Institution: University of Leeds

Unit of Assessment: UOA1 Clinical Medicine

Title of case study:
Case Study 4. Improving chemotherapy, radiotherapy and patient outcomes for colorectal cancer through patient-focused integrated clinical trials.

1. Summary of the impact

Colorectal cancer is a common disease, which frequently causes death or morbidity, either because of failure to control the primary tumour or failure to prevent distant metastases. Leeds researchers have devised new treatment approaches using chemotherapy and radiotherapy and tested them in large randomised controlled trials which have led to major changes in clinical practice in the management of rectal cancer and advanced colorectal cancer (aCRC), driving clinical decision-making and improving outcomes for patients. This includes better-evidenced treatment for elderly patients and patient stratification on the basis of molecular biomarkers.

2. Underpinning research

Colorectal cancer afflicts 40,000 people per year in the UK and this number is rising by 5,000 per decade. However the rates of cure and disease control are improving, with significant contributions from Leeds researchers.

Rectal cancer affects 14,000 patients in the UK a year. Local recurrence after surgical resection of rectal cancer is frequently incurable and leads to major debilitating symptoms. Strategies to reduce the risk of local recurrence included improved surgical technique and the use of adjuvant radiotherapy. Yet there had been uncertainty over whether the benefits from preoperative radiotherapy remained when it was combined with modern surgical technique. Between 1997 and 2005 David Sebag-Montefiore (Professor of Clinical Oncology, Leeds 1997-) led an international trial (CR07) of 1350 patients from 80 centres in four countries showing a one-week course of preoperative radiotherapy prior to surgery halved the risk of local recurrence and improved disease-free survival (1).

For all patients with colorectal cancer, even if the primary local disease is controlled, the risk of distant metastatic spread remains high, resulting in serious morbidity and 15,000 deaths per year in the UK. The mainstay of treatment for the large majority of patients with advanced colorectal cancer (aCRC) is chemotherapy. Between 1995 and 1999 Matthew Seymour (Professor of Gastrointestinal Cancer Medicine, Leeds 1995-), who was a co-investigator in trials which established two new drugs – irinotecan and oxaliplatin – in the treatment of aCRC, identified the need to develop better schedules combining these agents with established drugs to maximise effectiveness, reduce toxicity and allow their practicable and cost-effective use throughout the NHS. Between 2000 and 2008, in collaboration with the Colorectal Cancer Clinical Studies Group of the National Cancer Research Institute (NCRI) and the NIHR Cancer Research Network (NCRN), Seymour led or co-led a series of large national phase III randomised controlled trials (RCTs) to address the optimum sequencing of available drugs (2-4). The schedules he developed (MdG, OxMdG and IrMdG) have since become UK standards.

FOCUS (2) – with 2135 patients at 61 UK centres and at the time the largest ever trial of patients with aCRC – tested three strategies of sequential and combination chemotherapy. This was followed by FOCUS2 (3) assessing the adaptation of treatment for frail, elderly patients – a fast-growing population. The merits of intermittent or continuous therapy were studied in COIN (4) – the largest RCT in aCRC - which along with FOCUS2 also assessed the introduction of oral therapy. Together, these trials included 5000 patients and provided firm evidence to guide many aspects of day-to-day management and subsequent international meta-analyses.

Throughout this period, particularly from 2008 onwards, Seymour and Phil Quirke (Professor of Pathology 1982-), worked to identify molecular predictive biomarkers and introduce prospective

molecular stratification, especially in relation to novel targeted therapies. In FOCUS (2) we introduced, for the first time in aCRC, prospective consent for use of surplus tumour material, enabling the subsequent identification of potential predictors of treatment benefit (5). We then led PICCOLO, the first phase III trial internationally to introduce prospective genotyping with different randomisations based on *KRAS* mutation status. This identified a subpopulation of patients with *KRAS*-unmutated tumours who receive increased benefit from the addition of the anti-EGFR therapeutic antibody panitumumab, while around 30% of patients, with tumours unmutated for *KRAS* but having a mutation in a related gene, gain no benefit or are harmed (6).

3. References to the research

1) Sebag-Montefiore D, Stephens R, Steele R, Monson J, Grieve B, Khanna S, Quirke P, Couture J, de Metz C, Myint S, Bessell E, Griffiths G, Thompson L, Parmar M. A randomised trial comparing pre-operative radiotherapy and selective post-operative chemo-radiotherapy in rectal cancer. Results from the Medical Research Council CR07 and National Cancer Institute of Canada Clinical Trials Group C016 trial. Lancet 2009; 373: 811-20.

