

**Submission to the National Institute
for Health & Clinical Excellence**

**Laparoscopic Surgery for the
Treatment of Colorectal Cancer**

Review of Guidance No. 17

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1 Introduction

The EES submission is restricted to presenting the key issues identified for consideration, and presenting the context within which we feel those clinical and economic issues would be best considered. All of the clinical trials are in the public domain, or being provided to the Institute from their academic sponsors. Similarly, as the Review Group has already committed to developing a robust economic model we have not developed our own.


In summary, it is considered the evidence demonstrates that:

- Long-term clinical outcomes between open and laparoscopic (LAP) colorectal surgery are equivalent
- Short-term clinical outcomes favour the laparoscopic approach
- Hospital Episode Statistics demonstrate that there is significant room for improvement in terms of managing hospital length of stay for colorectal procedures, where the average length of stay is over 17 days
- The study by King *et al* demonstrates what can be achieved in the NHS, through the use of laparoscopic surgery and an enhanced recovery programme. A median length of stay of 5.2 days has been reported for LAP patients, 7.4 days for open patients. Mean NHS costs were equal in the 2 groups
- Review of published studies report that the conversion rate (*of intended LAP cases to open procedures*) is a key driver of total cost
- Conversion rates can be kept within single figures through appropriate training, preceptorship and case selection during the learning curve. Positive guidelines have been developed by the ALSGBI & ACPGBI
- Accepting the above conditions, the laparoscopic procedure would be a cost effective alternative for patients within the NHS, and cost saving from the societal perspective

2 Long Term Clinical Outcomes

2.1 3 year clinical outcomes from 4 key studies

The original guidance, no 17, identified that longer-term outcomes data were required. An (independent) patient level meta-analysis of 4 of the largest studies (COLOR, CLASICC, COST & Barcelona trials) has now been undertaken and reports on 1,536 patients.¹

 In the Barcelona trial, a benefit in oncological-related survival was also demonstrated for patients with stage III tumors, $p=0.006^2$. This study also demonstrated the lowest conversion rate, 11% compared with combined 19% average.

Short-term benefits of LAP surgery are summarised in section 4.

3 Contextual Issues Relevant to Review

3.1 Learning Curve, Education & Training

It is acknowledged that there is a significant learning curve for colorectal surgery, and that the learning curve is closely linked to the conversion rates in laparoscopic surgery.^{3,4} Specifically, the paper by Tekkis *et al* demonstrated that key predictors leading to conversion (from a laparoscopic to open procedure) are surgeon seniority, type of resection, and patient selection.

The Association of Laparoscopic Surgeons of Great Britain and Ireland (ALSGBI) and the Association of Coloproctology of Great Britain and Ireland (ACPGBI) give clear recommendations on training and mentoring. These include the advice that a Consultant surgeon attend two training courses and complete 10 live cases prior to taking a preceptorship in LAP surgery. In the UK, some of the medical device companies run courses and wet labs to support this recommendation. During the preceptorship, the surgeon should then perform 2-4 procedures in the hospital of the Preceptor (who themselves should have experience of > 100 resections). Following the preceptorship, surgeons should complete 20 or more uncomplicated resections before attempting more complex resections, to reduce the risk of conversions to open surgery. Industry has worked with the ALSGBI and ACPGBI to establish suitable preceptorship programmes.

3.2 Impact of learning curve on conversion rate: interpretation of CLASICC and COLOR

The CLASICC trial reported that the LAP procedure was not proven for routine use in rectal cancer.⁵ This a flawed interpretation of the evidence. There are no significant differences between open and LAP resections, so this conclusion is unjust and unproven. Letters from surgeons have been submitted to the journal.

