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Emergence of "Big Data" and Its Potential and Current Limitations in Medical Imaging

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Although electronic imaging was performed in the early 1950s in nuclear medicine, it was the introduction of computed tomography in 1972 that caused a revolution in medical imaging in that it marked the beginning of the inevitable transformation to digital imaging. This transformation is now more or less complete. While initially these CT images were relatively small, comprised of only about 6400 pixels per slice, the steady move toward higher spatial resolution, multislice imaging, digital radiography, and fluoroscopy rapidly increased the size of images and the amount of data required to be stored, processed, displayed, and moved about in a medical imaging department. The more recent introduction of digital pathology with submicron-sized pixels and the need for color further increases these demands. Rising work volumes in hospital, a push for cost containment, and a move toward greater precision in diagnosis and treatment of disease all work together to motivate the development of automated image analysis algorithms and techniques to improve efficiencies in in vivo imaging and pathology. This may require bringing together information from different imaging and nonimaging sources within the institution. While technological development has provided practical means for storage of the burgeoning data load and the use of multiple processors and high-speed networks has enabled more sophisticated analysis locally or in the cloud, challenges remain in terms of the ability to integrate data from different systems, the development of appropriately annotated image bases for training and testing of algorithms, and issues around privacy and ownership in obtaining access to patient-related data.

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Possibly the first capture of medical images via electronic signals occurred in the 1950s initially with the development of the rectilinear scanner[1] and then the Anger scintillation camera[2] for nuclear medicine imaging. Gamma rays emitted from a radionuclide administered to the patient were absorbed in a thallium-activated NaI crystal. The resulting burst of light quanta from each detected gamma ray produced electronic pulses in an array of photomultiplier tubes and in this way the gamma rays could be counted to represent a signal whose origin in the body could be localized, thereby providing information on the distribution of uptake of a radiopharmaceutical. This marked a major milestone in that it provided the ability not just to use radionuclides to obtain information through tracer studies but to perform actual in vivo functional imaging.

Initially, the electronic signals were recorded in an analog manner on paper or film and the processing and display of the images from the gamma camera were of necessity fairly simple. Subsequent developments resulted in creation of fully digital images and more elaborate processing and display were implemented as more sophisticated and powerful computers and display devices became available.

In the early 1960s, nuclear medicine gamma ray imaging was extended by Kuhl and Edwards to tomographic imaging of tissue slices or slabs within the body, although the method for image construction was entirely analogue.[3] This was the origin of gamma ray emission computed tomography (SPECT). These tomographic images showed the potential for improved specificity in reporting on distributions of radionuclide uptake in the body.

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Despite these important earlier milestones, it was the publication of results with the first clinical CT system in 1972 that aroused tremendous excitement and truly propelled the revolution toward digital imaging in medicine.[4,5] CT combined several key features. First, the images were captured in digital form. Second, they were not simply recordings of x-ray projection data, as in conventional radiography, but were reconstructed slices representing transverse sectional slabs of tissue within the patient. CT revolutionized medical imaging by providing images that depicted much more subtle changes in tissue than was possible with earlier technology. This came about (1) through the development of x-ray detectors, with higher x-ray absorption efficiency, wider dynamic range and lower noise for acquiring the data compared to the previous analogue film-based systems, (2) precise digitization, (3) the three dimensional nature of the reconstructed images which eliminated the detrimental effect of tissue superposition in conventional radiology, and (4) the ability to manipulate the digital image data and then view the images on a computer display where image brightness and contrast scales were adjustable. Furthermore, these images were quantitative and amenable to many types of subsequent refinements, such as dual energy for tissue composition analysis, contrast improvement, and artefact reduction[6,7-11] and quantitative analyses, higher speed and extended body coverage through helical and multislice imaging.[12,13]

Over the next three decades, a gradual transition to digital image acquisition and display occurred in all the other existing areas of medical imaging including vascular imaging, nuclear medicine, projection radiography, and ultrasound. More-recently-introduced imaging techniques based on reconstructed images like PET and MRI were digital at the outset.

Of necessity the earliest digital images were relatively small, limited by the available detector technology of the time. The first CT images, for example, had dimensions of only 80 × 80 pixels, 3 mm on a side and produced two adjacent slices simultaneously, each 13 mm thick. From the beginning, it was realized that the most important benefit from CT was not spatial resolution, but the ability to distinguish tissue changes on the basis of small differences in x-ray attenuation properties. This required precise measurement of signals over a wide range of intensities, possible only through the introduction of fast, analogue-to-digital conversion electronics with 12-16 bits of digitization depth capacities, depending on the application.[14]

While digital imaging represented a revolution in technology, the most important impact of that revolution has been in its opening the door to the use of quantitative techniques in medical imaging.

Big Data

As digital imaging took hold, technologies further developed and the amount of digital data associated with imaging increased. The amount of data is dependent on several factors and these vary among the different imaging applications. The data requirement for an examination is given by:

$$D = \left(LW/w^2\right)Bn$$

where L and W are the dimensions of the image field and w is the dimension of the side of a square pixel, B is the number of bytes required to digitize the information in a pixel, usually 2, and n is the number of images, image frames or slices acquired in an examination. L, W, and w must be specified in the same plane, which can be in the detector itself or referred back to a level within the patient. The data rate, which is the number of bytes per second that must be acquired, stored or transferred is also an important consideration and this can vary considerably depending on the type of detector and whether or not it can temporarily buffer data internally and the image frame rate defined by the clinical need. Therefore, although I am not really comfortable with the term whose definition will almost certainly change continuously as technology advances, the data become "big" when image fields are large, pixels are small, frame rates are high, or there are many images acquired per examination. The amount of data increase rapidly when more than one of these conditions applies to a particular imaging requirement. Typically, imaging modalities that provide primarily anatomical or morphological information tend to have small voxels (area of pixel × slice thickness), while those that convey functional measurements often use larger voxels, but with more bits per voxel to express the more-subtle changes or multi-spectral data.

Digital Mammography

The last radiographic modality to move from analogue to digital was mammography, where it was necessary to wait for the development of analogue-to-digital converters with adequate precision and very high spatial resolution (small pixel) x-ray detectors to accommodate the requirement of depicting the fine detail of microcalcifications and soft tissue spiculations. But, recognizing the potential of digital approaches in breast imaging, a conference on digital mammography was held in San Jose California in 1993,[15] seven years before the appearance of the first commercial digital mammography system. These meetings, originally known as The International Workshops on Digital Mammography (now The International Workshop on Breast Imaging) have taken place continually since that time at two-year intervals and have been a forum for science around the development of digital breast imaging.

Before the actual clinical systems became available, the discussions focused on the technological obstacles that had to be overcome for digital mammography to become a clinical reality, namely the required developments of detectors and display devices. There was also considerable interest on the potential of factors such as image processing, data compression and computer-aided detection, and diagnosis and their role in this future modality. The latter was applied to analysis of data from film mammograms that had been digitized by means of high spatial resolution optical scanning devices.

The ideas developed using these scanned images included definition of key features, segmentation, classification, and use of neural networks.

In Europe, the benefit of having more than a single interpretation of the mammographic examination has long been appreciated and double reading is commonly done to improve sensitivity and/or specificity. In North America, double reading is generally considered to be prohibitively costly. Nevertheless, the possibility of emulating a second reader by using computer-aided detection was very attractive, although the need to scan films for digitization was a major disincentive.

