Institution: University of Leeds

Unit of Assessment: UOA1 Clinical Medicine

Title of case study:

Case Study 3. Establishing the effectiveness of laparoscopic surgery for colorectal cancer leading to safer implementation into the NHS and world-wide for greater a patient benefit.

1. Summary of the impact

The MRC Conventional versus Laparoscopic-Assisted Surgery In Colorectal Cancer trial (CLASICC) is the largest and most successful UK trial of a technology applied to general surgery. It addressed an area of huge clinical uncertainty, providing a rigorous evaluation of a new technology and enabling its safe and widespread implementation. The impact of CLASICC has been global, confirming the advantages for patients (quicker recovery) and healthcare providers (cost-effectiveness) and so influencing national and international policy in favour of the laparoscopic technique. It informed NICE guidance and led to a major DH initiative that has seen the UK become one of the largest providers in the world of laparoscopic colorectal cancer surgery. CLASICC is regarded as a benchmark surgical trial, combining high quality trial design with rigorous quality assurance, which has informed the design of many subsequent colorectal cancer studies.

2. Underpinning research

The introduction of new technologies into surgical practice is seldom based on rigorous scientific evaluation. Such was the case for laparoscopic surgery in the 1980's. Although the potential benefits in terms of improved patient recovery were not in dispute, concerns were expressed regarding its safety, particularly in the treatment of malignant disease with early reports of unusual patterns of disease recurrence.

The MRC CLASICC trial was set up in 1996 to specifically address concerns regarding the safety and efficacy of the laparoscopic approach in colorectal cancer. Led by **Professor P.J.Guillou** (Prof. of Surgery - retired 2006), facilitated by **Professor D.G.Jayne** (Leeds/former MRC Clinical Research Fellow), and coordinated by **Professor J.M.B.Brown** (Director, Clinical Trials Research Unit, Leeds), this University of Leeds initiated, UK-wide, multicentre clinical trial recruited one of the largest cohorts of surgical patients (794 patients) to either laparoscopic or conventional open colorectal cancer surgery between 1996 and 2002.

The initial results, reported in the Lancet in 2005 (1), stimulated an Editorial and much exchange of international correspondence. Laparoscopic surgery was shown to be as safe as open surgery, but with short-term benefits for patients, and similar oncological outcomes. CLASICC was unique in the rigour of its trial design and quality control, combining for the first time centralised pathological review and evaluation of the quality of surgery (1, 2); a feature that has been widely adopted in the design of subsequent clinical trials and has become standard in routine NHS practice. The publication of the 3-year CLASICC results in 2007 (2), and subsequently the 5-year results in 2010 (3), confirmed long-term oncological safety and further reinforced positive world opinion towards laparoscopic surgery. It is now internationally acknowledged that laparoscopic surgery has benefits for patients without compromise to long-term outcomes. Any previous criticisms towards the laparoscopic approach have been dispelled, enabling its safe dissemination into routine care [A,B].

CLASICC was designed as a pragmatic trial, which has been instrumental in enabling the translation of its results to the wider surgical community. It was also comprehensive in its evaluation, which has enabled valuable information to be gained about the broader benefits of the laparoscopic approach. It has provided information on cost-effectiveness (4), predictors of conversion to open surgery (5), sexual and bladder function following rectal resection (6), and benefits of the laparoscopic approach in the prevention of adhesive bowel obstruction and incisional herniation. The outputs from CLASICC, showing improved cost-effectiveness and better functional outcomes, have subsequently been confirmed by other studies.

Until 2013, CLASICC was the only randomised, multicentre trial to evaluate the laparoscopic approach for rectal cancer and thus provided the only randomised data to inform healthcare policy. It showed that the laparoscopic approach was feasible and potentially beneficial in rectal cancer surgery, and that with certain caveats it could be recommended for routine application. The findings were endorsed in 2013 with the publication of a large, multicentre European study (COLOR II).

CLASICC set the standard for evaluating new surgical techniques by randomised comparison. As the foremost clinical trial in laparoscopic colorectal cancer surgery, it set the benchmark in trial design for other colorectal cancer studies around the world (NMRC-Singapore trial, European COLOR II [L],US NIH ACOSOG-Z6051) [K]. International collaboration led to a large transatlantic meta-analysis that revealed the biases present in other smaller, single institution studies. The expertise gained from CLASICC has been instrumental in developing follow-on research initiatives, which include the MRC/EME/NIHR ROLARR trial; a pan-World randomised controlled trial evaluating robotic-assisted with laparoscopic surgery for rectal cancer.

