Combined with 2D Digital Mammography in Screening Women for Breast Cancer

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BENEFITS OF 3D BREAT TOMOSYNTHESIS COMBINED WITH 2D DIGITAL MAMMOGRAPHY IN SCREENING WOMEN FOR BREAST CANCER

by

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Abstract

Breast cancer screening imaging options have progressed greatly over the years in sensitivity, specificity, and image quality. According to DynaMed Plus, in 2012 there were 522,000 deaths by breast cancer and 1,677,000 total cases of breast cancer documented (Dynamed, 2018). For years, traditional screening for breast cancer involved 2D digital mammography which obtains two views of each breast. With advances in technology, the use of 3D breast tomosynthesis has become an advantageous addition to routine breast cancer screening protocols at many health care facilities.

My literature review of articles was found in PubMed, DynaMed Plus, Cochrane Library, and Clinical Key from the year 2011 and on. These articles and resources focus on the current recommendations for breast cancer screening. The benefits of 2D digital mammography alone, 3D breast tomosynthesis alone, and 2D digital mammography combined with 3D breast tomosynthesis are compared. This study also compares the differences in radiation dose of each imaging option. The research demonstrated that 2D digital mammography combined with 3D breast tomosynthesis offers the lowest recall rates, the highest sensitivity and specificity, and increases the effectiveness of breast cancer screening. The risk of this type of screening is the potential increase in radiation dose depending on the type of imaging system and the minimal increase in time the patient is under compression.

Key Terms: breast cancer screening, age 40 and older, 2D mammography, 3D mammography, and radiation dose mammography.

Benefits of 3D Breast Tomosynthesis Combined With 2D Digital Mammography in Screening Women for Breast Cancer

When women reach the age of 40, they have the choice to start annual screening tests for detection of breast cancer. By age 45, it becomes a recommendation that women start annual screening for breast cancer. With advances in technology, screening for breast cancer can be done in many ways. Two imaging options for screening are 2D digital mammography and 3D breast tomosynthesis. Each healthcare facility develops its own protocol for breast cancer screening. Some facilities have the resources to combine 2D digital mammography and 3D breast tomosynthesis in one imaging system. 2D digital mammography has been considered the gold standard for breast cancer screening (Dynamed, 2018).

2D digital mammography consists of two views of each breast under compression. 3D breast tomosynthesis consists of the same views under compression for each breast. During 3D breast tomosynthesis, the patient is under compression while the machine moves in a semi-circular pattern to obtain many views from different angles. While the machine rotates around the breast obtaining these different views, it is ultimately capable of imaging the breast tissue with minimal superimposition. This is very helpful in patients who have dense breast tissue in which cancer can easily hide. The digital ability of the 3D breast tomosynthesis machine reconstructs the two views that are normally obtained by 2D digital mammography. There is question as to whether the reconstructed views obtained by 3D breast tomosynthesis are diagnostically comparable to those obtained by 2D digital mammography.

Most healthcare facilities who have access to the newest technology are changing their breast screening protocols from 2D digital mammography to 3D breast tomosynthesis combined with 2D digital mammography. In order to obtain the combination study, the patient undergoes compression in which the first 2D image is taken followed by the 3D breast tomosynthesis

images. These images are obtained under the same compression. Then the patient proceeds to undergo the second round of compression to obtain the second view which completes the 2D digital mammography series. The patient remains under compression while the machine rotates and obtains the second 3D tomosynthesis view, thus completing the 3D breast tomosynthesis series. When 2D digital mammography and 3D breast tomosynthesis are combined, the patient does not undergo any additional views under compression. The additional time under compression while obtaining the first 2D view and the 3D tomosynthesis view is minimal and often does not cause any added discomfort to the patient.

Thanks to the advances in technology, providers and patients have increased access to imaging modalities used for screening of breast cancer. These advances in technology allow patients and providers access to breast imaging which increases sensitivity and specificity while using a radiation dose as low as reasonably achievable. The purpose of this study is to compare the specificity, sensitivity, and radiation dose of 2D digital mammography alone, 3D breast tomosynthesis alone, and 2D digital mammography combined with 3D breast tomosynthesis. This study involves screening in women age 40 and older for breast cancer. The sensitivity and specificity of the imaging options weighs heavily on whether a patient is called back for further imaging, studies, or procedures. When a patient receives the phone call that more imaging is needed in addition to their annual screening, it causes a lot of anxiety and stress on the patient and their family. Reducing the number of call backs for patients is beneficial to the patient, their loved ones, and the institution in which the patient doctors.

