THE FUTURE OF MEDICAL IMAGING

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The organisers of this conference have kindly provided me with the forum to look forward and examine the future of medical imaging. My view of the future is informed by my own research directions; thus, I illustrate my vision of the future with results from my own research, and from the research that has motivated me over the last few years. As such, the results presented are specific to the field of breast imaging; however, I believe that the trends presented have general applicability, and hope that this discourse will motivate new research. My vision of the future can be summarised in accordance with three broad trends: (1) increased prevalence of low-dose tomographic X-ray imaging; (2) continuing advances in functional and molecular X-ray imaging; and (3) novel image-based biomarker discovery.

INTRODUCTION

Future predictions are fraught with uncertainty; yet researchers constantly attempt to discern the future in order to align their research with that which is most likely to have high scientific and clinical relevance. I have been charged with the task of discerning the future of medical imaging. I have attempted, to the best of my abilities, to present a cogent and concise portrait of the future of medical imaging. In this paper, I present three trends, which have begun and yet are far from their ultimate conclusion, that I believe are key features of the future.

TOMOGRAPHIC IMAGING

Medical radiography is undergoing a tomographic revolution with the concurrent development of digital tomosynthesis and low-dose computed tomography (CT). It is conceivable that in the near future, projection radiography will be restricted to a specific few examinations where the derived benefits of tomographic imaging do not justify the time, effort or radiation risk.

Tomographic breast X-ray imaging became feasible with the development of modern digital mammography detectors. During the 1990s, while imaging companies were developing digital mammography products, researchers were exploring innovative methods made possible with the new detector technologies. Stereomammography, digital breast tomosynthesis (DBT) and dedicated breast CT (BCT) have their origins from this period. However, these methods might have remained intellectual curiosities had it not been for the remarkable results, or perhaps more fittingly the lack of results, from the ACRIN DMIST trial. The DMIST trial enrolled 49 500 women who were imaged by both screen-film and digital mammography. In spite of this large number, no significant difference was seen in sensitivity or specificity of breast cancer detection between the two technologies[1]. In hindsight, this result is not surprising; however, at the time, many researchers were dismayed.

This result, more than any other, has stimulated the move towards tomographic imaging, because for the first time, we have conclusive evidence that cancer detection and discrimination is not limited by the detector performance, but rather by anatomic noise—the dominant structure of normal tissue superimposed upon breast lesions. As a result of this work, we now recognise that there are specific limitations to mammographic imaging that need to be overcome to improve cancer detection:

- Mammography is a projection imaging process whereby 2D images are produced of 3D objects, thus intrinsically information is lost.
- 2D images superimpose spatially non-adjacent tissues, thus the inter-relationship of breast tissues is diminished. This results in a loss of diagnostic sensitivity.
- 2D images cannot fully present the 3D arrangement of breast tissue. This results in a loss of morphologic image information. As a result, there is a loss of diagnostic specificity.

Two directions are being explored in tomographic X-ray imaging of the breast. The first is the use of CT; the second, is the development and implementation of tomosynthesis or limited-angle CT.

The work of John Boone[2] is exemplary of the development of dedicated BCT systems. In these systems, the woman lies prone on a table with one breast positioned through a central hole on the table top. An X-ray tube and an opposing detector rotate about the breast. The total dose to the breast is comparable to a two-view mammographic study. The images are then reconstructed into a 512^3 volume, and displayed on a dedicated review workstation. To

Figure 1. The Hologic Dimensions™ DBT prototype system is shown (image courtesy of Hologic).

Figure 2. A digital mammogram (**a**) and DBT image (**b**) of a large tumour. The lesion and the associated architectural distortion are more clearly evident in the DBT image.

date, more than 100 women have been imaged, and the results, while anecdotal, are encouraging.

The competing technology is DBT[3−5]. DBT is a form of limited-angle CT. As currently formulated, the early DBT prototypes and products derive their form from existing digital mammography systems. In these DBT systems, the breast is held in compression between a movable compression paddle and a stationary breast support containing the detector array (see Figure 1). An X-ray tube is rotated about the breast and a series of projection images is acquired while the breast is immobilised. These projection data are reconstructed, typically using either filtered backprojection or an iterative reconstruction method, into a set of images aligned perpendicular to the central ray of the central projection and most commonly spaced in 1-mm increments.

