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FULL PAPER

The potential use of ultra-low radiation dose images in digital mammography—a clinical proof-of-concept study in craniocaudal views

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Objective: To estimate the potential of low-dose images in digital mammography by analysing the effect of substantial dose reduction in craniocaudal (CC) views on clinical performance.
Methods: At routine mammography, additional CC views were obtained with about 10% of the standard dose. Five radiologists retrospectively read the standard [mediolateral oblique (MLO) + CC] and combination low-dose mammograms (standard MLO + low-dose CC). If present, lesion type, conspicuity and suggested work-up were recorded. Final diagnoses were made by histology or follow up. A *t*-test or χ^2 test was used to compare results.
Results: 421 cases were included, presenting 5 malignancies, 66 benign lesions and multiple non-specific radiologic features. Using MLO with low-dose CC, all lesions were detected by at least one reader, but altogether less often than with standard mammography (sensitivity, 73.9% *vs* 81.5%). Missed lesions concerned all types. Lesions detected with both protocols were described similarly ($p = 0.084$) with comparable work-up recommendations ($p = 0.658$).
Conclusion: Mammography with ultra-low-dose CC images particularly influences detection. While sensitivity decreased, specificity was unaffected. In this proof-of-concept study a lower limit was to be determined that is not intended nor applicable for clinical practice. This should facilitate further research in optimization of a low-dose approach, which has potential in a relatively young and largely asymptomatic population.
Advances in knowledge: Tungsten/silver-acquired mammography images might facilitate substantial dose reduction. Ultra-low-dose CC images reduce sensitivity, but not specificity. Low-dose images have potential in a largely young and asymptomatic population; a baseline is set for further research in optimization of a low-dose approach.

Mammography is the most widely used modality in breast imaging. An increasing number of females throughout the world undergo mammography frequently, either in the diagnostic or screening setting. With the growing incidence of breast cancer, and the decreasing age of onset, the demand for mammography, particularly in the younger population, is still rising. Also, a considerable number of high-risk females are identified and advised to have annual mammograms, as part of a multimodality approach, preceding regular screening. With this development, in a relatively young and largely asymptomatic population, every opportunity to lower radiation dose in mammography should be investigated.

Standard mammography is gradually being extended to tomosynthesis. When used with synthetic two-dimensional (2D) mammography, the mean radiation dose might be comparable to standard mammography,[1] but lower doses are not to be expected. Moreover, implementation of a new technology, in screening and diagnostic imaging practices, takes both time and money. Therefore, in low-income countries and countries in transition, 2D mammography will continue to play a significant role for many years. Hence, ongoing research in radiation protection in this field is of undiminished importance.

Since digitization of radiology, low-dose imaging is receiving increased attention. In digital mammography,

radiation dose can be easily adapted. Owing to image processing, the unfavourable effect of dose reduction on image quality can be compensated for to a certain level. This has the potential to decrease dose level with different X-ray spectra without impairing lesion detectability. Mammography studies on dosimetry suggested that the radiologists' performance in detecting abnormalities with standard radiation dose images and markedly dose-reduced images (33–55%) does not differ significantly.[2–4]

These results motivated us to perform a small-scale study on breast specimen with the objective to determine a threshold dose level for single views. The results of this experimental study show that application of a tungsten/silver (W/Ag) beam quality for low-dose imaging permits a substantial reduction of the average glandular dose (AGD), possibly up to 90%, in single digital mammographic images, irrespective of breast thickness, particularly in combination with post-process noise reduction.[5]

