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Synthesized 2D Mammographic Imaging

Theory and Clinical Performance

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Motivation for Synthesized 2D Images

Breast tomosynthesis in screening using the Hologic system has demonstrated superior clinical performance to conventional 2D mammography in a number of metrics, in particular showing improved detection of invasive cancers and reductions in recall rate.[1] The studies that demonstrated the maximal improvements all share one characteristic: they involve the availability of 2-view tomosynthesis (CC and MLO) and 2-view 2D images (CC and MLO). Studies using only one view tomosynthesis (MLO) have either not shown improvement over 2D[2] or have failed to demonstrate both improved cancer detection and simultaneous recall rate reduction.[3]

Because cancers are often better visualized in one tomosynthesis view or the other— sometimes the CC is superior and sometimes the MLO is superior— taking both tomosynthesis views increases the chances of seeing a lesion.[4] The 2D images in a tomosynthesis study are not rendered superfluous just because the tomosynthesis images are available. 2D images are useful for comparison to 2D priors, for detection of left/right asymmetries, and for the rapid detection of microcalcification clusters.

The original studies performed using 2-view combo mode imaging (2D and tomosynthesis in both CC and MLO) were performed by acquiring both the FFDM and the tomosynthesis images, and therefore increased the dose, approximately doubling the dose compared to 2D imaging.[5]

The goal of reducing radiation dose, while at the same time maximizing clinical performance, has led to the development of synthetic 2D images that are generated from the tomosynthesis datasets and do not require additional radiation exposures beyond those of the tomosynthesis images. Synthetic 2D images also offer the benefit of improved patient comfort, through the elimination of the FFDM acquisitions, by reducing breast compression time compared to a study acquiring both FFDM and tomosynthesis images.

Without the availability of synthetic 2D imaging, one cannot provide both two 2D views and two tomosynthesis views without increasing the dose beyond the two tomosynthesis views themselves.

To this end, Hologic has developed synthetic 2D algorithms, known as C-View™, and its 2D images are designed, clinically validated, and FDA approved to diagnostically replace the FFDM images in a combined 2D/tomo screening study.

C-View Algorithm Goals/Design Objectives

The primary design objective of the C-View algorithm was to create a synthetic 2D image of sufficient clinical value that it can replace the FFDM 2D image in a screening exam, while maintaining the tomosynthesis improvements in cancer detection and reduction of recall rate. It should be sufficiently similar to a conventional 2D image to facilitate comparison to 2D priors, but importantly, it does not need to look exactly like the FFDM 2D image that it is replacing. In fact, Hologic realized early on that a synthetic 2D image that looked identical to a FFDM 2D image would carry with it many of the negative characteristics of the FFDM 2D whose limitations encouraged the development of tomosynthesis in the first place. This realization led to a design goal whereby the visibility of mass and calcification lesions would be greater in the C-View 2D image than in the FFDM 2D image it was replacing, especially in denser regions in breasts where feature visibility is decreased due to the overlapping parenchyma.

Given the above, the design goals of the Hologic C-View software were to:

- Replace the FFDM 2D images in a tomosynthesis

screening exam, allowing 2-view CC and MLO tomo at similar doses to 2-view (CC and MLO) FFDM 2D imaging

- Facilitate high volume screening, including rapid identification of calcifications, architectural distortions and mass lesions. To help achieve this goal, increase the contrast of these characteristics to be higher than the contrast in typical FFDM 2D images
- Allow comparison to 2D priors
- Highlight calcification clusters to avoid the 'thin slice' effect of thin tomosynthesis slices
- Maintain the ability to assess parenchymal density
- Maintain similar clinical performance to combo mode (FFDM 2D+tomo) in the detection of invasive cancers and reducing recall rates

Tomosynthesis System Requirements

The C-View images are created solely from the tomosynthesis slices, so it is important that the tomosynthesis images are of adequate quality. One of the demanding challenges is the appearance of microcalcifications. There are several important system characteristics that allow tiny microcalcifications to be visualized, among them high spatial resolution and minimal patient motion.

Hologic generates reconstructed slices with resolutions of approximately 100 microns – adequate for visualizing microcalcifications. The very high spatial resolution of direct conversion amorphous selenium detectors mean that their spatial resolution as measured by Modulation Transfer Function (MTF), even when employing 140-micron pixel readout, is higher up to its Nyquist limit than the MTF resolution of 100-micron cesium iodide detectors[6], and facilitated the development of a tomosynthesis system with very short scan times.