The definitive trial showing benefits to patients with primary rectal cancer from modern radiotherapy and surgery combined

2) Seymour MT, Maughan TS, Ledermann JA, et al, for the FOCUS Trial Investigators and the National Cancer Research Institute Colorectal Clinical Studies Group. Different strategies of sequential and combination chemotherapy for patients with poor- prognosis advanced colorectal cancer (MRC FOCUS): a randomised controlled trial. Lancet 2007; 370: 143-52.

This was at the time of publication the largest-ever trial in aCRC. Multiple references in NICE guidance, reviews and meta-analyses.

3) Seymour MT, Thompson LC, Wasan H, et al, on behalf of the FOCUS2 Investigators and the National Cancer Research Institute Colorectal Cancer Clinical Studies Group. Chemotherapy options in elderly and frail patients with metastatic colorectal cancer (MRC FOCUS2): an open-label randomised factorial trial. Lancet 2011; 377: 1749-59.

The largest ever RCT focusing specifically on frail and elderly aCRC patients, who constitute around 40% of the aCRC population; extensively cited in SIOG guidance (the international society for geriatric oncology).

4) Maughan TS, Adams RA, Smith CG, Meade AM, Seymour MT, et al, for the MRC COIN Trial Investigators. Addition of cetuximab to oxaliplatin-based first-line combination chemotherapy for treatment of advanced colorectal cancer: results of the randomised phase 3 MRC COIN trial. Lancet 2011; 377: 2103-14.

This and a sister publication in Lancet Oncol (2011;12:642-53) together report COIN, which succeeded FOCUS as the largest-ever RCT in aCRC, and included two separate trial questions.

5) Braun MS, Richman SD, Quirke P, Daly C, Adlard JW, Elliott F, Barrett JH, Selby P, Meade AM, Stephens RJ, Parmar MK, Seymour MT. Predictive biomarkers of chemotherapy efficacy in colorectal cancer: results from the UK MRC FOCUS trial. J Clin Oncol 2008; 26: 2690-98.

Using samples collected in the FOCUS trial, we detected molecular correlates of treatment benefit which were then used to select stratification factors for the FOCUS3 trial.

6) Seymour MT, Brown SR, Middleton G, Maughan T, Richman S, Gwyther S, Lowe C, Seligmann JF, Wadsley J, Maisey N, Chau I, Hill M, Dawson L, Falk S, O'Callaghan A, Benstead K, Chambers P, Oliver A, Marshall H, Napp V, Quirke P. Panitumumab and irinotecan versus irinotecan alone for patients with KRAS wild-type, fluorouracil-resistant advanced colorectal cancer (PICCOLO): a prospectively stratified randomised trial. Lancet Oncol 2013; 14(8):749-59. doi 10.1016/S1470-2045(13)70163-3.

This was the first RCT in the world to use prospective molecular selection in advanced colorectal cancer. This publication reports the evaluation of anti-EGFR targeted therapy in patients with KRAS-unmutated tumours.

4. Details of the impact

This strategic programme of clinical and translational research into colorectal cancer led from Leeds has changed clinical guidelines and practice in this common cancer, nationally and internationally, benefitting thousands of patients.

Impacts on health and welfare

The MRC CRO7 trial (1) of preoperative radiotherapy, analysed together with a similar trial from The Netherlands, has changed clinical practice in the UK and across Europe by recommending its use in resectable rectal cancer [A, B]. Nationally this has resulted in an increase in the overall use of radiotherapy, and specifically in the one-week regimen used in CR07. Data from the National Bowel Cancer Audit for England & Wales [C] show that preoperative radiotherapy increased by 76% from 1022 patients in 2007/8 to 1803 patients in 2011. Over the same period, the use of the one-week radiotherapy regimen increased by 65% from 416 to 690 patients. In North America, where short-course radiotherapy was initially met with resistance, the 2013 National Comprehensive Cancer Network guidance now states: *"Short course RT gives effective local control and the same overall survival as more conventional RT schedules and may therefore be an appropriate choice"* [D]. Patient information from Cancer Research UK states: *"If your tumour can be operated on, you are likely to have a short course of five radiotherapy treatments in the week before surgery."*

Trials led by Seymour (2-4) established the "MdG" regimens for aCRC with high activity, good tolerability and reduced drug costs that are delivered on an outpatient basis. These regimens have been adopted in national guidelines [E] and, as well as being received by over 5,000 patients in trials, they underpin the non-trial management of aCRC in most NHS Units in England & Wales. Figures from the national Systemic Anti-cancer Therapy Audit (which captured around one-half of all chemotherapy prescribing over 1 year) suggest that around 40,000 cycles of MdG-based regimens are received by 7,000 patients each year in England & Wales [F].

