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State of art and optimization perspectives for breast imaging

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ABSTRACT

Breast screening with mammography is the most effective method of detecting early-stage breast cancer and reducing related mortality. Among the intrinsic limits of mammography, in terms of clinical performance, the overlapping of normal and pathological tissues is one of the most influential. Some new techniques as Digital Breast Tomosynthesis (DBT) is expected to overcome this limitation by providing a quasi-three-dimensional (3D) image that could lead to improve the accuracy of mammography. Another way to increase accuracy and sensitivity is represented by a double exposure of the patient before and after intravenous injection of contrast media, this technique is called Contrast-enhanced digital (or spectral) mammography (CEDM, CESM). Furthermore, highly specialized software has been developed which is able to detect suspicious mammographic findings. This technology is very interesting especially in the screening field, in fact there are multiple ongoing studies evaluating the use of Artificial Intelligence (AI) as a second reader.

To date, screening mammography is the only imaging modality that has proven to significantly lower breast cancer mortality. Tomosynthesis demonstrated excellent sensitivity and specificity but the technique did not meet the expectations given the risk of over diagnosis as well as the lack of reduction in the number of interval breast cancer. CESM could in some cases serve as an alternative imaging tool to MRI. AI, seems to be competing with the breast radiologist and its use as a second reader in breast screening programs is already being proposed.

1. Introduction

Breast screening with mammography is the most effective method of detecting early-stage breast cancer and reducing related mortality [1,2]. In Italy, screening for the early diagnosis of breast cancer is applied to women aged between 50 and 69 and it is performed with a mammogram every 2 years [3]. In some Italian regions effectiveness is being tested in a broader age range, between 45 and 74. According to the local health care authority the frequency has to be annual for women under 50 or for high risk patients (i.e. previous surgery or familiarity). A large study published in 2008, having reviewed the published researches on breast cancer screening programs active in Europe, showed that mortality is reduced by 45% for women who undergo the screening [4]. This mean that for one thousand women aged between 50 and 69, who are regularly screened and followed up to 79 years of age, screening can save between 7 and 9 lives, as stated by the Italian ministry of health [5]. In Ref. [6] is reported that at a mean glandular dose of 1.3 mGy per view, biennial mammography screening between age 50 and 74 was predicted to induce 1.6 breast cancer deaths per 100 000 women aged 0–100 (range 1.3–6.3 extra deaths at a glandular dose of 1–5 mGy per view), against 1121 avoided deaths in this population. Advancing the lower age limit for screening to include women aged 40–74 was predicted to induce 3.7 breast cancer deaths per 100 000 women aged 0–100 (range 2.9–14.4) at biennial screening, but would also prevent 1302 deaths. Over 100 000 women aged 0–100 in the absence of screening there would be 12 289 diagnoses of breast cancer. Of these 4330 would be fatal. In Italy, every year, the number of new patients increases of about 5000 new cases. The screening prevents 26% of these deaths for the 50–74 group with biennial exams, potentially causing 1.6 extra cancer deaths in the group with mean glandular dose (MGD) equal to 1.3 mGy. Thus the ratio between mortality without screening and the cases of fatal cancer potentially induced by radiation with screening would be equal to 2706. The ratio between prevented deaths and induced deaths is 704. Including the decade 40–49 with an annual screening frequency (at the same MGD of

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1.3 mGy) we have potentially 7.4 extra cancer deaths. Therefore it comes out that the ratio between prevented and potentially induced deadly cancers is reduced to 175:1 (prevention would rise to 29.9). The risk-benefit ratio decreases when MGD rises, as it happens when working with thicker breasts. Each year, millions of women in Europe have a screening mammogram. This may reduce the risk of dying from breast cancer up to 50% [4,7,8]. It may, on the other hand, also cause breast cancer and breast cancer deaths due to ionizing X-ray radiation. It has been shown that the risk of tumor induction is proportional to the dose of radiation absorbed in the breast [9–14]. Although radiation doses at mammography are much lower than the doses for which cancer induction is directly observed [15] screening a large population on a regular basis has the potential to harm. While saved life are clearly verified, induced cancers that lead to death are not demonstrable due to the non-specific nature of the stochastic damage. Moreover, the risk of radiation-induced tumors decrease with increasing age because the lower radiosensitive and the high latency period.

