HEI name: Queen's University Belfast

UOA name: 2

Title of case study: Re-assessment of Cancer risk in Barrett's oesophagus

1. Short summary of the impact

Research within the Northern Ireland Barrett's oesophagus Register demonstrated that cancer risk in this disease was substantially lower than previously thought. It identified clinico-pathological characteristics and potential biomarkers that allow Barrett's patients to be stratified into those with higher and lower cancer risk. This research has influenced recommendations from Gastroenterological Associations in the UK and USA and resulted in altered clinical practice nationally and internationally, in which costly routine endoscopic surveillance is now targeted to Barrett's oesophagus patients with the highest cancer risk.

2.Underpinning research

Barrett's oesophagus (BO) is the precursor of a lethal cancer of the oesophagus called oesophageal adenocarcinoma (OAC). Rapid increases in the last 30 years in OAC incidence led to the widespread practice of routine endoscopic surveillance in the UK, Europe and USA in patients diagnosed with BO. It has been a widely held premise that the cancer risk in BO patients is high and that regular endoscopy would lead to detection of cancer at an early or pre-invasive stage and thereby provide a cost-effective opportunity for surgery or other interventions; to improve outcomes for BO patients and reduce the public health burden associated with OAC.

A systematic review of the published literature in this field undertaken by Professor Liam Murray (Cancer Epidemiologist, Centre for Public Health, Queen's) identified that the case for surveillance of BO patients was primarily based on flawed evidence from small studies of biased high-risk BO populations, which provided inflated estimates of cancer risk.[1] The review identified that no unbiased population-based studies of cancer incidence in BO had been performed. Therefore, Professor Murray, Professor Brian Johnston (Gastroenterologist, Belfast Health and Social Care Trust (BHSCT), Honorary Clinical Professor, Queen's), Dr Damian McManus (Pathologist, BHSCT, Honorary Clinical Senior Lecturer, Queen's) and Dr Anna Gavin (Director, Northern Ireland Cancer Registry, Queen's) established the Northern Ireland Barrett's oesophagus Register (NIBR). The NIBR is a unique, population based register of every case of BO diagnosed in NI since 1993. NIBR reflects everyday practice within the NHS and avoids referral biases (e.g. to specialist centres), which afflict other studies in the field. The NIBR was followed up with minimal loss of follow-up (until 2010) for cancer incidence and death. Uniquely, it was possible to access diagnostic BO tissue and link to detailed clinical data.

The first NIBR publication was reported in *Gut* in 2003.[2] This study showed that, although the death rate from OAC was elevated, OAC accounted for only a small proportion of deaths and the overall mortality in BO patients was the same as in the general population. This was one of the first and most influential reports to query the prevailing view within the scientific and clinical community that BO carried a very high OAC incidence and mortality risk. In 2011, the group published the cancer incidence within NIBR.[3] The study confirmed that the cancer risk in BO was substantially lower than previously believed and was at a level where the cost-effectiveness of endoscopic surveillance of BO patients was questionable. The study underlined the importance of strategies to identify BO patients who are at the highest risk of developing cancer and in whom surveillance may be beneficial and cost-effective. Such strategies include the use of clinico-pathological characteristics and tissue biomarkers for cancer progression. Using NIBR resources, the research group and collaborators in the Universities of Cambridge (Dr Rebecca

Fitzgerald) and Leeds (Professor Chris Wild, now Director of the International Agency for Research on Cancer (IARC) and Professor David Forman, now Head of Information at IARC) and University College London (Dr Laurence Lovat) have published the first population-based biomarker studies in BO.[4,5] These studies identified several promising biomarkers of the cancer risk in BO that, once validated in other studies, can be applied in routine clinical settings.