DBT images differ from BCT images in two ways. First, DBT images have very high in-plane spatial resolution. This is completely analogous to conventional linear tomography; the in-plane spatial resolution is only limited by the spatial resolution of the detector. By comparison, the spatial resolution of BCT is poorer in-plane; however, BCT has markedly superior spatial resolution in the orthogonal direction. This leads to the second major difference, DBT has essentially no resolution out of plane; rather DBT blurs structures located above or below the focal plane. Thus, essentially only those structures in the plane of focus are displayed.

DBT has yet to be proved in a large randomised trial. However, there is already anecdotal evidence to show that DBT has clinical merit over digital mammography. By eliminating tissue superimposed upon
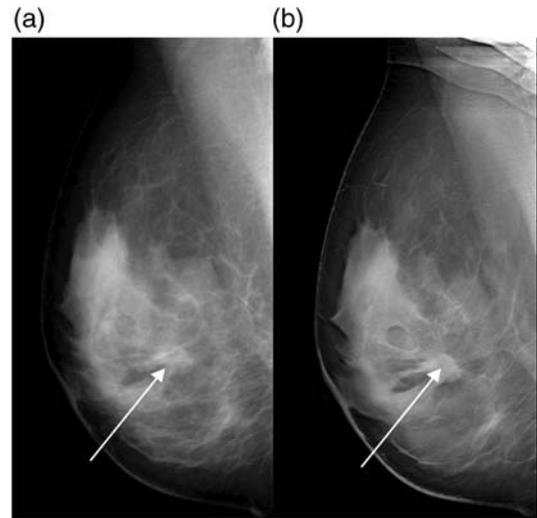
tumours, DBT can make tumours more conspicuous, potentially making DBT more sensitive than mammography. An example of this is given in Figure 2. DBT has also been shown to have value in resolving densities seen in one mammographic view when these densities solely consist of superimposed tissues. Another key advantage of DBT is the dose; DBT images can be acquired for a dose comparable to that required to produce a 2D digital mammogram, provided that the detector noise is minimised; this provision is nominally met with the current prototypes.

Today, it is not clear whether one technology (BCT or DBT) will dominate over the other; nor is it clear that any one technology need necessarily become dominant. It is quite possible that each technology will find an appropriate niche. As we move forward, the number of screening and diagnostic imaging technologies is likely to increase in number. Already, dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) is recommended for screening women at high risk (greater than a 20 % lifetime risk) of breast cancer. DCE-MRI has a number of diagnostic roles too. Whole breast screening ultrasound is currently being tested, and other imaging methods are on the horizon. Thus, a critical outstanding research question is to find a rational and practical method of triaging women into appropriate screening and diagnostic regimes. It is currently anticipated that genetic, demographic and image-based biomarkers will guide such decisions in the future.

FUNCTIONAL AND MOLECULAR IMAGING

In X-ray imaging, whether mammography, tomosynthesis or CT, disease diagnosis is largely achieved through observation of anatomic perturbations. X-ray images depict anatomic and morphologic information for diagnosis with high fidelity. However, organ morphology is often insufficient; for example, pathologic complete response to neoadjuvant chemotherapy is immediately evident in functional imaging, while morphologic changes may lag by a period of months. Therefore, functional imaging at macroscopic and molecular levels is essential to breast imaging.

Today, the undisputed champion of functional breast imaging is DCE-MRI. MRI is able to distinguish benign from malignant breast tissues on the basis of enhancement and washout temporal characteristics as well as tissue morphology. Tumours will rapidly take up the contrast agent, while the contrast agent washout is slow.

DCE-MRI has a role in breast cancer screening in women at high risk of developing breast cancer[6]. DCE-MRI is also used to evaluate the extent of disease for clinical disease management, including surveying for multifocal and multicentric ipsilateral disease, and contralateral disease. DCE-MRI is used to assess capsular rupture in women with breast implants. Finally, DCE-MRI has an increasing role in assessing therapeutic response, including risk-reducing therapies such as SERM and aromatase inhibitors, and neoadjuvant chemotherapy in treatment of women with locally advanced breast cancer[7].