Digital mammography enters the realm of "big data" primarily due to the small size that is required for the image pixels, typically between 50 and 100 μm (0.05-0.1 mm), resulting in pixel areas as small as 2.5×10^{-3} mm^2. For an 18 cm × 24 cm size mammography image field, this would require as many as 17.3 million pixels, or at 2 bytes per pixel approximately 35 MB per image. At an average of 4 images per examination and 100 examinations per day, this produces about 3.5 TB of data per year in a busy department and a significant impact on the network of moving these images around.

But by far, the greatest challenges for digital mammography were in developing x-ray detectors that could provide the small element sizes to support such high spatial resolution with an intensity range/precision of 12 or 14 bits (factor of 4096 or 16,384, while allowing coverage of an 18 cm × 24 cm (or today a 24 cm × 30 cm) field and then displaying so much data simultaneously.

The detector problem was solved through technological improvements in capabilities of creating readouts based on amorphous silicon pixel arrays (Fig. 1). These were coupled either to a high-resolution CsI(Tl) phosphor[16,17] or to a sheet of amorphous selenium photoconductor.[18,19] Alternatively, long, narrow single- or multiline strip detectors could be used to scan across the breast, gradually accumulating the image data. Systems that have been implemented were of two types. In one, a CsI(Tl) phosphor was coupled through fiber optics to a self-scanning charge-coupled device (CCD) array that recorded the light from the phosphor.[20] In another, individual x-ray quanta could be counted by collecting the electronic charge liberated in a silicon strip detector.[21]

One of the major advantages of digital acquisition was the ability to perform image processing to optimize the presentation of the image for the diagnostic task, in the case of mammography, the detection or characterization of subtle masses, architectural distortions and microcalcifications. Most display devices cannot render the 12-14 bits of acquired intensity with optimal contrast. In particular with film, the upper and lower ends of the recorded intensities were displayed with reduced contrast in the so-called "shoulder" and "toe," respectively of the characteristic display curve of the film. The simplest type of processing was adjustment of the displayed brightness and contrast to enhance the probability of detection of lesions, overcoming the restrictions of photographic film, and/or the human eye. An example of an almost universally used technique is linear clipping and scaling of the intensity scale, achieved by setting a window level to define the acquired signal intensity level that would be rendered as midtone gray. The window width then defined the range of recorded digital values that would be displayed between the black and white (minimum and maximum brightness levels) of the display device.

On the earliest digital mammography systems, the number of acquired pixels in the image was much greater than the capacity of available monitors and the solution was to print the digital image back onto film after adjustment of window level and width. While this helped to optimize the gray scale presentation, it was inflexible in that the display could not be further modified once the image had been printed. In addition, film is expensive, requires storage space and the image is only accessible for viewing in one physical location.

Another image processing technique that could be applied to the mammograms was used to reduce the dynamic range of signals that must be rendered by the display device. The interpretation of the mammogram focuses mainly on details at mid and high spatial frequencies. Low-frequency information that varied over a range of several centimeters was less important. High speed processing of these large images allowed various types of filtering to be applied to the

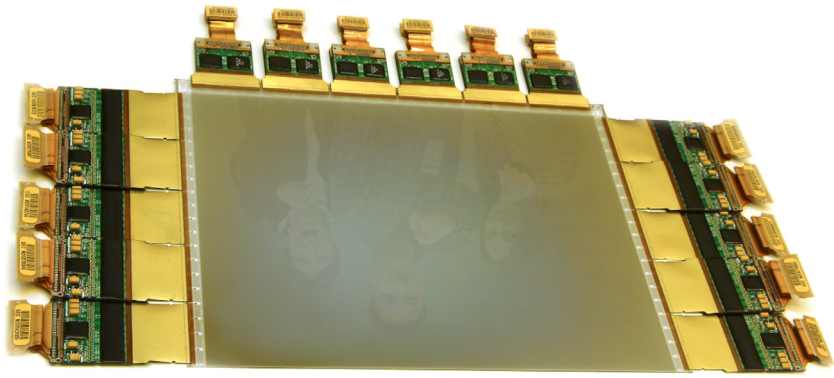

Figure 1 High-resolution amorphous silicon flat-panel x-ray detector for digital mammography. Detector elements (pixels) are 0.1 mm on a side. A CsI(Tl) phosphor is evaporated onto the surface to make this an x-ray sensitive device. Courtesy, General Electric Global Research Center, Niskayuna, NY.

images to allow small-area contrasts due to fine structures in the breast to be enhanced while suppressing changes at very low spatial frequency. This allowed preservation of good contrast both in the thicker denser areas of the breast and also near the skin edge of the image.[22] Another image processing technique called contrast-limited adaptive histogram equalization,[23] allowed local optimization of contrasts deemed important in radiological interpretation while reducing broad-area changes. Although this type of spatially-varying nonlinear processing was valuable in making lesions more conspicuous, it had the effect of transforming an image that was a fairly faithful representation of x-ray attenuation patterns in the patient to one in which the local signals were less closely related to a physical phenomenon. For some types of analysis, preserving the original unaltered data would be important. Recognition of the value of both the highly processed image and the original, more direct recording led the DICOM standards group to define the former as a "For Presentation" image and the latter as a "For Processing" or "Raw" image.[24]

Driven by developments in other fields, high-resolution electronic monitors became commercially available for medical imaging, first capable of displaying 3 million pixels, and later 5 million pixels, which have now become standard. The displays were initially CRT devices which were expensive and bulky and produced considerable heat, but allowed interactive manipulation of image gray scale display (brightness and contrast) by the radiologist during interpretation. These devices still could not simultaneously display all of the pixels provided by a detector with 50 μm elements, but this limitation could be mitigated by use of software that allowed zoom and scroll of the digital image on the display. Hardware acceleration of these functions soon became available to reduce latency in image manipulation, improving the radiologist's experience in interacting with the digital images. Eventually the CRT displays were replaced by flat panel LCD screens which were more energy efficient and allowed the design of more ergonomic reading stations for the radiologist.

Once mammograms were available in digital form, it was much easier to implement the algorithms originally developed with film mammography in computer-assisted detection (CAD_d) and/or diagnosis (CAD_x) systems. The former are used primarily in cancer screening to identify suspicious lesions[25] while the latter are tools that make use of large knowledge bases of annotated cases to give the probability that a lesion represents breast cancer rather than a benign condition[26,27] or in identifying one of the major significant features of cancer such as architectural distortion.[28]

The development of these CAD algorithms may have been one of the first examples of use of big data in medical imaging as the training and validation of these algorithms required very large sets of appropriately annotated images, indicating ground truth, location and type of lesion, etc. When these algorithms were designed to be applied to a breast cancer screening application, in principle, the number of images required for training could become extremely large. This is because in a screening cohort only about five women per 1000 screened would have breast cancer. To obtain enough cancers for statistical validity while including the range of morphological or textural features that would characterize breast cancer and at the same time represent the overwhelming number of normal variations, possibly hundreds of thousands of images would be required.

Interestingly, in an application like screening, the task is to reduce the information from the enormous amount of data associated with large, high-resolution digital images to just one bit: where "0" indicates suspicion of cancer and the need for further investigation and "1" denotes confidence that there is no disease and the patient can return at the next screening interval.

