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Monochromatic X-rays: The future of breast imaging

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ABSTRACT

Keywords: Innovative breast imaging Mammography Dose and image quality Screening mammography Digital breast tomosynthesis Disruptive technology Future of breast imaging *Purpose*: To present details about the innovative and disruptive technology of monochromatic X-rays and its application to breast imaging.

Methods: To analyze results of studies done using a prototype system for breast imaging that generates monochromatic X-rays through fluorescence emission. To assess signal-to-noise ratio (SNR) as a measure of image quality at different doses in breast phantoms of different sizes and review the comparison of parameters with a standard mammography system.

Results: Monochromatic X-rays reduce the radiation dose per mammogram by a factor of 5 to 10 times. For phantom simulating thick breast (9 cm), the SNR for monochromatic system was 2.6 times higher and the dose 4.2 times lower than the respective values obtained with the conventional system within the same 5 mm × 5 mm square area of the 100% glandular step wedge. For the conventional broadband system to equal the SNR of the monochromatic system, it would require a dose of 19 mGy, 29 times higher than the dose delivered by the monochromatic system. Contrast-enhanced digital mammography with monochromatic X-rays is shown to provide a simpler and more effective technique at substantially lower radiation dose.

Conclusions: Lowering radiation dose by a factor of 5 to 10 while maintaining image quality implies a major reduction in total exposure from breast cancer screening and dramatically less risk of radiation-induced cancers in at-risk women. The high SNRs for very thick breast phantoms provide strong evidence that screening with lower breast compression is possible while maintaining image quality.

1. Introduction

Screening mammography for breast cancer detection has led to the development of various imaging modalities. Some utilize ionizing and others non-ionizing radiation. The well-known advantages of X-rays have resulted in various imaging modalities with the intention of enhancing safety and efficacy. Digital mammography spawned the development of several derived technologies, including digital breast tomosynthesis (DBT) and contrast-enhanced digital mammography (CEDM) [1]. Combining DBT with CEDM has been shown to limit the effect of surrounding soft tissue and achieving higher contrast between malignancy and surrounding tissue [2].

Despite these advances, major problems remain in imaging of dense and thick breasts at acceptable radiation doses. Research in recent years has shown that DBT can more accurately assess breast cancer size and stage than conventional mammography [3]. It has been shown to improve the detection rate of cancers in women with dense breasts when using supplemental tomosynthesis in addition to standard digital mammography and has comparable sensitivity in the detection of noncalcified breast lesions when compared with digital mammography carried out with additional views.

X-ray mammography is the universally accepted method for breast cancer detection. It is widely available, relatively inexpensive, and repeatable. An estimated 39 million mammograms are performed annually in the United States [4]. The high radiosensitivity of breast tissue [5] has been the focus of frequent debates over the cancer risk associated with mammography [6] and increasing cumulative doses to patients [7]. That said, an innovative imaging technology using monochromatic X-rays recently has been developed [8] that has the potential for reducing radiation risks in mammographic exams. It is especially important for examining dense breast tissue where image quality frequently is suboptimal and limited in sensitivity.

This article summarizes the technology of monochromatic X-rays, results obtained so far and the potential for improving currently used mammographic techniques.

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2. Dose and image quality

Radiation doses and image quality are the major concerns in mammography. This is critical in breast cancer screening, when the majority of the asymptomatic women examined are healthy. Dose and image quality are interlinked, which is important to understand in the modern era dominated by digital mammography. In the past with analog mammography, the film turned black when overexposure occurred, but with digital imaging, overexposure results in crisper images with low noise [9]. As a result, not only are overexposures more common with digital imaging, but they remain undetected unless conscious efforts based on awareness and education are implemented [10]. The relationship between dose and image quality is further highlighted as the breast is a unique organ with only soft tissues, no bones. In a technical sense, it is one of the most demanding radiological examinations, as high-quality imaging is required in order to detect lesions that are normally very small in size. Mammography requires discrimination of soft tissues with minimal difference in X-ray attenuation and visualization of microscopic calcifications of varying shape [10]. In addition, it requires use of lower X-ray energies to enhance the image contrast, but at the expense of increasing the radiation dose.

There are clear guidelines provided by national organizations like the American College of Radiology (ACR) and the European Commission for maximum dose in mammography [11,12]. As per the ACR, the average glandular dose delivered by a single craniocaudal view of a 4.2cm thick, compressed breast consisting of 50% glandular and 50% adipose tissue must not exceed 3.0 mGy, although in practice, doses generally are much lower [11].

