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Dale Jonathan Waterhouse

Novel Optical Endoscopes for Early Cancer Diagnosis and Therapy

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Novel Optical Endoscopes for Early Cancer Diagnosis and Therapy

Doctoral Thesis accepted by
the University of Cambridge, Cambridge, UK

Springer

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To my mum and dad,
whose love gave me the strength to succeed,
and to my brother Aaron,
my best friend
...

Supervisor's Foreword

Optical imaging plays an important role in the early diagnosis of cancer. In particular, the use of optical endoscopes to relay image information from deep within the body to the external observer is widespread. At present, however, the optical information relayed is typically recorded using a standard colour camera, which integrates a Bayer filter array of red, green and blue colour filters to replicate the colour sensing capability of the human eye. This approach restricts the range of wavelengths that can be detected and the number of spectral features that can be resolved. Using standard colour cameras provides limited contrast for cancer within a background of normal tissue, which leads to high miss rates during endoscopic surveillance and difficulty in assessment of tumour margins during surgery.

The interactions of light with tissue go far beyond the simple red, green and blue. In addition to those interactions that occur intrinsically with different biomolecules in the tissue, it is also possible to use contrast agents that can specifically enhance the contrast between healthy and diseased tissues. These contrast agents may be untargeted and give rise to contrast due to differences in tissue structure or vascularisation, or they may be targeted to specific cell surface receptors or other biological processes that are known to change during disease progression. The detection of these contrast agents in tissue can often be difficult due to the high background signals that arise from the intrinsic tissue interactions.

In this thesis, Dale Waterhouse has begun to exploit these additional sources of contrast in a series of clinically motivated studies. The thesis begins with the development of an optical imaging biomarker road map, which critically reviews the opportunities and challenges for optical imaging in endoscopy and identifies common features of successful optical imaging biomarkers that have been deployed clinically. This defined framework is then kept at the forefront for the remainder of the thesis, in which the design, development, characterisation and application of several novel imaging systems are presented.

Dale then embarked upon the development of a bimodal white light and near-infrared endoscope for imaging of a targeted fluorescence contrast agent in the context of early detection of dysplasia in patients with Barrett's oesophagus. With the clinical translation in mind, the endoscope was built around an existing

CE-marked device, modifying only the back end of the system. He then extended the initial system further to resolve intrinsic contrast from different biomolecules by introducing a multispectral imaging capability using a spectrally resolved detector array as the camera within the system. Taking the approach of using a CE-marked imaging fibre bundle for these endoscopy experiments required the development of a number of computational methods to deal with comb artefacts and overcome challenges with demosaicking of images from the multispectral camera. In addition to applying these advanced optical imaging methods in flexible endoscopic imaging, Dale also created and clinically applied a multispectral imaging system that could be used to guide surgery for the removal of pituitary adenomas.

With his dissertation, Dale made an important contribution towards understanding how optical imaging can be applied in biomedicine. In particular, by developing a clear understanding of the characteristics shared by successful optical imaging biomarkers, Dale ensured the success of his own device development, with two of his systems being applied in 'first-in-human' clinical trials. This is a significant achievement within only a 4-year time frame and is a testament to the impact of Dale's thinking not only on the research of my own laboratory, but also on the field of biomedical optical imaging more generally.

Cambridge, UK
June 2019

Dr. Sarah Bohndiek

Abstract

Imaging is the only medical tool currently capable of non-invasively capturing detailed, real-time and spatially resolved biochemical information in vivo and thus delineating disease so that non-invasive curative resection or treatment of the affected area can take place. Though visible and near-infrared (NIR) light undergo a wide range of complex interactions in tissue—interactions which can be harnessed to yield useful information about the underlying pathology—optical imaging has yet to be fully utilised in clinic, with many existing techniques relying on standard colour imaging that replicates human vision.

This thesis describes my recent effort advancing novel optical endoscopic imaging techniques towards the clinical translation. Before embarking on the development of novel devices, an analysis was made of the common challenges in translating optical imaging techniques. Through this work, a streamlined road map to clinical translation was developed, and key translational characteristics were defined. These were used to guide the subsequent development of endoscopic devices.

Initial efforts were focused on the development of flexible endoscopes for detection of dysplasia in Barrett's oesophagus. To enable molecular imaging with a newly discovered targeted fluorescent contrast agent, a bimodal endoscope capable of capturing NIR fluorescence and white light reflectance was developed around a clinically translatable device architecture, and image artefacts were addressed by developing and evaluating image correction algorithms. This technique demonstrated significant potential for delineation of dysplasia in ex vivo samples. Next, a multispectral endoscope capable of imaging multiple fluorophores or endogenous tissue reflectance was developed. This device was successfully translated to a clinical pilot study, where initial results showed the promising potential of multispectral endoscopy for delineation of dysplasia based on endogenous reflectance from oesophageal tissue. Finally, multispectral imaging was explored for intraoperative delineation of adenoma and healthy pituitary tissue. A novel rigid multispectral endoscope was developed, preliminary technical characterisation of this device was performed, and a clinical pilot study was planned.