Short scan times are perhaps the single most important tomosynthesis characteristic that allow for high quality high resolution imaging. Hologic's tomosynthesis scan time of 3.7 seconds, even for the largest breasts, is similar to conventional mammographic exposure times, and much shorter than scan times for some other tomosynthesis systems that have scan times in the 10-20 second range.[7] Blurred images due to patient motion are more likely when scan times increase because it is more difficult for the patient to remain still during the entire scan. It is known that the likelihood of patient motion increases with increasing exposure time.[8] Patient motion may also be exacerbated in systems that employ a moving face shield, because the patient cannot rest comfortably against the face shield. Added benefits to the short Hologic tomosynthesis scan time are greater patient comfort through shorter compression time; and faster screening exams compared to slower systems using the same protocols.

The importance of reducing the possibility of patient motion is even more important when using synthetic 2D imaging than when relying on a FFDM 2D image such as part of a tomosynthesis screening exam. In a combo mode study, where both a FFDM 2D and a tomosynthesis image are available, if the patient should move during the tomosynthesis portion of the study, at least the FFDM 2D image is available and may not have motion. However, if the FFDM 2D image is dispensed with, if there is motion in the tomosynthesis images then there will be a degradation in the synthetic 2D image which is created from the tomosynthesis slices. Thus, short tomosynthesis time scans are critically important in synthetic 2D procedures.

Hologic made system design decisions specifically to address this need for high resolution images without patient motion, such as high resolution selenium detectors, a tomosynthesis stationary face shield, and the shortest scan time among FDA-approved tomosynthesis systems.[9]

C-View Algorithm Description

The C-View algorithm starts with a standard tomosynthesis acquisition, in any desired projection such as CC or MLO or LM etc. The scan is reconstructed into 1 mm slices. If the synthesized 2D image was designed to mimic a conventional FFDM 2D image exactly, these slices could be algebraically combined to create the synthesized 2D image, but as previously mentioned this would result in a synthesized 2D image with some of the same limitations as a conventional FFDM 2D image.

The Hologic C-View algorithm attempts to create an image whereby certain features of interest appear with greater conspicuity than they would in the conventional FFDM 2D image. This is accomplished by identifying slices and regions containing calcification-like and lesion-like characteristics such as linear structures, and then combining the tomosynthesis slices into the final C-View 2D image but giving these special regions extra weighting compared with normal fibroglandular and adipose breast tissue.

The objects of interest can be found using filters, for example a high-pass filter finds small objects such as microcalcifications.

Because of these enhancements, the C-View 2D image will not look identical to the FFDM 2D image it is replacing, just as different manufacturer's FFDM 2D images all look different. Sometimes this enhancing algorithm results in C-View 2D images that intentionally look quite different from a FFDM 2D image, but this should not be thought of as a limitation of C-View software. The difference can manifest itself as a difference in the appearance of fibroglandular tissue in addition to the difference due to the enhancement of linear and calcification-like structures.

The C-View algorithm places high value on the importance of contrast resolution, not dissimilar to the design goals of CT versus an x-ray radiograph. The final combined C-View image is then formatted to be saved and displayed as a conventional 2D DICOM image, with the one difference that the image has a burned in "C-View" mark so it can be distinguished from a FFDM 2D image.

