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Sir Michael Brady , Ralph Highnam , Benjamin Irving , Julia A. Schnabel

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## Highlights

- Medical image analysis applied to cancer has to date only addressed a very small subset of the “hallmarks of cancer”.
- A number of opportunities and challenges for research over the next decade in oncological image analysis are outlined.

# Oncological Image Analysis

Sir Michael Brady[1], Ralph Highnam[2], Benjamin Irving[3], Julia A. Schnabel[3,4]

[1]Department of Oncology, University of Oxford, UK http://www.oncology.ox.ac.uk/
[2]Volpara Health Technologies, Wellington 6011, NZ http://volparasolutions.com/
[3]Institute of Biomedical Engineering, Department of Engineering Science, University of Oxford, UK http://www.ibme.ox.ac.uk/
[4]Department of Biomedical Engineering, King's College London, UK
http://www.imagingcdt.com/

## Abstract

Cancer is one of the world's major healthcare challenges and, as such, an important application of medical image analysis. After a brief introduction to cancer, we summarise some of the the major developments in oncological image analysis over the past 20 years, but concentrating those in the authors' laboratories, and then outline opportunities and challenges for the next decade.

## Keywords

Cancer; mammography; angiogenesis; molecular imaging; radiotherapy

## Introduction

Medical image analysis is a continual interplay between: developments in the underpinning science; technological developments in imaging and intervention (including drug therapy); and clinical drivers. Example *scientific developments* during the lifetime of *Medical Image Analysis* include: image filtering (e.g. the monogenic signal), segmentation (e.g. level sets and atlases), deformable image registration, and, latterly, machine (deep) learning. Similarly, example *technological developments* have included: MRI – higher fields in clinical systems (3T, 7-9T); Diffusion Weighted Imaging; quantitative hyperpolarised imaging, especially of the lung; Ultrasound – 3D, microbubbles, Automated Breast Ultrasound; nuclear imaging - faster, more accurate reconstruction algorithms for PET, dynamic imaging, time-of-flight, and faster detectors. Though digital mammography is nowadays the dominant norm, it was only introduced in 2000. More recently, clinical deployment of quasi-3D mammography in the form of digital breast tomosynthesis (tomo) has increased rapidly. Unsurprisingly, the dominant *clinical drivers* have seen less change over the past 20 years. In 1996, three of the most important clinical applications were in: heart disease; cancer; and neurodegenerative diseases, and although there have been in each case major contributions from medical imaging, they continue to pose fundamental challenges and to be in desperate need of advances in medical image analysis. To these should now be added the looming pandemic in (non-alcoholic) fatty liver disease, leading to steatosis, cirrhosis, and hepatocellular carcinoma, and of course its close interaction with cardiovascular diseases. Work that concentrates on just one of these three forces, for example a fascination with the underpinning mathematical formulation of a problem is unlikely to make an impact.

Every researcher has their own individual motivation: ours is cancer, and is the focus of this article. Over the past 30 years, oncological imaging has evolved from imaging anatomy (e.g. $T_1$-weighted MRI) through imaging physiology (e.g. dynamic contrast-enhanced MRI), through imaging function and metabolism (e.g. functional MRI, primarily BOLD contrast, and PET), to molecular imaging (e.g. imaging cellular processes such as tyrosine kinase receptors (VEGFR 1-3) on the cell surface, for example by a PET/SPECT radioligand based on bevacizumab). Such developments, both clinical and pre-clinical, play an increasingly important role in cancer research: the UK alone has 4 national cancer imaging centres, namely in Oxford; the Institute of Cancer Research; UCL/KCL; and Cambridge/Manchester.

## Cancer

Cancer is one of the leading causes of morbidity and mortality worldwide, with approximately 14 million new cases (and 8.2 million cancer-related deaths) annually. Epidemiologically, approximately 1/3 of people in developed countries can expect to have cancer diagnosed during their lifetime, and, for a range of reasons, this figure is predicted to rise to 1/2 by 2025.
The increase in cancer rates is partly due to increased life expectancy, as well as reduced deaths from certain infections, and better care for some cardiovascular disease. Around one third of cancer deaths are due to the 5 leading behavioural and dietary risks: high body mass index, low fruit and vegetable intake, lack of physical activity, tobacco use, and alcohol consumption.