Statement of the Problem

Each radiology imaging modality has its own risks and benefits, especially pertaining to breast cancer screening. When a patient receives a 3D breast tomosynthesis scan, it can

reconstruct images that a 2D digital mammography scan would provide. This could ultimately eliminate the need for 2D digital mammography. Further investigation is needed to determine the specificity, sensitivity, and radiation dose of 2D digital mammography, 3D breast tomosynthesis, and these studies combined. This will help determine the safest and most effective imaging protocol for screening of breast cancer as this is an annual recommendation.

Research Questions

In women age 40 and older, does screening for breast cancer using 3D breast tomosynthesis alone versus 2D digital mammography alone offer increased accuracy, specificity, sensitivity, and less call back tests for patients?

In women age 40 and older, does screening for breast cancer using combination of 2D digital mammography with 3D breast tomosynthesis versus 2D digital mammography alone or 3D breast tomosynthesis alone offer increased accuracy, specificity, sensitivity, and less call back tests for patients?

Methodology

For this review, four databases were searched including DynaMed Plus, Cochrane, PubMed, and ClinicalKey from September 12, 2018 to September 30, 2018. The search method used for four of the articles from PubMed include mesh term search details: (2d[All Fields] AND ("mammography"[MeSH Terms] OR "mammography"[All Fields]) AND versus[All Fields] AND ("mammography"[MeSH Terms] OR "mammography"[All Fields] OR ("3d"[All Fields] AND "mammography"[All Fields]) OR "3d mammography"[All Fields])) AND ("2008/09/26"[PDat] : "2018/09/23"[PDat]). Search terms utilized for ClinicalKey included the following: breast cancer screening imaging, age 40 and older=-, full text, medline, systematic reviews, randomized control trials, and meta-analyses. Search term utilized for Cochrane database included: breast cancer screening imaging and tomosynthesis. The search terms, “breast

cancer screening" was utilized in the DynaMed Plus database. Sources used and chosen for this study are after the year 2011 and consist of randomized control trials, systematic reviews, and meta analyses. Works that were excluded included those published prior to 2011, studies performed on both men and women, and studies that included young women under the age of 18.

Review of the Literature

A review of literature has been conducted which provides evidence pertaining to the benefits of using 3D breast tomosynthesis in conjunction with 2D digital mammography in screening for breast cancer. The review demonstrates the increase in detection of suspicious lesions and the decrease in number of patients who are called back for further work up. The difference in radiation dosing between the two imaging options separately and combined is also demonstrated.

The drawbacks to the studies include: relatively small participant groups, the variability of patient's breast tissue, not all studies had the ability to follow up on patients with breast cancer providing sensitivity data, and different imaging systems were used from study to study.

Current screening recommendations and imaging options for breast cancer

It is considered a strong recommendation to start breast cancer screening for average-risk women aged 50-74. Patients are offered screening at age 40 but this screening should be based on shared decision making. Mammography is the imaging of choice for screening women with average-risk of breast cancer. Screening of mammography is recommended every two years, but annual screening should be discussed and considered with shared decision making. (Dynamed, 2018).

According to the American College of Radiology (ACR) Appropriateness Criteria for Breast Cancer Screening, average-risk women age 40 and older should begin annual screening mammography or 3D breast tomosynthesis (Mainiero et al., 2017). These guidelines are

reviewed annually by a multidisciplinary expert panel. The screening age recommendation of 40 years was concluded based on review of randomized trials and subsequent meta-analyses. Based on the articles and studies reviewed by the ACR, it was concluded that cancer detection rate increased with 3D breast tomosynthesis compared to 2D digital mammography alone. It was also found that recall rates for false-positive were decreased with the use of 3D breast tomosynthesis (Mainiero et al., 2017).

Comparing 2D digital mammography alone and 3D breast tomososynthesis (with 2D reconstruction) alone

Aase et al. (2018) published a randomized control study comparing 2D digital mammography to 3D breast tomosynthesis. This study targeted about 14,089 women aged 50-69 years old. Each woman was randomly assigned to screening with either 2D digital mammography or 3D breast tomosynthesis. The same imaging equipment was used on every patient as well as the same reading workstation equipment and screens. In order to keep the study consistent, each breast was assigned a score of 1-5 by the radiologist (1 being negative for abnormality and 5 being high suspicion for malignancy). If the patient was assigned a score of 2 or higher on one or both breasts, this meant the radiologists gathered to determine whether the patient needed to be called back for further imaging. This is often referred to as a recall. The recall rate for 3D breast tomosynthesis was 3.0% and 3.6% for 2D digital mammography (p = 0.03) (Aase et al., 2018). The recall rate for women with dense breasts was 2.2% for 3D breast tomosynthesis and 3.4% for 2D digital mammography (p = 0.04) (Aase et al., 2018). This statistical information pertaining to women with dense breasts is significant. One of the benefits of 3D breast tomosynthesis is that is eliminates superimposition. If a woman has dense breasts her breast tissue displays as white on a mammogram, as does cancer. This means that cancer can easily hide within dense breast tissue on a 2D digital mammogram. 3D breast tomosynthesis

allows the radiologist and provider to essentially scan through the breast looking between the dense breast tissue.

