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Clinical study in phase-contrast mammography: image-quality analysis

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The first clinical study of phase-contrast mammography (PCM) with synchrotron radiation was carried out at the Synchrotron Radiation for Medical Physics beamline of the Elettra synchrotron radiation facility in Trieste (Italy) in 2006–2009. The study involved 71 patients with unresolved breast abnormalities after conventional digital mammography and ultrasonography exams carried out at the Radiology Department of Trieste University Hospital. These cases were referred for mammography at the synchrotron radiation facility, with images acquired using a propagation-based phase-contrast imaging technique. To investigate the contribution of phase-contrast effects to the image quality, two experienced radiologists specialized in mammography assessed the visibility of breast abnormalities and of breast glandular structures. The images acquired at the hospital and at the synchrotron radiation facility were compared and graded according to a relative seven-grade visual scoring system. The statistical analysis highlighted that PCM with synchrotron radiation depicts normal structures and abnormal findings with higher image quality with respect to conventional digital mammography.

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1. Introduction

The first clinical study on phase-contrast mammography (PCM) was carried out at the Synchrotron Radiation for Medical Physics (SYRMEP) beamline of the Elettra Synchotron Radiation Laboratory in Trieste (Italy). The analysis of the first group of patients produced promising preliminary results reported in [1–3]. Propagation-based phase-contrast imaging (PPCI) [4] was applied, based on the high coherence of the synchrotron radiation (SR) beam. In fact, albeit other phase-sensitive techniques were successfully experimented in *in vitro* mammography [5–8], PPCI was preferred because of its simplicity in the experimental set-up, that allowed a straightforward translation to the *in vivo* application. Moreover, clinical mammography has very tight constraints in acquisition time because of the discomfort related to the breast compression and of the potential motion artefacts related to the physiologic motions of the human body (e.g. heart cycle and blood flow, breathing, etc.). PPCI technique meets this requirement because it does not need multiple image acquisitions, as typically happens in grating-based differential phase-contrast imaging or diffraction-enhanced imaging [7]. Analyser-based imaging can be applied in single acquisition mode, but the stability constraints and the temperature drifts of the crystal analyser increase the complexity of the instrumentation and of the patient safety system [9].

There are fundamental differences between *in vitro* and *in vivo* studies related not only to the limitations in glandular dose and acquisition time but also owing to the tissue property changes, before and after excision, such as the presence/absence of blood, fixation solution [10,11], tissue hydration, etc. Therefore, clinical trials are crucial steps for the evaluation of any new diagnostic imaging technique. In this paper, we present and discuss the results of an image-quality comparison between PCM, acquired at the Elettra SR facility, and digital mammography, obtained at the Azienda Ospedaliero Universitaria 'Ospedali Riuniti', hereafter Trieste University Hospital.

This first clinical trial on PCM had a very stringent enrolment protocol [1]: only subjects that could have had a direct benefit from the PCM were eligible; therefore no healthy volunteer was enrolled. In our study, we focused on the image-quality comparison between PCM and conventional clinical mammography and on the evaluation of the diagnostic improvement owing to phase contrast. Preliminary results were obtained from analysis of the first 49 patients and we have reported a significant increase of the specificity [1].

2. Material and methods

Seventy-one patients were selected on the basis of the enrolment criteria approved by the local ethics committee. In particular, the criteria include patients with an inconclusive diagnosis after mammography and ultrasonography (US), at the University Hospital. One of the following cases had to be satisfied:

— negative mammography results (Breast Imaging Reporting and Data System [12], BI-RADS category 1) but the presence of a palpable mass that was not clarified at US in a heterogeneously or homogeneously dense breast;
— focal asymmetry of tissue density between the two breasts on mammography (BI-RADS category 3 or 4) that was not clarified at US;
— architectural distortion on mammography (BI-RADS category 3 or 4) that was not clarified at US; and
— equivocal or suspicious mass on mammography (BI-RADS category 3 or 4) that was not clarified at US.

The digital mammographic images at the hospital were acquired with a direct radiography (DR) mammography unit (Senographe2000D, General Electric, Milwaukee, WI, USA).

In the next paragraphs, the main information about the clinical protocol and the mammography facility are presented. Detailed discussions are found in [1–3].
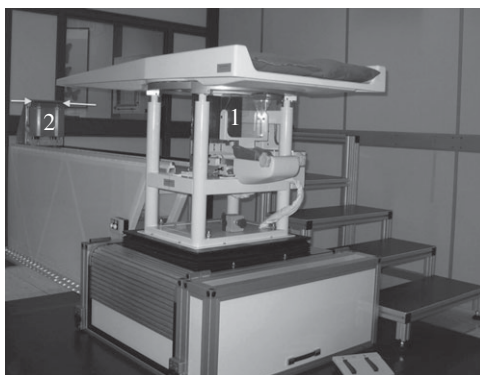
Figure 1. Patient support at the SYRMEP beamline. The compression system (1), under the support, in correspondence with the appropriately shaped aperture. On the left, the holder of the screen-film system (2) at a distance of 2 m from the compressor; on the top of the holder, which works as an antiscattering shield, the entrance slit of the beam (arrows).