Tomosynthesis

The clinical motivation for digital mammography was to improve the detectability of cancers, particularly in women with dense (ie, highly fibroglandular) breasts through more efficient acquisition of the x-ray image and image processing and manipulation. To some extent it succeeded in this goal, however, the sensitivity and specificity in cancer detection are still suboptimal. In the United States, for breast cancer screening, while sensitivity can exceed 90% in women with fatty breasts, it can be as low as 65% in very dense breasts.[29] Overall specificity is under 90% and can be as low as 85%, that is, 10%-15% of women will be recalled for further examinations after screening while only 0.5% will be found to have breast cancer.

Part of the problem is the inherent superposition of the information from overlapping structures in the breast in the two-dimensional projection images. Breast tomosynthesis is an imaging technique, built on the platform of digital mammography, that attempts to overcome the superposition problem, much in the way that computed tomography does this in other areas of radiography.[30-32] In fact, dedicated breast CT imagers have been built and one model is available commercially.[33-36]

Tomosynthesis is an intermediate approach between 2D radiography and CT. The gantry, which looks like that of a mammography system, has been modified to allow the x-ray tube assembly to rotate about the stationary compressed breast while a series of low-dose x-ray projection images is acquired. These views are reconstructed by a computer algorithm to produce a set of slice or slab (thicker slices) images of the attenuation of breast tissue, typically in the craniocaudal and/or mediolateral oblique planes.

Typically, tomosynthesis provides more or less the same spatial resolution as digital mammography in these planes (ie, similar pixel size) while the resolution in the orthogonal dimension tend to be coarse, 0.5 mm or greater. Because 9-25 angular views are acquired and the set of reconstructed tomosynthesis slices must be stored, the amount of data is considerably larger than for digital mammography with a single examination creating between 720 and 2000 MB, and a busy department producing up to 5 TB per year just from

breast tomosynthesis. Of course, reasonable levels of lossless compression can be applied to such image data.

Although some studies have shown impressive improvements in specificity and/or sensitivity of tomosynthesis in conjunction with digital mammography over digital mammography alone, these have mainly been ecological studies or single vendor studies. There has been some recent data demonstrating superior accuracy of tomosysnthesis alone vs digital mammography alone, but this has been a retrospective reader study. Many of these studies have taken place in Europe where double reading interpretation of mammograms is done and screening is biennial, resulting in a rather different situation than in North America.

The Tomosynthesis Mammography Imaging Screening Trial (TMIST) is a randomized trial of 165,000 women sponsored by the ECOG-ACRIN clinical trials group and funded by the US National Cancer Institute.[37,38] TMIST was designed to compare the detection accuracy of digital breast tomosynthesis (with or without digital mammography) to that of digital mammography alone. Each participant will receive 3-5 examinations at either annual or biennial intervals and both unprocessed and processed image data as well as details of their radiological interpretation and biopsy reports from more than 600,000 examinations, yielding several million images, will be archived centrally. Positive examinations will be annotated by a radiologist. Notably, TMIST includes systems from multiple vendors and outcomes will consider not only the accuracy of cancer detection but also potential impact, by examining biological differences between the types of cancers detected by the two imaging modalities. To this end, biological tissue samples are being collected for genetic and proteomic analysis.

This unique repository of both (annotated) imaging and biological data provides enormous potential for research in radiomics,[39-41] the use of image data to develop quantitative imaging biomarkers or radiogenomics,[42,43] and the integration of radiomic and genetic information for the purposes of more precise characterization of disease or guidance in prescribing therapy.

Digital Pathology

The definitive diagnosis of disease virtually always comes from the pathologic examination of tissue. To this day most pathology is performed by visual inspection of the tissue, treated with appropriate chemical stains, under the microscope. The examination is largely subjective and based on the extensive experience of the pathologist in distinguishing normal, benign changes, and diseased tissue. Quantitative techniques are fairly primitive and often very time consuming and labor-intensive. For example, cells are counted individually by visual inspection, by sampling over a specific subarea of the image on a glass slide.

The dramatic improvements in electro-optical devices such as high resolution, wide dynamic range CCDs, and in digitally controlled opto-electromechanical devices such as laser scanners have provided the ability to transform pathology to a science based on digital imaging and analysis. Digital pathology is still a very new field and the transition from over 150 years of microscopic pathology as pioneered by Virchow,[44] has been a slow and challenging one. Nevertheless, there is enormous excitement at the new capabilities that emerge when the microscope slide and many other aspects of pathology become available in digital form.

For example, in my laboratory we have been digitizing histopathology slides for over a decade and, along with many other academic and industrial groups, have been developing algorithms for quantifying important aspects of the pathology examination. In particular, my group has focused on techniques for creating whole-mount sections in digital form.[45,46] This involves many changes from historical protocols, in fixing, cutting, and processing the tissues, in microtomy, and of course, in producing and storing the digital image. Because histopathology images must capture microscopic detail, down to 0.5 μm or finer and the images are color (typically 3 bytes per pixel), even a single standard 1 × 3 in. (25 mm × 75 mm) digital slide requires approximately 22.5 GB. We have been working with slides as large as 125 mm × 170 mm (eg, Fig. 2), so that the image can be as much as 20 times larger. The enormous amount of data created immediately raises questions as to the type and degree of data compression that is acceptable. These issues are not only scientific, but because of the sensitive role that pathology plays in the final diagnosis of disease, there are also legal questions that must be addressed. In any case, digital whole-slide images are much larger than those typically encountered in in vivo medical imaging applications and, given that many of these slides would be produced each working day, there are key practical challenges in how to acquire and move such large amounts of data effectively within a clinical institution.

In our work we have been studying the potential impact of utilizing these larger more complete pictures of resected tissue to quantify the tumor burden of breast cancer in terms of linear size (dimensions) of disease, tumor volume,[47] and multifocality[48] and have found differences from diagnostic conclusions drawn when conventional smaller format slides are used.

There are many other valuable applications that can be built on the platform of digital pathology, both in terms of how information is acquired and how it can be analyzed to enhance diagnosis and possibly add prognostic and predictive information to guide treatment decisions.

One exciting application of digital imaging is the multiplexing of biomarkers in tissue specimens. We have been working with a system designed by General Electric Global Research Center (Niskayuna, NY) that allows imaging of multiple markers on the same tissue section. Antibodies to the protein of interest are directly conjugated with fluorophores (typically Cy3 and Cy5). The microscope slide is then imaged under fluorescence and a high-resolution digital image is captured and recorded. The fluorophores are then deactivated by bleaching and a second set of antibodies is imaged in a similar manner on the same tissue section. This process can be repeated multiple times, producing a multiplexed image of

