NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Overview

Laparoscopic surgery for the treatment of colorectal cancer (review of Technology Appraisal Guidance no. 17)

The overview is written by members of the Institute's team of technical analysts. It forms part of the information received by the Appraisal Committee members before the first committee meeting. The overview summarises the evidence and views that have been submitted by consultees and evaluated by the Assessment Group, and highlights key issues and uncertainties. To allow sufficient time for the overview to be circulated to Appraisal Committee members before the first Appraisal Committee meeting, it is prepared before the Institute receives consultees' comments on the Assessment Report. These comments are therefore not addressed in the overview.

A list of the sources of evidence used in the preparation of this document is given in Appendix A.

Please note: this overview contains confidential information (academic in confidence) which is removed.

1 Background

1.1 The condition

Colorectal cancer (CRC) is cancer that develops in the large intestine: the colon or rectum. Common modes of presentation include rectal bleeding associated with a change in bowel habit, abdominal or rectal mass, or iron-deficiency anaemia. Some patients may present as emergencies with bowel obstruction, perforation or bleeding.

CRC is a common malignancy. There were about 29,500 registrations of newly diagnosed malignant neoplasm of the colon, rectosigmoid junction and rectum in England and Wales (about 27,600 in England[1] and 1,900 in Wales[2]) in 2002. CRC accounted for about 12% of newly diagnosed cancers[3] and was the second most common newly diagnosed cancer for women and the third most common for men in 2003.[4] The age-standardised incidence in England in the same year was 51.8 and 32.3 per 100,000 for men and women, respectively.[5] The mean age at diagnosis in the UK is 65 years. The incidence of CRC rises sharply with age.

CRC is a major cause of morbidity and mortality, especially in the elderly. In 2004, there were about 14,000 registered deaths from malignant neoplasm of the colon, rectosigmoid junction, rectum and anus in England and Wales.[6] In the same year, the age-standardised mortality rates in men were 142 per million for colon cancer and 91 per million for cancer of the rectum and anus. The corresponding mortality rates in women were 96 and 47 per million, respectively.[7] The 5-year age-standardised relative survival rate was about 47% for adults diagnosed with colon cancer during the 1996–1999 period in England and Wales.[8]

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[1] Office for National Statistics (2005) *Cancer Statistics Registrations of Cancer Diagnosed in 2002, England. Series MB1 No. 33*. Available from: www.statistics.gov.uk/downloads/theme_health/MB1_33/MB1_33.pdf (Accessed on 16 November 2005.)

[2] Welsh Assembly Government (2005) *Key Health Statistics 2005*. Available from: www.wales.gov.uk/keypubstatisticsforwalesheadline/content/health/2005/hdw200506293-e.htm (Accessed on 16 November 2005)

[3] Excluding non-melanoma skin cancer.

[4] Office for National Statistics (2005) *Data: Cancer Registrations in England, 2003*. Available from: www.statistics.gov.uk/statbase/ssdataset.asp?vlnk=9096 (Accessed on: 16 November 2005).

[5] Ibid. The age-standardised incidences were calculated by direct standardisation using the European Standard Population.

[6] Office for National Statistics (2005) *Mortality Statistics - cause: Review of the Registrar General on deaths by cause, sex and age, in England and Wales, 2004*. National Statistics Series DH2 No.31. London: HMSO. Available from: www.statistics.gov.uk/downloads/theme_health/Dh2_31/DH2No31.pdf

[7] Ibid, Table 5. The age-standardised death rates were based on the European Standard Population.

[8] Office for National Statistics (2005) *Cancer Survival: England 1998–2003*. Available from: www.statistics.gov.uk/statbase/ssdataset.asp?vlnk=8982&More=Y (Accessed on 16 November 2005.) Adults refer to those aged 15 to 99 years. Relative survival was the ratio of crude survival to expected survival (obtained from a life table) in the age- and sex-corresponding group in the general population. The 5-year age-standardised relative survival rate was 46.9% for men and 47.9% for women.

1.2 Current management

Surgical resection of tumour is indicated in about 70–80% of patients diagnosed with CRC. The remaining 20–30% usually have advanced disease, either metastatic or locally invasive to the extent that surgical resection with curative intent is unlikely to be carried out. Among those who undergo surgery, a majority will have a good prognosis (with adjuvant chemotherapy in some cases) while about 30% will develop advanced disease and metastases despite having apparently complete initial resection. For those with advanced disease, treatment is mainly palliative, aiming at increasing the duration and quality of the patient's remaining life while controlling symptoms.