Among the intrinsic limits of mammography in terms of clinical performance the overlapping of normal and pathological tissues is one of the most effective. Indeed it can decrease the visibility of malignant abnormalities or simulate the appearance of an abnormality. Some new technique as Digital Breast Tomosynthesis (DBT) is expected to overcome this limitation by providing a quasi-three-dimensional (3D) image that could lead to improved accuracy of mammography [16–18]. Another way to increase accuracy and sensitivity is represented by a double exposure of the patient before and after intravenous injection of contrast media, this technique is called Contrast-enhanced digital (or spectral) mammography (CEDM, CESM) [19,20].

2. Dose and related risk

As stated in the European guidelines for quality assurance in breast cancer screening and diagnosis (EUREF [21]), the acceptable dose level for typical breast simulated with PMMA and relative equivalent breast thickness is reported in Table 1. For a 2-view acquisition with Full Field Digital Mammography (FFDM) the average MGD is 3.7 mGy [22] while the lifetime attributable risk (LAR) is 1.3 per 100 000 women aged 40 (at time of exposures) and 1 case per million for woman aged 80 (at time of exposures).

In the early 2000s the photon counting detector (PCD) technology in digital mammography was introduced. This led to a reduction of the delivered doses from one third [23] up to 50% [24,25] compared to traditional digital mammography.

An attempt to introduce a similar detecting technology in DBT was performed but no longer available on market at present time.

By counting individual x-ray quanta rather than accumulating total charge, it is possible to completely remove all background noise from the image. The detector counts only the number of peak pulses, with no conversion steps from x-ray photons to a digital signal leading to a complete removal of Swank noise, electronic noise and noise due to the quantification of the electrical signal from the detector. For the scintillator based detectors, Swank noise, introduced by the statistical variation of released light after the photon conversion [26], can be a serious cause of image degradation. Two photons of the same energy can have different responses in the detector, leading to an overall uncertainty in the integrated signal. This effect can be present also in direct conversion energy integrating detectors. The absence of Swank noise and the significant removal of electronic noise is the major advantage of PC technology.

A full field digital mammography equipped with photon counting detector, could produce good quality images for different breast thickness as showed hereafter in Table 2.

Table 1
Dose levels for typical breasts simulated with PMMA.

Thickness of PMMA (mm)	Equivalent breast thickness (mm)	Maximum average glandular dose to equivalent breast (mGy)	
		Acceptable level	Achievable level
20	21	≤1.0	≤0.6
30	32	≤1.5	≤1.0
40	45	≤2.0	≤1.6
45	53	≤2.5	≤2.0
50	60	≤3.0	≤2.4
60	75	≤4.5	≤3.6
70	90	≤6.5	≤5.1

3. Digital Breast Tomosynthesis

Breast screening with mammography is the most effective method of detecting early-stage breast cancer and reducing breast cancer mortality, as concluded by a meta-analysis of 11 randomized trials [27]. This study evaluated that there is a 20% relative risk reduction in breast cancer mortality in women invited to screening program. Nevertheless, 15–30% of cancers are not detected by standard screening [28], and this value is higher in women under 50 years old [29] and in women with dense breast [30]. One of the intrinsic limits of mammography clinical performances is the overlapping of normal and pathological tissues that can decrease the visibility of malignant abnormalities or simulate the appearance of an abnormality. This led to an increase in the number of false-positive recalls [31] and a reduction of screening program sensitivity.

Digital Breast Tomosynthesis (DBT) is expected to overcome this limitation providing a quasi-three-dimensional (3D) image that could improve the accuracy of mammography since it reduce overlapping shadows that could degrade the clinical image quality in standard 2D projection imaging. The logical outcome is that small size lesions and distortions, which may be hidden by normal tissues in standard 2D projection imaging, could be more readily detected using DBT, particularly in women with radiologically dense breast. This improved accuracy could lead to a decrease of false-positive recalls and associated healthcare costs and patient anxiety.

In DBT during the acquisition, 9 up to 25, depending on manufacturers, individual exposures are obtained at different angles, between 11 and 40°. The x-ray tube movement can be continuous or step-and-shoot. In the former, the tube moves continuously during the scan acquisition with pulsed x-ray minimizing blurring due to tube motion. In the latter, the tube stops at each location delivering pulsed x-ray beam, reducing in principle tube motion blurring but increasing the total scan time.

Tomosynthesis is a compromise between conventional digital mammography and CT: DBT system can provide a quasi-3D image improving the information of a digital mammography while minimizing the complexities and patient dose of a CT [32]. The readers, at cost of an additional time to read DBT images, are more able to identify lesions and to differentiate between malignant and benign features, as reported by F.J. Gilbert et al. [33].