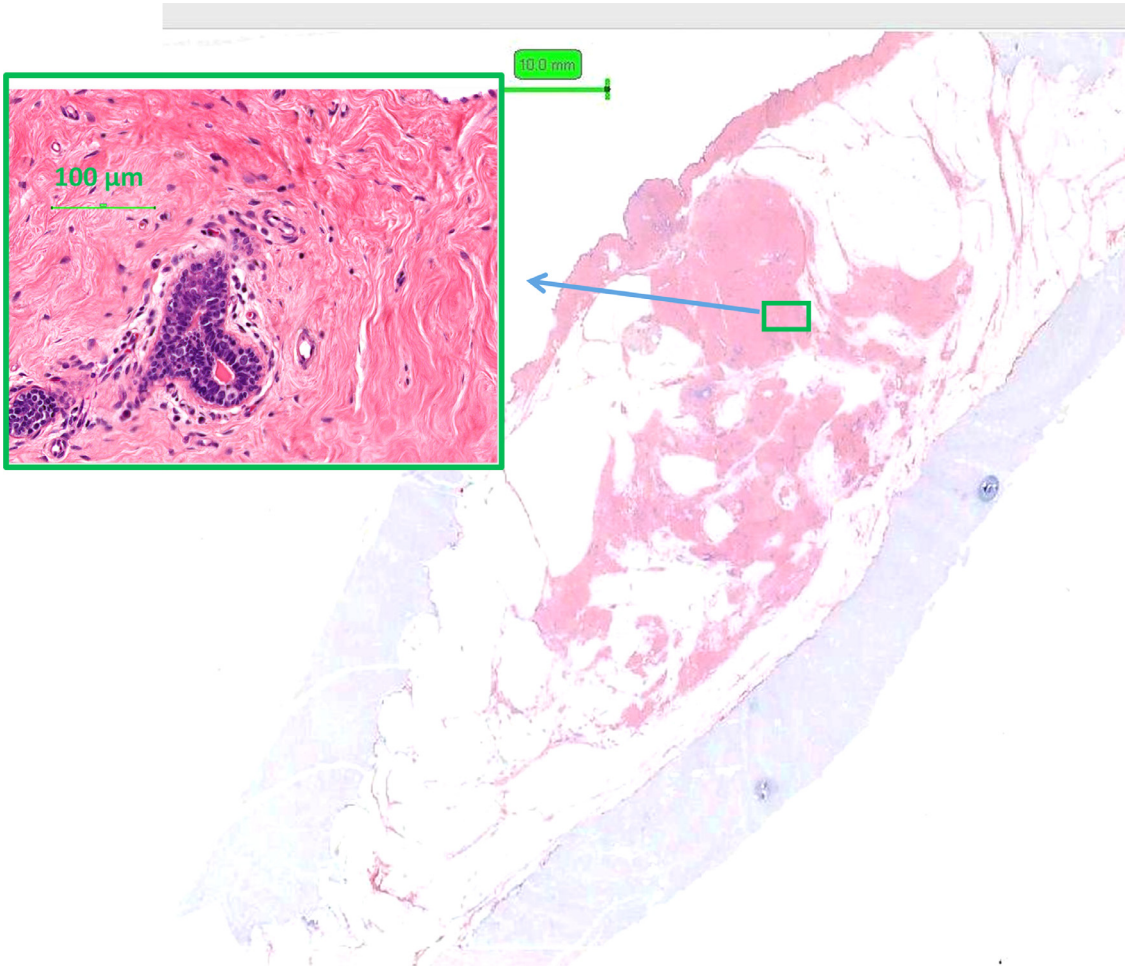

Figure 2 Whole-mount histopathology image of entire lumpectomy section. Region of interest displayed at higher spatial resolution is shown in the inset.

many (up to 64) markers. Because the tissue section remains stationary under the microscope, there is perfect spatial registration of the markers, allowing colocation analysis to be performed.[49] We are currently using this system to analyze spatial heterogeneity of the characteristics of breast cancer and to map the immune environment of different cancers to guide regimens for immunotherapy (Fig. 3).

The logical extension of this work is the integration of the protein data with genetic data obtained by RNA or DNA sequencing of spatial specific areas of interest. This would provide an excellent tool for investigation of the important problem of spatial heterogeneity of the characteristics of cancer.

In the application of multiplexed pathology the data become "big" because of the high spatial resolution of the microscopy, the use of multiple molecular-specific stains, color and the complexity of the analysis. Analysis consists of identification of features in the tissue and distinguishing the different cell types, nuclei and organelles. Again, as in digital in vivo imaging, this application lends itself to the use of artificial intelligence techniques to facilitate subtle classification tasks.[50,51] Although this is an exciting new approach, its ultimate value remains to be demonstrated, but may be both in the better understanding of disease and also in improved prognostic and predictive information for treatment.

Data Warehouses

The field of medicine is typically practiced as a set of siloed activities. In the area of cancer, the processes of detection, diagnosis, and treatment are often isolated from one another, often to the disadvantage of the patient. Each of these activities generates valuable information about the patient and the disease, information that could be valuable both in the management of disease and for research into cancer diagnosis, treatment, survivorship, and prevention. Often the information from the activities that occur in a health facility is collected on disparate computer systems in ways that impede the integration of that information and the potential synergies from such integration. Several institutions including ours have attempted to create systems that will facilitate such integration. A data warehouse, known as the Sunnybrook Research Biomatrix, has been designed initially to support cancer research activities only, but it is scalable to include other diseases and to be used for clinical management. Its design retains patient identifiers internally to preserve accuracy, but only allows extraction of data in pseudo-identified form by researchers. It has been built with safeguards to restrict access to authorized users, contains an audit trail mechanism and also can be configured to allow