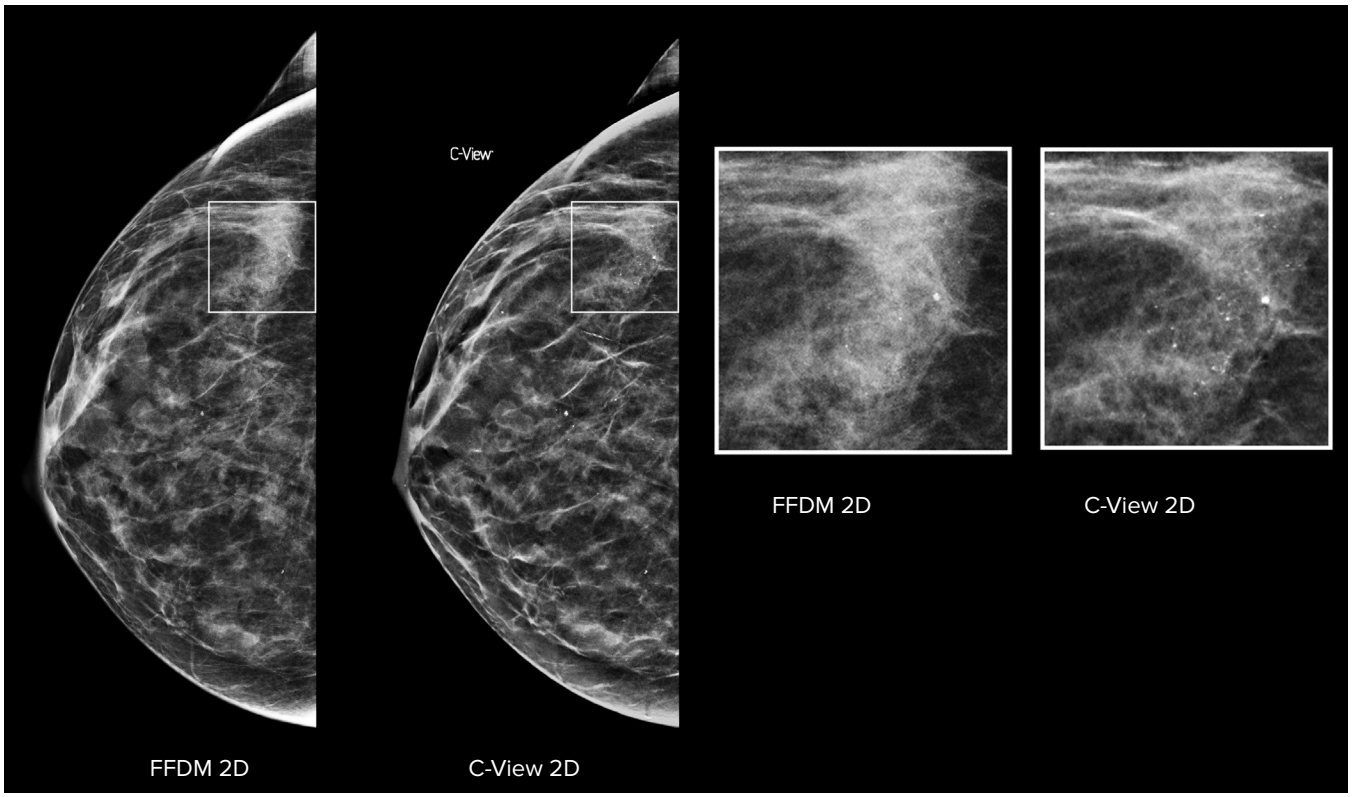

Figure 1: Visibility of calcifications as seen in C-View 2D and FFDM 2D images from the same study.

