**TOPGEAR**: the international trial on gastro-oesophageal cancer

**Drs Rebecca Wong** and **Chris O’Callaghan** discuss their important roles in conducting an international clinical trial to improve the outcomes for patients diagnosed with gastro-oesophageal cancer

Could you each provide an introduction to your respective backgrounds and explain what drew you to your specific research fields?

**RW:** After graduating from the University of Sheffield, UK, I obtained an MSc in Clinical Epidemiology from McMaster University, Canada. I then joined the University of Toronto’s Department of Radiation Oncology and was appointed Professor in 2010. My clinical research is focused on the care of patients with gastrointestinal (GI) malignancies, particularly those living with metastatic and gastro-oesophageal cancer. My goal, through well-designed research, is to improve patient outcomes, and do so with the least treatment-related morbidities.

**CO:** As a veterinarian with MSc and PhD degrees in clinical and analytical epidemiology, respectively, I came to the world of clinical cancer research primarily as a methodologist with comparative medical expertise. In my capacity as a senior investigator with the NCIC Clinical Trials Group (CTG) with an academic appointment as Associate Professor in the Department of Public Health Sciences at Queen’s University, Canada, I provide stewardship and oversight for the Gastrointestinal and Brain Disease Site Committees, as well as being simultaneously responsible for the development, execution and analysis of several studies in partnership with the external Clinical Study Chair.

**Dr Wong, you have multiple academic affiliations. Can you outline your duties and explain how you manage your time effectively?**

**RW:** In addition to my clinical practice, which occupies 50 per cent of my time, I have also been given opportunities to shape initiatives in other areas. As Director of Clinical Research for my department, I oversee the quality and efficiency of our clinical research programme. At the University of Toronto’s Department of Radiation Oncology, I serve on the executive committee representing professionalism and equity. As one of the co-chairs for the Program in Evidence-Based Care, I oversee the development of evidence-based practice guidelines in gastrointestinal malignancies for Ontario. As part of the faculty for the Institute of Health Policy Management and Evaluation, I provide formal training for graduates on evidence-based guidelines development. Within NCIC CTG, in addition to being Co-Chair for the gastro-oesophageal working group, I also chair the Symptom Control Committee, with the mandate of designing and conducting clinical trials addressing symptoms related to cancer and its treatments. I am still in search of the optimal and most effective way to manage time. Staying true to the most important goals and not giving up perhaps keeps me on track. On every vacation, I invariably re-evaluate and refresh my priorities, and take up a change that could make me work smarter.

**What are your respective involvements and designated duties in the randomised controlled trial (RCT)?**

**RW:** As the Canadian Principal Investigator for the study, my role is best described as an advocator. This involves clearly defined tasks such as provision of methodological input to the study, presentations at meetings, grant writing and submission, liaising with the various stakeholders and an anticipated strong accrual into the trial. More critically, the role requires effectiveness in building investigator networks and engagement.

**CO:** As the NCIC CTG Senior Investigator responsible for the GI Disease Site, my role is best described as coordinating the sponsorship and conduct of the trial in Canada. While my responsibilities do include methodological input on study design and ultimately analysis and interpretation, I will be principally involved in the logistics and processes necessary to open the trial at participating sites across Canada.

**This trial is conducted through the NCIC CTG, could you explain the Group’s importance to the study?**

**RW:** The NCIC CTG is a network of clinical researchers whose funding includes programmatic and project-specific peer-reviewed grants. Through our funding mechanisms, we are able to conduct national and international clinical trials. Our mission is to test interventions that demonstrate efficacy and/or relative effectiveness in preventing cancer or improving patient outcomes. The NCIC CTG includes more than 80 Canadian member institutions, including all major cancer centres and many community hospitals, and more than 1,200 investigators, research nurses, data managers and pharmacists. Between its inception in 1980 and January 2014, we have conducted 270 trials – some of which are still in progress – within our phase III programme (69,585 patients) and 197 phase I or II studies within our Investigational New Drug Program (5,627 patients).

Conducting the trial through NCIC CTG provides Canadian investigators with the critical expertise needed to mount and coordinate the Canadian portion of this trial.

**Speaking broadly, what are your hopes for the future of gastric cancer, and to what extent will your work help contribute to improving the outlook for patients?**

**RW:** The future of gastric cancer needs to involve improved prevention and early diagnosis. Enhanced understanding of the molecular basis of this disease along with advances in imaging and radiotherapy delivery may lend themselves to the development of better prevention strategies and diagnostic tools, as well as advances in patient selection and choice of personalised treatment strategies.
Changing protocol

As part of a wider international collaboration, a multidisciplinary team of Canadian researchers from the NCIC Clinical Trials Group is testing the effectiveness of preoperative chemoradiotherapy in the treatment of gastro-oesophageal cancers.

Although gastric and oesophageal cancers are relatively rare, they account for a substantial proportion of cancer-related morbidity and mortality, ranking as the 9th and 10th national leading causes of death respectively. In 2013, in Canada alone, approximately 3,650 patients were diagnosed with gastric or oesophageal cancers and around half of these cases will be fatal. While surgery is potentially curative in patients with local advanced disease, with a cure rate in the order of 30 per cent.

In the search to maximise the success of gastro-oesophageal resection surgery, two approaches have been shown to improve cure rates by approximately 10 per cent – perioperative ECF (epirubicin, cisplatin, fluorouracil) chemotherapy, and the delivery of postoperative chemoradiotherapy (CRT). Examining patterns of failure provides insight into how the best aspects of both approaches can be combined, delivering a strategy that is optimally effective.