In the present study, the potential of these low-dose images in a clinical setting was assessed. Physical image quality is not synonymous to perceived image quality or the clinical value of an image. The current information on this aspect of mammography is mainly based on phantom studies. As degradation of clinical performance caused by dose reduction is unacceptable, mammography systems use radiation dose levels that are set on the safe side. However, it is unclear at what point dose reduction starts to influence clinical performance negatively. Our study was set up to find information on this cross-over point, where dose reduction meets performance degradation. To investigate this, we set up a clinical observer study, evaluating the potential of low-dose imaging in digital mammography by analysing the effect of substantial dose reduction in craniocaudal (CC) views on clinical performance. We considered the CC view to be the most suitable candidate for this trial. As, in general, the CC view is most valuable for differentiation, for example, to distinguish suspect lesions from summation artefacts that concern as many as 83% of the one-view-only lesions,[6] but much less so for detection, particularly when microcalcifications are concerned.[7]

To determine the lower limit in dose reduction, we obtained additional images with an extremely low radiation dose. These images are meant to be compared with regular images and are not intended to set a baseline for clinical practice. Instead, this proof-of-concept study is intended to pave the way for further research. With data on both ends of the spectrum, intermediate dose levels can be simulated, generating a potential clinical alternative for the current protocols under specific circumstances. With this, we aim to do evidence-based and justified assessments of pragmatic dose reduction in mammography in the future. To our knowledge, this is the first clinical study dedicated to dose reduction in digital mammography.

METHODS AND MATERIALS

Setting

This observer performance study was approved by the institutional medical ethics committee. All examinations were performed at the St Elisabeth Hospital in Tilburg, Netherlands, with accepted protocols, including signed informed consent by the participants. In a single visit, a scheduled clinical mammography was complemented by the acquisition of a low-dose CC view of each breast. The standard digital mammography images used for this study were acquired for diagnostic purposes, followed by an additional low-dose CC view of each breast for research purposes only. A paired study design was used, with each female serving as her own control, by creating two sets of examinations per case for image interpretation [*i.e.* standard mediolateral oblique (MLO) with standard CC, and a combination protocol of standard MLO with low-dose CC].

Study population

During the study period, from 1 October 2010 to 1 May 2011, every female having mammography scheduled in our hospital was invited to participate, irrespective of medical complaints or history. Informed consent was the only pre-requisite. As this needs time, females with an urgent request for mammography could not be included in the study. In total, 438 females participated. The procedure had to be ceased four times because of perceived pain during (extended) compression. Seven cases were disqualified, because of incorrect parameter settings (two), incompleteness (two) and system errors (three). For the reviewing process, the images had to be uploaded onto a dedicated mammography workstation, which failed six times because of technical reasons. The remaining 421 females were enrolled in the observer study. The mean age was 52.7 years (range, 27–84 years). In 267 females, medical history was unremarkable; 14 had undergone (excision) biopsy; 11, cosmetic surgery; 59, breast conserving therapy; and 70, breast amputation. The reason for current mammography, according to the physician request form, was diverse. Most requests related to surveillance (262) or follow-up (78). The other mentioned complaints were 32 females had pain; 39, a palpable lump; 8, nipple discharge; and 2, nipple retraction.