Tumours of the colon have traditionally been removed through open laparotomy with a relatively long abdominal incision. Surgical resection of colon cancer may involve removal of the entire colon (total colectomy) or part of the colon (right hemicolectomy, left hemicolectomy, or sigmoid colectomy), depending on the location of the tumour. However this procedure is associated with significant morbidities such as postoperative pain and long hospital stay.

Tumours of the rectum are usually removed by anterior resection with total mesorectal excision (TME). TME involves the removal of the rectum and the surrounding fatty tissue known as the mesorectum which contains the draining lymph nodes. Tumours of the lower rectum are removed either by low anterior resection or by abdominoperineal resection. The latter includes the removal of the rectum and anus so that a permanent colostomy is required.

2 The technology

Laparoscopic colorectal surgery was first described in the early 1990s. It is thought to be associated with less pain and more rapid recovery from the operation. However, the surgery usually takes longer. There are also concerns regarding tumour recurrence at port sites, incomplete tumour clearance, and higher costs. It is also unclear whether laparoscopic surgery has an impact on long-term cure rates.

Laparoscopic colorectal surgery involves the use of laparoscopic instruments (inserted through a variable number of ports about 5–12 mm in diameter in the abdominal wall) to dissect tissues around the tumour. The tumour is then removed through a short abdominal incision whose length is dictated by the size of the tumour. Sometimes the incision is enlarged to complete the dissection before removal of the specimen; this may be referred to as laparoscopically assisted colectomy. However, the difference between laparoscopic and laparoscopically assisted colectomy is subtle, and both approaches have the advantage of a smaller incision. Hand-port-assisted laparoscopic surgery involves the use of a hand-port through which a gloved hand is inserted intracorporeally. It is suggested that this last method gives better tactile feedback and improves organ retraction.

Compared with conventional open surgery, laparoscopic surgery involves additional material costs (ports, staplers, diathermy and ultrasound instruments). The extent to which disposable (as opposed to reusable) instruments are used has a great impact on these additional costs.

Laparoscopic surgery is a technically more difficult procedure. From 1998 to 2001, only about 0.1% of people with CRC were treated with laparoscopic surgery in the UK. A recently published survey reported that only 45 of the existing members of the Association of Coloproctology of Great Britain and Ireland perform laparoscopic colorectal surgery.

The existing NICE technology appraisal guidance on the use of laparoscopic surgery for CRC states that open rather than laparoscopic resection should be the preferred surgical procedure, and that laparoscopic surgery should only be undertaken as part of a randomised controlled clinical trial. This original guidance was issued in December 2000 and is now due for review.

3 The evidence

3.1 Clinical effectiveness

3.1.1 The evidence base submitted

The original guidance issued in December 2000 was based on a systematic review[9] funded by the Institute. For this update, Aberdeen Technology Assessment Review Group conducted its own systematic review in 2005 on the clinical effectiveness of laparoscopic surgery for CRC

Nineteen randomised controlled trials (RCTs) and an unpublished meta-analysis (Bonjer 2005)[10] were included in the 2005 review. Only three of these 19 RCTs were included in the original review in 2000. The unpublished meta-analysis was based on individual patient data of subsamples from four of the 19 RCTs included in the Assessment Report. The sample size of the 19 RCTs ranged from 16 to 1082. Altogether there were about 2400 study participants in the laparoscopic surgery arms and about 2100 participants in the open surgery arms. Most RCTs predominantly recruited people with colon cancer. Three studies involved only patients with rectal cancer.

The quality of the trials varied. The method of randomisation used was regarded as appropriate and adequate in all studies except one. However, concealment of random allocation was judged to be adequate in only about one third of the studies. Nevertheless, the baseline characteristics of intervention and control groups were considered to be comparable in about three quarters of the studies.

Ethicon Endo-Surgery (EES) did not conduct its own systematic review of clinical effectiveness but rather submitted the unpublished meta-analysis mentioned above. [redacted]

[9] Vardulaki KA, Bennett-Lloyd BD, Parfitt J, et al. (2000). *A systematic review of the effectiveness and cost-effectiveness of laparoscopic surgery for colorectal cancer*. Available from: www.nice.org.uk/page.aspx?o=13507

[10] Bonjer et al. on behalf of the Trans-Atlantic Laparoscopically assisted versus Open Colectomy Trials Study Group (2005). Laparoscopically assisted versus open colectomy for colon cancer – a meta-analysis. (Unpublished.)