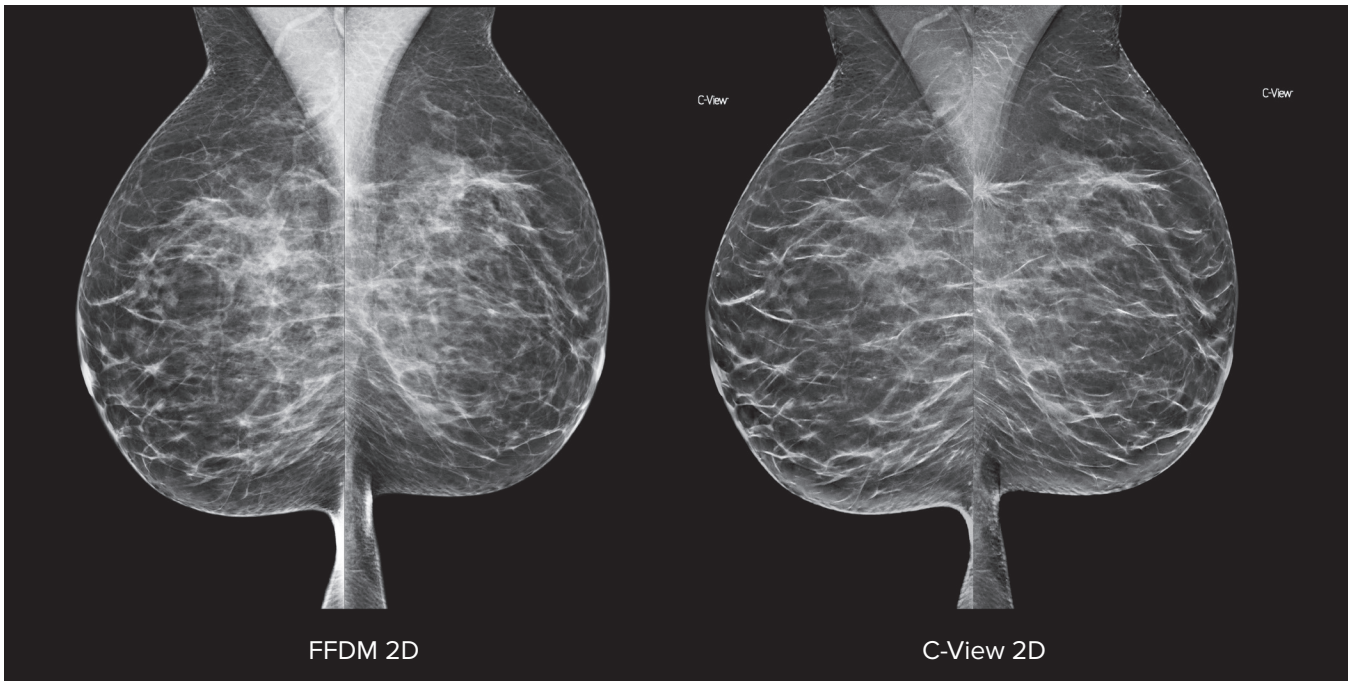

Figure 2: C-View 2D and FFDM 2D images can differ in contrast, resolution, parenchymal density, and skin line appearance.

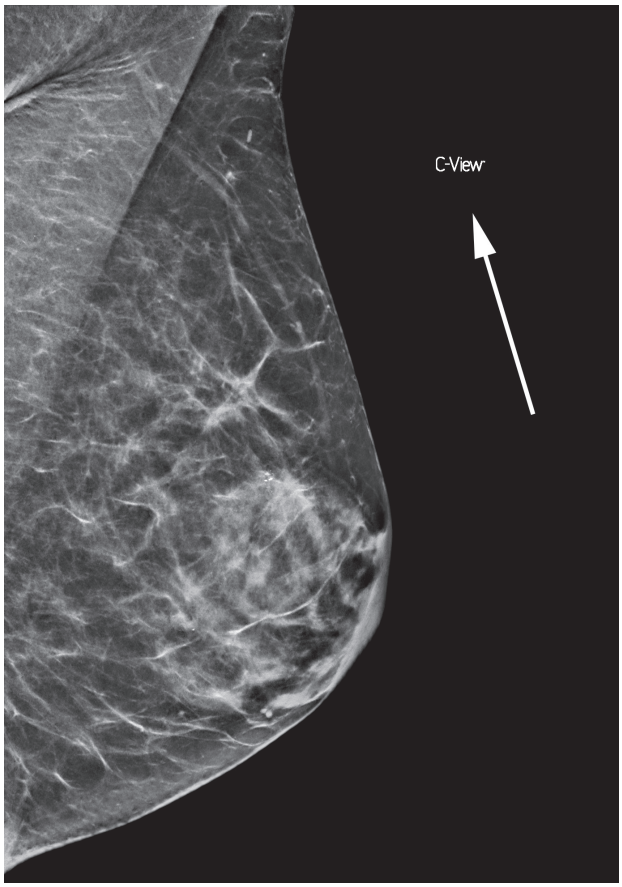

Figure 3: C-View 2D image with the burned-in "C-View" mark identifier.

Clinical Uses of Synthesized 2D Images

There are two main methods by which a synthesized 2D image can be used. One is simply as a navigation tool for the tomosynthesis images. The other, more demanding application, is for diagnostic use, to be able to replace the FFDM 2D image as part of a 2D/tomo screening study. Hologic's C-View 2D images were developed with the diagnostic use in mind, and has received FDA approval and CE mark for this purpose, although of course the C-View 2D image may also be used for navigation to expedite the tomosynthesis exam review. Because C-View 2D is approved to replace the FFDM 2D image in a tomosynthesis screening study, it allows the reduction of dose by eliminating the need for a separate 2D acquisition.

Dose of C-View 2D

There is no additional radiation dose for C-View 2D images beyond that of the standard tomosynthesis acquisition. Using C-View software allows the acquisition of 2-view tomo images and provides 2-view 2D images for a tomosynthesis screening exam at the same dose of a typical 2-view FFDM 2D study.[10]

Clinical Performance of C-View 2D

The clinical performance validating the ability of C-View 2D to diagnostically substitute for the FFDM 2D image in a tomosynthesis screening exam has been demonstrated and documented in several ways: as part of an ROC-analysis enriched reader study and in reports of the performance in clinical screening usage. Comparisons have been made of the C-View 2D/tomo (tomoHD mode) performance to 2D imaging and to FFDM 2D/tomo performance (combo mode).