3. Breast compression: the nuisance

In mammography, breast compression reduces radiation dose and improves image quality by increasing sharpness and decreasing motion [13,14]. However, optimal values for compression force are not known, with no uniform consensus in international guidelines [15–17], resulting in subjective interpretation and variability in clinical practice. Breast size and density composition contribute to this variability and many women find the mammography examinations very painful [18–21]. Increased breast compression with each mammogram perceived as uncomfortable or painful may impact screening compliance [22–24].

Recently the US Food and Drug Administration and the American College of Radiology linked breast compression to the relationship between image quality and poor positioning in mammography [25,26]. One method to reduce variability in compression is standardization of pressure and implementation of breast compression paddles that display the pressure to both technologist and patient [27-29]. However, use of such paddles remains highly dependent on positioning as the paddle itself does not guarantee similar breast compression. Recent studies have explored ways to decrease mammographic compression during digital breast tomosynthesis that showed that a substantial reduction in breast compression of \sim 50% is feasible [29,30]. Another recent study used a pressure-based, flexible paddle, with or without patient-assisted compression. It improved the patient and technologist experience dealing with reduced compression pressure variability, mean breast thickness, and glandular dose [31]. Image quality was similar when comparing patient-assisted and technologist compression [32]. These recent outcomes may result in significantly reducing pain during mammography with minimal impact on image quality, improved screening adherence and increased survival rates.

4. Thick and dense breasts: Limitations of current breast imaging

Mammography is the only imaging modality proven to reduce breast cancer mortality in both randomized controlled trials and observational studies [33,34]. However, the advantage of mammography in breast cancer detection is not shared equally across women, in part due to dependency of the performance on breast density. Breast density refers to the amount of fibroglandular tissue relative to fatty tissue, which is determined visually or quantitatively in a mammogram [35].

Dense breast tissue is present in approximately 40% of women over 40 years and generally decreases as women age due to glandular involution with fatty replacement [36,37]. In the many clinical practices and screening programs, including in the United States, the American College of Radiology Breast Imaging Reporting and Data System (BI-RADS) breast density (composition) categories are integrated into reporting for two primary reasons: 1) impact on mammography outcomes and 2) associated breast cancer risk [38].

- Breast density impacts mammographic cancer detection due to the masking effect of breast density, which can obscure detection of lesions and decrease mammographic sensitivity [39,40]. A representative case of breast density impacting the interpretation of mammogram is illustrated in Fig. 1. The impact of breast density extends from increased false-positive findings [40,41] and reduction in cancer detection [42] to higher interval cancer rates [43,44]. In addition, breast density results in increased risk of higher stage cancers [34,45] which can minimize the mortality reduction [46] benefit of mammographic screening.
- 2. Dense breast tissue is a moderate risk factor for breast cancer. Women with dense breasts have approximately 1.5 times higher risk than the average woman [47] and some publications indicating up to 6 fold greater lifetime risk [48].

While there are inherent limitations of mammography in breast cancer detection due to breast density, supplemental screening should be considered only after a comprehensive risk assessment, not as an automatic reaction to breast density alone. Digital breast tomosynthesis reduces overlap of normal breast tissue which may result in reduced false positive recalls across breast density categories [44,49,50], increased cancer detection rate [49], and reduction in interval cancer rate [51]. Contrast-enhanced digital mammography (CEDM) captures both high and low energy images within seconds after intravenous iodinated contrast administration. The post- processed image highlights a potential enhancing lesion without the density impact, similar to subtraction images, resulting in comparable sensitivity and specificity to MRI [52,53] and superior to mammography for cancer detection in women with dense breasts [54,55].

A key component of mammographic image quality is adequate compression thickness [56], as decreased sharpness and image contrast occur in thicker breasts [57,58]. Additionally, thicker compressed breasts have increased overlap of structures, decreased uniformity of breast tissue displayed, and increased beam hardening [22,23]. A recent study showed that in light of the obesity epidemic, an increased body mass index was associated with greater compressed breast thickness, increased potential for motion, and resulted in decreased sharpness, and image contrast [59].

5. Monochromatic X-rays

5.1. Past studies that demonstrated advantages of monochromatic X-rays

Conventional X-ray tubes emit a broadband spectrum of X-rays that typically includes some characteristic line radiation. For optimal quality in breast imaging, monochromatic X-rays are needed to avoid energies leading to degradation of image quality. Literature dating as far back as 1947 and in the 1950's [60–62] discuss the use of monochromatic X-rays. In later part of twentieth century, the focus shifted to exploring the potential of monochromatic X-rays obtained from synchrotrons [63,64]. In 1987, studies using monochromatic X rays from 20 to 100 keV showed that in the energy range of approximately 20–30 keV, cancerous breast tissues exhibit a higher attenuation than normal tissues [65].





