Precision imaging of lung cancer

Drs Elisabeth Weiss and Geoff Hugo discuss their multidisciplinary research into visualising lung cancers and the potential of their techniques for improving treatment success

Can you describe your research into the functional imaging of lung cancer?

EW: The current gold standard for functional imaging of lung tumours uses \(^{18}\text{F}\)-fluorodeoxyglucose positron emission tomography (FDG-PET), which is able to differentiate lung tumour volumes with active disease from non-metastatic conditions, as well as quantify changes in metabolic tumour activity as a response to therapy. Magnetic resonance imaging (MRI) is more readily available than FDG-PET, and has improved soft tissue visualisation and higher image resolution. It provides morphological and functional imaging information; in particular, diffusion-weighted MRI (DW-MRI) has been shown to be a promising biomarker to monitor therapy response in various tumour sites, such as rectum and cervical cancers. Our focus is therefore to investigate MRI for radiotherapy planning of lung cancer and, in particular, DW-MRI as a biomarker and predictor of tumour response to radiotherapy, enabling personalised treatment plans that can be adapted during the treatment process according to the early response findings.

Which challenges of radiotherapy in lung cancer do you hope to overcome with your image-guided treatment techniques?

EW: Despite many efforts to improve radiotherapy for locally advanced non-small cell lung cancer, therapeutic outcome is poor with a high rate of local recurrences in the radiation treatment field. More accurate characterisation of the individual patient’s tumour features and identification of markers that can predict local tumour response and treatment outcome would help to tailor the therapy, thereby avoiding overtreatment of well-responding tumours and undertreatment of aggressive tumours. Radiation oncologists, therefore, have an increasing interest in implementing diagnostic radiology and molecular imaging technology in their field for the benefit of more accurate tumour targeting.

How has your background enabled your current research?

EW: As a physician, I have always had active collaborations with other specialists, such as radiologists and medical physicists. Their training is complementary to my own, allowing us to approach research questions in a team with a multidisciplinary perspective.

Most of my research has been focused on geometric accuracy in radiotherapy planning and delivery. Typically, the way to measure accuracy is through repeated assessment, using a variety of imaging methodologies. I have, therefore, investigated different types of imaging techniques for their benefits in accurately treating cancer patients. For example, 4D computerised tomography (CT) for motion assessment of tumours during breathing, FDG-PET, MRI and cone beam CTs.

GH: My background is in image-guided radiotherapy, an area that already involves a great deal of image processing and analysis work. The data are too complicated for a physician alone to view the images and make a decision, so we try to use modelling and prediction algorithms to simplify and automate the process, which calls more on my physics background.

What technological advances have you seen in oncology imaging that have had an impact on the field of radiation oncology?

EW: While CT has, for many years, been the work horse imaging modality used for diagnosis and treatment planning in radiation oncology, recent integration of alternatives such as PET, single-photon emission computed tomography (SPECT) and MRI has been shown to provide a substantial benefit for improved targeting and individualisation of radiation therapy.

In particular, recent technological advances in MRI, for example multichannel imaging, strong gradients, fast pulse sequences, and cardiac pulsation- and respiration-triggered imaging, have significantly improved thoracic MR image quality and therefore its utility in planning and assessing successful treatment in cancer.

Can you elaborate on some of the biggest challenges you have faced?

EW: One major issue is the rather subjective interpretation of morphological and functional MR images. Evaluating images in consensus with experienced radiologists has certainly helped with the reproducibility of findings. However, automated or semi-automated techniques for determining tumour tissue, active and necrotic (dead) tumour and non-malignant tissue needs to be researched further, as the adequate definition of an active tumour is vital for determining DW-MRI as a reliable biomarker that can be used in a clinical environment.

GH: There is also the potential for measurement error to confound the results due to the sometimes subtle changes we are trying to detect. For example, drift of image intensity on a CT or MR scanner over time could mask true changes to tissue intensity, so careful quality assurance and measurement protocols must be observed.
WITH 1.59 MILLION deaths in 2012 alone, lung cancer is the most common cause of cancer mortality. A combination of radiotherapy and chemotherapy is the best course of treatment for inoperable lung cancers, but the five-year survival rate is just 20 per cent. Choosing the correct radiation dosage is also challenging – too much and it is possible to damage the healthy lung tissue surrounding the tumour, but too little and some cancerous cells could remain. Radiotherapy requires several weeks of daily treatments so, even if high-resolution images can be obtained, there can be many sources of error when repetitively targeting treatment; for example, patient position, tumour movement during respiration and tumour deformation.

As treatment progresses it is important to be able to accurately deliver radiation therapy to active and aggressive malignant cells while avoiding healthy ones, and track the position of dead tumour tissue that has already been effectively treated. High-resolution images are crucial for planning where in the lung to target treatment but complicated to acquire because the tumours move during imaging as the patient breathes in and out. Defining the microscopic boundary of the cancerous cells particularly difficult.

**A NOVEL APPROACH**

The current best practice for functional imaging in lung cancers uses 18F-fluorodeoxyglucose positron emission tomography (FDG-PET). A small amount of FDG radioactive trace is injected into the patient, where it is absorbed by the rapidly metabolising cancer cells more than by normal cells, labelling tumours for detection by the PET scanner. Unfortunately, FDG-PET has poor spatial resolution, can lack specificity where inflammation is present, and requires the injection of the FDG tracer every time imaging is performed, giving patients additional radiation exposure. Alternative imaging measures for lung cancers are urgently required.