ROC-analysis Reader Studies

This reader study was submitted as part of the C-View software's U.S. FDA approval process and CE mark.[11] The reader study involved 302 cases read by 15 board-certified radiologists. The study compared the performance of C-View 2D combined with tomo (tomoHD mode) to the performance of FFDM 2D. The primary endpoint of the study was met and exceeded. In this study, C-View 2D plus tomosynthesis was shown, using ROC analysis, to be statistically superior to 2D imaging alone.

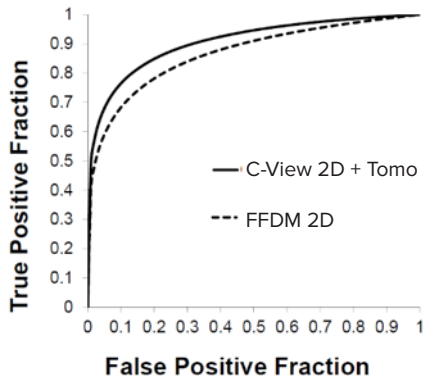

Figure 4: The ROC curve performance of C-View 2D plus tomo was superior to 2D.

There are other reader studies that reported on the performance of C-View 2D and affirm its positive performance. Zuley et al concluded that C-View 2D alone was comparable to 2D, and with tomosynthesis was comparable to 2D plus tomo.[12] Choi et al concluded that the diagnostic performance of C-View and 2D were comparable in the detection of T1-stage breast cancers.[13]

Clinical Results

It is also been shown that the use of C-View 2D plus tomosynthesis gives comparable clinical performance to 2D/tomo combo mode imaging.[14-16]

A large study reporting on the clinical performance of synthesized 2D imaging was published by Skaane et al and gave results for two years of experience in screening in Oslo County.[14] Two versions of synthesized 2D algorithm were studied. The first year employed a pre-commercial early version of the algorithm, and the second year documented the results using the released C-View version that was approved by the U.S. FDA in 2013.[15] The second year's results, with the commercial C-View software, were concluded to be 'substantially equivalent' to FFDM 2D/tomo combined imaging.

More recently, a series of presentations at the 2015 Radiological Society of North America (RSNA) annual meeting reported on the clinical experience of C-View, as C-View software became commercially widespread.

A summary of studies is given on the next page.

Study	Conclusion	Where Published	Title
C-View FDA reader study	C-View 2D/tomo is superior to 2D	FDA panel meeting	Hologic Selenia Dimensions C-View Software Module
Zuley, Guo, Catullio, et al.	C-View 2D alone or in combination with tomo is comparable in performance to 2D alone or in combination with tomo	*Radiology,* 2014	Comparison of Two-dimensional Synthesized Mammograms versus Original Digital Mammograms Alone, and in Combination with Tomosynthesis Images
Choi, Han, Ko, et al.	Diagnostic performance of C-View 2D and 2D are comparable for detecting T1-stage breast cancers	*European Radiology, 2015*	Comparison Between Two-dimensional Synthetic Mammography Reconstructed from Digital Breast Tomosynthesis and Full-field Figital Mammography for the Detection of T1 Breast Cancer
Skaane, Bandos, Eben, et al. (Oslo)	C-View 2D/tomo is comparable to 2D/tomo	*Radiology*, 2014	Two-View Digital Breast Tomosynthesis Screening with Synthetically Reconstructed Projection Images: Comparison with Digital Breast Tomosynthesis with Full-field Digital Mammographic Images
Bernardi, Pellegrini, Valentini, et al. (STORM II)	C-View 2D/tomo is comparable to 2D/tomo	RSNA 2014	The STORM II (Screening with Tomosynthesis or Mammography II) Trial: Interim Comparison of Screen-reading Strategies in Population Breast Screening
Zuckerman, Conant, Weinstein, et al.	Stable recall rates and lesion types were seen with the replacement of 2D with C-View 2D in combination with tomo	RSNA 2015	Impact on Recall Rates Following Implementation of Synthesized 2D Mammography in Digital Breast Tomosynthesis Screening
Choi, Ko, Kim, et al.	Diagnostic performance of C-View 2D and 2D are comparable for detection and classification of calcifications. Results indicate that C-View 2D may overcome the limitation that tomo may underestimate the calcifications during tomo-based screening.	RSNA 2015	Detection and Classification of Calcifications on Two-dimensional Mammography: Comparison of Synthetic Mammography Reconstructed from Digital Breast Tomosynthesis and Full-field Digital Mammography
Durand, Raghu, Geisel, et al.	C-View 2D+tomo shows the majority of mammographic findings equally well/better than 2D+tomo, regardless of breast density or age, with equitable recall rates and cancer detection.	RSNA 2015	Synthesized 2D Mammography+Tomosynthesis: Can We See Clearly?
Mariscotti, Durando, Bogetti	C-View 2D alone is comparable in performance to 2D, demonstrating a similar sensitivity, specificity and area under the ROC curve; C-View 2D could be used instead of 2D in addition to tomo images as part of routine clinical study.	RSNA 2015	Synthetized Digital Mammography Compared to Conventional Digital Mammography in a Diagnostic Setting
Woo, Choi, Shin, et al.	C-View 2D showed equivalent diagnostic values as compared with 2D. Overall characterization of the lesion was better in C-View 2D, and especially C-View 2D showed statistically significant superiority in evaluation of spiculated margin and architectural distortion.	RSNA 2015	Comparative Diagnostic Value of Two-dimensional Synthesized Mammogram and Conventional Full-field Digital Mammogram for Evaluation of Breast Cancer