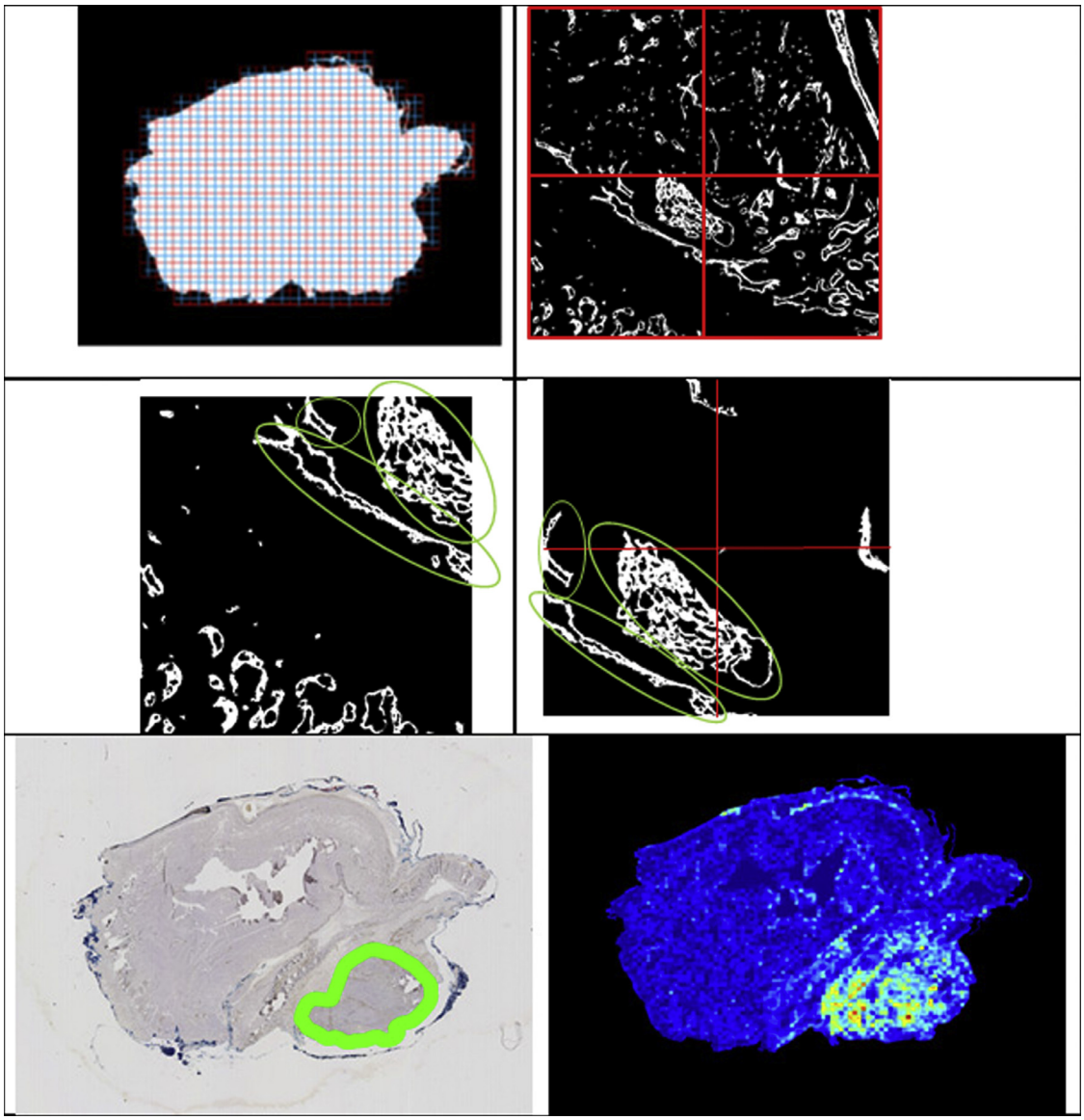

Figure 3 Processing of very large digital pathology images. Top: Region of interest to be processed applied with two grids, round 1 processing grid (red) and round 2 processing grid (shifted half a block grid vertically and horizontally). Middle: In round 1 processing, only objects that are completely captured by the block are counted. Objects touching the block borders (circled) were removed. In round 2 processing, objects touching the seam between round 1 blocks are counted. Also, objects touching the tips of the cross are often counted twice and thus they are counted as half-objects. Bottom: After block processing, images are tiled back to original position. (Left) Original color image of CD31 whole-mount VX2 tumor is highlighted in green. (Right) Final vessel-density map taken with an 800 pixel block-width. Lighter pixels represent higher density regions.

collaborations between institutions. The Biomatrix includes a data server and an image server. The data server contains demographics, imaging, pathology, and treatment reports as well as outcome data, while the image server is a large DICOM image base with links to the textual data.

Data are entered on the basis of patient consent. While some patients provide consent for their data to be used only for one specific study, there is also a prospective consent mechanism in place where the patient can choose to allow any of his/her data to be used in ethics board-approved research studies to be designed in the future. Currently data from over 12,000 Sunnybrook patients reside in the Biomatrix. As much of the data are synoptic values and text, the storage requirements for this wealth of data are modest, on the order of hundreds of megabytes. The corresponding image archive which is much more data intensive occupies 40 TB.

Currently basic scientist and clinician scientists are utilizing the Biomatrix to address a wide assortment of problems. These range from studying the toxicities associated with delivery of radiation therapy in different geometrical configurations, to selection of patients on the basis of multiple radiogenomic markers to predict the therapy that would elicit the best tumor response to optimization of diagnostic imaging procedures.[52]

Image Data Analysis

The aims associated with development of the Biomatrix and of algorithms for image analysis are to allow more precise and less labor-intensive assessment of in vivo and/or pathology images.

One example of such activity is an attempt to develop a radiomic approach to stratification in breast cancer screening. Mammography is an effective tool with excellent sensitivity and sensitivity for detection for most women. Both sensitivity and specificity may be dramatically diminished in women with dense breasts. Such women may benefit by receiving alternative or supplementary screening using a modality less affected by density. One way of stratifying screening for these women is by subjective assessment of breast density from the mammogram. It has been shown, however, that this approach is rather inefficient. Not all of the women whose cancers would be missed are selected for supplementary screening and many women whose cancers could be satisfactorily detected on mammography would be sent for additional more costly procedures. We have been developing a more sophisticated approach based on an index for cancer "masking" that predicts the probability that a cancer would be missed. This would take into account both the amount of dense tissue and its location and features such as the texture and complexity of the image background due to surrounding normal tissue.[53] To arrive at truly-efficient algorithms that could be implemented in clinical screening programs, it is likely that we will have to turn to artificial intelligence methods that would identify which women should be recommended for supplementary imaging. Deep learning using convolutional neural networks is being investigated for this purpose. Convolutional neural networks learn by training on a very large number of images that have been at least partially annotated. These images would include women with cancers that were missed because of masking on the mammograms, women whose cancers were detectable and women without cancer. The algorithm would learn subtle features that would help identify the first group and ignore as many images as possible in the other two. To overcome statistical variability and other factors that cause uncertainty, it is possible that over 100,000 images would be required to train the network. At 10 MB per image, this is a terabyte of data that must be stored, managed, and processed.

Precision Medicine—Multimodality, Multiparametric, and Molecular Imaging

Each imaging modality is based on the interaction between a specific form of energy and biological structures in the patient at the gross, molecular, atomic, or nuclear levels. From these interactions important information can be inferred that report on normal phenomena or pathologic changes. The potential value of integrating complementary information obtained through the use of multiple imaging modalities has been recognized for some time, mainly for the combination of anatomical or morphological information with information on functional properties.[54,55]

Classic examples of the synergy between imaging modalities are in SPECT/CT and PET/CT where the CT image provides excellent, relatively-high spatial resolution, 3-dimensional anatomic information and the SPECT or PET reports on physiological activity associated with the uptake or kinetics of a specific radiopharmaceutical. Because of the nature of gamma ray interactions, their relatively high energy and the desire to achieve high signal-to-noise ratio in SPECT and PET images at acceptably low radiation doses, the voxel size for these images is relatively large and, therefore, their spatial resolution is modest. The complementary value of the CT is to provide excellent spatial resolution with anatomical features registered to these sensitive functional images. CT data have also been used to facilitate attenuation correction of the nuclear medicine images to improve their accuracy.[56]

Another way in which imaging data are enriched is through multiparameter (mp) imaging. Extraction of multiple data parameters has been widely exploited in MRI, where pulse sequences can be designed to produce images that report on different phenomena, such as vascularity, perfusion, diffusion, oxygen utilization, etc. and where spectroscopy and imaging have been combined. One example of mp imaging is in prostate cancer where overtreatment is a major challenge. Image measurements can be made, not only of the traditional relaxation coefficients like T2, but also of diffusion through the apparent diffusion coefficient, perfusion (K_{trans}) and of vascular characteristics such as angiogenesis through dynamic contrast enhanced pulse sequences as illustrated in Figure 4.[57-60]

The goal in such imaging studies is to be able to characterize the potential aggressiveness of a cancer, taking into account the spatial heterogeneity that may exist at the mm scale level. There is a risk in conventional biopsy of missing key information due to undersampling. Quantitative imaging is well suited to this task as it provides continuous sampling, albeit at a macroscopic scale.