The developing world is catching up quickly, in large part as a result of changes of lifestyle, diet, and exposure to many new toxins. For example, though its use is in decline (among males) in developed countries, tobacco consumption is increasing in several developing countries. A particularly tragic case study in the making is afforded by asbestos, which is well known to be a toxin. Perhaps the most notable and notorious health complication associated with asbestos is Malignant Pleural Mesothelioma (MPM), an aggressive tumour found in the pleura, or the outer lining, of the lungs. Etiological studies have identified prior exposure to asbestos, usually but not exclusively occupational, as the primary cause of the malignancy. In mesothelioma, malignant cells develop mostly in the pleura of the lungs and internal chest wall. Responsible for over 47,000 deaths worldwide each year, MPM poses a serious threat to global public health. It is also the greatest single cause of work-related death in many countries. Given the gradual phasing out of asbestos production in the 1980s and the disease's long latency period, typically between 30 to 40 years, the incidence of mesothelioma in the EU is expected to continue to increase and ultimately peak in 2020. However, asbestos production is still rising in China and India, and MPM is likely to emerge as a more serious health concern in the years to come. Moreover the average age of developing the disease in developed countries is 60 years, whereas in China it is 45.2 years. Chen and Brady have developed a method of automatically segmenting and measuring mesothelioma in lung CT images.

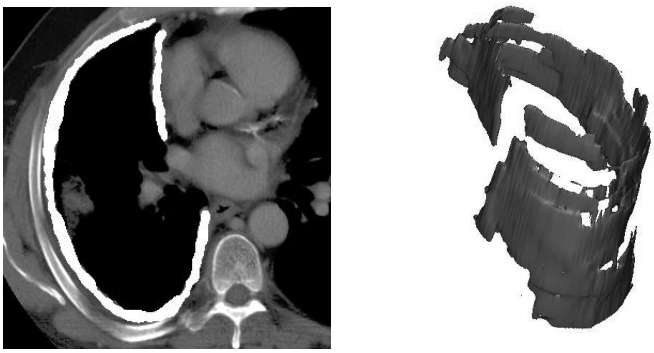

Figure 1. Left: Malignant pleural mesothelioma (MPM, white) shown superimposed on a lung CT image. Right: the thin, curved nature of the MPM is shown in a projection of the 3D volume (Chen and Brady, 2014).

It is known [Weinberg 2014] that the overwhelming majority of solid cancers (which account for approximately 93% of cancers) are epithelial and are ***not*** genetic in origin. Of course, there may be a significant epigenetic component; but the extent of this is not known. Among women, the 5 most common sites of cancer are breast, colorectum, lung, cervix, and stomach. Among men, the most common 5 are: prostate, lung, colorectum, stomach, and liver. Ten years ago, almost all liver cancers were secondaries, most often spread from the colorectum through the portal vein; this situation is changing rapidly, as the looming pandemic of liver disease referred to above is generating a surge in primary hepatocellular tumours.

In developed countries, one woman in 8 will develop breast cancer at some point in her life; 25 years ago it was one in 12. Breast cancer accounts for 23% cancers in women, and this is projected to rise to 29% by 2030. The peak incidence is age 60, a point we return to in the next Section. Again, 25 years ago, breast cancer was virtually unknown in developing countries, now it is rising rapidly with over 500,000 cases annually. It was initially suggested that this rise in the developing countries was due in large part to sharply increased awareness of breast cancer, and/or to increasing life expectancy coupled to reduced mortality rates from previously deadly diseases. Evidently, both can explain in part the very rapid rise that has been seen; but only in part.

