Institution: University of Southampton		
Unit of Assessment: 01 Clinical Medicine		
Title of case study: 01-08 Changing treatment paradigms in gastrointestinal cancers		
Period when the underpinning research was undertaken: 2003 – 2019		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	**Role(s) (e.g. job title):**	**Period(s) employed by submitting HEI:**
John Primrose	Professor of Surgery	October 1993 – present
Timothy Iveson	Honorary Senior Lecturer (Category C, RAE 2008); Professor of Gastro-intestinal Oncology	October 2002 – July 2020 July 2020 – present
Period when the claimed impact occurred: January 2014 – December 2020		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the impact

University of Southampton research has defined new standards of care and changed clinical practice for cancers of the gastrointestinal (GI) tract worldwide.

Through large scale clinical trials and other studies, Southampton research has improved follow up protocols for patients with colorectal cancer; defined new standards of care for biliary tract cancer; reduced chemotherapy treatment time; demonstrated harm from the use of epidermal growth factor receptor antibodies in the neo-adjuvant treatment of operable colorectal liver metastases and developed an evidence base and standards of training and care for minimally invasive surgery of the liver and pancreas.

Through these trials around 1.5 million patients annually now experience better treatment and care resulting in improved survival rates and substantial annual cost savings for global health care systems in the region of GBP2 billion.

2. Underpinning research

The University of Southampton's medical and surgical oncology research teams have together pursued a strategy of undertaking large-scale multicentre clinical trials combining clinical end point with exploratory translational analyses. The work has focused on colorectal cancer, a common cancer with high societal impact, and rarer conditions of unmet need such as biliary tract cancer, resulting in clinical trials that have changed clinical practice around the world.

The Follow-up After Colorectal Surgery (**FACS**) trial (2003–2014) [**3.1**], led by Professor John Primrose, was a 2x2 factorial UK wide trial examining the use of CT and tumour marker examination, serum carcinoembryonic antigen (CEA). In the follow up of 1,202 patients with completely resected colorectal cancer, results showed that more intensive monitoring is of no benefit to the patient, so cost and patient inconvenience can be reduced markedly.

The MRC Short Course Oncology Therapy (**SCOT**) study (2008 to date), led by Professor Tim Iveson, is the largest trial of adjuvant chemotherapy in colorectal cancer ever conducted (6,088 patients from 244 centres in six countries) and has demonstrated that for most patients, three months treatment after surgery is enough compared to the previous treatment duration of six months [**3.2**]. Combining the findings in the SCOT study with five other concurrently conducted randomised controlled trials in a predefined analysis, Iveson went on to define a new worldwide standard of sub-dividing Stage III colon cancer according to risk of recurrence. The pre-planned pooled analysis of the adjuvant studies (the IDEA Collaboration [**3.3**]) included 13,025 patients and was subject to a linked editorial by Richard L. Schilsky on behalf of the American Society of Clinical Oncology, the pre-eminent oncology association globally.

The New EPOC trial (Primrose/Iveson, 2005 to date), involving 257 patients with metastatic colorectal cancer, demonstrated that adding the epidermal growth factor receptor antibody cetuximab to conventional chemotherapy (as commonly practiced globally until now) counter-intuitively resulted in a two-year detriment in overall survival in patients with resectable colorectal

liver metastases [**3.4**, **3.5**]. Analysis shows that this is due to rapidly progressive multisite recurrence. A biomarker for "harm" (Mir-31-3p) has been identified, in work led by Southampton researchers and this biomarker has wider application [**3.6**].

The BILCAP trial (2004–2009, Primrose/Iveson) examined the use of capecitabine chemotherapy in patients with resected biliary tract cancer. Up to this point patients had not received any post-operative treatment and were subject to clinical observation only. In total 447 patients were enrolled between 2006 and 2014 from 44 UK centres. In a pre-planned analysis conducted in March 2017 when median follow-up had reached 60 months (five years), the BILCAP study demonstrated a 16-month improvement in overall survival with adjuvant chemotherapy but no major toxicity [**3.7**].

Primrose and colleagues have critically examined the development of minimally invasive surgery in liver and pancreas [**3.8**] including within two CRUK-funded trials (ORANGE 2 and ORANGE SEGMENTS). They have established guidelines to enable safer introduction of the technologies through two global consensus conferences.

3. References to the research

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phase 3 study. Lancet Oncol. 2019 May;20(5):663-673. Epub 2019 Mar 25. https://doi.org/10.1016/S1470-2045(18)30915-X

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Related grants, Primrose

- FACS Trial HTA 2003 GBP1.5m over 10 years, extension 2012, two grants of GBP120,000 each for translational proposals
- New EPOC (perioperative chemotherapy in patients with operable colorectal liver metastases). CRUK 2006, 6 years GBP495,000
- BILCAP Trial (adjuvant chemotherapy and resected biliary tract cancer) CRUK 2004, 5 years, GBP300,000, extension 2011 GBP50,000
- EPOC B (an exploratory trial examining the scheduling of perioperative chemotherapy for colorectal liver metastases). CRUK 2010, 2 years GBP47,000
- Trans EPOC. CRUK 2008, funding of GBP138,000 over 5 years
- Trans-BILCAP. CRUK 2007 funding of GBP34,000 over 3 years for sample collection associated with the BILCAP trial
- Orange 2 Trial (laparoscopic v open liver resection), CRUK GBP80,000, 2015
- ACTICCA-01:Adjuvant chemotherapy with gemcitabine and cisplatin compared to observation. CRUK GBP483,000, 2013
- Orange Segments Trial, CRUK, GBP83,000, 2017

Related grants, Iveson

- SCOT 2008 MRC GBP3,061,732 (subsequently transferred to NIHR NETSCC) 96 months
- SCOT 2013, Extension NIHR HTA, GBP274,695, 36 months

4. Details of the impact

Gastrointestinal clinical cancer research designed, led and delivered by University of Southampton researchers has, since 2014, directly included over 14,000 people and changed practice in multiple domains, resulting in better patient outcomes and estimated world-wide cost savings of approximately GBP2,000,000,000 per year.