The amount of information and its complexity coming from mp imaging imposes a challenge in trying to determine how various elements of image data could optimally be used to infer the characteristics of a cancer. The potential role of radiogenomics is obvious here, but as the amount of information increases so does the complexity of the analysis. For this reason, researchers often turn to the techniques of artificial intelligence to assist in unraveling the connections between measurable variables and the disease state.[61,62] Because annotated case material from a single site is always limited, such studies are greatly facilitated if they can draw on data from multiple institutions.

In the quest for tools to enable the delivery of precision medicine, there is a pressing need for imaging methods that provide molecular specificity to targets for the disease. Early work focused on detecting changes in metabolism associated with tumor growth using ^{99m}Tc sestamibi or FDG. Now, more precisely targeted agents are being considered for use in detection of disease, characterization of its subtype or its potential aggressiveness, guidance in delivery of therapy and

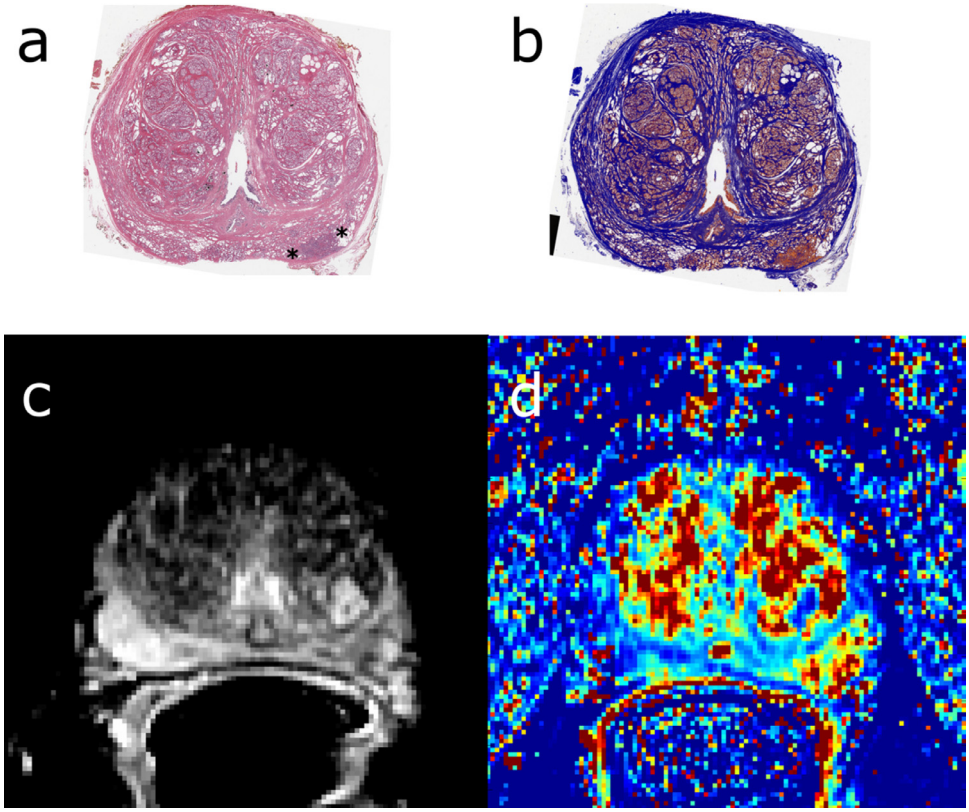

Figure 4 Representative prostate histologic sections (a, b) with corresponding ADC (c) and K^{trans} (d) maps. The tumor, located between the two '*' in (a), is seen on H&E as a region with increased density, and corresponds to an increase in cytoplasm and nuclei in (b) (orange), a decrease in ADC (c), and increase in K^{trans} (d). Courtesy, Dr. Masoom Haider, University Health Network, Toronto.

monitoring of response to treatment. This area deserves much more extensive discussion than can be accommodated here, but the most obvious way to achieve molecular specificity with diagnostic sensitivity is through molecularly-targeted radionuclides. There is an enormous amount of work being done in this area. Within my own area of interest, breast cancer, colleagues have developed multiple agents to probe the different subtypes of the disease including labeled trastuzumab, pertuzumab, and TDM1 for variants that over-express different HER2 neu receptors[63,64] and others have been investigating targeted imaging agents for other sites such as radiolabeled prostate-specific membrane antigen for prostate.[65] In many cases there is interest in modifying these targeted diagnostic agents to make them suitable for therapeutic applications. An excellent review of molecular breast imaging was published by Specht and Mankoff in 2012,[66] however, rapid development is expected in this field.

Needs

Only a few years ago the pressing needs in medical imaging were for greater storage capacity to handle larger images, greater processing speed, and faster networks. These limitations have largely disappeared with the availability of affordable multiterabyte image stores, gigabit networks, GPUs, and the ability to cluster computers and processors.

There are still bottlenecks with respect to speed, usually due to slower, legacy networks and hardware in institutions, that may restrict capacity of faster, more powerful systems that are part of the same pipeline. Largely, however, needs have changed.

Currently, there is an enormous demand for medical images that have been annotated to identify key features and/or where ground truth or outcome is known for the training and validation of machine learning systems. Much of the medical knowledge base associated with images is still contained in reports, many of which are handwritten or in free text. Fax may be still used to transmit these reports within or between institutions and when digitized, this often occurs by optical scanning. Greater standardization in the structure of reports[67,68] and effective natural language processing systems that would provide the ability to search, analyze, and extract meaningful synoptic information from free text would be of great value for research and to allow better quantitative use of medical information.[69]

Another area for improvement is in the standardization of medical images and of the staining characteristics in pathology images. Historically, they have been considered by their users simply as "pictures." Today, however, the wealth of additional radiomic information which they contain is better appreciated.[39] Such information may be difficult to be perceived directly by a human observer and even more difficult

to quantify subjectively, but may be extracted by various analytic techniques.[70] These analytic approaches are often more effective when performed on images that have been standardized such that the pixel values have clear meaning and are reproducible.[71] A number of efforts are in place in this direction, notably the Quantitative Imaging Network sponsored by the US NIH.[72]

Finally, a major challenge relates to what in some cases may be an overzealous preoccupation with privacy. While protection of patients should always be paramount in healthcare and medical research, most patients want to contribute to improvements that will help others in the future. Reasonable policies and an effective environment that addresses concerns regarding data security and privacy while allowing more flexible access to data are sorely needed if medical research is to flourish and bring forth those improvements. For example, greater ease in linkages to disease outcomes such as cancer registries, death registries, etc. is required and realistic risk: benefit assessments should take the place of rigid, restrictive policies that benefit nobody. Especially when the incidence of certain conditions is low or when specific subsets (race, age groups, comorbidities, etc.) are of interest, adequate numbers of cases and images to conduct meaningful studies can only be accrued through multi-institutional studies. Therefore, effective and practical mechanisms to allow safe sharing of such data across institutional (and in some cases, international) boundaries would be of enormous value in moving research forward.