Verification of Synthesized Image Performance

Not all synthesized images are created equal. The importance of clinically validating the performance of a synthesized 2D is are given in the instructive results from the Oslo study as reported by Skaane.[14] As previously noted, they reported on two year's synthesized 2D experience, one with an early pre-commercial version and the second year with the final commercially-released C-View version. The cancer detection rates seen in the various arms of the study are given in the table below. Using the pre-commercial synthesized 2D images, the synthesized mammography (SM) + tomo had a cancer detection rate of 7.4/1000, higher than the FFDM 2D arm at 6.1/1000, but lower than the 2D+tomo arm which had a cancer detection rate of 8.0/1000. The arm using the C-View software commercial version showed a rate of 7.7/1000, which was not statistically significant from the 2D+tomo arm with 7.8/1000. The authors reported that use of C-View 2D to replace FFDM 2D in a tomosynthesis screening exam offered comparable clinical performance to the FFDM 2D/tomo combo mode imaging. Similar results were seen in the STORM II data, which showed an even higher cancer detection rate using C-View/tomo compared to FFDM 2D/tomo, although this was not statistically significant.[16]

The commercial C-View algorithm has been shown to be comparable to the cancer detection performance of a combo mode study,[11-16] although an early pre-release version was not. Clinical validation of a synthetic 2D algorithm should be demonstrated before any decision is made to implement it in screening.

	Cancer detection rates		
Algorithm	**FFDM 2D**	**FFDM 2D + tomo**	**SM + tomo**
Synthesized 2D pre-commercial early version	6.1/1000	8.0/1000	7.4/1000
C-View 2D commercial version (Oslo)	Not published	7.8/1000	7.7/1000
C-View 2D commercial version (STORM II)	5.7/1000	6.3/1000	8.2/1000

Clinical Use of C-View 2D

The clinical use of C-View 2D is determined by the medical professional, however, here are some general thoughts and guidelines that may be useful.

C-View 2D is approved and validated to replace the FFDM 2D images in a tomosynthesis screening study. Even though the C-View 2D images replace the FFDM 2D images, they are not treated identically to FFDM 2D images in a combined study. This is because, whereas a FFDM 2D image is a separately-acquired image independent from the tomo dataset, the C-View 2D is not independent of the tomosynthesis data, because it is created from the tomosynthesis slices.

As such, the tomosynthesis slices represent the primary diagnostic image set. Findings in a C-View 2D image should be reviewed in the tomo slices, and one would not make clinical decisions on the basis of the C-View 2D images alone without reviewing the corresponding tomosynthesis dataset. Finally, findings in one C-View 2D image may not appear identically in another view of the same breast, just as findings in one 2D image may not be apparent in another 2D view.