[redacted]

3.1.2 Short-term outcomes

The main results for short-term outcomes (see page 12 of the Assessment Report for definition) are shown in Table 1 below. The 2005 systematic review reported that when compared with open surgery, laparoscopic surgery was significantly associated with longer operation time (by 40 minutes, 95% CI 32 to 48 minutes, based on three studies) and shorter hospital stay (by 2.58 days, 95% CI 2.0 to 3.1, based on four studies). Laparoscopic surgery might also be associated with a slight decrease in number of lymph nodes retrieved (WMD = –0.41, 95% CI –1.42 to 0.59, three studies), an increase in risk of anastomotic leakage (pooled RR = 1.13, 95% CI 0.74 to 1.73, eight studies), and a slight decrease in risk of operative and 30-day mortality (three studies), though these differences did not reach statistical significance. Note that the number of studies contributing to synthesis was in general small. [redacted]

[11] The Clinical Outcomes of Surgical Therapy Study Group (2004). A comparison of laparoscopically-assisted and open colectomy for colon cancer. *New England Journal of Medicine* 350:2050–9.
[12] The COlon cancer Laparoscopic or Open Resection Study Group (2005). Laparoscopic surgery versus open surgery for colon cancer: short-term outcomes of a randomised trial. *Lancet* 6:477–84.
[13] Guillou PJ, Quirke P, Thorpe H et al. for the MRC CLASICC trial group (2005). Short-term endpoints of conventional versus laparoscopic assisted surgery in patients with colorectal cancer (MRC CLASICC trial): multicentre, randomised controlled trial. *Lancet* 365:1718–26.
[14] Lacy AM, Garcia-Valdecasas JC, Delgado S et al. (2002). Laparoscopy-assisted colectomy versus open colectomy for treatment of nonmetastatic colon cancer: a randomised trial. *Lancet* 359:2224–9.

Table 1 Short-term outcomes from the Assessment Report and Bonjer's unpublished meta-analysis

	Assessment Group's systematic review			Bonjer 2005 meta-analysis
	Number of RCTs providing information	Number of RCTs contributing to synthesis	Results of meta-analysis (95% CI, p-value)	
Difference in duration of surgery (minutes, LS – OS)	16	3	WMD = 40 (32 to 48, p < 0.001)	[redacted]
Conversion rate of LS to OS	11	-	Mean = 20% (sd 12%, range 0%–46%, median 17%)	[redacted]
Difference in number of lymph nodes removed during surgery (LS – OS)	13	3	WMD = –0.41 (–1.42 to 0.59, p = 0.42)	[redacted]
Risk of anastomotic leakage	8	8	Pooled RR = 1.13 (0.74 to 1.73, p = 0.58)	[redacted]
Difference in length of hospital stay (days) (LS – OS)	14	4	WMD = –2.58 (–3.12 to –2.03, p < 0.001)	[redacted]
Risk of operative mortality	3	3	Pooled RR = 0.84 (0.29 to 2.47, p = 0.75)	[redacted]
Risk of 30-day mortality	3	3	Number of events: LS = 9/1011, OS = 15/992 Pooled RR = 0.57 (0.25 to 1.29, p = 0.18)	[redacted]

LS, laparoscopic surgery; OS, open surgery; RR, pooled relative risk (fixed effect model); sd, standard deviation; WMD, weighted mean difference.

3.1.3 Long-term outcomes

In terms of overall survival and disease-free survival, quantitative synthesis of the evidence identified did not show a statistically significant difference between laparoscopic and open surgery (see Table 2 below). Note, however, that the six studies that contributed to meta-analysis for overall survival had widely varied follow-up periods (1 to 108 months). Two of the six studies also excluded 5% and 16% of the randomised population from analysis, respectively (one study reported the reason for exclusion as being detection of metastasis intraoperatively). It is not clear how these factors might influence the pooled effect estimates. [redacted]

In terms of total tumour recurrence, quantitative synthesis of five studies gave a pooled risk ratio of 0.92 (95% CI 0.74 to 1.14). Again, the result did not reach statistical significance. [redacted]

Table 2 Long-term outcomes from the Assessment Report and Bonjer's unpublished meta-analysis

	Assessment Group's systematic review			Bonjer 2005 meta-analysis
	Number of RCTs providing information	Number of RCTs contributing to synthesis	Results of meta-analysis (95% CI and p-value)	
Overall survival	7	6	No. of events: LS = 836/1111, OS = 973/1353 (length of follow-up ranged from 1 to 108 months) Pooled RR = 1.03 (0.98 to 1.09, p = 0.28) One of the studies reported 100% survival in both arms. [redacted]	[redacted]
Disease-free survival	5	4	No. of events: LS = 513/683, OS = 496/666 Pooled RR = 1.01 (0.95 to 1.07, p = 0.83) [redacted]	[redacted]
Tumour recurrence (total)	7	7	No. of events: LS = 135/789, OS = 144/765 (length of follow-up ranged from 3 to 108 months) Pooled RR = 0.92 (0.74 to 1.14, p = 0.44) Two of the studies reported zero rates in both arms.	[redacted]
Tumour recurrence (wound)	4	4	No. of events: LS = 2/435 (0.5%), OS = 1/428 (0.2%) (n = 1) Three of the studies reported zero rates in both arms.	[redacted]
Port-site recurrence	8	8	No. of events: LS = 3/483 (n = 8) Six of the studies reported zero event rates in both arms.	[redacted]

Data regarding the long-term survival outcomes of the CLASICC trial were from personal communication of the Assessment Group with CLASICC trial investigator (Prof PJ Guillou, the University of Leeds, 2005).