Colorectal cancer

In colorectal cancer, a disease that affects 1.4 million people a year globally, Southampton researchers have performed the definitive studies in treatment and follow-up after surgery. The FACS trial has set the standard on the follow up of patients with resected colorectal cancer and has informed all guidance on colorectal cancer follow up globally since the results were published in 2014, including NICE Guidance NG151 [**5.1**]. This recommends the follow-up protocol tested in the FACS trial: “For people who have had potentially curative surgical treatment for non-metastatic colorectal cancer, offer follow-up for detection of local recurrence and distant metastases for the first 3 years. Follow-up should include serum CEA and CT scan of the chest, abdomen and pelvis”. In a 2018 analysis of 21 national guidelines from countries represented in the European Society of Coloproctology [**5.2**], the guidelines committee recognised the singular importance of the FACS trial findings as underpinning follow up protocols including CEA testing and CT scans. Adherence to these protocols has been subject to published nation-level audits in countries including the Netherlands, where guidance is based specifically on FACS, and Norway which is proposing reducing intensity of guideline. The lower intensities of follow up have equal efficacy in detecting recurrence and have identical overall survival. A 2017 economic analysis [**5.3**] suggests a saving of around GBP2,000 per patient suitable for reduced surveillance (20,000 annually) resulting in around GBP40,000,000 per year saving in the UK alone, mainly by reducing the number of CTs. Globally around a million patients will suffer colorectal cancer requiring follow-up, and hence very substantial global savings could be expected depending on local practices.

Chemotherapy following potentially curative surgery has been shown to improve survival in many cases of colorectal cancer, but at the cost of significant toxicity. The toxicity relates to duration of chemotherapy but until now the duration to achieve efficacy was unknown. In combination the MRC SCOT and the IDEA Collaboration studies included over 13,000 people with stage III colorectal cancer from around the world. Results were immediately incorporated into national and international guidelines 2018-2019 [**5.4**, **5.5**]. NICE Guidance NG151 (2020) [**5.1**], makes recommendations based directly on the SCOT study findings: "Halving the standard care from six months to three months (for people who can have CAPOX) will reduce treatment time and costs, meaning people have chemotherapy side effects for a shorter time, and will lower the incidence of long-term toxicity (neuropathy) and its consequences". Analysis undertaken in 2020 of these findings [**5.6**] concluded that the survival difference between three and six months was minimal, especially if CAPOX is used, but the toxicity markedly reduced with three months treatment. An economic analysis of SCOT [**5.7**] suggests a saving of GBP4,881 which, applied globally to 700,000 stage 3 patients annually (based on a conservative estimate of 50% of patients receiving post-operative chemotherapy) results in a saving of approximately GBP1,700,000,000 per year.

There are around 3,200 patients annually in the UK with operable colorectal liver metastases. These patients were commonly treated with neoadjuvant chemotherapy to treat micro-metastatic disease, and increasingly with an anti-epidermal growth factor receptor antibody, cetuximab. The New EPOC study demonstrated the harm in the use of cetuximab in patients with operable colorectal liver metastases, resulting in a two-year reduction in median overall survival and a 15% reduction in survival at five years. As this schedule was commonly used, changing practice has had major impact on the survival of patients in this cohort globally. The 2016 guidelines of the European Society of Medical Oncology (ESMO) [**5.8**] makes the change in practice clear, stating: "EGFR-targeting monoclonal antibodies (cetuximab and panitumumab) are not to be used in this setting, based on the data from the New EPOC trial". This is further supported by a 2020 Lancet editorial [**5.9**]. Based on UK rates of operable colorectal liver metastases, 240 lives are saved every year by not using cetuximab. This increases into the thousands when applied globally.

Biliary Tract cancer

The BILCAP trial showed that adjuvant capecitabine following surgery for biliary tract cancer improved median overall survival by 16% with no measurable reduction in quality of life. Treatment was well tolerated. The result of the study was published in 2019 [**5.10**] and immediately incorporated into standard of care in EUROPE and the USA; American Society of Clinical Oncology (ASCO) guidelines were also produced as a result of the trial outcome [**5.11**]. Based on a conservative estimate of 500,000 annual biliary tract cancer cases globally, implementation of this process around the world could result in a saving more than 4,000 lives every year in a disease with large unmet need and no major Pharma interest. A heath economic assessment suggested treatment was also highly cost effective at GBP2,725 per Quality Adjusted Life Year (QALY) [**5.10**].

Minimally invasive surgery

Minimally invasive surgery (MIS) is developing rapidly in surgery of the liver and pancreas but this is technology-driven with little evidence of patient benefit. Primrose and colleagues have led efforts in the UK to develop an evidence base and standards of training and care in this area. The group have led three randomised trials, one completed (ORANGE 2), and two ongoing (ORANGE SEGMENTS and DIPLOMA). The University of Southampton (Primrose, Cook and colleagues) organised two global consensus conferences in MIS in liver (Southampton) and pancreas (Miami), which were attended by approximately 100 leading cancer experts. Guidelines have been developed from the events and set global standards for safe practice and training in these areas [**5.12**, **5.13**]. The recommendation for more research in MIS is included in the 2018 NICE guidance NG85 on pancreas cancer, which was chaired by Primrose [**5.14**].

5. Sources to corroborate the impact

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