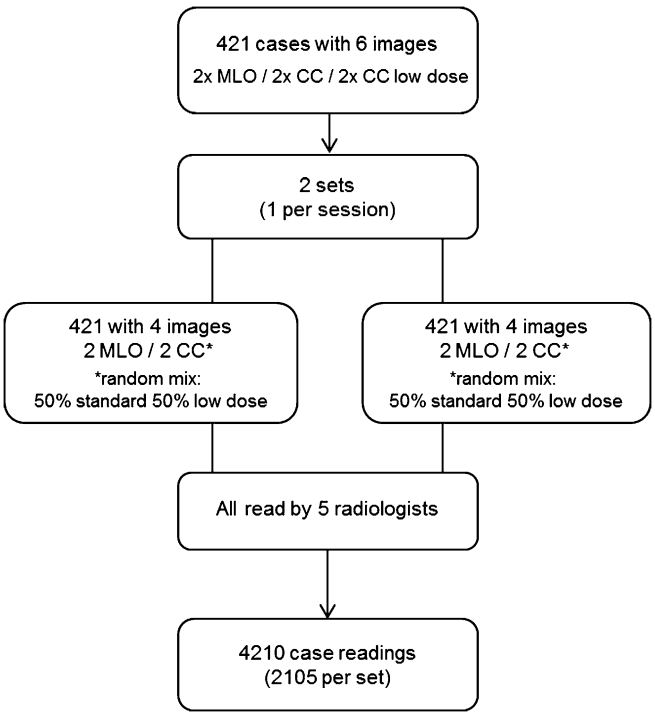
Image acquisition and processing

All images were acquired on a Lorad Selenia full-field digital mammography system (Hologic Inc., Danbury, CT) with 70-μm pixel size and 24 × 29-cm field of view. Standard mammography images were acquired under automatic exposure control (AEC) conditions. The acquisition of a standard CC view was directly followed by a low-dose image of the compressed breast, to create a similar pair. Based on previous study results,[5] low-dose images were acquired with a W/Ag target-filter combination at 35 kV and a tube current of 4, 5 or 8 mAs, depending on breast thickness. Doses, calculated based on the model by Dance et al,[8] were read from the digital imaging and communications in medicine header. Post-process noise reduction was applied to these raw images by 3 × 3-pixel binning implemented in a home-made algorithm using a gaussian kernel.

Image interpretation

Each case consisted of six images, out of which two mammography examinations were created: one standard dose protocol (SDP) and one combination low-dose protocol (LDP) with a standard MLO and ultra-low-dose CC. These were separated into two sets and randomized in order to offer a mix of standard and combination low-dose examinations per reading session (Figure 1). To overcome memory bias, at least 6 weeks had passed before the complementary set was offered for reading.

Figure 1. Reading set-up with 421 cases resulting in 4210 case readings. CC, craniocaudal; MLO, mediolateral oblique.



A team of 5 experienced (screening) radiologists, reading an average 8500 screens per year apart from their clinical practice, was involved in reading the anonymized image sets. They had worked with digital mammography for at least 2 years before the start of the study. Review was performed independently; hence, every set was read five times in total, without the knowledge of other readers' results. Images were viewed on a dedicated mammography workstation (SecurView DX; Hologic Inc.) with customized software (MeVis Medical Solutions, Bremen, Germany) and two high-resolution 5-megapixel portrait monitors (Barco N.V., Kortrijk, Belgium). The setting of our retrospective reading study design was aimed to resemble the clinical setting. Therefore, relevant data such as age and reason for the examination were presented. Moreover, observers were free to use all the available options of the digital viewing system. Prior mammograms, however, were left out, as these could contain information that might influence the outcome of the study.

All examinations were read as regular clinical mammograms with detection of pathology as the major outcome parameter. To this end, readers were instructed to report all (probable) lesions, including benign lesions. Breast density was scored according to the American College of Radiology (ACR) Breast Imaging Reporting and Data System (BI-RADS) classification. In case of perceived pathology, localization and type of lesion (well-defined mass, less/ill-defined mass with or without microcalcifications, spiculated mass with or without microcalcifications, microcalcifications only, distortion, asymmetry and post-operative changes) were recorded. For a more sophisticated evaluation, rather than using the BI-RADS classification, the level of suspicion was indicated on a 0–100 visual analogue scale, where 0 is not suspicious for malignancy and 100 is undoubtedly malignant. Also, a recommendation was given regarding the need for further imaging (no further imaging needed, additional mammography projection, ultrasound assessment or other). In case of multiple lesions, readers were asked to describe the most conspicuous only.

Further diagnostic work up was not performed or interpreted by any of the readers. Final diagnoses, by biopsy or imaging only, were recorded after a follow-up period of 1 year. This allowed us to distinguish true- and false-positive feature reports, that is, true lesions—features with a pathological substrate—and non-true, or pseudo, lesions.

Variables representing practical outcome measures, such as reading time, were not addressed. Reading conditions were, however, similar to daily practice.

Analysis

Sets were compared for diagnostic performance and clinical benefit. Thereto, we compared the SDP and LDP with respect to lesion detection and lesion interpretation (type, conspicuity and possible further imaging).