One factor to consider when comparing imaging modalities, is the amount of time the patient spends under compression and in the exam room. This aspect was measured during this study and it was found that the women who had 3D breast tomosynthesis spent an additional one minute and five seconds in the exam room. According to the study, the time radiologists spent reading and meeting for consensus was longer for 3D breast tomosynthesis than 2D digital mammography. The average reading time was one minute and 11 seconds for 3D breast tomosynthesis and 41 seconds for 2D digital mammography ($p < 0.01$) (Aase et al., 2018).

Mall et al. (2018) composed a study of 144 women aged 40 years and over in which 48 cases of cancers were randomly assigned to either 2D digital mammography or 3D breast tomosynthesis for workup. Fifteen radiologists were recruited, and each radiologist read the 48 cases. The study compared the sensitivity, specificity, and positive (PPV) and negative predictive value (NPV) (Mall et al., 2018). The radiologists' performances were calculated using the receiver-operating characteristics area under the curve (AUC). Radiologists had improved performance (AUC = 0.927) with the use of 3D breast tomosynthesis when compared to 2D digital mammography (AUC = 0.872). Similarly, the sensitivity, specificity, PPV, and NPV of 3D breast tomosynthesis (0.93, 0.75, 0.64, 0.96) were higher than 2D digital mammography (0.90, 0.56, 0.49, 0.92). It was concluded that there was a significant reduction in the need for additional views with 3D breast tomosynthesis (Mall et al., 2018).

The findings of the two trials coincide with results found in a meta-analysis performed by Marinovich et al. (2018). The meta-analysis included 17 studies, 1,009,790 participants, from 433 citations and compared breast cancer screening detection and recall rate in asymptomatic women for 3D breast tomosynthesis versus 2D digital mammography. In conclusion, 3D breast

tomosynthesis improved cancer detection rates and reduced the recall rate (Marinovich et al., 2018). The recall rate for 3D breast tomosynthesis was lower than 2D digital mammography (pooled absolute reduction = -2.2%, 98% CI = -3.0 to -1.4, $P < .001$, $I^2 = 98.2\%$) (Marinovich et al., 2018). The findings of this meta-analysis, again, demonstrates the benefits of 3D breast tomosynthesis.

Comparing 2D digital mammography combined with 3D breast tomosynthesis

Twenty-one articles were analyzed in the systematic review constructed by Coop et al. (2016). The review ultimately investigates whether 3D breast tomosynthesis should be used as a screening tool, diagnostic tool, or both. It also considers whether 3D breast tomosynthesis could potentially replaced 2D digital mammography or if it should be used alongside of it.

When 3D breast tomosynthesis is integrated with 2D digital mammography for screening, it was found that results from various studies demonstrated a reduction in false-positive recalls and positive predictive values raised. To state it simply, fewer women were recalled, and of those who were recalled a greater percentage were found to have cancer. This again demonstrates that cancer can easily hide behind tissue, especially dense breast tissue, and this superimposition of breast tissue and cancer is one of the downfalls of 2D digital mammography. 3D breast tomosynthesis reduces tissue superimposition making interpretation more accurate (Coop et al., 2016).

The findings of Coop et al.'s (2016) systematic review was parallel with the findings of another systematic review and a meta-analysis by Hodgson et al. (2016). Both reviews concluded that when 2D digital mammography and 3D breast tomosynthesis are in conjunction with one another, it results in the safest and most accurate screening protocol for breast cancer. Hodgson et al.'s systematic review compared the two screening options; 3D with 2D digital mammography versus 2D digital mammography alone. One study determined there was, "a

statistically significant higher invasive cancer detection rate in favor of 3D breast tomosynthesis + 2D digital mammography" (Hodgson et al., 2016 p.9). Results demonstrated more false positives in 2D digital mammography groups with higher recall rates. The evidence from this systematic review determined that 3D breast tomosynthesis combined with 2D digital mammography increased invasive cancer detection rates and increased the effectiveness of breast cancer screening.