The SYRMEP beamline allowed mammography to be carried out using a laminar beam with a cross section of $21 \times 0.35\,cm^2$ at the breast position. The size of the beam required a vertical scan to produce a two-dimensional image. As the beam was fixed, the breast and the detector were moved synchronously during the acquisition. The radiology room was equipped with a support on which the patient lay prone, with the breast placed in correspondence with an appropriately shaped aperture, under which a compression system, similar to that used in conventional units, was mounted (figure 1). Compression in mammography is necessary in order to equalize the breast tissue thickness and to stretch the tissue, increasing the glandular structure visibility and lesion detectability.

The main features of the SR beam were as follows: monochromaticity (0.2% bandwidth), tuneable energy range of 8–35 keV and photon flux of the order of 10^8 photons $mm^{-2}\,s^{-1}$. The distance between the SR source and the patient's breast was about 30 m, and the detector was located about 2 m from the breast.

In this study, the PCM images were acquired at the SYRMEP beamline using a Kodak Min-R 2000 screen-film system. The mammographic screen-film system was selected on the basis of its high intrinsic spatial resolution necessary for the detection of the interference fringes resulting in the edge-enhancement effect typical of the PPCI [4,13]. The cassette holder worked as an antiscattering shield so that only the primary beam reached the film by the entrance slit (figure 1). Owing to both the breast and the long path in the air, the scattered radiation around the primary beam was not negligible. The image contrast decreases if scattered radiation is not rejected.

The monochromatic beam energy used for PCM was in the range of 17–22 keV. It was selected for each patient, considering compressed breast varying thickness and density. It was the lowest energy allowing image acquisition that delivered a dose lower than the dose delivered during the hospital examination. Per each beam energy, the optimal exposure level of the film-screen system was carefully obtained. In such a way the PCM images presented an absorption contrast similar to that of the conventional mammography plus the edge-enhancement effects typical of the PPCI.

Two experienced radiologists specialized in mammography diagnosis assessed the visibility of both the breast abnormalities (calcifications, masses, focal asymmetries or architectural distortions) and the breast gland structures depicted from DR mammography and from PCM. They graded the overall image quality on the basis of the visibility of the breast gland and abnormalities relative to the background tissue according to a seven-grade visual scoring system. A score of 1 meant visibility of the breast gland and abnormalities excellent at DR and poor at PCM; a score of 2 or 3, visibility of the breast gland and abnormalities progressively lower at DR but better than that at PCM; a score of 4, equal visibility of the breast gland and abnormalities with
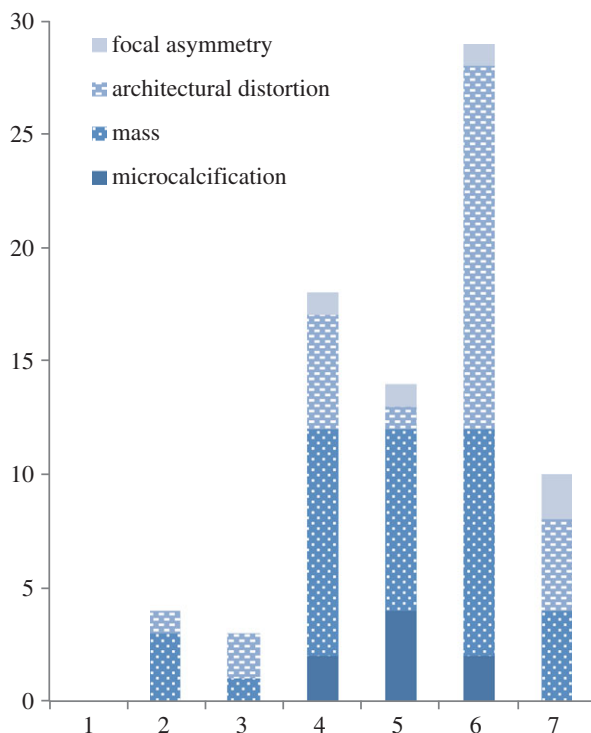
Figure 2. Histogram of the scores of lesion relative visibility. Score of 1: visibility of the abnormalities excellent in DR and poor in PCM. Score of 2 or 3: visibility of the abnormalities progressively lower in DR but better than that in PCM. Score of 4: equal visibility of the abnormalities with the two techniques. Score of 5 or 6: visibility of the abnormalities progressively better in PCM than in DR. Score of 7: excellent visibility in PCM and poor visibility in DR. (Online version in colour.)

the two techniques; a score of 5 or 6, visibility of the breast gland and abnormalities progressively better at PCM than at DR; and a score of 7, excellent visibility at PCM and poor visibility at DR. Multiple abnormalities in the same patient were evaluated independently.