Furthermore, benefits of laparoscopic surgery were offset in the CLASICC trial due to the high conversion rate. However **the study also reported that the rate of conversions fell by year of study, from 38% in year 1 to 16% in year 6**, thus showing the link between experience and outcomes, Figure 2. As the conversion rates decrease, the better clinical outcomes for the LAP group will be observed. Any potential differences are therefore considered to be an outcome of surgeon experience rather than any clinically relevant difference between colon and rectal disease. **The COLOR I trial⁶ also found that hospitals with higher caseloads appeared to be associated with lower conversion rates** and better short term outcomes compared to hospitals with medium and low caseloads, Figure 3.

Figure 2: CLASICC Conversion rate by Study Year

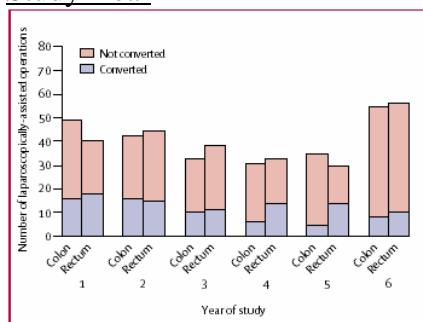
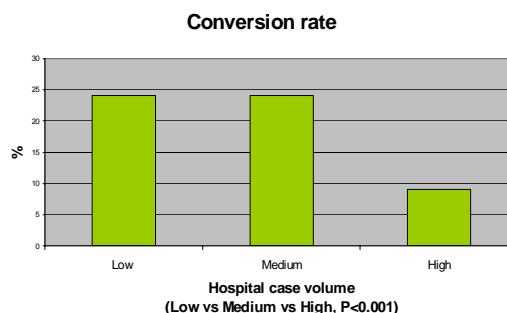


Figure 2: Intraoperative conversions by year of study

Figure 3: COLOR1 Conversion Rate by Recruitment Level



(Low vs Medium vs High, P<0.001)

3.3 Enhanced Recovery Programme

Fast track combines various techniques such as epidural analgesia, early enteral (oral) nutrition, early mobilization and revision of the surgical care program to facilitate early recovery after surgical procedures. Four studies^{7,8,9,10} have demonstrated that length of stay is reduced after open surgery by an enhanced recovery programme, and two studies^{11,12} reported that this programme could also be implemented with laparoscopic surgery accentuating the benefits of LAP surgery.

One RCT has compared open versus LAP procedures within an enhanced recovery programme.¹³ **This study demonstrates that LAP surgery still delivers benefits over open surgery in what could be considered to be best clinical practice in this area in the UK.**

3.4 The role of Hand-Assisted LAP Surgery

Virtually all LAP colorectal surgery for cancer involves some degree of ‘open assistance’ to the LAP procedure to facilitate specimen removal. How the specimen is removed depends on size, the bowel resection site, and the operation performed.

There are also devices available that allow the surgeon to use one hand as part of the laparoscopic procedure (e.g., LAPDISC distributed by EES). These devices are not widely used in the UK. Where used, they tend to be confined to specific circumstances, such as during complex cases when the alternative would be to convert to a full open procedure.

Two studies have been undertaken to compare the use of hand-assisted surgery with traditional LAP.^{14,15} These studies should however be interpreted within the light of how a device such as HALS is being used in clinical practice. It is not viewed as a device to replace standard LAP surgery, and therefore the studies do not reflect the average case hand-assist might be used in. The clinical trials demonstrate the general effectiveness of the approach, whereas current surgical opinion is that these devices may offer advantages in some specific areas, such as that mentioned above.

3.5 Economic Drivers of Laparoscopic Colorectal Surgery

Twenty-four papers and 4 reviews have reported on costs in LAP colorectal surgery. None of the papers attempt any cost effectiveness analysis. Most simply report cost minimization analyses. Although the longer-term outcomes of surgery are equivalent, if decisions are made purely on which procedure is cheaper, this in effect puts no value on the range of short-term benefits of LP surgery, which are discussed in section 4. Key economic drivers are presented below.