A breast cancer research and treatment meta-analysis was completed by Yun et al. (2017). This meta-analysis, again, paralleled the findings of Coop et al. and Hodgson et al.'s systematic reviews. In conclusion of this meta-analysis, it demonstrates that while 3D breast tomosynthesis does provide optimal results and better detection of breast cancer, it is not yet found to be enough to replace 2D digital mammography. Rather, the two studies should be combined and integrated into a routine screening protocol (Yun et al., 2017). This meta-analysis demonstrates results from 11 eligible studies to conclude that risk ratios showed an increase in cancer detection for 3D breast tomosynthesis plus 2D digital mammography than 2D digital mammography alone for invasive cancer (1.327; 95% CI, 1.168-1.508), stage T1 (1.388; 95% CI, 1.137-1.695), nodal-negative (1.451; 95% CI, 1.209-1.742), all histologic grades (grade I, 1.812; grade II/III, 1.403), and histologic types of invasive cancer (ductal, 1.437; lobular, 1.901) (Yun et al., 2017). Combining 3D breast tomosynthesis with 2D digital mammography did not increase detection of carcinoma in situ or nodal-positive cancer (Yun et al., 2017). Still, with the increase in detection of other cancers and decrease in recall rates, 3D breast tomosynthesis combined with 2D digital mammography offers a more reliable screening protocol for breast cancer.

A randomized control trial was conducted by Pattacini et al. (2018). This involved 9,777 women ages 45-70 years old. Each woman was randomly assigned to undergo either 2D digital

mammography combined with 3D breast tomosynthesis or 2D digital mammography alone. The detection rate was about 90% higher with 3D breast tomosynthesis combined with 2D digital mammography than with 2D digital mammography alone. The recall rate was 3.5% in both arms (Pattacini et al., 2018).

Comparison of radiation doses between 2D digital mammography alone, 3D breast tomosynthesis alone, and 2D digital mammography combined with 3D breast tomosynthesis

Gennaro et al. (2017) published a per-view analysis comparing the radiation doses between 3D breast tomosynthesis and 2D digital mammography. The analysis included 4,780 2D digital mammography studies and 4,798 3D breast tomosynthesis studies from a total of 1,208 women. All in all, it found that there is a modest increase in dose for 3D breast tomosynthesis (Gennaro et al., 2017). The estimated mean glandular dose (per view) was 1.36mGy (SD 0.51) for 2D digital mammography, 1.87mGy (SD 0.67) from 3D breast tomosynthesis, and 3.22mGy (SD 1.16) from combining the two imaging methods (Gennaro et al., 2017).

The ACR has a criterion mentioned earlier created by Mainiero et al. (2017) which also states the increase in dose is either the same or a modest increase depending on the imaging system being used (Mainiero et al., 2017). The randomized controlled study conducted by Aase et al. (2018) reported that the mean glandular dose for 3D digital breast tomosynthesis was 2.96mGy and 2.95 for 2D digital mammography ($p = 0.433$) (Aase et al., 2018). Physicists work with the imaging systems purchased by a health care facility in order to calibrate them appropriately. The key is to deliver the lowest dose of radiation possible while maintaining diagnostic quality of the images. Some imaging systems offer both 2D digital mammography and 3D breast tomosynthesis with little to no increase in radiation dose to the patient. This is

significant when integrating 2D digital mammography and 3D breast tomosynthesis because often patients assume the radiation dose is doubled.

Discussion

In women age 40 and older, does screening for breast cancer using 3D breast tomosynthesis alone versus 2D digital mammography alone offer increased accuracy, specificity, sensitivity, and less call back tests for patients?

3D breast tomosynthesis has the ability to digitally reconstruct the images provided by 2D digital mammography. Due to this advance in technology, it has been studied whether 3D breast tomosynthesis could potentially replace 2D digital mammography. According to a meta-analysis included in this study, 3D breast tomosynthesis has not yet been found to be reliable enough to replace 2D digital mammography and rather they should be combined and integrated (Yun et al., 2017).

Mall et al. (2018) reported that 3D breast tomosynthesis demonstrates increased sensitivity, specificity, positive predictive value, and negative predictive value when compared to 2D digital mammography. It also included that radiologists had improved performance when reading 3D breast tomosynthesis compared to 2D digital mammography. In conclusion of the study conducted by Mall et al. (2018), 3D breast tomosynthesis is superior to 2D digital mammography and reduces the need for additional views which increases the patient's radiation exposure.