The “central dogma” in oncology is that early detection and diagnosis improves prognosis. This has encouraged mass screening of asymptomatic populations: cervix, breast, and increasingly lung; though not all have enjoyed the success of breast cancer screening. To the extent that cancer is “cured”, which typically means disease-free survival for 5 years, approximately 49% of cures are effected by surgery; 40% by radiotherapy; and just 11% by chemotherapy. However, there is increasing interest in combination therapies: radiotherapy + chemotherapy; or minimally-invasive surgery + chemo/radiotherapy. In a landmark paper, Hanrahan and Weinberg [2011] identified a number of “hallmarks of cancer”: resisting cell death; genome instability and mutation; inducing angiogenesis; activating invasion and metastasis; tumour promoting inflammation; enabling replicative immortality; avoiding immune destruction; evading growth suppressors; sustaining proliferative signalling; and deregulating cellular energetics. Associated with each of these (e.g. inducing angiogenesis), are a set of key processes (e.g. inhibition of vascular endothelial growth factor (VEGF) signalling). This in turn provides for therapeutic opportunities (e.g. bevacizumab, which aims to achieve such inhibition). More details on all of these issues can be found in the superb introduction *The Biology of Cancer* by Robert A. Weinberg [2014]. (A wonderful popular account of the history of cancer can be found in the Pulitzer Prize winning book *The Emperor of All Maladies: a Biography of Cancer*, by Siddhartha Mukherjee [2010].)

## Developments during the lifetime of Medical Image Analysis

Inevitably, in a brief article like this, a list of developments in Oncological Image Analysis over the past 20 years is inevitably selective and fragmentary, and our list features our own work, not least in breast cancer. In view of the bibliography restrictions, we invite interested readers to contact us for more details and references.

Perhaps the best known application of image analysis in breast cancer is to computer-aided detection (CAD) of microcalcifications and masses. The proceedings of the *International Workshops on Digital Mammography*, and the collection of articles edited by Li and Nishikawa [2015] and Geiger et. al. [2013], provide excellent introductions to the subject.

Over the past 20 years, CAD systems have developed to the point where a number of successful (and several unsuccessful) companies have been launched, primarily in the USA, driven by reimbursement. Separately, it has become clear that breast cancer risk is closely related to the post-menopausal process of involution, in which stromal tissue converts to "fat[5]". When involution proceeds normally, the breast contents become primarily fatty, and since fat is essentially transparent to x-rays, mammography is then 98% effective (specificity, sensitivity, …). However, in approximately 40% women involution does not proceed "normally" and the breast remains stubbornly dense. In such a case, mammography is considerably less effective. Indeed, dense breasts create what Dr. Bruce Schroeder has called the "perfect storm": tumours are far more difficult to detect, and the risk of a woman with dense breasts getting breast cancer increases up to six-fold relative that of women with fatty breasts. As a result of women's action groups, most states in the USA now require that a woman be told her breast density when she has a mammogram. Of course, this poses the challenge of what a clinician should report, and in turn the challenge of developing a robust, repeatable, ideally quantitative measure of breast density. This is what Highnam and Brady [1999], and subsequently jointly with Karssemeijer (see [Brady, Highnam and Karssemeijer, 2015], have developed and commercialised in *VolparaDensity*[6]. The *VolparaDensity* software enables stratification and personalised screening: the woman has a mammogram and her breast density is measured; if it is "low", it is assumed that mammography findings are sufficient; if, on the other hand, the breasts are dense, then MRI or ultrasound is recommended.

One of Hanrahan and Weinberg's [2011] hallmarks concerns angiogenesis, where the tumour constructs a chaotic network of leaky blood vessels (the neovasculature) to fuel the tumour's uncontrolled growth. Dynamic contrast-enhanced MRI, where the contrast agent is a chelate of gadolinium, has developed to highlight the neovasculature. The breast is imaged prior to bolus injection of the contrast agent, and then breast volumes are imaged as rapidly as possible, typically over a 10 minute period. Since the breast may move during this extended acquisition period, if only as a result of breathing, the succession of imaged volumes requires alignment by deformable image registration. Registration results in a time-activity curve for each voxel, and these can be analysed to detect angiogenesis. To this end, a number of pharmacokinetic (PK) models of contrast agent uptake have been developed, in principle enabling the estimation of biologically meaningful parameters at each voxel. These include $K^{trans}$ which is generally taken to refer to the endothelial permeability surface area product, which is considered to be a physiologically meaningful quantity, though the precise meaning varies with anatomical structure. Technically, the observed time activity curve is the convolution of the PK function (which is, typically, a weighted sum of exponentials) with the arterial input function. Unfortunately, the latter is both hard to estimate and has a substantial nonlinear effect on the estimation of the biological parameters. An alternative approach is to dispense (largely, or altogether) with the PK model, and to assign to each voxel a tissue class (tumour, fat, normal tissue, …), for example using principal or independent component analysis. The situation is more complex – and largely unsolved - in the liver, where there is both an arterial, and later venal, blood supply. Despite all of these challenges, a number of software systems have been developed, some even commercialised, and are used increasingly by clinicians.