3.5.1 Length of Stay (LOS)

The majority of studies that have reported data on length of stay demonstrate a statistically significant reduction in favour of laparoscopic patients compared with open patients. The actual LOS and difference between the two groups varies widely across studies, however the trend to shorter LOS for LAP procedures is consistent. It is important to remember that length of stay will be influenced by many parameters, and not just the difference between the LAP and open procedures. Hospital discharge policies will also impact LOS.

A review of the English Hospital Episode Statistics data suggests that current clinical practice for colorectal surgery results in variable lengths of stay, and that there is room for the average

length of stay to be reduced substantially. The data reports the mean length of stay is approximately 17 days.^{1, 16}

Data from 2 UK centres confirm the ability of the LAP procedure to discharge patients in a shorter length of time, in a variety of settings. First, under traditional surgical practice, a review of treatment patterns at a UK teaching hospital confirms the HES open length of stay as 19.7 days, compared with 14.9 days in LAP patients (138 & 17 patients respectively, using the OPCS codes in 'i').¹⁷ Second, an RCT from a prominent UK centre demonstrated that a median length of stay of 7.4 days for open patients is achievable when used as part of an enhanced recovery programme (*Section 3.3*), which can be reduced further to 5.2 days when laparoscopic surgery is used in conjunction with the enhanced recovery programme.¹³

Note: A list of all studies identified reporting LOS, and a tabular output of their findings is available on request.

3.5.2 Conversion Rates

The conversion rate is potentially the biggest single cost driver in the relative cost effectiveness of the LAP procedure compared with open surgery, and so ensuring a low conversion rate is to the benefit of both the patient and the provider.

Of all papers reporting costs, 9 studies explicitly report costs according to an intention to treat analysis.^{13,18,19,20,21,22,23,24,25} Five of these studies demonstrated lower hospital cost for laparoscopic resection.^{13,19,20,21,25} Two demonstrated comparable cost,^{18,21} and two reported higher total hospital costs for the laparoscopic technique.^{23,24} When these studies are ranked by their reported conversion rate, a correlation appears.

Table 1: Conversion rate and impact on Total Hospital Cost

| Studies | Conversion rate | Hospital cost |
|-----------------------|-----------------|----------------------|
| Duepre et al.(2002) | 4.8% | <i>Lower for lap</i> |
| Yount-Fadok(2001) | 5.9% | |
| Senagore et al.(2002) | 6.6% | |
| King et al | 7.5% | |
| Delaney et al (2003) | NA | |
| Khalili et al.(1998) | 8% | Similar |
| Joo et al.(1998) | 17.4% | |
| Janson et al.(2004) | 14% | Higher for lap |
| Leung et al.(2004) | 23.2% | |

It is therefore considered that with the control of conversion rates, through appropriate training, mentoring and case-mix selection, the cost of laparoscopic surgery should be similar with or lower than open surgery.

Note: A complete reference list and tables highlighting total costs reported for each study and a list of all studies that report hospital length of stay is available on request. It is excluded here for brevity.

¹ Colorectal cancer surgery is normally captured in the clinical procedure OPCS4 codes H04 to H11 and H33. These clinical procedure codes map to HRGs F31 and F32, and the Hospital Episode Statistics (HES) data for 2003-2004 reports a mean length of stay of 18 and 17 days respectively.

3.5.3 Incisional hernia & adhesions

Incisional hernia and adhesion are two well-recognized consequences of surgery. **Five studies have reported high incidence rates of incisional hernia after open abdominal surgery ranging from 4.3% to 16.9%**^{26,27,28,29,30} **compared with under 1% port site hernia after laparoscopic surgery.**^{30,31,32,33,34} Furthermore, when reviewing the cause of adhesions, prior open surgery was found to be the cause in 93% of cases.³⁵ It has been suggested that LAP surgery might reduce the formation and the reformation of adhesion.^{36,37} Costs associated with the treatment of bowel obstruction caused by postoperative adhesions and incisional hernias are substantial.^{38,39,40,41,42,43,44} In particular, there are no ideal treatments for incisional hernia and recurrence rates after primary repair remain high.^{45,46,47,48,49,50,51} The Data from Scottish National Health Service indicated that one in three patients (34.6%) of 29,790 patients in the open surgery group experienced at least one further admission over a 10 year period.⁴⁴ **The costs of adhesions and incisional hernia should therefore be taken into consideration in any economic modeling undertaken for this review.**