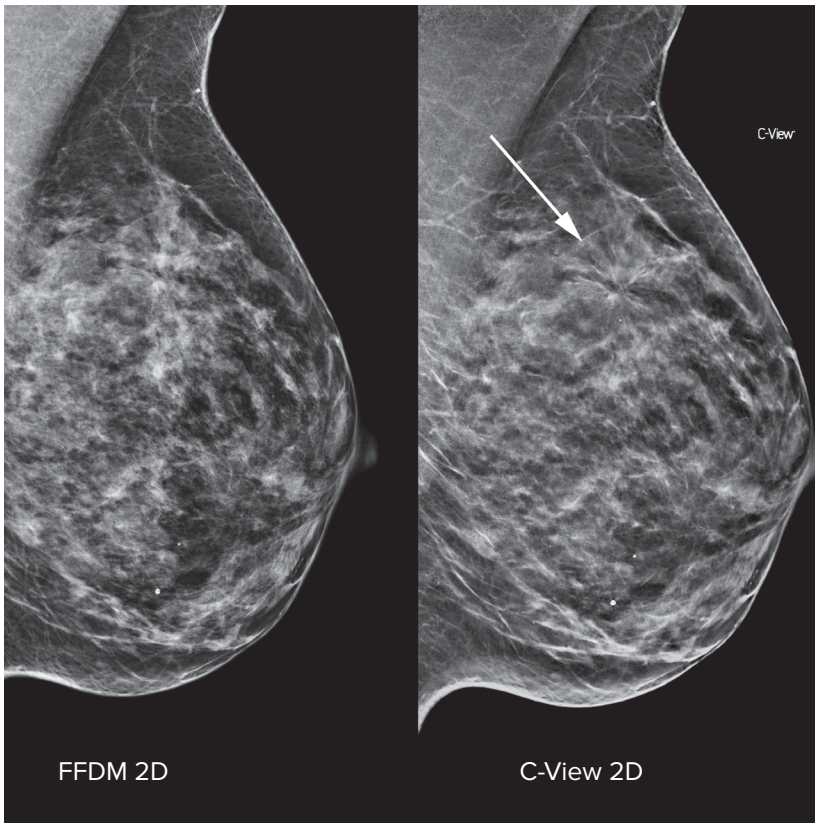

Figure 5: Invasive ductal carcinoma as seen in FFDM 2D and C-View 2D.

Site Implementation Suggestions

One should consider development of an implementation plan that may ease the transition from using FFDM 2D to using C-View 2D, such as:

- Suggest your staff review the CME available on the use of C-View 2D within tomosynthesis exams (www.hologic.com/training).
- Prepare your staff by describing how its images will differ from your current FFDM 2D images, not unlike the issues faced when switching FFDM 2D vendors.
- Many customers report that the transition from combo or comboHD (FFDM 2D + C-View 2D+ Tomo) mode to tomoHD mode is easiest when a transition timeline is developed and held to.
- Finally, remember that even though sometimes C-View 2D images may differ in look from FFDM 2D images, one can have confidence that tomoHD has been clinically validated.[11-16]

Developments in C-View Software

Hologic is committed to continually evolving our tomosynthesis and C-View algorithms, to further improve the clinical performance of our 3D MAMMOGRAPHY™ imaging. One recent example is improved imaging for breasts when there are large calcifications or metal clips present. Another example under development reduces the likelihood of enhancing features that may not be of clinical interest.[17] We are also investigating how to use the C-View 2D image to reduce reading time in a tomosynthesis study.[17]

Routine Quality Control of the C-View 2D Image

C-View 2D QC is treated differently from FFDM 2D QC. C-View 2D images do not need to be part of routine QC procedures. This is sometimes seen as surprising to users familiar with performing routine QC on FFDM 2D images and tomosynthesis datasets. QC on FFDM 2D and tomosynthesis images are routinely performed, usually using standard test phantoms, to ensure proper system operation.

The C-View 2D images, on the other hand, are created from the tomosynthesis dataset, so if the tomosynthesis images pass QC, then the C-View 2D image will process properly, and there is no need to QC the C-View 2D images. The proper processing of the tomosynthesis images into the C-View 2D image is tested and verified and validated (V&V) through Hologic's software V&V process. Once the algorithm is verified to be operating properly, it will work consistently, because software does not degrade over time. Software installations and upgrades are confirmed using standard software checksum methods by the engineer installing the software, guaranteeing proper installation.

