

<p>Institution: University of Leeds</p>
<p>Unit of Assessment: UOA1 Clinical Medicine</p>
<p>Title of case study: Case Study 5. Pathology research led to an international reduction in rectal cancer recurrence and death by improving multidisciplinary clinical practice</p>
<p>1. Summary of the impact</p> <p>Postoperative local recurrence affects 20-30% of patients with rectal cancer. Between 1993 and 2013, University of Leeds researchers identified the importance of pathology studies to show a disease-free margin around the excised tumour and how to predict this margin routinely and accurately using simple histopathology and preoperative MRI.</p> <p>We also used photography in the pathological assessment of the quality of surgery and were instrumental in the adoption of modern techniques by professional organisations around the world.</p> <p>Following adoption of our techniques in England and Scotland, local recurrence has halved with 10% better survival and cost savings of £60 million. Our methods have also become the gold standard in the treatment of rectal cancer patients around the world.</p>
<p>2. Underpinning research</p> <p>Rectal cancer is common with 14,999 cases annually in the UK and 446,400 globally. Around 20-30% of patients develop pelvic local recurrence, which can lead to a very painful and unpleasant death six to nine months later. More than 90% of individuals with pelvic local recurrence die within three years of initial surgery.</p> <p>In 1994 Phillip Quirke (Professor of Pathology 1982 to present), Michael Dixon (Professor of Gastrointestinal Pathology 1970 to 2001), David Johnston (Professor of Surgery, 1977-1998) and others at the University of Leeds published research showing that local recurrence of rectal cancers was due to inadequate resection at the circumferential surgical margin.¹ In this prospective study of 190 patients with rectal cancer we developed a simple routine dissection method for identifying tumour at the circumferential margin and showed that it was present in 25% of specimens where the surgeon thought the resection was potentially curative and 36% of all cases. This work also showed that inadequate resection at the circumferential surgical margin predicted local recurrence and survival fell from 66% to 15% and that NHS histopathologists could use this method to predict prognosis.</p> <p>Subsequent work (also by Professors Quirke, Johnston and Dixon) published in 2002 showed that frequency of circumferential surgical margin involvement varied between surgeons and was dependent on how well total mesorectal excision was performed.² Our work showed surgical skill was associated with rates of local recurrence and individual patient survival both of which could be improved with better dissection technique.</p> <p>Professor Quirke developed a simple photographic method for grading the quality of total mesorectal excision. The MRC CR07 trial in 2009 showed quality of surgery assessed this way predicted outcomes at three years³, and this was confirmed in the Dutch Total Mesorectal excision +/- radiotherapy trial surgical specimens reviewed by Quirke.</p> <p>In collaboration with Professor Bill Heald and Mr Brendan Moran (Pelican Centre, Basingstoke) and Dr Gina Brown (Royal Marsden Hospital, London) we conducted the Mercury study showing circumferential surgical margin status can be accurately assessed and outcome predicted preoperatively by MRI.⁴</p> <p>One issue that became apparent during these studies in the early 2000s was that outcomes in patients with low rectal cancer did not improve with improved total mesorectal excision technique. Work by Professors Quirke, Johnston and Dixon, showed this was due to on going high rates of</p>

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circumferential surgical margin involvement (20-30%) and high perforation rates (20%) during abdominoperineal excision.⁵ This was confirmed in the Mercury trial in tumours < 6cm from anal verge.

In 2008, Professor **Quirke** with Paul **Finan** (Professor of Surgery, Leeds Teaching Hospitals NHS Trust [2010-present]) and Nicholas West (PhD student/Lecturer 2009-present) then showed through work in Leeds and a collaborative multinational study that a newer more radical approach (extralevator abdominoperineal excision) developed by Swedish surgeon Torbjorn Holm (Karolinska Hospital, Stockholm) reduced circumferential surgical margin positivity and perforations by excising more tissue around the tumour.⁶ The Mercury2 study has shown a relative reduction in CRM involvement by 55% based on this approach.

