Medical Image Analysis 33 (2016) 7–12

Contents lists available at ScienceDirect

Medical Image Analysis

journal homepage: www.elsevier.com/locate/media

Editorial

Oncological image analysis

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ARTICLE INFO

Article history:
Received 5 April 2016
Revised 9 June 2016
Accepted 13 June 2016
Available online 23 June 2016

Keywords:
Cancer
Mammography
Angiogenesis
Molecular imaging
Radiotherapy

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 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.

1. 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.

2. Cancer

Cancer is one of the leading causes of morbidity and mortality worldwide, with approximately 14 million new cases (and

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[1] http://www.oncology.ox.ac.uk/.
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[3] http://www.ibme.ox.ac.uk/.
[4] http://www.imagingcdt.com/.

http://dx.doi.org/10.1016/j.media.2016.06.012
1361-8415/

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 1980 s and the disease's long latency period, typically between 30 and 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.

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. 10 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 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 Mukherjee (2010).)

3. 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".[1] 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*.[2] 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

[1] 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.

[2] JMB and RPH are founders of Volpara Health Technologies, http://volparasolutions.com/.