3. References to the research

1. Yousef F, Cardwell CC, Cantwell MM, Galway K, **Johnston BT, Murray LJ**. The incidence of oesophageal cancer in Barrett's oesophagus. A systematic review and meta-analysis. *American Journal of Epidemiology* 2008;168(3):237-49. Doi: 10.1093/aje/kwn121.
Main findings: Very substantial variation in the reported incidence of OAC in BO. Available estimates of incidence are generally from small studies of biased high risk populations. 113 citations:
2. Anderson LA, **Murray LJ**, Murphy SJ, Fitzpatrick DA, **Johnston BT, Watson RG, Gavin A**. Mortality in Barrett's Oesophagus: results of a population-based study. *Gut* 2003;52:1081-4. Doi:10.1136/gut.52.8.1081.
Main findings: Low mortality from OAC in BO patients and overall mortality not different from the general population. 108 citations
3. Bhat S, Mulholland H, Yousef F, **Johnston B, McManus D, Gavin A, Murray L.** Risk of Malignant Progression in Barrett's Esophagus Patients: Results from a Large Population-Based Study. *Journal of the National Cancer Institute* 2011;103(13):1049-57. Doi: 10.1093/jnci/djr203.
Main findings: Cancer risk in BO lower than previously reported. Clinico-pathological characteristics including male gender, aged 60-79 at BO diagnosis, presence of Specialised Intestinal Metaplasia, long segment length were associated with higher cancer risk. 71 citations
4. **Murray L**, Sedo A, Scott M, **McManus D**, Sloan JM, Hardie LJ, Forman D, Wild CP. TP53 and progression from Barrett's metaplasia to oesophageal adenocarcinoma in a UK population cohort. *Gut* 2006;55(10):1390-7. Doi: 10.1136/gut.2005.083295.
Main findings: Expression of TP53, measured by immunohistochemistry, identified as a biomarker of progression from BO to OAC. 54 citations
5. Bird-Lieberman EL, Dunn JM, Coleman HG, Lao-Sirieix P, Oukrif D, Moore CM, Varghese S, Johnston BT, Arthur K, McManus DT, Novelli MR, O'Donovan M, Cardwell CR, Lovat LB, **Murray LJ** and Fitzgerald RC. Phase 3 population-based study reveals new risk-stratification biomarker panel for Barrett's esophagus. *Gastroenterology* 2012;143(4):927-35. Doi: 10.1053/j.gastro.2012.06.041.
Main findings: A biomarker panel comprising low grade dysplasia as defined by expert pathologists, abnormal DNA ploidy measured using image cytometry, and immunohistochemical staining for Aspergillus oryzae lectin expression predicted cancer risk in BO patients. 11 citations

4. Details of the impact

The effect of the NIBR research has been an increased recognition of the lower cancer risk in BO than previously thought, the importance of using clinicopathological characteristics (and potentially biomarkers) to stratify BO patients according to cancer risk and tailoring endoscopic surveillance of BO patients accordingly. The principal aim of the register was to determine the true clinical and public health importance of BO and to influence clinical practice in the UK and internationally by providing unbiased estimates of cancer incidence and mortality in patients diagnosed with this condition. The research has informed changes in influential clinical gastroenterology guidelines. An important additional aim was to identify clinico-pathological characteristics and tissue biomarkers associated with a high risk of progression to cancer to enable effective targeting of endoscopic surveillance or other clinical interventions to high risk patients.

The central findings of this research is that cancer incidence in BO patients, although raised compared to the general population, is lower than has been previously believed and is at a level where routine surveillance of all BO patients is very unlikely to be a cost-effective use of health care resources. This work has resulted in a paradigm shift in the thinking of clinicians and health service providers involved in the management of BO. It is now recognised that BO patients should be stratified according to cancer risk and endoscopic surveillance and associated interventions targeted at those with higher cancer risk. Work in NIBR based on clinico-pathological factors has identified some groups at higher cancer risk[3] and seminal publications have also identified tissue biomarkers that may be applied within routine clinical settings to aid targeting of surveillance practice.

The importance of the research undertaken within the register to the shaping of scientific and clinical thinking with respect to BO is evidenced by the fact that the main publications have been accompanied by editorials from leading practitioners in the field.[1,2,4]. These editorials have, for example, pointed out that the finding that cancer mortality in BO patients is low '*has direct clinical relevance as well as public health significance*'. The '*population based epidemiology*' approach used was recognised as '*the only way the much needed quantitative information about the condition (BO) and its natural history can be gained'*.