3. References to the research

1) **Guillou PJ, Quirke P, Thorpe H, Walker J, Jayne DG, Smith AHM, Heath RM, Brown JM**. Short-term endpoints of conventional versus laparoscopic-assisted surgery in patients with colorectal cancer (MRC CLASICC Trial): multicentre randomised controlled trial. The Lancet 2005; 365:1718-1726.
Publication showing that laparoscopic surgery is as effective as open surgery for the treatment of colorectal cancer. Unique pathological assessment demonstrating high quality laparoscopic resections.

2) **Jayne DG, Guillou PJ, Thorpe H, Quirke P, Copeland J, Smith AHM, Heath RM, and Brown JM**. Randomized Trial of Laparoscopic-Assisted Resection of Colorectal Carcinoma: 3-Year Results of the UK MRC CLASICC Trial Group. J Clin Oncology 2007; 25: 3061-68.

doi:10.1200/JCO.2006.09.7758.
Publication showing that the mid-term results of laparoscopic surgery are at least as good as open surgery for colorectal cancer. Concerns about higher local recurrence following laparoscopic rectal cancer resection disproven.

3) **Jayne DG, Thorpe HC, Copeland J, Quirke P, Brown JM, Guillou PJ.** Five year follow-up of the Medical Research Council CLASICC trial of laparoscopically assisted versus open surgery for colorectal cancer. Br J Surg. 2010; 97: 1638-45. doi:10.1002/bjs.7160.
Publication showing that the use of laparoscopic surgery to maximise short-term outcomes for colorectal cancer does not compromise long-term oncological results. Conversion from laparoscopic to open surgery associated with worse overall but not disease-free survival.

4) Franks PJ. Bosanquet N. **Thorpe H. Brown JM. Copeland J. Smith AM. Quirke P. Guillou PJ.** CLASICC trial participants. Short-term costs of conventional vs laparoscopic assisted surgery in patients with colorectal cancer (MRC CLASICC trial). British Journal of Cancer. 95(1):6-12, 2006. doi:10.1038/sj.bjc.6603203.
Publication documenting the short-term cost effectiveness of laparoscopic surgery for colorectal cancer.

5) **Thorpe H, Jayne DG, Guillou PJ, Quirke P, Copeland J, Brown JM**. Patient factors influencing conversion from laparoscopic assisted to open surgery for colorectal cancer. Br J Surg. 2008; 95: 199-205. PMID:17696215
Publication identifying those patients most likely to benefit from laparoscopic surgery for colorectal cancer. Establishes selection criteria for the laparoscopic approach, helping to avoid unplanned conversion to open surgery with documented worse overall survival (established in [4], above).

6) **Jayne DG**, **Brown JM**, **Thorpe H, Walker J, Quirke P, Guillou PJ.** Bladder and sexual function following resection for rectal cancer in a randomized clinical trial of laparoscopic versus open technique. Br J Surg. 2005; 92(9): 1124-32. PMID:15997446
Publication highlighting the need for high quality laparoscopic rectal cancer surgery to minimise the risk of postoperative bladder and sexual dysfunction.

Further **successful grant applications** which built on the success of CLASICC include:

- MRC: Adhesive complications after open and laparoscopic surgery. (CI: **Prof. PJ Guillou**)
- MRC/EME/NIHR: ROLARR trial: Robotic rectal cancer surgery (CI: **Prof. D.G.Jayne**).
- MRC/EME/NIHR GLiSten trial: Fluorescence guide surgery (CI: **Prof. D.G.Jayne**).

4. Details of the impact

CLASICC conclusively demonstrated: the technical and oncological safety of laparoscopic colorectal cancer surgery; benefits for patients (including improvements to quality of life outcomes) and healthcare providers (including health economics needed to guide policy decisions and

effective criteria for patient selection for laparoscopic surgery).