The recent recommendations published by the Italian College of Breast Radiology (ICBR) by the Italian Society of Medical Radiology (SIRM) [34] summarize the evidences on DBT and provide recommendations for its use. This publication underlines that DBT combined with 2D FFDM allows a better diagnostic performance than mammography

Table 2
Dose levels for typical breasts simulated with PMMA for Sectra MicroDose L30.

Thickness of PMMA (mm)	Equivalent breast thickness (mm)	Sectra MicroDose L30 AGD (mGy)
20	21	0.4
30	32	0.6
40	45	0.6
45	53	0.6
50	60	0.8
60	75	0.9
70	90	0.8

alone by means of eight prospective trials [17,18,35] and retrospective studies [36–41]. In the important Houssami review [42], it is reported that DBT plus 2D digital mammography provides an increase in cancer detection rate from 0.5 to 2.7 per thousand screened woman and a reduction in false positive recall rate from 3.6 to 0.8 per 100 screened women.

Some studies as the OTST trial [18,35,43], the Italian STORM trial [17], the Malmo Breast Tomosynthesis Screening Trial [36,44], the work of Rose et al. [45], and Friedwald et al. [37] confirm that DBT combined with mammography allows a better diagnostic performance than mammography alone as confirmed by the results summarized in Table 3 show that coupling FFDM with DBT increases sensitivity and specificity.

Radiation dose delivered with DBT plus 2D digital mammography is clearly higher than that delivered with standard mammography alone. In the last years, manufacturers improved detector technical features and introduced a 2D synthetic image reconstructed from the DBT projections and this led to a sensible reduction of delivered doses. There is an opportunity to use synthetic 2D images in combination with DBT instead of conventional FFDM with only a slight increase in dose compared with FFDM and DBT. Today, the radiation dose delivered in a DBT exam are comparable to that delivered with digital mammography [46]. Once synthetic 2D images have been shown as an acceptable alternative, the marginal increase in radiation dose becomes much less of an issue.

However it seems to be unrealistic for a large part of the breast radiologist community, at present, to justify a screening program based on substituting traditional digital mammography with DBT because there is a demonstrated issue of over diagnosis and there is no evidence of reduction of interval cancer (developed cancer between two consecutive screening rounds) [43].

4. Contrast enhanced spectral mammography (CESM)

Currently, there are some FFDM units with devices and software able to perform breast examinations after contrast medium intravenous injection, subtracting the high and low energy acquisition mammograms - CESM or CEDM (contrast enhanced digital mammography). In some cases, this technique, still considered experimental, might replace Breast MRI exam at a lower cost and logistic advantage.

CESM is a novel breast imaging technique that combines standard full field digital mammography (FFDM) with contrast-enhanced high- and low-energy images. The iodinated contrast agent tends to highlight regions with vasculature that is increased and leaky—two characteristics of malignant lesions. The low-energy images provides detail of soft tissue and calcifications similar to standard FFDM. Digitally subtracted images remove the normal mammary glandular tissue and highlight areas of angiogenesis to help detect breast malignancies.

As reported in Ref. [47] CESM results in higher radiation exposure compared with conventional 2D FFDM and 3D tomosynthesis. Although radiation dose is increased, CESM provides the radiologist with both a standard low-energy image (similar to 2D FFDM) and a contrast-enhanced image that highlights areas of angiogenesis. Initial evaluation suggests a clinical benefit with CESM because of added physiologic information. The added imaging detail gained from CESM likely offsets the incremental increase in AGD, which is still within the range permitted by applicable regulations. However, further studies must be performed, particularly to quantify CESM radiation dose as a function of varying breast density and in subpopulations of patients appropriate for this examination.

In [48] results indicate that CESM has the potential to be a valuable diagnostic method that enables accurate detection of malignant breast lesions, has high negative predictive value, and a false-positive rate similar to that of breast MRI. CESM and MRI examinations were performed in 102 patients who had suspicious lesions described in conventional mammography. All visible lesions were evaluated independently by 2 experienced radiologists using BI-RADS classifications. A comparison between CESM and MRI, a CESM sensitivity of 100% compared to 93% of MRI was found, while accuracy raised up 79% compared to 73% of MRI. In Ref. [49] CESM has comparable diagnostic performance (ROC-AUC) to MRI for breast cancer diagnostics, in combination with MG does not improve diagnostic performance and a lower sensitivity but higher specificity than MRI was found with CESM. Furthermore sensitivity differences are more pronounced in dense and not significant in non-dense breasts.