HR, hazard ratio (laparoscopic versus open surgery); LS, laparoscopic surgery; n, number of studies; OS, open surgery; RR, relative risk.

3.1.4 Assessment of subgroup differences

3.1.4.1 Patients who underwent conversion to open surgery

The Assessment Group identified only three studies[15] that recorded separate outcome data for patients randomised to receive laparoscopic surgery but who underwent conversion to open surgery. From the limited data available, the Assessment Group observed that patients who underwent conversion to open procedures appeared to have higher blood loss, longer hospital stay and a greater risk of tumour recurrence, when compared with patients who received a laparoscopic or open procedure as planned. The incidence of urinary tract and wound infection, and overall survival appeared to be similar (see Assessment Report page 165 Appendix 10 for details). [redacted]

3.1.4.2 Location of cancer

Limited data were available. Anastomotic leakage was the only outcome for which there were sufficient data to conduct stratified meta-analysis by location of cancer. The pooled RR was 1.27 (95% CI 0.70 to 2.31, four studies) for colon cancer and 1.25 (95% CI 0.63 to 2.46, two studies) for rectal cancer (see Assessment Report page 164 Appendix 9 Outcome 15).

3.1.4.3 Stage of cancer

The Assessment Group identified two RCTs that conducted subgroup analysis by stage of cancer for overall survival. Both reported that there was no statistically significant difference in overall survival of patients undergoing laparoscopic surgery compared to open surgery for cancer stages I, II or III. [redacted]

[15] One was a large UK study (CLASICC trial) with over 500 patients allocated to the laparoscopic surgery group while the other two were small studies with fewer than 30 participants in each group.

[redacted]

3.1.5 Conclusion

Regarding short-term outcomes, evidence suggests that laparoscopic surgery is significantly associated with an increase in operation time (by about 30–40 minutes) and a decrease in length of hospital stay (by about 2 days), when compared with open surgery. Laparoscopic surgery may also be associated with a slight decrease in the number of lymph nodes retrieved, an increase in risk of anastomotic leakage, and a slightly lower risk of operative and 30-day mortality. However, the number of relevant studies is small and the difference is not statistically significant.

Regarding long-term outcomes, existing evidence available does not seem to suggest the presence of a statistically significant difference between laparoscopic and open surgery in terms of total tumour recurrence, overall survival and disease-free survival. However, the follow-up period among the studies varied widely and this might have had an effect on the direction and magnitude of the effect estimate. It is also not clear whether there is a difference between laparoscopic and open surgery in terms of tumour recurrence at wound or port site, as observed events were rare (see Table 2 above).

Regarding subgroup differences, existing evidence available is limited. Patients who were converted to open surgery appeared to have higher blood loss, longer surgery, longer hospital stay and higher risk of tumour recurrence, when compared with patients who underwent procedures as planned.

3.1.6 Issues that may influence the interpretation of evidence

Although a total of 19 RCTs were identified and included in the Assessment Group's systematic review, the number of studies that reported on outcomes of specific importance to this appraisal was limited. In particular, existing studies that reported on survival outcomes had a wide range of follow-up. There is also very limited evidence on survival outcomes beyond 3 years.

Possibility of potentially important clinical difference between laparoscopic and open surgery cannot be excluded with certainty at this stage.

The Bonjer (2005) study has potentially important weaknesses. [redacted]

[redacted]

The mean rate of conversion in the studies identified by the assessment group was 20% (range 0–46%). [redacted] The CLASICC trial reported that 29% patients were converted from laparoscopic to open surgery, with excessive tumour fixity or uncertainty about tumour clearance being cited as the most common causes for conversion. It also reported that patients who underwent conversion were significantly associated with higher intraoperative complication rates, greater transfusion requirements, longer hospital stays and higher death rates. It is therefore likely to be important to be able to identify patients at high risk of conversion in advance, especially while surgeons are gaining experience in laparoscopic colorectal surgery.