Combined treatment

Incorporating radiotherapy may augment the success of curative drugs and surgery through improving arrest of malignant cell growth at the site of origin. The use of a strategy that incorporates treatment in the preoperative setting has a number of advantages and is expected to benefit more patients, as many are simply not candidates for additional treatment in the postoperative state. Radiotherapy delivered in the preoperative setting is expected to be more efficacious for dose as there is a lower risk of hypoxia (which would limit the therapy’s effect) at this stage. The treatment volumes are typically smaller, resulting in less normal tissue being irradiated and fewer side effects. Combining these features, the use of preoperative CRT represents a promising strategy. Indeed, there is already evidence that suggests this method may be effective. A meta-analysis of four trials comparing preoperative radiotherapy with surgery alone suggests a superior survival rate; moreover, two phase II studies suggest preoperative CRT to be safe and efficacious, with significant tumour downsizing and complete responses in the order of 30 per cent.

An alternative approach

Having considered the results of these clinical trials, Canadian researchers Drs Rebecca Wong and Chris O’Callaghan believe that the alternative treatment strategy – the use of preoperative CRT in addition to perioperative chemotherapy – will increase overall survival of gastric and oesophageal cancer patients undergoing surgical resection, compared to just using perioperative chemotherapy. In a large, international and collaborative clinical trial, Wong and O’Callaghan are working alongside the Australian Gastro-Intestinal Trials Group (AGITG – Lead Investigator Dr Trevor Leong), the European Organisation for Research and Treatment of Cancer (EORTC – Lead Investigator Dr Karin Hausmann), the Trans-Tasman Radiation Oncology Group (TROG) and the National Health and Medical Research Council (NHMRC) Clinical Trials Centre at the University of Sydney, on TOPGEAR: Trial Of Preoperative therapy for Gastric and Esophagogastric junction Adenocarcinoma.

Canadian contribution

The Canadian facet of the trial is being conducted by the NCIC Clinical Trials Group (CTG). Chief Investigator Wong and Senior Investigator O’Callaghan are overseeing the work and anticipate around 250-375 patients across 15 Canadian centres, out of a total 750 participants. The study concept was first introduced to Canadian researchers in 2011, and despite various challenges, the proposal was prioritised by Canadian investigators as the most important question for investigation.

“its approval at NCIC CTG reflects the importance of the research question, quality of the science and strength of the investigator networks. This is further reflected in the successful grant application securing CAD $1.7 million from the Canadian Institutes of Health Research,” Wong enthuses.

There are a number of reasons why preoperative CRT is thought to have the ability to improve patient outcomes. Primarily, the use of therapy prior to surgery provides opportunity for tumour downsizing, which could increase the success rate of the resection and reduce the chance of cancer recurrence. Furthermore, due to the inherent toxicity of cancer therapies, they are often better tolerated by patients when administered before surgery. Postoperative therapy can be disrupted by patient morbidity so the full intended treatment is sometimes not administered, limiting its effect.

Trial objectives

The primary objective of the trial is to determine whether CRT prior to surgical abscission improves patient survival compared to the sole use of perioperative chemotherapy. Analysing the results in more detail, the researchers will be looking to evaluate how the addition of CRT improves pathological response rate, surgical cure rate and disease-free survival. Furthermore, its effect on toxicity, quality of life and economic perspective will also be considered.

Overcoming hurdles

Currently, the trial is open and recruiting participants across Canada. It is estimated that recruitment will be completed in around five years’ time, with follow-up of an additional three years to consider survivor outcomes. Looking forward to the results of the trial, Wong hypothesises: “I predict radiotherapy has an important role to play in the management of gastric cancer, and that it is more efficiently used when applied preoperatively”. It is also thought that although postoperative CRT has been associated with significant toxicities, the present trial will show that, when used preoperatively and in combination with modern radiotherapy techniques, it will be well tolerated and acceptable to patients.
In 2013, in Canada alone, approximately 3,650 patients were diagnosed with gastric or oesophageal cancers and around half of these cases will be fatal.

From the Canadian perspective, Wong has led the development of the study from concept through design and into the implementation phase. Attaining trial approval and funding support for the required level of patient participation has its difficulties. “Sustaining investigator enthusiasm across the country is probably one of the key challenges,” she elaborates. Managing such large numbers of scientists and clinicians from a wide variety of disciplines requires significant network development and engagement.

GLOBAL IMPLICATIONS

The involvement of such an internationally diverse array of researchers and participants has ensured the results will be widely applicable across different nationalities. A critical feature of the study is the pre- and post-treatment samples that will be collected from consenting patients. Once the data have been fully analysed and amalgamated, the results will become part of a highly valuable biobank, containing well-documented clinical outcomes for different individuals. This will be an important tool, allowing researchers to better predict the behaviour of gastroesophageal cancers.

The insights gained will be used to guide future clinical trials that further probe the most effective treatment methods for patients with gastro-oesophageal cancer. “The improved understanding of the predictors of response and outcome to surgery, radiotherapy and chemotherapy would lend itself to better patient selection, perhaps guided by biological markers, so that the next generation of treatment strategies would be more effective and appropriate for specific patients,” Wong concludes.

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DR CHRIS O’CALLAGHAN is a veterinarian with MSc and PhD degrees in clinical and analytical epidemiology who came to the world of clinical cancer research principally as a methodologist with comparative medical expertise. In his capacity as a senior investigator with the NCIC CTG he provides stewardship and oversight for the development, execution and analysis of multiple clinical trials in gastrointestinal and central nervous system cancers.

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Over a period of more than 30 years, the NCIC CTG has applied for and secured a Major Program Grant from CCS, which has provided the Group with crucial support.