Medical images often have poor signal-to-noise and are bandwidth limited, resulting in poor spatial and temporal sampling. Evidently, in such cases, image segmentation and registration can be combined to advantage as Brady, Xiao Hua, and Lo showed in IPMI 2005, as can the estimation of dynamic information such as contrast take-up at each voxel. A case in point is the assessment of neoadjuvant therapy in colorectal cancer: the

[5] The biochemistry of breast fat is highly complex and involves a mix of hormones, not least Estrogen. There is no room in this article to explore further fat, its measurement, and the process of involution.
[6] JMB and RPH are founders of Volpara Health Technologies, http://volparasolutions.com/

suspicious region is assessed prior to, and following, such therapy, informing the decision whether or not to resect the tumour. It has been estimated that in clinical practice, as many as 10% of cases show complete response to therapy, as judged by histological analysis of resected specimens, implying that the resection was not in fact necessary. Working with Bhushan and Jenkinson, Brady and Schnabel have developed an initial system that addresses this issue, though much remains to be done [Bhushan *et. al.* 2013].

There is substantial, and continuing, interest in therapy planning, not least of minimally-invasive surgery. This is an extensive subject in its own right, and the interested reader is directed in the first instance to the annual *MICCAI* proceedings. Systems have been developed for endoscopic delivery, and for local energy deposition using electromagnetic (EM) waves (HIFU, and laser, RF, and microwave ablation). There is increasing application of robotic systems for specialised tool deployment, as well as the further development of such tools and for task planning. There is growing interest in the use of EM to deliver cytotoxic drugs locally to tumours. Separately, the past 20 years have seen the development of image-guided and image-modulated radiation therapy (RT), to date of x-rays, and in the future of protons. Though there have been substantial developments in minimally-invasive surgery, and in local resection (which has been shown to give outcomes equivalent to mastectomy for localised breast cancer), a great deal of surgery is far from minimally invasive. An example is total mesorectal excision, for which the key parameter is the circumferential resection margin. Joshi, Bond, and Brady [2010] reported a system based on level segmentation, constrained by detection of parts of the mesorectum boundary using the monogenic signal.

Radiotherapy (RT) kills cells by destroying their DNA. Cells have remarkable abilities to detect and auto-correct damage to DNA. The particular double helix structure (in which Adenine is always paired with Thymine, and Cytosine always with Guanine) enables damage to one strand of DNA to be detected and repaired automatically. RT aims at double strand breaks, where proteins are recruited to form DNA repair complexes. This includes recruitment of the histone $\gamma H_2AX$ that must be modified by phosphorylation to function. Colleagues in Oxford have shown that by coupling the anti-$p\gamma H_2AX$ antibody to the transport peptide TAT, the antibody could gain access to the nucleus and be used to detect DNA damage and labelled for SPECT imaging.

Another of the “hallmarks” is deregulated cellular energetics, which is associated with the inhibition of aerobic glycolysis and, via the Warburg effect, hypoxia. It is a remarkable fact that tumours can grow uncontrollably, even when starved of oxygen. To do this, the cell’s microenvironment becomes mildly acidic. There has been substantial work, including imaging, on both the estimation of glycolysis (and the cycling of the cellular state that can result) and on molecular imaging applied to hypoxia. In particular, there has been encouraging work on combining cellular modelling (based on the HIF – hypoxia inducible fraction - complex of proteins) and PET imaging, primarily using the F-MISO ($F^{18}$-misonidazole) radioligand. This remains an active area of research for modelling, radioligand development, and image analysis.

Such is the complexity and variability of human physiology and metabolism, and of disease, that it is rarely the case that any one imaging modality suffices. Image fusion, incorporating (deformable) image registration, is an increasingly key clinical requirement, particularly in oncology. A number of software systems for medical image fusion are available commercially and installed in thousands of hospitals worldwide[7]. The commercialisation of image fusion was originally boosted by the development of integrated PET-CT systems. The current challenge is PET-MR whole body imaging, for which commercial systems are available but which also has open research challenges. Whole body imaging is of

[7] JMB is founder and a non-executive director of Mirada Medical http://www.mirada-medical.com/

fundamental importance in oncology, since it can provide early information about metastatic spread to anatomical sites far removed from the primary tumour (another of Hanrahan and Weinberg's hallmarks). In most cases, in fact, it is metastatic disease that kills. Whole body imaging has inspired the development of whole body atlases. For example, Potesil, Kadir, and Brady [2014, 2015] have shown how such atlases may be constructed using pictorial structures.