3.2 Cost effectiveness

Ethicon Endo-Surgery (EES) did not submit a systematic review or economic model but rather a narrative account highlighting issues that it considered as important for this appraisal. Two consultees, the Association of Laparoscopic Surgeons of Great Britain and Ireland (ALSGBI) and the Association of Coloproctology of Great Britain and Ireland (ACPGBI), each made a submission, neither of which included an economic model. The Assessment Group conducted a systematic review of relevant economic evaluations published from 2000 to 2005. It also conducted its own economic evaluation using first a balance sheet approach and then a modelling approach. Table 3 below shows a summary of the arguments and recommendations in the EES submission. Broadly similar arguments and recommendations were submitted by the ALSGBI and ACPGBI.

Table 3 Summary of Ethicon Endo-Surgery submission

Source of evidence as stated in EES submission	Conclusion
Bonjer (2005) meta-analysis	[redacted]
Abraham 2004[16]	Short-term clinical outcomes favour the laparoscopic approach.
Hospital Episode Statistics 2003/2004	Average length of hospital stay for colorectal procedures (HRG F31 and F32) is >17 days. There is therefore significant room for improvement.
King (2005)[17]	What NHS could achieve by using laparoscopic surgery in the context of an enhanced recovery programme: shorter length of hospital stay in laparoscopic surgery patients (5.2 days, 4.2 to 6.5)* than in open surgery patients (7.4 days, 6.0 to 9.2)*.
EES's non-systematic review of published studies	Conversion rate of laparoscopic to open surgery is a key driver of total cost (the other key driver is length of hospital stay).
CLASICC trial & Tekkis 2005[18]	Learning curve is closely linked to conversion rate.
Not stated	With appropriate training, conversion rate can be kept at a single-digit percentage.
EES's non-systematic review of nine studies that reported on costs	With the control of conversion rates, through appropriate training, mentoring and case-mix selection, the cost of laparoscopic surgery should be similar to or lower than that of open surgery.
King (2005)	Laparoscopic surgery still delivers benefits over open surgery in the context of an enhanced recovery programme (considered to be best clinical practice in the UK).
Accepting all the conclusions above	Laparoscopic surgery would be a cost-effective alternative for patients within the NHS, and cost saving from the societal perspective.

*Numbers in brackets are geometric means and 95% confidence intervals.

[16] Abraham NS, Young JM, Solomon MJ (2004). Meta-analysis of short-term outcomes after laparoscopic resection for colorectal cancer. *British Journal of Surgery* 91:1111–24.
[17] King PM, Blazeby JM, Ewings P et al. (2005). Randomised clinical trial comparing laparoscopic and open surgery for colorectal cancer within an enhanced recovery programme. *Colorectal Disease* 7 (Suppl 1):69 (abstract).
[18] Tekkis PP, Senagore AJ, Delaney CP (2005). Conversion rates in laparoscopic colorectal surgery. *Surgical Endoscopy* 19: 47–54.

3.2.1 Assessment Group's systematic review and critique of submissions

3.2.1.1 Systematic review

The Assessment Group identified five relevant primary studies (see Assessment Report Table 4.2). Two of the five studies were RCT-based studies on colorectal cancer in the UK: one was an unpublished draft paper (Franks 2005[19]) on the short-term economic evaluation of a subset of patients in the CLASICC trial, and the other was a small RCT-based study in the context of an enhanced recovery programme (King 2005).

When compared with open surgery, the mean cost for laparoscopic surgery was higher in all of the studies except one (King 2005). Overall, there was considerable variation in the reported differences in mean costs of laparoscopic and open surgery in the studies (see Assessment Report page 48 Table 4.4 for details). The number of complications was the only common measure of effectiveness across all five studies. The direction of effect of laparoscopic surgery on the risk of complications was not consistent across the studies. Nevertheless, using the cost data in each individual study, the incremental cost per complication avoided was calculated for each study (see Assessment Report Table 4.6). [redacted]

3.2.1.2 Critique of submissions

None of the submissions contained a systematic review or an economic model. EES contended that the total cost of laparoscopic surgery will decrease as conversion rate becomes lower. While this is likely, direct evidence is limited. It is also not clear how a reduction in conversion rate would affect the difference in cost between laparoscopic and open surgery.

[19] Franks PJ, Bosanquet N on behalf of the CLASICC trial participants (2005). Short term costs of conventional versus laparoscopic assisted surgery in patients with colorectal cancer (MRC CLASICC trial). (Unpublished.)

With regard to the ALSGBI submission, the Assessment Group reported that its own review of cost effectiveness did not support ALSGBI's claim that the additional operative costs of laparoscopic surgery were offset by cost savings from lower complication rates and shorter hospital stays with laparoscopic surgery. There was no comment on the ACPGBI submission in the Assessment Report.