The advent of digital mammography has stimulated interest in contrast-enhanced (CE) mammography. However, as with morphologic imaging, quantitative functional and molecular imaging is best performed tomographically; the removal of superimposed anatomy results in more accurate and precise quantification and localisation. Thus, the emergence of two tomographic X-ray imaging techniques has spawned interest in both CE-DBT and CE-BCT.

Researchers at the University of Pennsylvania, including the author, have pioneered CE-DBT[8,9]. There are two basic approaches to CE-DBT: temporal subtraction and dual-energy subtraction. In temporal subtraction, a pre-contrast DBT image of the breast is acquired; this image will form the mask used in later subtractions. The woman, with her breast still held in compression, is then administered a radiographic contrast agent. In our experiments, Visipaque-320 (Amersham, Chalfont-St.Giles, UK) is administered at a dose of 1 ml kg^{-1}. Subsequently, one or more post-contrast DBT images of the breast are acquired. These images are processed by subtraction of the mask image to create one or more difference images for which the primary source of image contrast is the uptake of iodine (Figure 3).
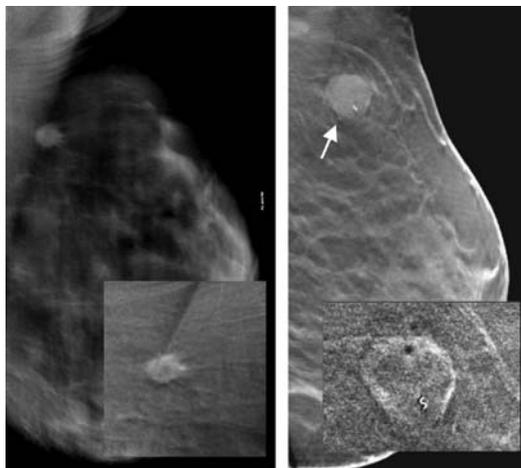

Figure 3. Two CE-DBT images are shown with subtraction images of the lesions inset. The left inset image is created with temporal subtraction and the right with dual-energy subtraction.

Temporal subtraction DBT is typically performed with a high-energy (45–49 kV) X-ray beam, which is heavily filtered (typically 0.25–0.30 mm Cu). The result is an X-ray spectrum practically matched to the K-edge of iodine. The result has the beneficial consequence of reducing the radiation dose to the breast, but the acquired mask image (being a high-energy image) is not of diagnostic quality in terms of the morphologic appearance of the breast parenchyma. Temporal subtraction imaging is also fraught with motion artefacts. Thus, some form of motion correction is typically required.

Dual-energy subtraction is the alternative technique for CE-DBT. In dual-energy subtraction, one acquires images in pairs—one with a mean energy below the K-edge of iodine and one with a mean energy above the K-edge of iodine. In theory, monoenergetic spectra immediately bracketing the K-edge energy would work best; thus, only the presence of iodine in the beam would alter the attenuation to any degree. In practice, the spectra overlap, and hence there is a change in the attenuation from both the soft tissues and the iodine. The result is that for the same radiation dose to the breast, the signal-to-noise ratio of a DE subtraction image will be poorer than a temporal subtraction image. However, the DE subtraction image will not demonstrate motion artefacts. Moreover, the low-energy image of the DE subtraction pair is typically suited for diagnostic imaging. In addition, DE imaging provides practical advantages including the ability to inject the contrast agent prior to breast compression and the ability to image the contralateral breast in a single contrast injection, albeit delayed with respect to the

ipsilateral image. In the same way, it is possible to obtain multiple projection images of the same breast in different orientations with one injection.

Both temporal subtraction and dual-energy subtraction are applicable to digital mammography, digital tomosynthesis and dedicated breast CT.