References

1. Cassen B, Curtis L, Reed C, et al: Instrumentation for 131I use in medical studies. Nucleonics 9:46-50, 1951
2. Anger HO: Scintillation camera. Rev Sci Instrum 29:27-33, 1958
3. Kuhl DE, Edwards RQ: Image separation radioisotope scanning. Radiology 80:653-662, 1963
4. Hounsfield GN: Computerized transverse axial scanning (tomography): Part 1. Description of system. BJR 46:1016-1022, 1973
5. Ambrose J: Computerized transverse axial scanning (tomography): Part 2. Clinical application. BJR 46, 1023-1047.
6. Honda N, Osada H, Watanabe W, et al: Imaging of ventilation with dual-energy CT during breath hold after single vital-capacity inspiration of stable xenon. Radiology 262:262-268, 2012
7. Kim WW, Lee CH, Goo JM, et al: Xenon-enhanced dual-energy CT of patients with asthma: Dynamic ventilation changes after methacholine and salbutamol inhalation. AJR Am J Roentgenol 199:975-981, 2012
8. Jin KN, De Cecco CN, Caruso D, et al: Myocardial perfusion imaging with dual energy CT. Eur J Radiol 85:1914-1921, 2016
9. McCollough CH, Leng S, Yu L, et al: Dual- and multi-energy CT: principles, technical approaches, and clinical applications. Radiology 276:637-653, 2015
10. Tijssen MP, Hofman PA, Stadler AA, et al: The role of dual energy CT in differentiating between brain haemorrhage and contrast medium after mechanical revascularisation in acute ischaemic stroke. Eur Radiol 24:834-840, 2014
11. Agrawal MD, Pinho DF, Kulkarni NM, et al: Oncologic applications of dual-energy CT in the abdomen. Radiographics 34:589-612, 2014
12. Goldman LW: Principles of CT: Multislice CT. J Nucl Med Technol 36:57-68, June 2008
13. Zeman RK, Fox SH, Silverman PM, et al: Helical (spiral) CT of the abdomen. AJR 160:719-725, 1993
14. Dolazza E, Poulo L: Optimal quantization of noisy signals. Proc. SPIE 454:403-417, 1984. Zhao, W., Deych, R., Dolazza, E. Optimization of operational conditions for direct digital mammography detectors for digital tomosynthesis. Proc SPIE—Int Soc Opt Eng, vol. 5745. 10.1117/12.597301
15. Proc. SPIE 1905, Biomedical Image Processing and Biomedical Visualization, (29 July 1993)
16. Rougeot HM, Opsahl-Ong B, Castleberry DE, et al: Performance evaluation of a flat-panel filmless full-field digital mammography system. Radiology 201:190, 1996
17. Antonuk LE, Yorkston A, Huang W, et al: A real-time, flat-panel, amorphous silicon. digital x-ray imager. Radiographics 209(4):993-1000, 1995.
18. Zhao W, Rowlands JA: Digital radiology using active matrix readout of amorphous selenium: Theoretical analysis of detective quantum efficiency. Med Phys 24:1819-1833, 1997
19. Zhao B, Zhao W: Imaging performance of an amorphous selenium digital mammography detector in a breast tomosynthesis system. Med Phys 35:1978-1987, 2008
20. Nishikawa RM, Mawdsley GE, Fenster A, et al: Scanned-projection digital mammography. Med Phys 14:717-727, 1987
21. Åslund M, Cederström M, Lundqvist M, et al: Physical characterization of a scanning photon counting digital mammography system based on Si−strip detectors. Med Phys 34:1918-1925, 2007
22. Byng JW, Critten JP, Yaffe MJ: Thickness-equalization processing for mammographic images. Radiology 203:564-568, 1997
23. Pisano ED, Zong S, Hemminger BM, et al: Contrast limited adaptive histogram equalization image processing to improve the detection of simulated spiculations in dense mammograms. J Digit Imaging 11:193-200, 1998
24. NEMA PS3 / ISO 12052, Digital Imaging and Communications in Medicine (DICOM) Standard, National Electrical Manufacturers Association, Rosslyn, VA, USA (available free at: http://medical.nema.org/)
25. Nishikawa RM: Current status and future directions of computer-aided diagnosis in mammography. Comput Med Imaging Graph 31:224-235, 2007. Jun-Jul
26. Doi K: Computer-aided diagnosis in medical imaging: historical review, current status and future potential. Comput Med Imaging Graph. 31:198-211, 2007. https://doi.org/10.1016/j.compmedimag.2007.02.002. PMCID: PMC1955762 NIHMSID: NIHMS25740 PMID: 17349778
27. Kooi T, Litjens G, van Ginneken B, et al: Large scale deep learning for computer aided detection of mammographic lesions. Med Image Anal 35:303-312, 2017
28. Baker JA, Rosen EL, Lo JY, et al: Computer-aided detection (CAD) in screening mammography: Sensitivity of commercial CAD systems for detecting architectural distortion. Am J Roentgenol 181:1083-1088, 2003. https://doi.org/10.2214/ajr.181.4.1811083
29. Stout NS, Lee SJ, Schechter CB, et al: Benefits, harms, and costs for breast cancer screening after US implementation of digital mammography. JNCI J Natl Cancer Inst 106, 2014. https://doi.org/10.1093/jnci/dju092. dju092
30. Niklason LT, Christian BT, Niklason LE, et al: Digital tomosynthesis in breast imaging. Radiology 205:399-406, 1997
31. Kopans DB: Digital breast tomosynthesis from concept to clinical care. Am J Roentgenol 202:299-308, 2014. https://doi.org/10.2214/AJR.13.11520
32. Hooley RJ, Durand MA, Philpotts LE: Advances in digital breast tomosynthesis. Am J Roentgenol 208:256-266, 2017. https://doi.org/10.2214/AJR.16.17127
33. Lindfors KK, Boone JM, Nelson TM, et al: Dedicated breast CT: Initial clinical experience. Radiology 246: 725-733
34. Ning R, Conover D, Yu Y, et al: A novel cone beam CT breast-imaging scanner: Preliminary system evaluation. SPIE Phys Med Imaging 6142:614211, 2006
35. O'Connell A, Conover D, Zhang Y, et al: Cone beam computed tomography (CT) for breast imaging: Radiation dose, breast coverage, and image quality". Am J Roentgenol 195:496-509, 2010
36. Kalender WA, Kolditz D, Steiding C, et al: Technical feasibility proof for high-resolution low-dose photon-counting CT of the breast. Eur Radiol