## Looking Forward

The first observation that one can make, with absolute confidence, is that none of the topics identified as progress in the previous Section are anywhere near final solutions. We may expect to see substantial advances in: CAD, not least for the breast and lung; personalised risk estimation for breast and other cancers; dynamic contrast-enhanced MRI and its application to detecting and measuring angiogenesis; measuring the effect of therapy and/or disease progression, in particular identifying complete responders; therapy planning and increasing the scope of closed-loop control of treatment; modelling and analysis of more of Hanrahan and Weinberg's hallmarks than the two referred to in the previous Section; and better systems for whole-body image fusion and atlas generation. In this Section, we highlight a number of key problems. First, however, some general remarks.

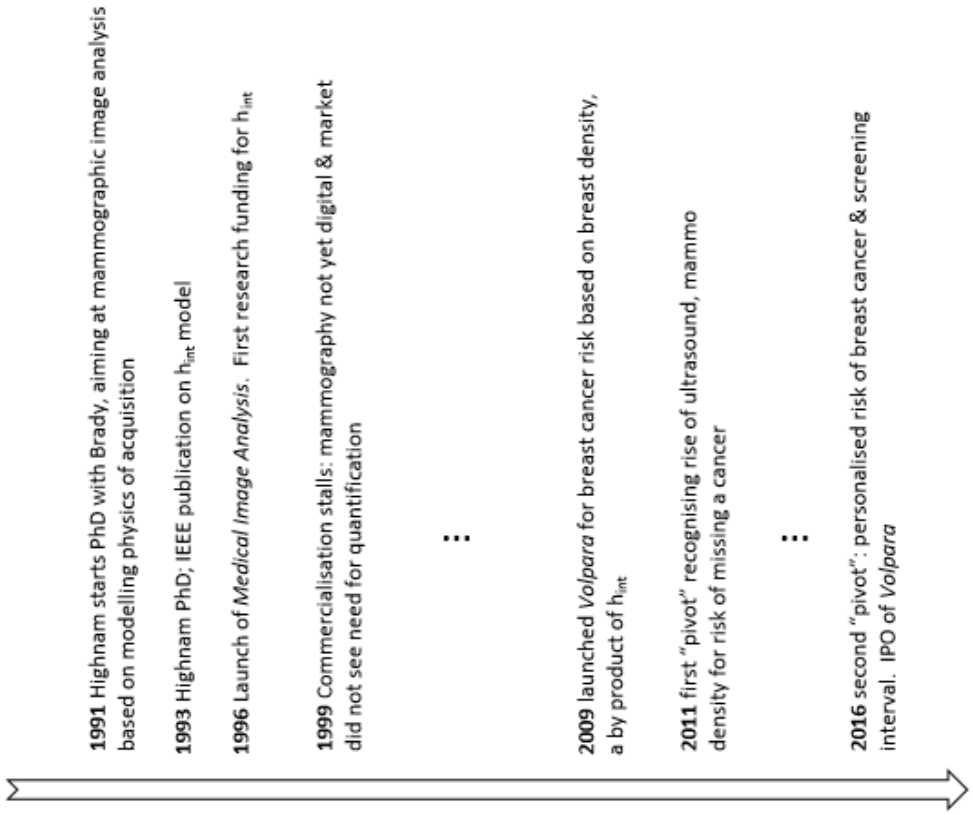


Figure 2: 25 years in the development of a scientific idea to commercial success. *Volpara*'s breast density products are currently installed in 34 countries in hundreds of hospitals centres and have processed 10 million mammograms.