Researchers at Virginia Commonwealth University, USA, are investigating a novel functional imaging approach that could revolutionise radiotherapy targeting and individualised treatment of lung cancer.

Dr Elisabeth Weiss, Professor of Radiation Oncology at Virginia Commonwealth University, USA, is dedicated to improving the functional imaging of lung cancers for radiotherapy planning and treatment response assessment and adaptation. Over the course of her career, she has evaluated many different imaging methodologies before focusing her attention on diffusion-weighted magnetic resonance imaging (DW-MRI), which she hopes can solve some of the problems with existing imaging techniques in lung cancer. “DW-MRI for lung cancer staging has been reported to have similar sensitivity (70-90 per cent) and specificity (up to 100 per cent) as standard functional imaging with FDG-PET,” Weiss explains. “However, compared to FDG-PET, DW-MRI has better spatial resolution and soft tissue visualisation, is generally more widely available, and does not require additional radiation. The value of DW-MRI for the diagnosis and therapy of lung cancer is the subject of our current research.”
Radiotherapy results in tumour cell death, which increases the ability of water to penetrate the tissue and causes a subsequent rise in the diffusion of water observable by diffusion-weighted magnetic resonance imaging.

PLANNING RADIOThERAPY

MRI uses a magnetic field and pulses of radiowaves to create high-resolution images of the body. Where FDG-PET measures metabolic activity of a tissue, DW-MRI measures water diffusion (apparent diffusion coefficient – ADC) as a proxy for a tissue’s microstructural composition. It is particularly useful for functional imaging of potential tumours because the size and density of cells within a tissue affect the ability of water to diffuse through the tumour. This is because they have a higher cell density, larger nucleus to cytoplasm cell ratio and less extracellular space than healthy tissue, which results in a low ADC. Weiss’ preliminary research, carried out in collaboration with her medical physics colleague Dr Geoff Hugo, showed tumour delineation by DW-MRI has comparable accuracy and is similarly specific as PET imaging, which facilitates accurate targeting of radiotherapy to tumours, allowing radiation oncologists to focus radiation at the tumour while reducing the dose to limit damage to healthy tissues.

A BENEFICIAL BIOMARKER

DW-MRI is a promising biomarker for therapy response in a variety of cancers, including those of the rectum and cervix. Radiotherapy results in tumour cell death, which increases the ability of water to penetrate the tissue and causes a subsequent rise in the diffusion of water observable by DW-MRI. Weiss and Hugo have evaluated whether this increase could be used to assess the tumour’s ongoing response to radiotherapy: “In our initial set of patients that were imaged with DW-MRI, we noticed significant increases in ADC values during treatment. In addition, these changes did not seem to be correlated with volumetric tumour shrinkage, indicating that DW-MRI could potentially be used as an independent marker of response”. These results will be used to develop standard protocols for the use of DW-MRI in a clinical setting, for example, how often imaging is required to monitor the tumour’s response to treatment.

Weiss is also interested in whether early ADC value change can predict how well a patient will respond to radiotherapy treatment in the long term. By studying the tumour’s response, it could be possible to model the change in tumour volume and adapt treatment where necessary. “While it is too early to confirm this relationship, we observed that patients with a small ADC increase appear to have a poor outcome,” summaries Weiss. The researchers are planning further experiments to elucidate the use of DW-MRI as a biomarker for predicting tumour response, which would allow physicians to adapt radiotherapy to an individual’s needs; for example with localised dose intensification for improved tumour control. This use of DW-MRI would help treatmet predict outcome so treatment can be modulated accordingly.

THE FUTURE OF DW-MRI

DW-MRI is a promising functional imaging technique for identification of active tumour and treatment response assessment, and Weiss and Hugo are continuing to develop it for use as a clinically validated tool for routine treatment planning and adaptive radiotherapy. Weiss and her multidisciplinary team are enthusiastic and positive that these objectives are achievable in the near future, offering patients and their physicians a powerful new technique for planning and adapting their radiotherapy for the best possible outcomes.

KEY COLLABORATORS

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Dr Jeffrey Williamson, Virginia Commonwealth University, USA

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CONTACT

Dr Elisabeth Weiss
Professor of Radiation Oncology
Virginia Commonwealth University
401 College Street
Richmond, Virginia, 23298
T +1 804 828 7232
E eweiss@mcv.vcu.edu

ELISABETH WEISS received her MD in Germany in 1990 and her medical doctorate degree in 1991. She completed her residency training in radiation oncology in 1997 after attending programmes in Berne, Switzerland, as well as Wuerzburg, Tuebingen and Goettingen, Germany. Following this, she held a position on the faculty at Goettingen University from 1997 to 2009 and received an academic teacher’s degree in 2004. Since then, she has been performing research at VCU Department of Radiation Oncology and joined the clinical faculty in 2008.

GEOFFREY HUGO received his PhD in Biomedical Physics from the University of California, Los Angeles, USA, in 2003. He then joined the staff of William Beaumont Hospital, where he participated in the clinical implementation of cone beam CT and was actively involved in developing an adaptive radiotherapy programme for lung cancer. Subsequently, he joined the Virginia Commonwealth University (VCU) Department of Radiation Oncology in 2008 as Assistant Professor. Hugo is also Director of the medical physics PhD and MS graduate programmes.