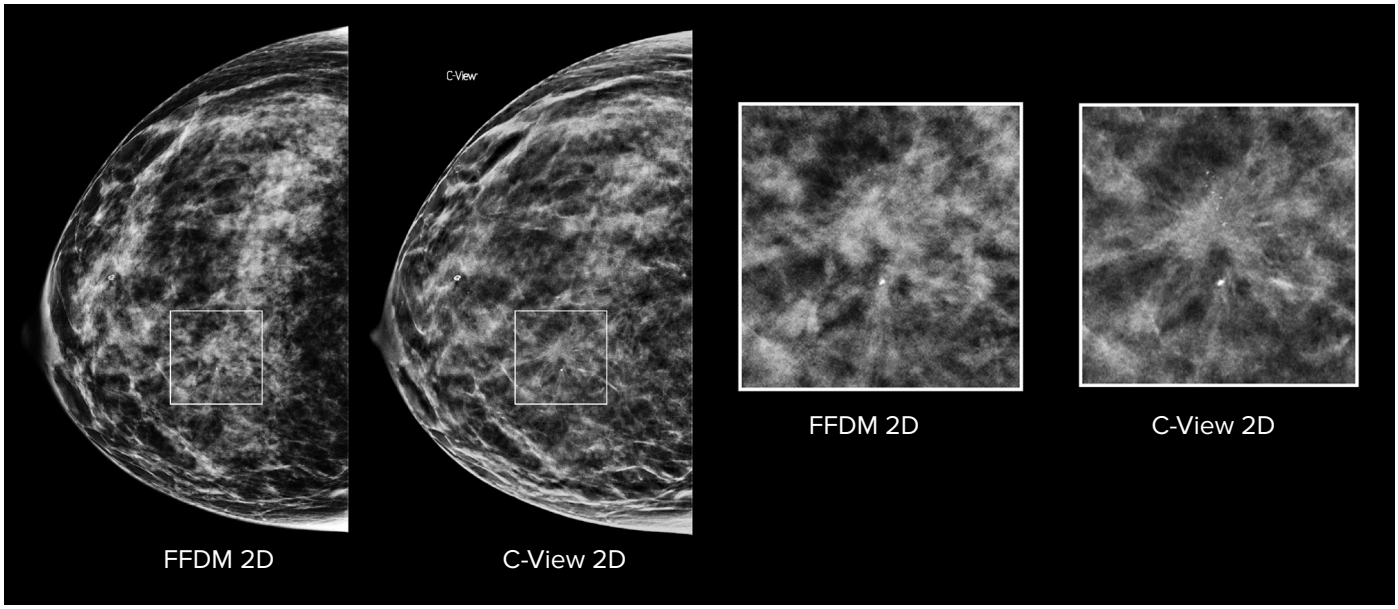

Figure 6: Invasive ductal carcinoma as seen in FFDM 2D and C-View 2D.

Conclusions

The safety and efficacy of C-View 2D to replace the FFDM 2D image in a tomosynthesis screening exam has been validated through multiple clinical evaluations.[11-16] The use of C-View software allows performing a 2-view tomo exam that provides all the views (2D-CC, 2D-MLO, Tomo-CC, Tomo-MLO) shown to increase invasive cancer detection and decrease recall rates, and at the same time lowering dose and patient compression time.

Glossary

2D	FFDM
2D/Tomo	Combo mode procedure where the 2D image is a standard FFDM exposure
Combo	Procedure where tomo and 2D images are acquired in the same projection
ComboHD mode	Procedure where tomo and 2D images are acquired in the same projection and, additionally, C-View 2D images are generated
C-View™	Hologic's name for synthesized 2D images and software
C-View 2D/Tomo	Known as tomoHD procedure, mode where the 2D image is synthesized from the tomo exposure
FFDM	Full Field Digital Mammogram
MTF	Modulation Transfer Function
ROC Curve	Receiver Operating Characteristics curve
RSNA	Radiological Society of North America
SM	Synthesized 2D Mammogram, same as Synthesized 2D
Synthesized 2D	A 2D image generated from the tomo slices, without the need for a 2D radiation exposure
Tomo	Shorthand for tomosynthesis
TomoHD mode	Procedure where tomo alone is acquired and C-View 2D images are generated

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[17] Research, development and evaluation projects are presented for informational purposes only and do not necessarily indicate that the items will be commercialized. These items are not available for use and are subject to FDA and country regulatory approvals. If/when commercialized, they may be subject to additional license, software and/or hardware purchases.

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