We chose to compare the total amount of lesions reported with each protocol to point out the information that might be missed when using very low-dose CC imaging. We regarded the clinical work-up (and 1-year follow-up) as a surrogate gold standard to determine a proxy variable for sensitivity, specificity and diagnostic accuracy only to allow comparison of both protocols. Concordant cases (where a feature has been reported in both protocols of one case) and discordant cases (where a feature has been reported in only one of the case protocols) were evaluated separately. Furthermore, results were stratified by reader.

For data management and analysis, SPSS® v. 16.0 for Windows (SPSS Inc., Chicago, IL) was used. Descriptive statistics were applied to explore the radiological and pathological characteristics of the lesions. Means were compared with a paired sample *t*-test. For categorical variables, the Pearson χ^2 test was used. A *p*-value ≤ 0.05 was considered indicative of a statistically significant difference.

RESULTS

The AGD of mammography images depends on breast volume and composition. In this study, the standard CC images were obtained with an AGD ranging from 0.71 to 4.24 mGy. For the acquisition of the low-dose images, 0.05–0.24 mGy was used. This was an average dose fraction of 10.4% of the AEC dose [standard deviation (SD), 3.48], meaning an average decrease in radiation dose of 89.6%. Doses were similar for both breasts with mean breast thicknesses of 54.9 mm (SD, 12.79) and 55.6 mm (SD, 12.77) of the right and left breast, respectively.

Table 1 shows that significantly less mammographic features were reported in the LDP group ($p = 0.020$). In 357 (84.8%) of the SDP examinations, a feature was reported by at least 1 of the readers, while this was true for 331 (78.6%) of the LDP examinations.

Table 1. Overall performance—standard *vs* combination low-dose mammography

Variable	SDP	LDP	*p*-value
Total number of cases, *n*	421	421	
Cases with reported features, *n* (%)	357 (84.8)	331 (78.6)	0.020 (χ^2)
Total number of case readings, *n*	2105	2105	
Total number of features reported, *n* (%)	988 (46.9)	887 (42.1)	0.002 (χ^2)
ACR BI-RADS density Type 1	392 (39.7)	357 (40.2)	
ACR BI-RADS density Type 2	288 (29.1)	252 (28.4)	
ACR BI-RADS density Type 3	233 (23.6)	222 (25.0)	
ACR BI-RADS density Type 4	75 (7.6)	56 (6.3)	0.279
Mean suspicion level 0–100, *n* (standard deviation)	11.8 (17.7)	10.8 (16.5)	0.084 (*t*-test)
ACR BI-RADS density Type 1	11.9	10.7	0.332
ACR BI-RADS density Type 2	9.5	8.9	0.528
ACR BI-RADS density Type 3	13.6	12.4	0.505
ACR BI-RADS density Type 4	14.6	13.9	0.851
Work-up, *n* (%)	608 (61.5)	537 (60.5)	0.658 (χ^2)
ACR BI-RADS density Type 1	230 (37.8)	188 (35.0)	
ACR BI-RADS density Type 2	177 (29.1)	154 (28.7)	
ACR BI-RADS density Type 3	155 (25.5)	156 (29.1)	
ACR BI-RADS density Type 4	46 (7.6)	39 (7.3)	

ACR, American College of Radiology; BI-RADS, Breast Imaging Reporting and Data System; LDP, low-dose protocol; SDP, standard dose protocol.

Per protocol, 2105 (5×421) case readings have been performed. In SDP examinations, 988 (46.9%) noteworthy features were reported and 887 (42.1%; $p = 0.002$) in LDP examinations. For all features that have been described, the mean level of suspicion ($p = 0.084$) and work-up ($p = 0.658$) did not differ significantly for both protocols. Also, distribution of lesion detection and interpretability throughout the density spectrum was similar.