Impact on guidance and service delivery

These outcomes had a direct bearing on the attitudes of surgeons and healthcare providers. In 2000, at the time CLASICC was recruiting, NICE guidance recommended "*open rather than laparoscopic resection should be the preferred surgical procedure*" for patients with colorectal cancer [A]. Six years later, CLASICC was one of only 7 RCTs, and the only RCT to include rectal cancer, included in a NICE meta-analysis that subsequently informed the updated NICE 2006 guidance [B]. The result was a step change in recommendation to "*laparoscopic surgery [should now be] recommended as an alternative to open resection for individuals with colorectal cancer*". The implication was that, where appropriate, laparoscopic surgery should be made available throughout the NHS for all patients with colorectal cancer. Given that colorectal cancer is the third most common cancer in the UK, affecting just under 40,000 people a year, this has far reaching implications for the NHS. CLASICC documented the potential benefits to health care providers through improved efficiency and cost-savings [J], corroborating those outlined in the NICE 2006 meta-analysis: laparoscopic surgery results in a reduction in hospital stay of 1.4 bed-days/patient, with the potential to increase to 4-10 bed-days/patient [B, F]. With ~ 30,000 patients undergoing colorectal cancer surgery every year, at a bed-day saving of 1.4 days per patient, this equates to ~17,000 bed-days saved per year, or around £7.5M saved per annum. Society at large has also benefited with patients and families returning to normal activity sooner, and a quicker return to work for those in employment.

Impact on Policy

CLASICC played an instrumental role in changing healthcare policy throughout the UK and internationally. Without the rigorous evaluation of all aspects of laparoscopic colorectal cancer surgery (technical, oncological, functional, health economics) it is unlikely that its implementation would have quadrupled from 10% in 2009 to over 40% in 2012. The change in NICE guidance in 2006 persuaded the Department of Health (DH) to launch a £20 million initiative in 2008 to promote laparoscopic colorectal cancer surgery throughout the NHS (LAPCO) [E]. A letter to NHS Chief Executives from the National Cancer Director outlined the need for a national training programme, and highlighted the potential cost-savings and the obligation of PCTs to fund and to make laparoscopic colorectal cancer surgery "normally available" [F]. LAPCO has successfully trained over 300 colorectal surgeons in laparoscopic colorectal cancer surgery.

Impact on clinical practice and patient outcomes

CLASICC has allowed laparoscopic colorectal cancer surgery to be safely disseminated throughout the NHS, in accordance with NICE guidance. More patients now enjoy the benefits of the laparoscopic approach. Laparoscopic resections undertaken in the NHS have increased from 10% in 2009 to 40% by 2012, which equates to ~9,000 additional patients per annum benefitting from the laparoscopic approach; a trend that has been confirmed using national NHS HES data [G]. This means that ~9,000 patients per annum are recovering quicker from surgery, spending 1 - 2 days less in hospital, and returning to normal activities several weeks earlier. Laparoscopic surgery for colorectal cancer is fast becoming the standard of care throughout the NHS, with the 40% UK adoption rate being one of the highest in the world. The realisation that minimally invasive techniques, such as laparoscopic surgery, reduces surgical trauma and facilitates patient recovery was embraced as a central component of the National Enhanced Recovery Programme, supported by the NHS Institute for Innovation and Improvement and the NHS Cancer Action Team [H]. The combination of laparoscopic surgery and improved perioperative management is considered the current gold standard for major colorectal surgery, with the potential to further reduce in-patient stays.

The successful implementation of laparoscopic surgery, supported by CLASICC, has lead to the evaluation of other technologies to further improve patient outcomes in colorectal cancer surgery. Robotic-assistance may improve the capabilities of laparoscopic surgery and increase the number of suitable patients. This is currently being tested in a follow-on study to CLASICC undertaken by the University of Leeds: the MRC/EME/NIHR ROLARR trial, a pan-World randomised controlled trial comparing robotic-assisted with laparoscopic surgery for rectal cancer [I]. ROLARR is at the forefront of surgical clinical trials research and is likely to be as influential as CLASICC.