Table 2: Financial cost of adhesions after open surgery

| Study | Country | Year | Admission Rate or Cost |
|---------|---------|---------|---|
| Wilson | UK | 1990-96 | Conservative £815/pt operative £1,965/pt |
| Menzies | UK | | Conservative: £1,606/pt operative: £4,677/pt |
| Ellis | UK | 1986-94 | 53.8% - 1 admission; 41.4% - 2-5 admissions 4.8% - >5 admissions |

3.6 King et al: Study demonstrating what can be achieved in the NHS

We propose that the most appropriate study that demonstrates what is achievable within the NHS, and the most appropriate cost analysis to inform this review is that recently undertaken by the East Somerset NHS Trust.¹³ This study reports an RCT comparing open surgery versus laparoscopic surgery for colorectal cancer embedded within an enhanced recovery programme. This is considered the most informative for the following reasons:

- All procedures were undertaken by one experienced surgeon – therefore removing confounders of learning curve and differences in practice
- Discharge policy was identical for all patients, and could not vary between centres as all were treated in the same centre
- The study was embedded in an enhanced recovery programme, so the emphasis was to discharge all patients as soon as possible. Even with this, the LAP procedure still managed to demonstrate a benefit

The results demonstrate that short term outcomes were better with LAP surgery, and that the LAP procedure, even when embedded within an enhanced recovery programme, still demonstrated equal costs from the NHS perspective compared with open surgery (LAP £5,986, Open £6,068). The LAP approach was cost saving when societal costs are taken in to consideration (LAP £6,433, Open £6,790). Finally, this result needs to be considered within the wider context of the NHS, where the average length of stay is presently longer, and therefore potential benefits of implementing LAP surgery are greater.

4 Short term Clinical benefits of Laparoscopic approach

The benefits of the LAP procedure observed in the short term are numerous, and evidence to support each outcome is listed below. The outcomes are difficult to roll in to a traditional

“QALY” estimate, and we request this be considered when the Committee is making its deliberations.

A large meta-analysis from Abraham *et al* has been conducted on 12 RCTs including 2,512 procedures.⁵² It confirms the numerous short-term benefits of LAP surgery regarding reduced wound infection rates, shorter time to passage of first flatus, to tolerance of solid diet, and to recovery of peak expiratory flow. Early narcotic analgesia requirements, pain at rest and during coughing and length of stay were also reduced.

4.1 GI function

Seven studies reported gastro-intestinal function resumption.^{24,53,54,55,56,57,58} Resumption of intestinal function is measured by several parameters: time to first bowel movement, first passage of flatus or defecation and time to resume intake of liquid or solid foods. **All seven studies demonstrated that that first passage of flatus or defecation was significantly faster after laparoscopic colorectal surgery compared with open surgery.**

4.2 Pulmonary function

Pulmonary function is impaired postoperatively after any abdominal surgery. Decline in pulmonary function in the immediate postoperative period is the major factor leading to postoperative morbidity after abdominal surgery and may lead to complications, such as atelectasis (collapsed lung), pneumonia, pulmonary embolism, hypoxemia leading to respiratory failure, and other complications, including death.

Two RCTs have investigated pulmonary function post surgery.^{57,59} **Both studies reported significantly less impaired pulmonary functions in comparison with open colorectal surgery;** they reported significantly better FEV1 for the LAP approach, and Schwenk *et al* also reported benefits in terms of FVC, PEF and FEF.

4.3 Immune Function & Stress Response

Immunosuppression is a decline in the functioning of the immune system and therefore results in less protection for the body from disease. Patients with more trauma induced by surgery are more likely to experience immunosuppression.