27:1081-1086, 2017. https://doi.org/10.1007/s00330-016-4459-3. Epub 2016 Jun 15
37. https://ecog-acrin.org/tmist
38. https://clinicaltrials.gov/ct2/show/NCT02616432
39. Lambin P, Rios-Velazquez E, Leijenaar R, et al: Radiomics: Extracting more information from medical images using advanced feature analysis. Eur J Cancer 48:441-446, 2012
40. Gillies RJ, Kinahan PE, Hricak H: Radiomics: Images are more than pictures, they are data. Radiology 278:563-577, 2016. https://doi.org/10.1038/npjbcancer.2016.12
41. Abrol S, Kotrotsou A, Salem A, et al: Radiomic phenotyping in brain cancer to Unravel hidden information in medical images. Top Magn Reson Imaging 26:43-53, 2017. https://doi.org/10.1097/RMR.0000000000000117
42. Li H, Zhu Y, Burnside ES, et al: Quantitative MRI radiomics in the prediction of molecular classifications of breast cancer subtypes in the TCGA/TCIA data set. npj Breast Cancer 2, 2016. Article number: 16012
43. Wu J, Li B, Sun X, et al: Heterogeneous enhancement patterns of tumor-adjacent parenchyma at MR imaging are associated with dysregulated signaling pathways and poor survival in breast cancer. Radiology 285:401-413, 2017
44. Hajdu SI: A note from history: Rudolf Virchow, pathologist, armed revolutionist, politician, and anthropologist. Ann Clin Lab Med 35:203-205, 2005
45. Clarke GM, Peressotti C, Mawdsley GE, et al: Design and characterization of a system for three-dimensional digital breast histopathology imaging. Phys Med Biol 51:5089-5103, 2006
46. Clarke GM, Eidt S, Sun L, et al: Whole-specimen histopathology: A method to produce whole-mount breast serial sections for 3-D digital histopathology imaging. Histopathology 50:232-242, 2007
47. Clarke GM, Liu K, Murray M, et al: 3-D pathology volumetric technique: A method for calculating breast tumour volume from whole-mount serial section images. International Journal of Breast Cancer, vol. 2012, Article ID 691205, 9 pages, 2012. https://doi.org/10.1155/2012/691205.
48. Clarke GM, Holloway CMB, Zubovits JT, et al: Whole-mount pathology of breast lumpectomy specimens improves detection of tumour margins and focality. Histopathology 2015. https://doi.org/10.1111/his.12912. [Epub ahead of print] PMID: 266443
49. Clarke GM, Zubovits JT, Shaikh KA, et al: A novel, automated technology for multiplex biomarker imaging and application to breast cancer. Histopathology 64:242-255, 2014
50. Janowczyk S, Madabhushi A: Deep learning for digital pathology image analysis: A comprehensive tutorial with selected use cases. J Pathol Inform 7:29, 2016. https://doi.org/10.4103/2153-3539.186902. PMCID: PMC4977982 PMID: 27563488
51. Holzinger A, Malle B, Kieseberg P, et al: Machine learning and knowledge extraction in digital pathology needs an integrative approach. Towards Integrative Machine Learning and Knowledge Extraction, Springer Lecture Notes in Artificial Intelligence Volume LNAI 10344. Cham: Springer, 13-50, 2017. https://doi.org/10.1007/978-3-319-69775-82
52. Blanchette PS, Desautels DN, Pond GR, et al: Factors influencing survival among patients with HER2-positive metastatic breast cancer treated with trastuzumab. Breast Cancer Res Treat 170:169-177, 2018. https://doi.org/10.1007/s10549-018-4734-x. Epub 2018 Mar 8
53. Mainprize JG, Alonzo-Proulx O, Alshafeiy TI, et al: Prediction of cancer masking in screening mammography using density and textural features. Acad Radiol 2018. https://doi.org/10.1016/j.acra.2018.06.011. pii: S1076-6332(18)30325-8 [Epub ahead of print]
54. Stokking R, Zubal IG, Viergever MA: Display of fused images: methods, interpretation, and diagnostic improvements. Semin Nucl Med 33:219-227, 2003
55. James AP, Dasarathy BV: Medical image fusion: A survey of the state of the art. In: James AP, Thiruvenkadam S, Paul JS (eds): Braun M Information Fusion, Elsevier, 19:4-19, 2014. https://doi.org/10.1016/j.inffus.2013.12.002
56. van Dalen JA, Vogel WV, Corstens FH, et al: Multi-modality nuclear medicine imaging: artefacts, pitfalls and recommendations. Cancer Imaging 7:77-83, 2007
57. Shukla-Dave A, Hricak H, Akin O, et al: Preoperative nomograms incorporating magnetic resonance imaging and spectroscopy for prediction of insignificant prostate cancer. BJU Int 109:1315-1322, 2012. https://doi.org/10.1111/j.1464-410X.2011.10612.x. Epub 2011 Sep 20
58. Fütterer JJ, Briganti A, De Visschere P, et al: Can clinically significant prostate cancer be detected with multiparametric magnetic resonance imaging? A systematic review of the literature. Eur Urol 68:1045-1053, 2015. https://doi.org/10.1016/j.eururo.2015.01.013. Epub 2015 Feb 2
59. Langer DL, van der Kwast TH, Evans AJ, et al: Prostate tissue composition and MR measurements: Investigating the relationships between ADC, T2, K trans, v e, and corresponding histologic features. Radiology 255:485-494, 2010
60. Wallis CJD, Haider MA, Nam RK: Role of mpMRI of the prostate in screening for prostate cancer. Transl Androl Urol 6:464-471, 2017. https://doi.org/10.21037/tau.2017.04.31. PMID: 28725588
61. Giannini V, Mazzetti S, Vignati A, et al: A fully automatic computer aided diagnosis system for peripheral zone prostate cancer detection using multi-parametric magnetic resonance imaging. Comput Med Imaging Graph 2:219-226, 2015. https://doi.org/10.1016/j.compmedimag.2015.09.001. Epub 2015 Sep 12
62. Ghafoorian M, Mehrtash A, Kapur T, et al: Transfer learning for domain adaptation in MRI: Application in brain lesion segmentation. Med Image Comput Comput-Assisted Interv 10435:516-524, 2017
63. Al-Saden N, Lam K, Chan C, et al: Positron-emission tomography of HER2-positive breast cancer xenografts in mice with $_{89}$Zr-labeled trastuzumab-DM1: A comparison with $_{89}$Zr-labeled trastuzumab. Mol Pharm 15:3383-3393, 2018. https://doi.org/10.1021/acs.molpharmaceut.8b00392. Epub 2018 Jul 16. PMID:29957952
64. McLarty K, Cornelissen B, Cai Z, et al: Micro-SPECT/CT with 111In-DTPA-pertuzumab sensitively detects trastuzumab-mediated HER2 downregulation and tumor response in athymic mice bearing MDA-MB-361 human breast cancerxenografts. J Nucl Med 50:1340-1348, 2009. https://doi.org/10.2967/jnumed.109.062224. Epub 2009 Jul 17. PMID:19617342
65. Schwarzenboeck SM, Rauscher I, Bluemel C, et al: PSMA ligands for PET imaging of prostate cancer. J Nucl Med 58:1545-1552, 2017
66. Specht JM, Mankoff DA: Advances in molecular imaging for breast cancer detection and characterization. Breast Cancer Res 14:206, 2012. https://doi.org/10.1186/bcr3094
67. Reiner BI: The challenges, opportunities, and imperative of structured reporting in medical imaging. J Digit Imaging 22:562-568, 2009
68. Schwartz LH, Panicek DM, Berk AR, et al: Improving communication of diagnostic radiology findings through structured reporting. Radiology 260:174-181, 2011
69. Pons E, Braun LMM, Hunink MGM, et al: Natural language processing in radiology: A systematic review. Radiology 279:329-343, 2016. 10.1148
70. Scalco E, Rizzo G: Texture analysis of medical images for radiotherapy applications. Br J Radiol 90:20160642, 2017. https://doi.org/10.1259/bjr.20160642. Epub 2016 Nov 25
71. Yang H, Schwartz LH, Zhao B: A response assessment platform for development and validation of imaging biomarkers in oncology. Tomography 2:406-410, 2016
72. National Cancer Institute. Quantitative imaging for evaluation of responses to cancer therapies. NCI QIN Web site: http://imaging.cancer.gov/programsandresources/specializedinitiatives/qin. Accessed 11 October 2018.