The work has also drawn much attention from the scientific media[3,4,6]. For example the main cancer incidence paper was heralded as a '*Game Changer in Gastroenterology 2011'* by Medscape International, the influential and widely read web resource for physicians and other health professionals.[3]

Most importantly with respect to impact on clinical practice, NIBR research has been among key publications referenced in recent guidelines for the diagnosis and management of BO issued by the two most influential gastroenterological societies worldwide, the American Gastroenterological Association[7] and the British Society for Gastroenterology (BSG). The most recent BSG guidelines 'Diagnosis and Management of Barrett's oesophagus' (Gut, In Press)[8] reference six papers from the NIBR research group, with NIBR research providing key evidence underpinning six of the practice recommendations made, especially the following three:

- *Surveillance regimens should take into account the presence of IM and length of the Barrett's oesophagus segment*
- *For patients with segments <3cm without intestinal metaplasia or dysplasia a repeat endoscopy with quadrantic biopsies is recommended to confirm the diagnosis. If repeat endoscopy confirms the absence of intestinal metaplasia consideration should be given to discharge from surveillance as the risks for endoscopy likely outweigh the benefits*
- *The addition of a p53 immunostaining to the histopathological assessment may improve the diagnostic reproducibility of a diagnosis of dysplasia in Barrett's oesophagus and should be considered as an adjunct to routine clinical diagnosis*

Furthermore, The National Clinical Lead for Endoscopy, Department of Health, England stated[9]. "*It (the register) provides one of the few unbiased samples of the natural history of Barrett's and factors that predict the development of malignancy. As such, it is of huge importance to the ongoing controversies surrounding the management of Barrett's. It has been uncomfortable reading for the advocates of surveillance of Barrett's and it has undoubtedly influenced recent guidelines in the UK and North America"*.

5. Sources to corroborate the impact

1) Heading RC. Barrett's oesophagus: epidemiology comes up with a surprise. *Gut* 2003;52(8):1079-80
This editorial emphasises the importance of the population based epidemiological studies such as NIBR in understanding the natural history and clinical and public health relevance of BO.

2) Corley DA. Understanding cancer incidence in Barrett's esophagus: light at the end of the tunnel. *Journal of the National Cancer Institute* 2011;103(13):994-5
This editorial emphasises the importance of NIBR research as the first work to provide robust population based evidence addressing crucial issues related to the clinical management of Barrett's e.g. cancer risk according to presence of intestinal metaplasia, age and sex and time since diagnosis.

3) Medscape. Game Changer in Gastroenterology 2011.
http://www.medscape.com/viewarticle/753828_8
This commentary on the NIBR paper published in Journal of the National Cancer Institute in 2011 (Reference 3) states that the paper is a game changer in the Gastroenterology field because it identifies extremely low cancer rates in the BO patients without intestinal metaplasia and raises questions about the value and cost-effectiveness of endoscopic surveillance in BO patients.

4) http://www.cancerresearchuk.org/cancer-info/news/archive/cancernews/2011-06-20-Current-UK-system-of-Barretts-oesophagus-monitoring-not-cost-effective
This comment on Reference 3 concludes that the NIBR data calls into question the cost effectiveness of current BO surveillance practice in the UK.

5) Preston SL, Jankowski JA. *Gut* 2006 Oct;55(10):1377-9. Drinking from the fountain of promise: biomarkers in the surveillance of Barrett's oesophagus--the glass is half full!
This editorial emphasises the importance of exploring biomarkers of cancer risk in BO patients, as undertaken within NIBR, to assist the identification of patients at high risk that will benefit most from surveillance or interventions to reduce cancer risk.

6) http://www.gastrohep.com/news/news.asp?id=109128
This scientific news piece drew the attention of the Clinical Gastroenterology community to the biomarker work undertaken by the NIBR group in collaboration with the University of Cambridge and University College London, which identified an increased cancer risk in biomarker defined subgroups of BO patients.

7) American Gastroenterological Association Technical Review on the Management of Barrett's Esophagus. Gastroenterology 2011;140:e18–e52
These guidelines on the management of BO quote NIBR research (Reference 2) as key work examining the impact of BO on life expectancy.

8) British Society of Gastroenterology guidelines. Diagnosis and Management of Barrett's oesophagus. In Press, *Gut,* August 2013. (Discussed in Section 4)

9) Letter from National Clinical Lead for Endoscopy, Department of Health, England. (Discussed in Section 4).