True lesions were diagnosed, by biopsy or (additional) imaging only, in 66 cases (15.7%). These included 61 benign lesions (7, adenosis/sclerosis; 7, fibrocystic changes; 19, cyst; 9, fibroadenoma; and 19, other) and 5 malignancies (2, ductal carcinoma *in situ*; 2, invasive ductal carcinoma; and 1, tubular carcinoma). Pseudolesions related to ectopic fibroglandular tissue, intramammary lymph nodes, post-operative architectural changes or summation artefacts.

Significantly more lesions were reported in the SDP group (Table 2). However, in either group, all lesions were detected by at least one of the readers and malignancies by at least two (Figure 2). If detected, mean suspicion level ($p = 0.228$, all lesions; $p = 0.098$, malignancies only) and work-up ($p = 0.578$, all lesions; $p = 0.851$, malignancies only) were comparable for both protocols. Overall, the unreported lesions were evenly distributed among all lesion types, that is, a specific type of lesion that is prone to be missed with the LDP could not be identified.

As more lesions were detected with the SDP, the sensitivity was higher (81.5%) than that of the LDP (73.9%). Specificity, on the other hand, was higher with the use of the LDP (63.8% *vs* 59.3%), resulting in a slightly better diagnostic accuracy (65.4% *vs* 62.6%).

Discordant cases were seen in both groups, with 10.0% ($n = 210$) of the features reported on the SDP mammogram only and 5.2% ($n = 109$) reported only on the LDP mammogram. The overall distribution of feature types that have been reported in one of both sets only was similar, mostly concerning features from the category "other", such as architectural distortion and asymmetry.

Well-defined masses were reported more often with the use of the LDP ($p = 0.405$). In the SDP group, more spiculate masses ($p = 0.395$) and clustered microcalcifications ($p = 0.393$) were seen. However, none of these differences was statistically significant.

In concordant cases, additional imaging was requested in approximately 60% of the lesions reported, irrespective of the mammography protocol (Table 3). However, the suggested imaging modality showed intra- and interobserver differences. In about 30% of cases, the suggested work-up plan was different for both protocols. Overall, when using the LDP, supplementary mammography projections were significantly more often requested as the first step in additional imaging.

Table 2. Diagnostic performance—standard *vs* combination low-dose mammography in all true lesions, including malignancies and malignant lesions only

Variable	SDP	LDP	*p*-value
Total number of case readings, *n*	2105	2105	
All true lesions (*n*)	330	330	
Detected, *n* (%)	269 (81.5)	244 (73.9)	0.019 (χ^2)
Mean suspicion level, *n* (SD)	21.8 (25.7)	19.1 (23.7)	0.228 (*t*-test)
Work-up, *n* (%)	213 (79.2)	198 (81.1)	0.578 (χ^2)
Total number of case readings, *n*	2105	2105	
Malignant lesions (*n*)	25	25	
Detected, *n* (%)	22 (88.0)	17 (68.0)	0.000 (χ^2)
Mean suspicion level, *n* (SD)	66.0 (29.4)	56.5 (36.4)	0.098 (*t*-test)
Work-up, *n* (%)	21 (95.5)	16 (94.1)	0.851 (χ^2)

LDP, low-dose protocol; SD, standard deviation; SDP, standard dose protocol.

DISCUSSION

Incremental dose reduction, or adding noise otherwise, is presumed to cause loss of relevant information in clinical decision-making. But, to our knowledge, in clinical digital mammography its extent has never been objectified. In this study, we compared two similar sets of mammograms with dose level of the CC view as the only variable. It is the first study to evaluate the loss of information and, with it, lesion detectability, in the low end of the X-ray spectrum, by observing its impact on clinical performance.