3.2.2 Assessment Group's economic evaluation using a balance sheet approach

The Assessment Group presented the differences between laparoscopic and open surgery in the form of a balance sheet. Outcomes that favoured laparoscopic surgery included length of hospital stay, amount of blood loss, time away from usual activities, postoperative pain and analgesia. The outcome that did not favour laparoscopic surgery was duration of operation. There was also a substantial conversion rate from laparoscopic to open surgery. Outcomes for which no statistically significance difference between laparoscopic and open surgery was found included costs[20], anastomotic leakage, wound infection, incisional hernia, 30-day mortality, overall survival and disease-free survival (see Assessment Report page 62 Table 5.3).

Although the difference in estimated costs between laparoscopic and open surgery did not reach statistical significance, it was likely that laparoscopic surgery was associated with a slightly higher cost (around £260) than open surgery. As for the outcomes for which data were available for quantitative synthesis, the confidence intervals were so wide that potentially important clinical and economic differences could not be ruled out. Assuming that the long-term outcomes are equivalent, a judgement is therefore required as to whether the short-term benefits associated with earlier recovery are worth the extra cost.

[20] Using cost components and mean cost estimates reported in a small UK study (King 2005), and the estimated difference in length of hospital stay between laparoscopic and open surgery from its own systematic review, the Assessment Group generated a distribution of the incremental cost of laparoscopic surgery as compared with open surgery: mean £265, 2.5 and 97.5 percentiles –£3829 to £4405 (see Assessment Report Table 2).

In addition, a difference in length of hospital stay was identified as one of the key determinants of cost difference. Threshold analysis suggested that the cost difference would decrease to zero if laparoscopic surgery decreased the average length of hospital stay by just over 4 days when compared with open surgery. However, this magnitude of difference was not observed in any of the studies included in the systematic review. The Assessment Group also highlighted that should the difference in length of stay between the two types of surgery decrease to as little as 1 day (for example, in an enhanced recovery programme), then the incremental cost would increase to over £500.

3.2.3 Assessment Group's economic model

3.2.3.1 Methods

A Markov model was used to estimate the long-term costs and benefits in a cohort of 65-year-old patients with colorectal cancer undergoing surgical resection of tumour (Assessment Report page 182 Appendix 13). After the initial surgery, a patient would enter one of the following five states: disease-free, recurrence, disease-free (after recurrence), non-operable recurrence and death. The cycle length was set at 6 months as this was considered to be the first instance at which a recurrence might be detected. The maximum number of cycles that a patient could go through was 50 (25 years). Outcomes were presented as incremental cost per additional life year and incremental cost per quality-adjusted life year (QALY). Appendix B shows a list of assumptions used by the Assessment Group in its economic model. Sensitivity analyses were conducted by varying assumptions and parameter estimates and costs and utility values in the base-case model (Appendix C).

3.2.3.2 Base-case analysis

In terms of incremental cost per additional life year and incremental cost per additional QALY, laparoscopic surgery was dominated (that is, associated with higher costs but no more effective) by open surgery (see Assessment Report page 79 Tables 5.9 and 5.10). Note, however, that few data on quality of life were available to inform any difference between the two types of surgery. If society's maximum willingness to pay for an additional QALY is £30,000, then the probability that laparoscopic surgery is the more cost-

effective intervention is about 0.4 (see Assessment Report page 80 Figure 5.3). If, however, equal overall and disease-free survival is assumed, then this probability would increase to about 0.5 (see Assessment Report page 82 Figure 5.5).

The Assessment Group warned that these results did not capture the QALY gain that might be associated with an earlier recovery for which little data were available. Assuming that society's willingness to pay is £30,000 for an additional QALY, and that the incremental costs for laparoscopic surgery were as estimated above, then in order for laparoscopic surgery to be considered worthwhile, the QALY gain associated with laparoscopic surgery would have to be 0.009 in the base case and 0.010 in the case of equal overall and disease-free survival.

3.2.3.3 Sensitivity analyses

Broadly similar results were obtained: laparoscopic surgery was dominated by open surgery in almost all of the sensitivity analyses.

3.2.3.4 Subgroup analysis

Using mortality and recurrence data (by stage of disease) obtained from the survival curves in Bonjer (2005), the Assessment Group assessed the cost effectiveness of the two types of surgery by stage of cancer. For patients with stage I or stage II disease, laparoscopic surgery was dominated (associated with higher costs but fewer QALYs). For patients with stage III disease, laparoscopic surgery was associated with a very slight increase in cost but a gain in QALYs (see Assessment Report pages 97–8 Tables 5.20 and 5.21). However, the Assessment Group warned that these results were at odds with clinical opinion which normally suggests laparoscopic surgery is recommended for patients with early-stage cancer and therefore should be treated cautiously.