Table 3
Clinical studies comparing FFDM with DBT-FFDM in screening population. CDR: cancer detection rate; FPR: false positive rate; RR: recall rate.

Study	FFDM	DBT (one view)	FFDM + DBT
OTST trial	FPR: 6.1% CDR: 6.3‰ RR: 6.7%		FPR: 5.3% CDR: 9.3‰ RR: 3.6%
STORM trial	FPR: CDR: 5.3‰ RR: 4.4%		FPR: + 17% CDR: 8.1‰ RR: 3.5%
Malmo	RR: 2.5% CDR: 6.5‰	RR: 3.6% CDR: 8.7‰	
Rose	CDR: 2.8‰ RR: 8.7%		CDR: 4.3‰ RR: 5.5%
Friedewald	CDR: 4.2‰ RR: 10.7%		CDR: 5.4‰ RR: 9.1%

5. Artificial Intelligence

Computer-aided detection (CAD) systems were introduced in the last decades as an aid for radiologists, in order to improve human detection performance. No study has found any direct improvement in performance [50,51]. To date, highly specialized software has been developed which is able to detect suspicious mammographic findings. This technology is very interesting especially in the screening field, in fact there are multiple ongoing studies evaluating the use of Artificial Intelligence (AI) as a second reader. New developments in deep learning algorithms are leading to an improvement of the performances of this kind of systems [52].

In [53] screening digital mammographic examinations from 240 women were interpreted by 14 radiologists, with and without AI support. This support provided radiologists with interactive decision support, traditional lesion markers for computer-detected abnormalities, and an examination-based cancer likelihood score. This study demonstrated that sensitivity improved from 83% to 86% with aid of AI and specificity improved from 77% to 79%. No increment of reading time was highlighted.

Rodriguez-Ruiz et al. [54] used nine multi-reader, multi-case study datasets of digital mammography for an amount of more than 2000 exams, of which more than 600 malignant, interpreted by one hundred radiologists and one AI system. The evaluated system achieved a performance statistically comparable to radiologists one.

Watanabe et al. [55] performed a blinded retrospective study using a cancer-enriched data set from 122 patients including 90 false-negative mammograms. The readers detected, averagely, 51% of early cancers without aid of AI software and this percentage raised up to 62% with assistance of AI while less than 1% increase in false positive recalls was found using AI.

The mentioned studies, and more, seems to led to an improvement of the performances of AI based software. This could be a great contribution to cancer detection in screening program without an increase in radiation dose to the patients.

6. Conclusions

Screening mammography is the only imaging modality that has proven to significantly lower breast cancer mortality to date. Digital mammography, specifically Full Field Digital Mammography is the obligatory requisite technique. Approximately 10 years ago, tomosynthesis, a pseudo 3D mammography technique was introduced (as an adjunct to 2D mammography), aiming to reduce the limitations of the 2D mammogram. Tomosynthesis demonstrated excellent sensitivity and specificity and came across as the best breast cancer screening tool. However, the technique did not meet the expectations given the risk of over diagnosis as well as the lack of reduction in the number of interval breast cancer. Conversely, the recent fine adjustments made to dual-energy subtraction and Artificial Intelligence (AI) software, in combination with FFDM, are revolutionizing the world of breast imaging. Dual-energy subtraction or CESM enables the acquisition of mammography post intravenous iodinated contrast administration. Same as in MRI, a vascularized lesion would demonstrate increased contrast enhancement secondary to the phenomenon of neo-angiogenesis that occurs in cancerous lesions, making the lesion visible even if the breast is dense. In the near future, this technique could in some cases serve as an alternative imaging tool to MRI. On the other hand, AI, seems to be competing with the breast radiologist in identifying suspicious findings on mammogram, and its use as a second reader in breast screening programs is already being proposed.

CRediT authorship contribution statement

Riccardo Calandrino: Conceptualization, Methodology, Writing – original draft, preparation. **Alessandro Loria:** Conceptualization, Methodology, Writing – original draft, preparation. **Pietro Panizza:** Conceptualization, Methodology. **Angelo Taibi:** Conceptualization, Methodology. **Antonella del Vecchio:** Conceptualization, Methodology, Validation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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