Impacts on International development

Internationally, the CLASICC has become a benchmark study for the design of other colorectal cancer trials. These included an NCI multi-centre US trial to gain further information about laparoscopic surgery in rectal cancer [C] and the European COLOR II study. CLASICC has informed policy decisions across the globe, for example being cited in the 2012 US Position Statement on laparoscopic surgery for curable colon and rectal cancer [D]. It has lead to laparoscopic surgery being accepted in many different healthcare systems as the preferred treatment for colorectal cancer. CLASICC is frequently cited as a point of reference in many colorectal cancer publications and continues to be upheld as example of rigorous evaluation of surgical technology that influenced surgical cancer care.

5. Sources to corroborate the impact

[A] NICE Technology Appraisal Guidance TA17. Guidance on the use of laparoscopic surgery for colorectal cancer. December 2000. http://publications.nice.org.uk/laparoscopic-surgery-for-colorectal-cancer-ta17 *National guidance against the use of laparoscopic surgery for colorectal cancer, issued in 2000 prior to the publication of CLASICC.* (Guidance 1.1)

[B] NICE Technology Appraisal Guidance TA105. Laparoscopic surgery for colorectal cancer. August 2006. *National guidance in support of the use of laparoscopic colorectal cancer surgery, issued following CLASICC – a step change from previous guidance issued in 2000.* (Guidance 1.1) http://publications.nice.org.uk/laparoscopic-surgery-for-colorectal-cancer-ta105, page 4.

[C] Laparoscopic-assisted resection or open resection in treating patients with stage IIA, stage IIIA, or stage IIIB rectal cancer. www.clinicaltrials.gov NCT00726622. *The US multi-centre trial, set-up in 2008, and inspired by CLASICC to evaluate laparoscopic with open surgery for rectal cancer.*

[D] Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) Evidence-Based Guidelines for the Laparoscopic Resection of Curable Colon and Rectal Cancer. http://www.sages.org/publication/id/32/ *2012 US guidance in support of laparoscopic surgery for colorectal cancer, citing CLASICC outcomes.*

[E] LAPCO: National training programme in laparoscopic colorectal surgery http://www.lapco.nhs.uk/ *The national training programme in laparoscopic colorectal cancer instigated by the National Cancer Director following the reporting of CLASICC and evidence of the influence of CLASICC in changing national strategic health policy. Over 300 UK colorectal surgeons trained in laparoscopic surgery.*

[F] Letter from DH National Cancer Director to NHS Chief Executives - *outlining the need for a national training programme in laparoscopic colorectal cancer surgery based on NICE evidence, the potential cost-savings, and the obligation of PCTs to fund the programme to make laparoscopic colorectal cancer surgery "normally available" (2008).* DH gateway 10945

[G] Morris,E.J; Jordan,C; Thomas,J.D; Cooper,M; Brown,J.M; Thorpe,H; Cameron,D; Forman,D; Jayne,D; Quirke,P; CLASICC trialists Comparison of treatment and outcome information between a clinical trial and the National Cancer Data Repository. Br J Surg 2011; 98: 299-307. *Evidence of the trend to increased penetration of laparoscopic colorectal cancer surgery performed within the NHS subsequent to CLASICC.* PMID: 20981742

[H] Department of Health, Enhanced Recovery Programme http://webarchive.nationalarchives.gov.uk/+/www.dh.gov.uk/en/Healthcare/Electivecare/Enhancedrecovery/index.htm *Department of Health policy, initiated in 2011, to integrate laparoscopic surgery with enhanced recovery programmes for major surgery. Highlights the beneficial role of laparoscopic surgery in a package as standard of best care.*

[I] Collinson FJ, Jayne DG, Pigazzi A et al. An international, prospective, multicentre, randomised, controlled, unblended, parallel group trial of robotic-assisted versus standard laparoscopic surgery for the curative treatment of rectal cancer. Int J Colorectal Dis. 2012. 27(2): 233-241. *ROLARR trial protocol. ROLARR builds on the success of CLASICC, has only been possible as a result of its success, and will likely be as influential as CLASICC.* PMID: 21912876

[J] Franks PJ. Bosanquet N. Thorpe H. Brown JM. Copeland J. Smith AM. Quirke P. Guillou PJ. CLASICC trial participants. Short-term costs of conventional vs laparoscopic assisted surgery in patients with colorectal cancer (MRC CLASICC trial). British Journal of Cancer. 95(1):6-12, 2006. *Manuscript from CLASICC detailing health economic benefits arising from laparoscopic surgery.* PMID: 16755298