3D breast tomosynthesis increased and improved cancer detection rates and reduced recall rates for false-positives in a study conducted by Mainiero et al. (2017). As discussed in the introduction, the compression a woman endures for 2D digital mammography is the same compression needed to obtain 3D breast tomosynthesis but slightly increased in amount of time. The only harm to the patient is the risk of increased radiation dose when comparing 2D digital

mammography to 3D breast tomosynthesis. According to Gennaro et al. (2017) and Mainiero et al. (2018), there is only a modest increase in radiation dose when replacing 2D digital mammography with 3D breast tomosynthesis. The randomized controlled study conducted by Aase et al. (2018) demonstrated a 0.01mGy increase in radiation dose with 3D breast tomosynthesis compared to 2D digital mammography. Gennaro et al. (2017) reported an increase dose of 0.51mGy with 3D breast tomosynthesis. It is important to mention that the radiation dose is different for each imaging system used. The radiation dose also depends on how the machine is calibrated by the facility's physicists.

In women age 40 and older, does screening for breast cancer using combination of 2D digital mammography with 3D breast tomosynthesis versus 2D digital mammography alone or 3D breast tomosynthesis alone offer increased accuracy, specificity, sensitivity, and less call back tests for patients?

When 3D breast tomosynthesis is combine with 2D digital mammography instead of digitally constructing the views obtained by 2D digital mammography, this results in higher invasive cancer detection rates and increased effectiveness of breast cancer screening making it the superior screening protocol (Hodgson et al., 2016).

As stated previously, the study conducted by Yun et al. (2017) suggests that 3D breast tomosynthesis is not yet proven to be diagnostically equivalent to 2D digital mammography therefore it cannot replace it. Rather, these two modalities should be combined for optimal screening of breast cancer. When 3D breast tomosynthesis is combine with 2D digital mammography, cancer detection rate is 90% higher and most imaging vendors have developed machines in which the dose of combining 3D and 2D is only slightly increased when compared to 3D breast tomosynthesis alone (Pattacini et al., 2018). The study conducted by Pattacini et al. (2018) does state in conclusion that the recall rates were not significantly different when

comparing 3D breast tomosynthesis combined with 2D digital mammography versus 2D digital mammography alone.

Overall, the review of the literature demonstrates that the combination of 3D breast tomosynthesis and 2D digital mammography provides the most accurate detection of breast cancer and the highest specificity, sensitivity, positive predictive value, negative predictive value, and the lowest recall rate for further imaging. The only risk and negative side to this combination being standard screening, is a modest increase in radiation dose and a slight increase in time that the patient is under compression.

Applicability to Clinical Practice

When screening for breast cancer in women age 40 and up, the information provided in this literature review assesses the most accurate tests available to patients. Traditionally, screening for breast cancer involved 2 views of each breast using a 2D digital mammography system. As health care facilities gain access to new types of technology and imaging systems, 3D breast tomosynthesis is commonly combined with 2D digital mammography as part of the screening protocol for breast cancer. Although adding the tomosynthesis view onto the 2D digital mammography series slightly increases reading time by radiologists, radiologists have reported that it is worth the increased reading time due to the increased specificity and sensitivity on the patient's test results.

When 3D breast tomosynthesis is combined with 2D digital mammography, the rate of patients who got called back for further imaging were lower than the rate compared to 2D digital mammography alone and 3D breast tomosynthesis alone. The greatest benefit of 3D breast tomosynthesis is the technology it uses to look at tissue in the breast without superimposition. This increase in specificity and sensitivity saves the patient from unnecessary anxiety, time taken

out of their daily lives, and increased cost to the patient and facility. There have been instances where 3D breast tomosynthesis has saved a patient from addition procedures that, in some cases, can be invasive. This is especially important and significant in women with dense breast tissue. Cancer hides easily in dense breast tissue on 2D digital mammography.

Some studies reported a slight increase in radiation dose when combining 3D breast tomosynthesis with 2D digital mammography while other studies did not report an increase in radiation. The radiation dose depends on the imaging system and the physicists who work together to calibrate the system in order to deliver a radiation dose as low as reasonably achievable. There are some imaging systems in which there is no increase in radiation dose when 3D breast tomosynthesis is combined with 2D digital mammography. This information is incredibly valuable to providers when ordering screening mammography studies for women. When a patient expresses concern about the added radiation or added compression they will undergo, the information included in this literature review helps to better explain the mammographic study including the risks and benefits.

If a health care facility's protocol for breast cancer screening involves 3D breast tomosynthesis combined with 2D digital mammography, it is proven in this literature review that this offers the most accurate and safest imaging option for breast cancer screening in women 40 and older.

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