Until relatively recently, biology and medicine have primarily been qualitative: the observation and description of phenomena, and relying upon the perceptual judgements of (clinical) experts. There is increasing recognition of the need to incorporate the methodology of the physical sciences: robust, repeatable measurements with low error bars and

mathematical models of complex phenomena, ranging nanometre sized cellular processes to entire structures such as a tumour, and from nanoseconds to months. To be deployed in clinical practice, there is a need for processes that work almost always, 24/7, and which fail gracefully. This necessitates quality processes (e.g. GMP laboratories), regulatory approval, and maintenance/support. A system can be useful, in that it performs a necessary task well, but that does not mean that it will be used: this requires an appreciation of work flow and clinical practice. These considerations may seem far removed from medical imaging research; but not if the aim is to get the fruits of research used in routine clinical practice. A cautionary statement: research is already a complex undertaking; but the many and mysterious workings of markets throw up even more road blocks to successful deployment. Even in research, there are considerable difficulties to be overcome in order to progress an idea from *in vitro* analysis (e.g. of spheroids) to preclinical studies, and from there to clinical studies. Figure 2 shows 25 years (1991-2016) in the development of a scientific idea and its subsequent commercialisation.

We noted in Section 2 that radiation therapy and chemotherapy are increasingly used in combination. There are now several reported instances in which such a combination is more effective than either radiation therapy alone or chemotherapy alone. It is believed that combination therapy is effective because it impacts the tumour microenvironment, for example enabling chemotherapy to overcome the tumour's remarkable resistance to toxicity once the tissue characteristics have been altered by radiation therapy. However, we lack precise models of how combination therapies impact the tumour microenvironment, and so knowledge of which combination therapies will work in any given situation is weak. Moreover, the progress that has been made over the past 20 years in radiotherapy have relied in part on substantial developments in our understanding of the interactions between x-ray photons and cells, including cellular DNA and repair processes, as noted in the previous Section. One of the most significant recent developments in RT is Proton Beam Therapy (PBT), in which x-ray photons are replaced by highly energetic hydrogen nuclei. The huge advantage is that the Bragg peak of protons, which ultimately determines the margin of healthy surrounding tissue that is destroyed during therapy, is very much smaller than for x-rays. However, considerably less is known about the interaction of protons and cells, and this will need intensive research if PBT is to realise its clinical potential. More generally, to date therapies for cancer have been applied to late stage disease. Several recent studies have shown that in most cases, death is postponed by as little as 9 weeks. An alternative approach, now being pursued with vigour, is to apply therapies in "window" trials, ideally to therapy naïve patients. Imaging will play a key role in measuring responsiveness.

To date, the complexity of the tumour microvasculature, together with very limited spatiotemporal imaging, have precluded the development of predictive mathematical models of tumour growth. Advances in microscopy (e.g. multiphase microscopy), allied to computing power, advances in medical imaging (e.g. segmentation), and mathematical modelling, offer the promise that such growth models will soon be available, enabling simulation, prediction, and measurement of therapeutic targets. Such mathematical models should also have a biomechanical component, at least at a certain spatial scale. It is known that tumour tissue is biomechanically dense relative to normal tissue, and it is known that the tumour stiffens surrounding tissue. There are rudimentary theories why this is so. Wessel, Schnabel and Brady [2012] have begun the development of a biomechanical model of a spiculated tumour that includes such stiffening of normal tissue; but much remains to be done.

The chaotic nature of the leaky neovasculature constructed by a tumour, and the complexity of the spatiotemporal growth of a tumour as it builds from the epithelium, are the basis of the tumour's appearance in images, either at a radiological (dceMRI, PET, ultrasound, …) or microscopic scale (conformal, multiphoton). Clinicians refer to a tumour's "heterogeneity",

though, when pressed, this term is generally as vague as “texture” and means “not homogeneous”. However, as in the case of texture, giving a precise image-based definition of heterogeneity is increasingly important in oncology. We have recently made a start on this [Irving et. al., 2016] by developing a pieces-of-parts representation of a tumour, and our current work builds on this to define “heterogeneity” (see Figure 3, reproduced from part of Irving 2016, Figure 3).