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Fig. 1. 47-year old woman presenting with left breast lump. Metallic BB placed in left breast area of concern by patient. CC (A,B) and MLO (C,D) views show extremely dense breast tissue which lowers the sensitivity of mammography. In the left breast CC view (B) there is an asymmetry underlying the dense tissue (oval). Targeted left breast ultrasound (E) performed in the area of clinical concern demonstrates an irregular hypoechoic mass with heterogeneous internal echoes and indistinct margins. Subsequent biopsy confirmed Invasive Ductal Carcinoma (IDC) grade 3, ER negative, PR negative, Her2-neu positive. Breast MRI axial vibrant post contrast fat saturated image (F) confirms the irregular left breast mass with avid enhancement and containing susceptibility artifact from biopsy clip. Currently, the patient is receiving neo-adjuvant chemotherapy.

With malignant lesions exhibiting, on average, a 10.9% increase in relative linear attenuation versus normal tissues, they should be easier to visualize using monochromatic beams in the range of 14–30 keV [65]. The effective energy of current mammography units (Mo-Mo, Mo-Rh, W-Rh) is in the 16.8- to 19.7-keV range.

Hoheisel et al. used an ordinary X-ray tube, a highly oriented pyrolytic graphite (HOPG) crystal, and an exit slit defining the Bragg angle for the desired energy that served as a virtual source [66]. They demonstrated contrast enhancement for monochromatic X-rays compared to polychromatic X-rays for existing iodine-based contrast media. They speculated that this contrast enhancement would also be experimentally verified in the detection of micro-calcifications.

Inverse Compton scattering involves the head-on collision of an energetic electron beam (traveling at approximately the speed of light) with an intense beam of light—in this case, infrared light. Both beams are focused to an exceptionally small spot at the point of collision. Light scatters off the electrons, picking up some of their energy and deflected back out of the interaction zone as X-ray photons along an axis almost collinear with the trajectory of the electron beam [67,68]. Investigators postulated that this would provide access to pulsed tunable X-rays to a wider range of users and ultimately accrue benefits for clinical patients, X-ray crystallographers, industrial radiographers, and others who routinely use X rays. A recent review presented the potential of spectroscopic imaging using compact inverse Compton X-ray sources [69].

5.2. Wish list for the future

X-ray tubes have evolved for over 125 years, since the experimental Crookes tubes that led to the discovery of X-rays on Nov 8, 1895, by Wilhelm Conrad Röentgen. These first-generation cold cathode or Crookes X-ray tubes were used until the 1920s. The Crookes tube or hot cathode tube was improved by William Coolidge in 1913 and has been the most widely used tube for the last century. If the century old technology is to be replaced by the advent of a monochromatic source, the positive aspects of the current technology should be retained and included in the wish list for the new source, as given below:

- 1. Monochromatic X-rays: Ideally with more than 90% monochromaticity
- 2. Facility size: It should not be synchrotron based which is impractical for use in the clinic
- 3. Source size: It should be suitable for the current day X-ray room
- 4. Source: Ideal if it can fit in standard X-ray systems
- 5. Cost should not be more than current tubes
- 6. X-ray energy: Ideal if it can be selectable and preferably auto selectable
- 7. X-ray spatial profile should be uniform with a wide field of view
- 8. X-ray flux sufficient to image thick and dense breasts and (if possible) for computed tomography (CT) and interventional fluoroscopy
- 9. Image quality and dose: The image quality should either be maintained with substantial reduction in dose as compared to conventional techniques or higher for the same dose as in current systems.

5.3. Most recent developments with futuristic potential

A most recent development in a monochromatic source fortunately meets all of the above 9 points in the wish list [8]. This innovative technology has garnered many patents as referenced in the paper. The technology is slated to be a disruptive as it has the potential to replace the more than century-old technology currently in use.

The new tube can be fitted in all current X-ray and CT imaging systems. It can produce a selectable monoenergetic X-ray energy spectrum with sufficient intensity over a wide field-of-view, enabling high quality images at low dose, all within the footprint of existing conventional mammography systems.

The technology combines two X-ray emission processes to generate

monochromatic X-ray beams. The first is similar to the conventional Xray tube where high energy electrons bombard metal to emit broadband X-ray energies. The second part is different and entails the concentration of these X-rays onto a compact, thin-foil, metallic target. The foil subsequently emits monochromatic X-rays via fluorescence with an energy that uniquely identifies its elemental composition. For example, the foil target of tin (Sn) produces two monochromatic emission lines, one very strong Kα line at 25.27 keV and a much weaker Kβ line at 28.49 keV. The emission from the tin target is 96% monochromatic. The complete setup including both parts occupies the space of the current day X-ray tube. The monochromatic energy can be selected by changing the material of the fluorescence target. Molybdenum, palladium, silver, and antimony generate similar monochromatic fluxes, and all are potentially useful in mammography. Higher energy monochromatic fluxes can be generated with target materials such as neodymium, samarium, dysprosium, tungsten and gold [70]. The tube allows for easy manual exchange of the fluorescence target to select the monochromatic energy because the target is located outside the vacuum of the X-ray tube. Automated target replacement is under development.