According to the BI-RADS classes for breast density [9], the radiologists associated each patient with a breast density score: (1) almost entirely fatty breast, (2) scattered fibroglandular densities, (3) heterogeneous dense and (4) extremely dense.

The results are in the form of ordinal data; therefore median and mode were used for presenting and summarizing, according to the usual definitions [14]. The Wilcoxon signed-rank test [15] was performed by using the Matlab software package (The MathWorks, Natick, MA, USA) to compare the visualization capability at PCM with that at DR. $p < 0.01$ was considered to indicate a significant difference.

3. Results

In figure 2, the histogram of the scores of lesion relative visibility is presented: the mode is 6 of 7 and the median is 5.5. In 10 cases, the visibility score is 7, which means excellent visibility at PCM and poor visibility at DR. According to the inclusion criteria of the study, different breast abnormalities were present in the enrolled patients; therefore, in the histogram each abnormality type is shown with specific colour grade. The statistical analysis demonstrates that the visibility of the abnormalities is significantly better in PCM when all the abnormalities are evaluated together (78 lesions, $p < 0.001$) and when the architectural distortions are studied (29 cases, $p < 0.001$, both mode and median are 6). The masses are significantly better evaluated by PCM as well (36 cases,
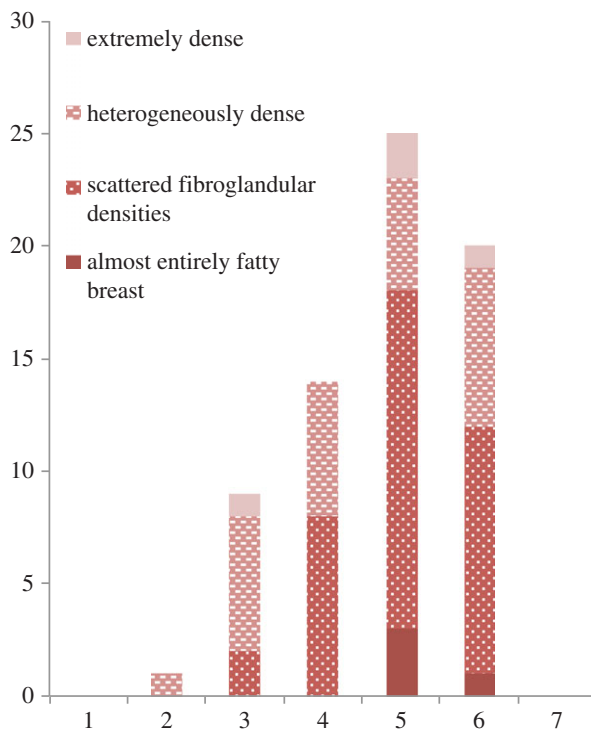
Figure 3. Histogram of the scores of glandular structure relative visibility. Score of 1: visibility of the breast gland excellent in DR and poor in PCM. Score of 2 or 3: visibility of the breast gland progressively lower in DR but better than that in PCM. Score of 4: equal visibility of the breast gland with the two techniques. Score of 5 or 6: visibility of the gland progressively better in PCM than in DR. Score of 7: excellent visibility in PCM and poor visibility in DR. (Online version in colour.)

$p = 0.0015$), their distribution having two peaks at 4 and 6, and therefore the mode value is not defined by a unique value and the median is 5.

The visibility of the microcalcifications is better, but only of marginal significance, in PCM: this result may be affected by the very small data sample (eight patients investigated, $p = 0.03$, both mode and median values are 5).

A focal asymmetry was present in five patients only. In one of the cases, the visibility is the same both in DM and PCM, while the rest presents better visibility in PCM. The mode is 7 (two cases of five) and the median is 6, but the number of cases is too small to be statistically significant.

In figure 3, the histogram of the scores of glandular structure relative visibility is presented: both mode and median values are 5 of 7. The statistical analysis demonstrates that the visibility of the glandular structure is significantly improved in PCM when all the patients are evaluated together (71 patients, $p < 0.001$). If only extremely dense breasts are considered, one out of four cases presents better glandular structure visibility using the screen-film system. Both modal and median values are 5: again, there is no significant difference between the two techniques mainly owing to the very small number of cases in this class.