Molecular imaging has so far addressed only a tiny number of the cellular processes that have been identified as potential targets in oncology. The number of potentially interesting molecular targets is growing faster than our capacity to image them. Though novel processes continue to be developed in radiochemistry, enabling higher purities, less noxious side-effects, and greater yields, the translation of such work to pre-clinical and clinical practice remains stubbornly slow. At the same, perhaps the exciting development in the molecular biology of cancer is immunotherapy, in which the body’s immune system in enlisted in the fight against a cancer growing. There have been a number of very promising examples, including increasing relationships with inflammatory disease and the TNF-α drugs; but this is approach remains very much in its infancy. For medical imaging, the interest is that immunotherapy implies continuing therapy and monitoring over many months, encouraging use of MRI and other imaging techniques that do not involve radiation. There is a major, growing need for MRI to be extended and applied to molecular imaging. Recently, a consensus position has been published for imaging biomarkers in cancer [O’Connor *et. al.* 2016].

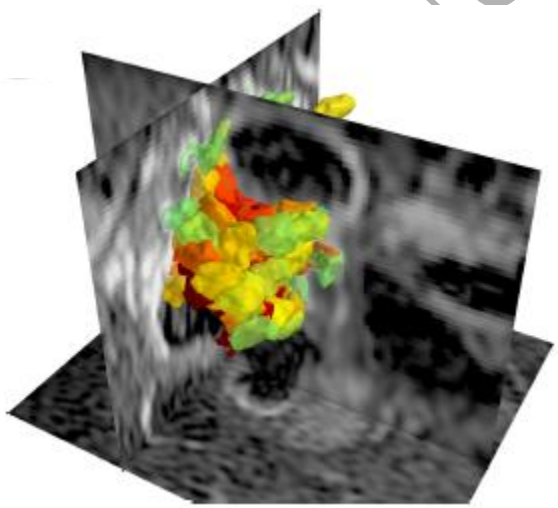

Figure 3: Pieces of parts representation of a colorectal tumour to improve tumour delineation and forming a basis for a precise definition of “heterogeneity” (reproduced from Irving et. al. [2016]).

A major claim for molecular imaging, as yet unrealised but none the less cogent, is that it will be the basis for personalised therapy. The long term goal, one of the most fundamental in biology and medical imaging, is to integrate information from molecular biology (a person’s genome, epigenome, cellular processes, …) with imaging to derive a diagnosis and therapy that is specialised to that individual’s metabolism and disease. We are currently far from realising this dream; but an important practical step that is being realised is stratification of therapy. We noted that *VolparaDensity* enables stratification in mammography: the woman has a mammogram and her breast density is measured; if the value is “low” (relative to what is a good question, beyond the scope of this paper), it is assumed that the breast is predominantly “fatty”, hence that mammography findings are sufficient; if, on the other hand, it is high, then the breasts are “dense”, indicating that the breasts should be imaged using MRI/ultrasound. Building on this, the x-ray dose administered to the individual woman’s breast, and her personal risk of getting breast cancer, can be estimated based on the

density measures and those computed from previous mammograms. We may confidently expect such stratification and personalisation of risk to be developed more generally.

Artificial Intelligence can make substantial contributions to cancer informatics analysis, including image analysis. For example, a number of decision support systems have been constructed, for breast, colorectal cancer, and lung cancer [Kelly, 2011, Patkar et. al., 2012, Sesen 2015]. The integration of such systems with state-of-the-art image analysis remains an elusive goal; but one that would have enormous practical benefits.

Finally, the armamentarium of the medical image analyst has recently been afforced by the development of advances in machine learning (random forests, convolutional "deep" neural networks, …). The initial hubris that machine learning leads inevitably to "black boxes" and obviates the need for segmentation, image filtering, motion estimation and other prior information will soon pass, and machine learning will rightly be regarded as an important tool in the medical image analyst's toolbox. Machine learning will prosper in the context of "big data", where datasets are processed that are orders of magnitude greater than those that have been analysed to date, leading to novel statistical methods that are based on (nonlinear) methods of machine learning. Such big data analyses will provide fresh insights in genomics, epigenomics, digital pathology, and large population studies such as the UK's BioBank (in which 100,000 nominally healthy volunteers are scanned, measured, and probed). The deployment of such methods in medical imaging will need to take account of the already limited availability of experts to provide "ground truth", necessitating a fresh look at statistical inference.

## Disclosure Statement

Highnam and Brady are co-founders of *Volpara Health Technologies*. Brady is also co-founder of *Mirada Medical*, *Perspectum Diagnostics, Optellum,* and, together with N. Karssemeijer, *ScreenPoint bv.*

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