Similar to a previous experimental study,[2] we found a marked reduction in mammographic sensitivity with the reduced dose protocol compared with the standard examination. We did not observe a significant effect of dose reduction on other test characteristics, like specificity and accuracy. While performance of individual observers varied, all showed similar trends. The observed 73.9% sensitivity of LDP mammography seems comparable with clinical screen-film mammography,[9,10] but the sensitivity as determined in this study, including detection of benign pathology, makes it hard to compare these results directly. In general, a relatively low sensitivity was observed. This might be owing to the relatively large share (20%) of females included in the study who previously underwent breast conserving procedures, as this is known to have a significant impact on the sensitivity of mammography.[11,12] Yet, all lesions were reported by at least one of the observers using the LDP. This suggests that, although lesions might have been more concealed, the information needed to detect a lesion was still available. The overall specificity was rather low. To some extent, this is inherent to the clinical setting, where additional imaging is easily accessible. Moreover, for this study, observers were encouraged to report all (possibly) aberrant features, which might have lowered the threshold for requesting further imaging even more. As these were constant factors, it is not expected to have had an impact on specificity comparison.

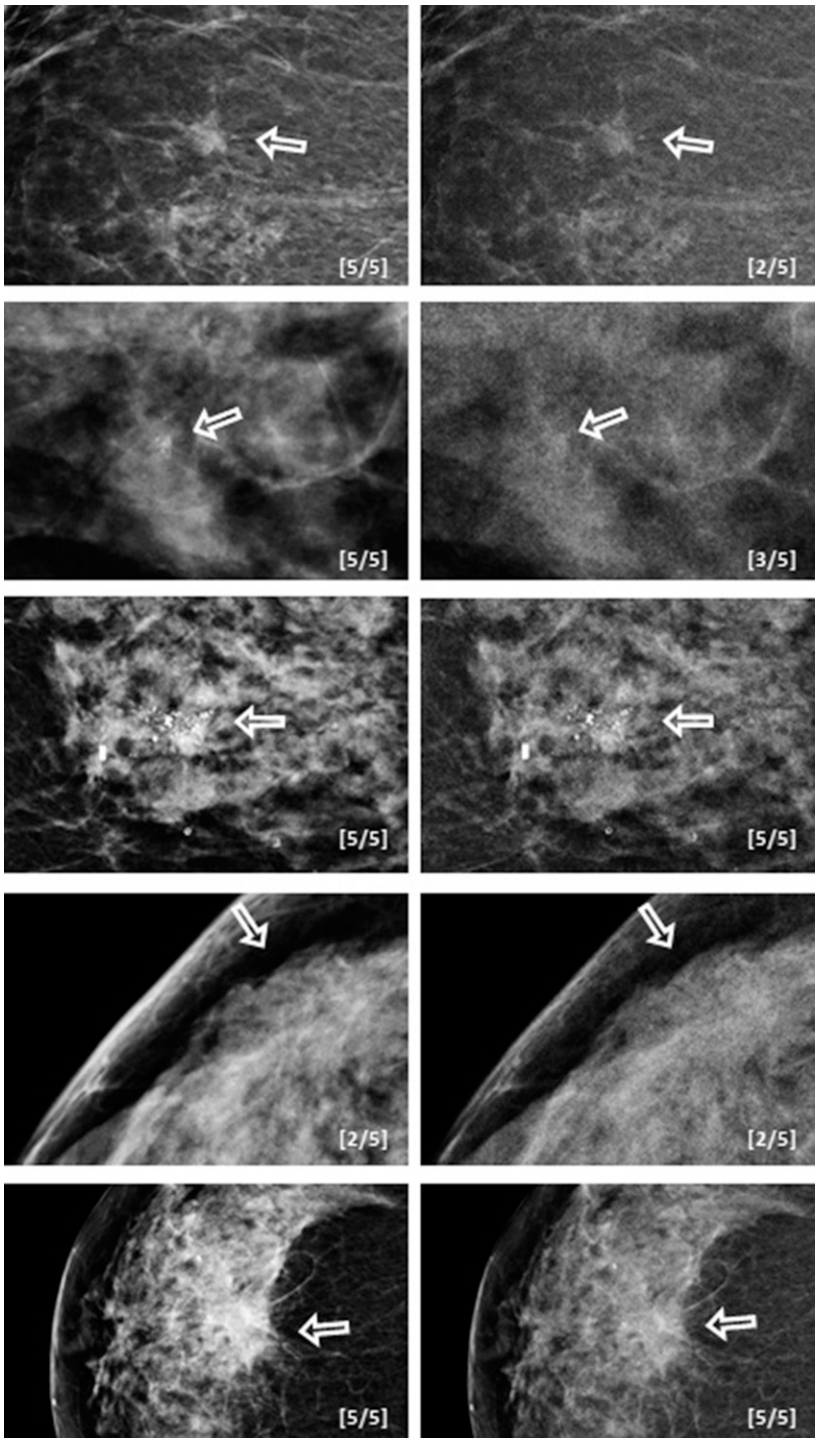
We found that lesion characterization by the radiologists was comparable for both mammography protocols. Therefore, image interpretability did not seem to be affected by the dose reduction in this setting. As a consequence, for a similar fraction of cases additional work-up was requested. While the decision on whether or not to perform diagnostic work up did not depend on the imaging protocol that was used, the LDP led to significantly more requests for additional mammography projections before another modality, such as ultrasound, was recommended. This suggests that a certain loss of information has been perceived by the observers when reading these mammograms. When these images appear to be inconclusive, they might require additional mammographic imaging that would cancel out the advantages of low-dose imaging. This should be kept in mind when planning future studies on this topic.