Concurrent with the emergence of CE breast radiography and tomography is a revolution in radiographic contrast agents. Taking inspiration from nuclear medicine and optical imaging, a significant increase is expected in research into radiographic contrast agents. These developments are made possible given recent advances in nanoparticles such as designer liposomes, polymersomes and nanospheres. Both blood-pool and targeted contrast agents are under investigation. As a result, it is now possible to envision molecular X-ray imaging

Molecular imaging, in a broad sense, implies visualising normal and abnormal cellular functions by utilising either biochemical or pharmacological probes. Ideally, the imaging technique should not perturb the function that is being assessed. Nanoparticles are small polymeric colloidal particles with therapeutic and/or imaging agent(s) either dispersed in the polymer matrix or encapsulated in the polymer. In our preliminary work, we have explored the role of targeted and blood-pool gold nanoparticle contrast agents for X-ray imaging. Karathanasis *et al.*[10] have published more advanced work demonstrating the potential of liposome-encapsulated iodine contrast agents. One key advantage of such agents is that the clearance route is altered, significantly reducing the risk of nephrotoxicity. At the same time, the clearance rate can be reduced significantly, providing greater diagnostic utility based on longer circulation times.

The field of molecular radiography is just beginning to emerge; yet, I personally believe that it will have a revolutionary role in the future of imaging.

IMAGE-BASED BIOMARKERS

A biomarker is a quantitative metric of the disease state. Appropriately validated biomarkers can be used to determine disease risk, indicate presence of disease in an individual, tailor treatments for the disease in an individual and monitor the course of that treatment. Although originally proposed with reference to protein and other biochemical markers, the term *biomarker* has become ubiquitous and is equally applicable to imaging measures.

As currently practiced, quantitative imaging involves the extraction of quantifiable features from images; these features add to the clinical assessment of the severity, degree of change or relative status of a disease or injury. Such measures are thus rightly called *image-based biomarkers*. The field of quantitative imaging includes the development,
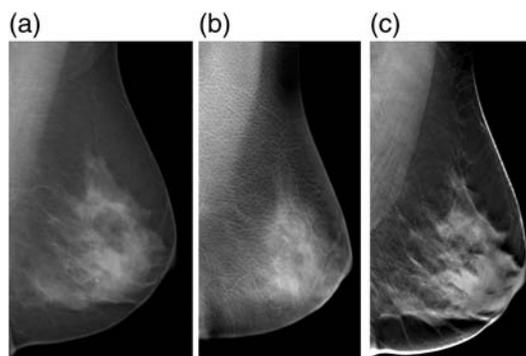

Figure 4. A digital mammogram (**a**) is shown in comparison with DBT images of the skin (**b**) and midline (**c**) of the breast. The texture in the mammogram arises from structures throughout the breast and hence is less discriminative than the texture of the midline DBT image.

standardisation and optimisation of anatomical, functional and molecular image acquisition, data analyses, display methods and reporting. Substantial research efforts are focused on the development and validation of precise image-derived metrics (image-based biomarkers) with physiologically relevant parameters, including treatment response to interventions and clinical outcomes.

One example of image-based biomarkers in breast imaging is parenchymal density (PD). Research by Boyd *et al.*[11, 12] have repeatedly shown that increased PD is associated with an increased risk of breast cancer. More recently, researchers at the University of Chicago have shown that retro-areolar texture is indicative of breast cancer gene expression (BRCA1/2) in digital mammography[13]. In extension of that work to DBT, we have shown that texture is inherent to a woman, that texture encodes unique information regarding risk and is indicative of the perceived quality of the acquired image[14]. While these associations were true in digital mammography, they showed stronger associations with DBT. This can be understood by examining Figure 4. Note that the texture seen in the digital mammogram is an admixture of the skin texture and the glandular parenchymal texture visualised separately in the DBT images. Thus, while such efforts are nascent, one expects these biomarkers to precede many other successful image-based biomarker discoveries.

CONCLUSIONS

In summary, as time moves forward it seems reasonable to expect that radiography will continue the move from projection to tomographic methods. With the increasingly common statement of concern regarding the dose of CT (refering to traditional CT

and not dedicated breast CT), one can reasonable expect that tomosynthesis will become increasingly common both for breast imaging and for other radiographic tasks.

Functional and molecular imaging is also reasonably expected to become more prevalent. This statement is true whether or not CE or molecular DBT is successful. Finally, it is safe to expect that many new quantitative metrics (image-based biomarkers) will arise in the course of the next few years.

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