In a prototype system obtained by substituting the normal X-ray tube in a commercial mammography machine with the above monochromatic source, the image quality was evaluated as a function of radiation dose using the signal-to-noise ratio (SNR) measured for high and low contrast masses and microcalcifications in standard breast phantoms with a variety of thicknesses. Spatial imaging properties were assessed from these images as well as from modulation transfer analysis (MTF). Measurements using an iodine contrast agent were also performed.

The measurements were done on 4 breast phantoms with thicknesses of 4.1, 4.5, 7.1 and 9 cm. Just as an example, the image quality of a 4.5 cm thick phantom with a 50% glandular-50% adipose equivalent tissue composition was evaluated by a standard, commercial, broadband mammography, and the monochromatic system. For equal SNR of the high contrast 100% glandular step wedge measured within a 5 mm \times 5 mm region, the dose of the monochromatic image (0.18 mGy) was 7 times lower than that of the conventional image (1.26 mGy) [8]. Overall, the prototype system reduced radiation dose by factors of 5 to 10 times for the same SNRs as obtained from a conventional system. This performance was demonstrated in phantoms simulating a wide range of lesion sizes and microcalcifications in a variety of breast thicknesses.

6. Thick breasts and breast compression

While the benefit of compression on image quality is well described, the use of compression is objectionable to most women, painful to many [71], and lacks reproducibility on a yearly basis [19].

In this respect, and in addition to advantages of image quality and radiation dose for the 4.5 cm breast phantom mentioned above, the monochromatic X-rays system showed superiority for the 9 cm compressed breast phantom. The SNR of 418 for monochromatic system was 2.6 times higher and the dose (0.65 mGy) 4.2 times lower than the respective values (158 and 2.75 mGy) obtained with the conventional system within the same 5 mm \times 5 mm square area of the 100% glandular step wedge [70]. For the conventional broadband system to equal the SNR of the monochromatic system, it would require a dose of 19 mGy, 29 times higher than the dose delivered by the monochromatic system. The high SNRs for very thick breast phantoms provide evidence that screening with less breast compression is possible while maintaining image quality.

Similar superiority in SNR and low dose are also characteristic for measurements of low contrast masses and microcalcifications. Again, comparing monochromatic and broadband imaging for equal SNRs, the conventional system requires 5-8 times the dose of the monochromatic system to image low contrast lesions in 4.1 cm and 7.1 cm thick phantoms. When imaging microcalcifications ranging in diameters from 330 μ m to 170 μ m, the dose delivered by the monochromatic system is 6.6

times lower. This is further evidence that that screening with less breast compression is possible while maintaining image quality.

7. Contrast enhanced digital mammography (CEDM)

CEDM is receiving increased attention in the screening of women at high risk of developing breast cancer and as a diagnostic tool when suspicious lesions are seen in routine screening mammograms. In addition to implementing the conventional two-image, dual energy subtraction technique commonly used with broadband systems, the recent study [8] showed how CEDM using monochromatic X-rays can be performed simply and effectively with a single image using monochromatic X-ray energies either below or above the iodine K absorption edge. The single and dual energy method used with monochromatic Xrays each has its advantages, and both reduce the radiation dose compared to conventional procedures while providing high contrast and SNR. Notably, a single image acquisition typically has less statistical noise and requires less dose.

Dual Energy subtraction using monochromatic X-rays can increase the contrast by a factor of 5 times by using a monochromatic energy below and above the iodine K-edge. This assumes that the imaging detector has a quantum efficiency of at least 85% at energies immediately above the iodine K edge. These results indicate that monochromatic Xrays enhance the potential for widespread use in CEDM while substantially reducing radiation exposure. Furthermore, single images with monochromatic X-rays could enable dynamic studies of the rate of contrast uptake by the lesion and surrounding tissue since several images can be taken in succession while still keeping the total dose at acceptable levels.

Conclusions: The monochromatic X-ray system is more sensitive for imaging a wide range of breast sizes and compositions than conventional broadband mammography. High image quality and lower dose are its hallmarks. It also makes CEDM much more effective than current methods developed for use with conventional broadband mammography systems.

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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