Several studies have been published that evaluated the effect of dose reduction upon detection of mammographic lesions in digital images.[2,13] As increased noise associated with dose reduction mostly affects the high-frequency features, they found the detection of microcalcifications to be impaired most. In contrast to these studies, we did not observe an effect in detection of a particular lesion type, while the loss of information was equal across the lesion spectrum. We assume this to be the effect of the availability of the standard MLO view in our study. Also, the use of a higher energy spectrum obtained with a W/Ag combination and post-process pixel binning are expected to have contributed to the depiction of microcalcifications in the low-dose images.

The added value of a CC view in mammography is beyond dispute. Our study underlines this by the fact that compromising on the image quality of a CC view already results in a decrease in the accuracy of mammography. It does not seem likely that most of the image information in the combined protocol came from the MLO view only. In that case, we would expect to have seen a stronger decrease in the detection of less and ill-defined lesions, as in one-view mammography, irregular masses are the type of lesions that are most at risk of being missed.[14,15]

Our study has some limitations that should be acknowledged. Firstly, it should be noted that this study was performed on one

Figure 2. Depiction and detection of malignancies (arrows) in standard dose protocol (left column) and low-dose protocol (right column). In brackets, the number of observers out of five who reported the lesion.



type of mammography system, with its specific acquisition, processing and display. It is, therefore, unclear how these results translate to other systems. This should be kept in mind when further research is being considered.

Secondly, the low-dose images were acquired using an existing imaging processing algorithm that was not optimized for the selected exposure parameters. In future research, we are planning to investigate possible improvements based on the raw data. This also applies to optimization of the detector.

Thirdly, it was not possible to obtain images at a very low level of radiation with AEC. Alternatively, tube currents had to be put in manually. For this purpose, an application scheme for tube current (mAs) values was developed depending on compression thickness. Compared with AEC, this method is suboptimal,

Table 3. Work-up—standard *vs* combination low-dose mammography in all concordant cases [*n* (%)]

All reviewers	SDP	LDP	*p*-value (χ^2)
Case readings with reported features, *n*	988	887	
Concordant cases	778	778	
No additional examinations	293 (37.7)	305 (39.2)	
Additional examinations	485 (62.3)	473 (60.8)	0.532
Additional views	148	180	0.014
Ultrasound	269	232	
Stereotactic biopsy	27	18	
Other	41	43	

LDP, low-dose protocol; SDP, standard dose protocol.

mostly because it did not comprise breast composition. This resulted in relatively large differences in received dose fractions.