3. References to the research

- [1] Adam IJ, Mohamdee MO, Martin IG, Scott N, Finan PJ, **Johnston D, Dixon MF, Quirke P**. Role of circumferential margin involvement in the local recurrence of rectal cancer. *Lancet*. 1994; 10; 344(8924): 707-11.
- [2] Birbeck KF, Macklin CP, Tiffin NJ, Parsons W, **Dixon MF**, Mapstone NP, Abbott CR, Scott N, Finan PJ, **Johnston D, Quirke P**. Rates of circumferential resection margin involvement vary between surgeons and predict outcomes in rectal cancer surgery. *Ann Surg*. 2002; 235(4): 449-57.
- [3] **Quirke P**, Steele R, Monson J, Grieve R, Khanna S, Couture J, O'Callaghan C, Myint AS, Bessell E, Thompson LC, Parmar M, Stephens RJ, **Sebag-Montefiore D**; NCRI Colorectal Cancer Study Group. Effect of the plane of surgery achieved on local recurrence in patients with operable rectal cancer: a prospective study using data from the MRC CR07 and NCIC-CTG CO16 randomised clinical trial. *Lancet*. 2009; 373(9666): 821-28.
- [4] MERCURY Study Group. Diagnostic accuracy of preoperative magnetic resonance imaging in predicting curative resection of rectal cancer: prospective observational study. *BMJ*. 2006; 333: 779-78. **Quirke P** lead pathologist.
- [5] Marr R, Birbeck K, Garvican J, Macklin CP, Tiffin NJ, Parsons WJ, **Dixon MF**, Mapstone NP, **Sebag-Montefiore D**, Scott N, **Johnston D**, Sagar P, Finan P, **Quirke P**. The modern abdominoperineal excision: the next challenge after total mesorectal excision. *Ann Surg*. 2005; 242(1): 74-82.
- [6] **West NP, Finan PJ**, Anderin C, Lindholm J, Holm T, **Quirke P**. Evidence of the oncologic superiority of cylindrical abdominoperineal excision for low rectal cancer. *J Clin Oncol*. 2008; 26(21): 3517-22.

4. Details of the impact

Researchers at the University of Leeds clearly identified that widely used surgical techniques were associated with local recurrence and death in patients with rectal cancer. We developed simple routine methods for assessing tumour involvement in the circumferential surgical margin and showed how these could be used to predict local recurrence and survival and improve surgical performance. Our concepts of the importance of the circumferential surgical margin, Leeds dissection methods, photography of the quality of surgery, introduction of routine preoperative MRI, and best practice total mesorectal excision and extra levator excision methods have become the gold standard in the treatment of rectal cancer patients around the world.

Health and welfare

In the 1990s, patients diagnosed with rectal cancer faced a 20-30% risk of local recurrence, which in turn is associated with high rates of mortality and can be a very painful and unpleasant way to

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die.^{a,b} We were the first to conclusively show that not properly excising the tumour in the circumferential surgical margin strongly influenced local recurrence and death, involvement was found in 25% of cases where the surgeon believed the operation had been curative. We also highlighted the importance of histological assessment in predicting recurrence and survival.

Our work has improved the surgical skills and techniques used in total mesorectal excision, abdominoperineal excision and the histology and imaging required to support and guide treatment. Through our studies showing MRI could be used before surgery to assess the circumferential surgical margin and predict outcome, this has become the standard approach in Europe^c and around the world. Patients can now be reassured that they are receiving the best possible surgical techniques which can be easily monitored and their chance of cure and survival have improved dramatically from that seen two decades ago.

In 2013 our techniques have led to an impressive 40-50% reduction in rates of local recurrence in curative surgery across England, Scotland, Sweden, Denmark, British Columbia, Slovenia, Belgium Norway^d and Spain^e and survival in curative cases improved by 8%^d. This means >1800 fewer patients suffering the consequences of local recurrence and >1,000 more surviving each year in the UK.

Society, culture and productivity

Between 2003-2006 we received £6 million in Department of Health funding to roll out the use of the histological, MRI and surgical techniques we had developed to 1,639 individuals from 183/186 English bowel cancer teams.^f Professor Quirke led the pathology training, Dr Gina Brown MRI and Professor Heald at the Pelican Centre, Basingstoke led on the surgery education programme. Between 2011 and 2013 funded by the NHS (£1 million) to provide LOW RECTal cancer courses throughout England training 1,045 staff of 147/151 English Trusts.

We conservatively calculate that each local recurrence costs the NHS more than £40,000 in direct medical expenses alone^f saving £60,000,000 per annum

NICE has recommended use of our concepts^g and the practice of all members of the multidisciplinary team in the NHS from surgeons, pathologists, radiologists and oncologists has radically changed.