Although aCRC is moderately chemo-sensitive, eradication or permanent control of disease by drugs alone is rare. Because of the unwanted effects of drug therapy, and the development of drug resistance, oncologists and patients need to make informed choices of strategy, including the integration of drug and surgical therapy, the sequencing of available drugs and the option of drug-free treatment breaks. The series of national trials led and co-led by Seymour has made many contributions to the evidence-base to guide these decisions. Complex decision-making involves synthesis of data from many sources, but the contribution of his work is highlighted by the 16 references to FOCUS (2) alone in the current NICE colorectal guidance evidence review [E]. Similarly, the data from these trials is cited extensively in guidance documents outside the UK, in Europe, North America and elsewhere [G, H].

Survival for patients with metastatic colorectal cancer has improved from median of under a year in the 1990s to over 2 years today. Many factors have contributed to this, including the safe and practicable regimens and patient-centred management strategies developed and promulgated through Seymour's research [I].

The median age at death from colorectal cancer in the UK is 75 years, and median age at diagnosis of aCRC is around 73 years. However, the median age of participants in most RCTs in aCRC, even those without formal age restrictions, is 60-65 years. A UK survey in 2002 established that in research-active units around 50% of aCRC patients were being treated off-trial with lower-intensity schedules than those used in trials because of concerns from oncologists or patients themselves that full-intensity regimens would be unsuitable for them. FOCUS2, with a median age of 75, was the first RCT to target this population, using adapted lower-intensity regimens. It provides a unique data source and is used by many oncologists to guide treatment choices. Evidence from FOCUS2 is included in international colorectal guidance documents, including in the USA and Europe [G, J].

Seymour and Quirke initiated predictive biomarker studies from 1997, and in 2000 pioneered the inclusion of prospective consent for future translational research within a trial, FOCUS. This

practice is now standard in cancer trials. The translational outputs from FOCUS led to the design of two pioneering prospective stratified medicine trials, FOCUS3 and FOCUS4. In PICCOLO we identified, within the KRAS-wt population, 30% patients with mutations predicting non-response or harm with anti-EGFR antibody therapy – a finding with important consequences for influencing future practice. Commercial laboratories worldwide, responding to these and other corroborating data, have expanded their mutation panels for molecular stratification of colorectal cancer patients [K].

Impacts on practitioners and services

Sebag-Montefiore and Quirke are members of the Steering Committee and Teaching Faculty for the national programme for low rectal cancer (LOREC) in England. Between 2010 and 2012 it trained 147/164 multidisciplinary rectal cancer teams in England in improved surgical techniques and selection of patients for preoperative radiotherapy.

5. Sources to corroborate the impact

A) Scottish Intercollegiate Guidelines Network (SIGN) 126, 2011: Diagnosis and Management of colorectal cancer. (www.sign.ac.uk/guidelines/fulltext/126/index.html)

B) ESMO Clinical Practice Guidelines - Rectal cancer; diagnosis treatment and follow-up, 2013. (http://www.esmo.org/Guidelines-Practice/Clinical-Practice-Guidelines/Gastrointestinal-Cancers/Rectal-Cancer)

C) National Bowel Cancer Audit (please compare data for successive years from 2007). (http://www.hscic.gov.uk/searchcatalogue?q=title%3A%22bowel+cancer%22&area=&size=10&sort=Relevance)

D) National Comprehensive Cancer Network (NCCN) Clinical practice guidelines in Rectal Cancer, V.1.2014, MS-16 (http://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf)

E) NICE review of colorectal cancer management (http://www.nice.org.uk/nicemedia/live/13597/57047/57047.pdf)

F) Systemic Anti-cancer Therapy Audit. Go to http://www.chemodataset.nhs.uk/home and select “Top Regimens” then “Lower GI” and “colorectal” to show data.

G) European Society for Medical Oncology (ESMO) Consensus Guidelines: management of patients with colon and rectal cancer – a personalised approach to clinical decision making. doi: 10.1093/annonc/mds236 (http://annonc.oxfordjournals.org/content/23/10/2479.long)

H) National Comprehensive Cancer Network (NCCN) Clinical Practice guidelines in Colon Cancer, Version 1.2014. (http://www.nccn.org/professionals/physician_gls/pdf/colon.pdf)

I) Letter from National Cancer Director to corroborate contributions in colorectal cancer and attribute improved outcomes to a significant degree to Leeds-led research.

J) National Comprehensive Cancer Network (NCCN) Clinical practice guidelines in Senior Adult Oncology, version 2.2014, SAO.B-9 & MS-26 (available at http://www.nccn.org).

K) Recommendations of the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group. (http://www.nature.com/gim/journal/v15/n7/full/gim2012184a.html)