Fourth, one of the observers recorded five times more mammographic features than the other four. The discrepancy was owing to excessive scores of "asymmetry" and a consequent high amount of follow-up procedures, particularly additional mammography images. We cannot explain this deviant scoring behaviour except by diligence, since every observer was instructed before the study started and during the reading sessions, an instruction booklet, as well as telephone support, was available. Despite the difference in numbers, all observers showed a similar trend. As including or excluding the data from this reviewer did not show significant differences in the results, we felt reassured that aggregation of data would not compromise the validity of our study.

Finally, the relative lack of pathological cases can be regarded as a drawback. Although the study cohort represents clinical practice well, it offers only a small percentage of current pathology. Therefore, performance parameters, as sensitivity and specificity, were based on the detection of pathology in general and not on cancer detection. Furthermore, analysis of missed carcinomas was not substantial. Cases of particular interest, however, such as cancers that are only visible on the CC view, comprising approximately 8% of the cancers missed on the MLO view,[15] would have added value to this evaluation. Further research might want to focus on this by using an enriched study sample.

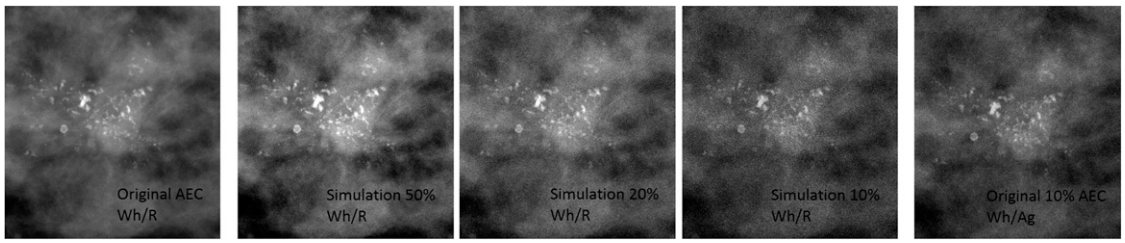
This baseline study was set up with ultra-low-dose images trying to avoid an indeterminate outcome as much as possible. It was not our goal to investigate whether a policy with CC views with a mean dose of 10% of the standard dose is feasible but rather to determine the loss of information in a clinical setting. With this study, we created a data set, with clinical images at both ends of the dose spectrum, from which point we can validate and compare simulated lower dose images by introducing noise (Figure 3). Herewith, a dose level feasible for additional mammography images for future research can be determined. Also, it generates the opportunity to analyse the discordant cases in detail in specific dose level steps. We expect that after further optimization, additional low-dose images in mammography can have a role in the clinical as well as the screening setting.

CONCLUSION

This study was designed to validate clinical aspects of low-dose imaging, in contrast to phantom and modelling studies, by comparing two similar sets of mammograms with a difference in CC dose level only. Obtaining images with ultra-low radiation doses (about 10% of the AEC dose) caused, as we expected, a shift of the detectability threshold. Nevertheless, the images obtained with such a low-dose fraction generally appeared to be of clinical value in combination with standard images. Results were not specifically affected by breast density, suggesting that further research in the younger population, for whom radiation protection is most relevant, might be worthwhile.

In this proof-of-concept study, we tried to identify a lower limit that is not intended nor applicable for clinical practice. Future

Figure 3. Image quality in standard mammography and different levels of (simulated) dose reduction using the same spectrum as the original image compared with tungsten/silver (W/Ag) low-dose imaging. AEC, automatic exposure control; W/Rh, tungsten/rhodium.



research with higher dose images, to be simulated on the basis of these data, will help us identify the dose level for additional images where the sensitivity of the examination is no longer affected. This knowledge may effectuate substantial dose reduction in digital mammography under specific circumstances, being of great value in controlling the radiation burden in a relatively young and largely asymptomatic population.

A baseline is set for further research in optimization of low-dose images in digital mammography before this imaging approach can find its way in the clinical environment. Herewith, it is also important that manufacturers make low-dose imaging more easily accessible with the implementation of dedicated LDPs.

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