Of 5 studies that have evaluated postoperative stress response,^{15,54,60,61,62} 3 report significantly less intense inflammatory response after laparoscopic surgery.^{54,60,61} Acute phase-reaction has been measured in most studies by monitoring the levels of C-reactive protein (CRP) and interleukin-6 (IL-6). It is considered that the improved responses are an indicator of the milder surgical trauma inflicted by LAP than open colorectal resection.

4.4 Pain

Laparoscopic surgery causes less trauma, predominantly to the abdominal wall, than open surgery, and therefore is considered to result in less postoperative pain. The lower stress response after LAP colorectal surgery suggests that this approach might be less aggressive to the intra-abdominal organs as well.

Eight studies have reported on evaluations of postoperative pain.^{24,54,57,58,59,62,63,64} **All studies noted a significantly shorter need for parenteral or oral analgesia.** All studies report either less analgesia immediately after surgery, or less total analgesia used.

4.5 Blood loss

The quantity of blood loss depends on different factors, the surgical technique being one of them. High blood loss may lead to a higher need for transfusion, which in turn can lead to undesirable postoperative events such as greater alteration to the immune system.

Nine studies have reported on intra-operative blood loss,^{24,53,54,55,57,58,65,66,67} of which 6 have demonstrated significantly lower blood loss with LAP surgery.^{53,54,55,65,66,67}

4.6 Complications

A number of studies have reported on post-operative complications.^{24,54,55,57,63,68,69} Their findings confirm that **LAP surgery was not associated with an increase in overall complications.** Furthermore, the studies report a benefit with the LAP approach with respect to a reduction in post-operative infections.^{4,52,53}

4.7 Quality of life

The clinical benefits of the LAP approach result in less postoperative pain, a faster recovery and a shorter hospital stay. These factors contribute to a better and enhanced quality of life (QoL) for patients undergoing laparoscopic surgery. Four randomized controlled trials have reported QoL outcomes in LAP versus open colorectal procedures.^{53,70,71,72} The results, presented below, **all report QoL benefits for the LAP procedure,** but not in terms that are easily converted to utility scores.

Table 3: Quality of Life Studies in Laparoscopic Surgery

| Study | Questionnaires | Consequences |
|----------------|---|---|
| Weeks et al. | Symptoms Distress Scale QoL index, a single-item global rating scale | QoL global rating score was significantly higher for LAP group at 2 weeks post-surgery (p=0.03) LAP group also required shorter duration of analgesia (p<0.001) |
| Schwenk et al. | EORTC QLQ-C30 (European Organisation for Research and Treatment of cancer, Quality of Life Questionnaire) | 1. Global QoL was significantly better in LAP group compared to the conventional group 1 week and 4 weeks after surgery (p=0.05) 2. Better physical and emotional functions in LAP group 1 week after surgery (p<0.05) 3. Pain, dyspnea and loss of appetite were more severe 1 week after open compared with LAP surgery (each p<0.05) |
| Braga et al. | Specific adaptation of the SF-36 Questionnaire | LAP group returned to full physical and social activities in 32.1 days compared with 65.3 days for open group (p=0.0001) |
| Liang et al. | - | LAP group returned to work-2 weeks earlier than open (p<0.05) |

In addition, one study has also reported significantly better satisfaction with the cosmetic results of the scar in the LAP group compared with the conventional group.⁷³

5 Conclusion

In summary, it is considered that the available evidence demonstrates that the long-term clinical outcomes between open and laparoscopic colorectal surgery are equivalent, however the short-term benefits demonstrate less trauma & pain, an improved quality of life, and a faster return to normal activities. A recent RCT run in a regional District General Hospital demonstrates that the LAP procedure can be cost neutral with the open procedure, and this perspective is supported by the literature in cases where the conversion rate is appropriately low. This is achievable in the UK if the joint initiative from the ALSGBI & ACPGBI is implemented. Under these conditions, laparoscopic surgery for colorectal cancer should be a cost effective alternative for patients within the NHS.

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