3.2.3.5 Limitations

The Assessment Group reported that a major limitation of its analysis was that there were very limited data on utilities (such as the QALY gain associated with earlier recovery from laparoscopic surgery). The model was also

sensitive to patient pathways and their associated probabilities, costs and utilities after recurrence.

4 Issues for consideration

- Based on existing evidence available, the possibility of potentially important clinical difference between laparoscopic and open surgery cannot be excluded with certainty. This is particularly the case with regard to long-term clinical outcomes. There are no data on long-term clinical outcomes beyond 3 years and existing data at 3 years are limited. For example, the sample size of the CLASICC trial did not have enough statistical power to detect whether the two types of surgery were equivalent in short- and long-term endpoints[21]. Regarding the Bonjer meta-analysis, the precision of the survival curves for overall and disease-free survival at 3 years is not reported. It is also unclear whether the patients excluded from meta-analysis had similar outcomes to those included.

- Several consultees suggest that laparoscopic surgery offers better short-term outcomes which may not be easily captured by QALY estimation. It is also suggested that the higher costs of laparoscopic surgery may be offset by shorter length of hospital stay and quicker return to work among working patients. However, the Assessment Group have concluded that current evidence does not support the claim that the observed decreased length of hospital stay is sufficient to make a difference big enough to offset the extra costs associated with laparoscopic surgery.

- There is some evidence suggesting that patients who undergo intraoperative conversion from laparoscopic to open surgery may be worse off than those who do not, in terms of some short-term outcomes. While conversion rate from laparoscopic to open surgery

[21] Guillou PJ, Quirke P, Thorpe H et al. for the MRC CLASICC trial group (2005). Short-term endpoints of conventional versus laparoscopic assisted surgery in patients with colorectal cancer (MRC CLASICC trial): multicentre, randomised controlled trial. *Lancet* 365:1718–26.

would be expected to decrease as surgeons become more experienced in the technique, it is not clear how a lower conversion rate will affect the difference in cost between laparoscopic and open surgery.

- Existing evidence regarding the long-term clinical outcomes of patients converted to open procedures is not established. There is the need to establish criteria for screening patients at risk of conversion and selecting patients for laparoscopic surgery.

- Existing evidence regarding possible subgroup differences (such as location of cancer and stage of disease) is limited.

- Data on costs of training of surgeons to carry out laparoscopic colorectal surgery are limited. It is also not certain how incorporating estimation of these costs may affect the cost-effectiveness evaluation of laparoscopic and open surgery.

- Evidence regarding any differences in clinical and cost effectiveness between laparoscopic, laparoscopic-assisted and hand-assisted laparoscopic surgery is limited.

- The impact of implementation of the technology may be an issue worth assessing (for example, surgeon training costs, disinvestment costs should guidance be reversed in the future, equity issues for converted patients who may be suffering from worse outcomes from the technology).

- There is a need for further research:

    - to establish long-term clinical safety of the technology, especially beyond 3 years

    - to identify important subgroup differences and establish patient selection criteria

- to assess any differences in clinical and cost effectiveness among the different types of laparoscopic surgery.

5 Ongoing research

The UK-based multicentre CLASICC trial is now closed and is due to publish results regarding long-term clinical outcomes and economic evaluation. While the Assessment Group received an unpublished preliminary paper on cost analysis of a subset of the CLASICC study population and incorporated the data in its sensitivity analysis, additional UK-specific utility data would help overcoming a key limitation of the economic model used in the Assessment Report. It is not clear when the actual results will be published.

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Appendix A: Sources of evidence considered in the preparation of the overview

A The Assessment Report: Alison M, Lourenco T, de Verteuil R et al. (Aberdeen Technology Assessment Review Group). *Systematic review of the clinical effectiveness and cost-effectiveness of laparoscopic surgery for colorectal cancer*, November, 2005.

B Submissions from the following organisations:

I Manufacturers/sponsors:

- Ethicon Endo-Surgery

II Professional/specialist and patient/carer groups:

- The Association of Laparoscopic Surgeons of Great Britain and Ireland
- The Association of Coloproctology of Great Britain and Ireland
- Beating Bowel Cancer

III Commentator organisations (without the right of appeal):

- None

Appendix B: List of major assumptions used in Assessment Group's economic model

1. The main cost components in the model were (a) costs of the initial operation and (b) costs of any subsequent reoperation or management.

2. If a patient had a recurrence and reoperation was indicated, then the second operation would be open surgery irrespective of whether the initial operation was laparoscopic or open surgery.

3. The risk of death, risk of recurrence, risk of death for patients with non-curative cancer and risk of hernia (incisional or port site) remained constant from one cycle to another.

4. Postoperative complications were categorised according to whether operative management was required or not. The costs of complications requiring operative management were captured through the costs of emergency operation and the costs associated with hernia. The costs of complications requiring non-operative management were captured through costs of increased operating times and longer hospitalisation.