By defining the planes of surgery seen after operations for rectal cancer and showing in a major clinical trial that rapid simple photographic audit (using low cost digital cameras or good quality mobile phones) of the quality of rectal cancer surgery was possible, we have revolutionised how these procedures are performed and assessed. This is now being investigated as a tool in other cancers such as pancreas, oesophageal and prostate.

Our methods have now been introduced into many professional guidelines around the world – both surgical^h and pathologicalⁱ and Trial protocols in England^j and Europe

In addition, we have actively disseminated these techniques and standards on six continents in conjunction with the Pelican Cancer Charity. Protocols, trial protocols and educational material have been made freely available on the web and by DVD. Countries we have run education programmes include many in Europe as well as Argentina, Chile, Russia, Toronto, USA with demand continuing to rise.

5. Sources to corroborate the impact

[a] **Medical Research Council Rectal Cancer Working Party. Randomised trial of surgery alone versus surgery followed by radiotherapy for mobile cancer of the rectum.**

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Lancet. 1996 Dec 14;348(9042):1610-4.

Describes the low survival and high local recurrence rate in this trial before knowledge of the importance of CRM, MRI and improved surgery.

[b] [Kodeda K](#), [Derwinger K](#), [Gustavsson B](#), [Nordgren S](#). Colorectal Dis. 2012 May;14(5):e230-7. doi: 10.1111/j.1463-1318.2011.02895.x. **Local recurrence of rectal cancer: a population-based cohort study of diagnosis, treatment and outcome.**

Describes the severity of local recurrence and the difficulty managing it even today if it is not avoided

[c] Valentini V et al; Scientific Committee. Multidisciplinary Rectal Cancer Management: 2nd European Rectal Cancer Consensus Conference (EURECA – CC2). Radiother Oncol. 2009 Aug; 92 (2): 148-63.

European consensus conference mandating our pathology, MRI and TME surgery to be updated in 2013

[d] [Bernstein TE](#), [Endreseth BH](#), [Romundstad P](#), [Wibe A](#); [Norwegian Colorectal Cancer Registry](#).

Improved local control of rectal cancer reduces distant metastases.

Colorectal Dis. 2012 Oct;14(10):e668-78. doi: 10.1111/j.1463-1318.2012.03089.x.

Description of local recurrence and survival in Norway over this period PQ trained Norwegian pathologists in his techniques

[e] [Impact Of A Multidisciplinary Team Training Programme On Rectal Cancer Outcomes In Spain](#).

Ortiz H, **Wibe A**, Ciga MA, Lujan J, Codina A, Biondo S; The Spanish Rectal Cancer Project. Colorectal Dis. 2013 Jan 25. doi: 10.1111/codi.12141.

Description of a repeat of the Norwegian project in Spain reproducing the improvements in Norway using our Pathology techniques, MRI and TME surgery

[f] [Miller AR](#), [Cantor SB](#), [Peoples GE](#), [Pearlstone DB](#), [Skibber JM](#).

Dis Colon Rectum. 2000 Dec;43(12):1695-1701; discussion 1701-3.

Quality of life and cost effectiveness analysis of therapy for locally recurrent rectal cancer.

[g] The National Institute for Health and Clinical Excellence (NICE). Colorectal cancer: the diagnosis and management of colorectal cancer. 2011.

<http://www.nice.org.uk/nicemedia/live/13597/56957/56957.pdf>

Recommends the use of our pathology techniques, preoperative MRI and TME surgery

[h] [Practice parameters for the management of rectal cancer \(revised\)](#).

Monson JR, **Weiser MR**, **Buie WD**, Chang GJ, Rafferty JF, **Buie WD**, Rafferty J; Standards Practice Task Force of the American Society of Colon and Rectal Surgeons.

Dis Colon Rectum. 2013 May;56(5):535-50. doi: 10.1097/DCR.0b013e31828cb66c.

Recommends the use of our methods for standard care in USA

[i] Royal College of Pathologists. Guidelines for dissection and reporting of colorectal cancer 2007.

<http://www.rcpath.org/resources/pdf/G049-ColorectalDataset-Sep07.pdf> (update due 2013) and College of American Pathologists Protocol for the Examination of Specimens From Patients With Primary Carcinoma of the Colon and Rectum

http://www.cap.org/apps/docs/committees/cancer/cancer_protocols/2012/Colon_12protocol_3200.pdf

[j] <http://www.philipquirke.com> Trial protocols of past and current phase III rectal cancer trials MRC Classic, MRC CR07, EME Rolar, NCRI Aristotle, NCRI Enrol, Trec, LOREC