With the continuation of this work as outlined at the end of this thesis, the novel techniques described here have the potential to improve the standard of care in their respective indications.

List of Publications

Publications

Jonghee Yoon, James Joseph, **Dale J. Waterhouse**, A. Siri Luthman, George S. D. Gordon and Massimiliano di Pietro, Wladyslaw Januszewicz, Rebecca C. Fitzgerald, Sarah E. Bohndiek, *A clinically translatable hyperspectral endoscopy (HySE) system for imaging the gastrointestinal tract.* Nature Communications, 10, 1902, (2019).

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Dale J. Waterhouse, A. Siri Luthman, Jonghee Yoon, George S. D. Gordon and Sarah E. Bohndiek, *Quantitative evaluation of comb-structure removal methods for multispectral fiberscopic imaging.* Scientific Reports, 8, 17801, (2018).

A. Siri Luthman, **Dale J. Waterhouse**, Laura Ansel-Bollepalli, Jonghee Yoon, George S. D. Gordon, James Joseph, Massimiliano di Pietro, Wladyslaw Januszewicz and Sarah E. Bohndiek, *Bimodal Reflectance and Fluorescence Multispectral Endoscopy based on Spectrally Resolving Detector Arrays.* Journal of Biomedical Optics, 24(3), (2018).

Dale J. Waterhouse, Catherine R. M. Fitzpatrick, Massimiliano di Pietro and Sarah E. Bohndiek, *Emerging Optical Methods for Endoscopic Barrett's Surveillance.* The Lancet Gastroenterology and Hepatology, 3(5), (2018).

André A. Neves, Massimiliano di Pietro, Maria O'Donovan, **Dale J. Waterhouse**, Sarah E. Bohndiek, Kevin M. Brindle and Rebecca C. Fitzgerald, *Detection of early neoplasia in Barrett's esophagus using lectin-based near-infrared imaging: an ex vivo study on human tissue.* Endoscopy, 50(6), (2018).

Dale J. Waterhouse, James Joseph, André A. Neves, Massimiliano di Pietro, Kevin M. Brindle, Rebecca C. Fitzgerald and Sarah E. Bohndiek, *Design and validation of a near-infrared fluorescence endoscope for detection of early esophageal malignancy*. Journal of Biomedical Optics, 21(8), (2016).

Conference Proceedings

A. Siri Luthman, **Dale J. Waterhouse**, Laura Bollepalli, James Joseph and Sarah E. Bohndiek, *A multispectral endoscope based on spectrally resolved detector arrays.* Proc. SPIE 10411, Clinical and Preclinical Optical Diagnostics, 104110A (2017).

Dale J. Waterhouse, A. Siri Luthman and Sarah E. Bohndiek, *Spectral band optimization for multispectral fluorescence imaging.* SPIE BiOS (2017).

Massimiliano di Pietro, André A. Neves, Maria O'Donovan, **Dale J. Waterhouse**, Sarah E. Bohndiek, Kevin M. Brindle and Rebecca C. Fitzgerald, *Detection of dysplasia in Barrett's oesophagus using lectin-based near infra-red molecular imaging: an ex-vivo study on human tissue*. Proceedings of the British Society of Gastroenterology Meeting (2016).

Dale J. Waterhouse, James Joseph, André A. Neves, Massimiliano di Pietro, Kevin M. Brindle, Rebecca C. Fitzgerald and Sarah E. Bohndiek, *Design and validation of a near-infrared fluorescence endoscope for detection of early esophageal malignancy using a targeted imaging probe*. SPIE BiOS (2016).

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Still, experiments failed. Equipment broke. Code crashed. During these times, I am grateful to have been surrounded by supportive colleagues. As a novice to the research, I am thankful that James Joseph and George Gordon were so willing to show me the ropes. I would also like to acknowledge the support of my exceptional clinical collaborators, especially Massimiliano di Pietro, Wladyslaw Januszewicz and James Tysome, whose support and patience have helped facilitate the clinical translation of my work. I am grateful to have worked alongside Siri Luthman, tackling our problems together in an otherwise desolate optics laboratory.

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Sadly, my big nan-nan is not here to see me complete my thesis. She is dearly missed, and I am sure she would be immensely proud, as are my other grandparents. Their pride and love have spurred me on throughout my research. I express immense gratitude to my mum, dad and brother, Aaron. The weekends we spent in

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