The heterogeneously dense breast scores are in the range between 2 and 6. In 12 cases of 25, the visibility was better in PCM, whereas in seven cases the opposite. No significant difference can be demonstrated, even if in this density class the mode is the highest (mode = 6) but the median value is 4.

In the class of the scattered fibroglandular dense breasts (36 patients), the glandular visibility is significantly better using PCM ($p < 0.001$). The class of almost entirely fatty breasts contains only four cases and their scores are 5 and 6. The very small number of cases prevents one from attributing any statistical significance (median and mode values are 5).

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4. Discussion

The PCM images acquired in this study presented both absorption contrast, as in conventional mammography, and the edge-enhancement effect owing to the use of the propagation-based phase-contrast technique. The image-quality analysis demonstrated that the relative visibilities of both the glandular structure and the abnormalities were significantly better in PCM with SR than in conventional mammography obtained at the hospital. Several experimental details of the set-up contributed to enhance the image quality of mammography with SR, in addition to the phase contrast: owing to the monochromatic beam and the very good scattering rejection, the contrast was higher than that in conventional mammography. Pioneering SR mamographic studies, without phase-sensitive techniques, demonstrated the superior image quality at a dose level comparable to or lower than conventional mammography [16–18]. In this study, no attempt was made to separate the contribution of the phase contrast from the others to the image quality.

To understand the possible role of PCM in clinical application, the relative visibilities of both the glandular structure and the abnormalities were studied in detail. In our analysis, all the lesions classes including more than 20 cases (masses and architectural distortion) were significantly better visible using PCM. The presence of microcalcifications was not in the inclusion criteria. They were observed in some patients enrolled for other breast abnormalities and they were included in the analysis: the limited number of the cases (eight only) was most likely the reason for the lack of significance.

The study of the relative visibility of the glandular structure of each of the four BI-RADS breast density classes suggested that PCM is a powerful tool for breasts with scattered fibroglandular densities (BI-RADS breast density = 2), while the lack of significance was verified in the heterogeneous dense breasts (BI-RADS breast density = 3, 25 subjects). This result needs attention because breasts with high fraction of dense tissue are difficult to evaluate with mammography owing to the complex anatomical structures that affect the lesion detectability. Digital mammography is significantly better than film-screen conventional mammography in women with dense breasts [19]. In dense-breast images, the very low contrast between cancer and complex anatomical background can be overcome in part by the image processing, exploiting the high dynamic range of the digital detectors. Therefore, new clinical studies are necessary to investigate whether the image quality of the PCM with SR may be improved using the digital detectors or whether the mammographic film-screen system is an essential element of our set-up, owing to its spatial resolution higher than digital detectors.

The results of our preliminary investigation using a mammographic computed radiography (CR) system, based on photostimulable granular phosphors and dual-side reading [20], demonstrated good results in both contrast and spatial resolution [2]. A single photon counting detector has been designed for mammography at the SYRMEP beamline and is now under commissioning. The sensor is based on a silicon strip detector in edge-on configuration, obtaining very high efficiency and low noise, while the spatial resolution is defined by the strip pitch (50 μm) and the scanning velocity [21].

Our clinical study at the Elettra SR laboratory was done in order to investigate the impact of the PPCI on mammography, but the application of phase-sensitive techniques in clinical practice is related to the development of compact units that will be based on high intensity X-ray tubes or on compact sources of coherent X-ray beams different from SR, as in the Thomson-scattering sources [22,23]. A conventional PCM unit is available on the market, which applies the PPCI and it is based on a conventional mammography unit, a CR detector and an optimized geometry: a mild edge-enhancement effect is visible that slightly increases the image quality [24,25]. Recently, Thomson-scattering sources, or inverse Compton X-ray sources, have been proposed as an alternative source for PPCI, possibly compatible with the space available for a radiology department in a large hospital; some very preliminary results have been obtained at the Brookhaven National Laboratory [26]. The first Thomson-scattering source designed for mammography is under commissioning at the INFN national laboratory in Frascati (Rome, Italy)

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and both PPCI and grating-based differential phase-contrast imaging will be studied using the 20 keV coherent beam [27].

5. Conclusion

The first clinical study of PCM based on PPCI with SR demonstrated significant improvements in the visibility of the breast abnormalities and the glandular structure; these results were obtained in a challenging group of patients with inconclusive diagnosis after mammography and US. In order to improve the image quality of PCM, especially in dense breast, further clinical studies are designed using new digital detectors with high resolution, low noise and high efficiency.

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