5. The risk of an emergency operation was the same as the risk of an anastomotic leakage.

6. The relative risk of (a) mortality for a patient with non-curative cancer, (b) hernia, and (c) reoperation after a recurrence, was 1.

7. The relative effect sizes remained constant over time.

8. Disease-free patients would receive regular review. Patients would receive a CT scan and an outpatient appointment at 12 and 24 months postoperatively. Patients would also be reviewed and undergo colonoscopy after 3 years, and have subsequent colonoscopy every 5 years until the age of about 70.

Appendix C: Estimates of parameters, costs and QALYs that Assessment Group used in its economic model in the base case and in sensitivity analyses.

	Base case				Sensitivity analysis			
Parameter	**Baseline estimate**	**Data source**	**Relative effect estimate**	**Data source**	**Baseline estimate**	**Relative effect estimate**	**Combined**	**Data source**
Mortality	0.030, constant	Estimated from Bonjer (2005) overall survival curve	1.016 (0.958 to 1.054), normal distribution	Estimated from 3-year overall survival reported in Bonjer (2005)	-	-	-	-
Recurrence of local or distant metastasis	0.046, constant	Estimated from Bonjer (2005) disease-free survival curve	0.993 (0.943 to 1.06), normal distribution	Estimated from 3-year disease-free survival reported in Bonjer (2005)	-	-	-	-
Mortality (after recurrence of non-operative cancer)	0.2, β-distribution	Estimated from survival curve for 'chemotherapy group' in Benoist (2005) study	1	Based on the assumption that prognosis is the same once a recurrence occurs irrespective of method of initial resection	High rate of 0.31 Low rate of 0.11	0.5 or 1.5	Combining high mortality rate of 0.31 with relative effect size of 1.5 Combining low mortality rate of 0.11 with relative effect size of 0.5	-
Emergency operation	0.019, triangular distribution (α = 5.4, β = 21.6), IQR: 0.008–0.034	Median rate of anastomotic leakage in open arms in trials identified in systematic review	1.13 (0.74 to 1.73), lognormal distribution	Based on the relative risk of anastomotic leakage derived from systematic review	-	-	-	-

	Base case				Sensitivity analysis			
Parameter	**Baseline estimate**	**Data source**	**Relative effect estimate**	**Data source**	**Baseline estimate**	**Relative effect estimate**	**Combined**	**Data source**
Risk of hernia (incisional or port site)	0.003, triangular distribution, IQR: 0.002–0.012	Median rate from open arms in trials identified in systematic review and non-randomised studies included in ALSGBI submission	1	The limited evidence from systematic review revealed no statistically significant difference between LS and OS	0.003	0.5 or 2	-	-
Reoperation after recurrence	0.05, β-distribution (α = 15, β = 285)	Grampian University Hospitals NHS Trust	1	Expert opinion (assuming that method of initial resection would not affect post-recurrence management)	High rate of 10% Low rate of 1%	0.5 or 2	Combining high reoperation rate of 10% with relative effect size of 2 Combining low reoperation rate of 1% with relative effect size of 0.5	-
Cost of open surgery	£5852, triangular distribution with high and low based on IQR (£4968–£6272)	Estimated from data in King (2005)	Relative cost of LS = 1.05, lognormal distribution, sd 0.33	-	[redacted]	[redacted]	-	Franks (2005) (CLASICC)
					[redacted]	[redacted]	-	Recalculated by using length of stay for OS in Franks (2005) and the WMD in systematic review to calculate length

	Base case				Sensitivity analysis			
Parameter	**Baseline estimate**	**Data source**	**Relative effect estimate**	**Data source**	**Baseline estimate**	**Relative effect estimate**	**Combined**	**Data source**
								of stay for LS
					For OS, additional cost of preoperative staging using an ultrasound scan: £32, triangular distribution with high and low based on IQR £26–£39	For LS, additional cost of preoperative staging using a CT scan: £73, triangular distribution with high and low based on IQR £56–£91	-	National Reference costs
Cost of emergency operation	£1615, triangular distribution with high and low based on IQR (£1132–£2322)	National reference cost for HRG F42 (a general abdominal, very major or major procedure)	-	-	-	-	-	-
Cost of re-operation	£5852, triangular distribution with high and low based on IQR (£4968–£6272)	Same as costs of open surgery (expert opinion)	-	-	-	-	-	-
Cost of an outpatient visit at 6 months	£99	King (2005)	-	-	-	-	-	-
Cost of CT scan	£73, triangular distribution with	National reference	-	-	-	-	-	-

	Base case				Sensitivity analysis			
Parameter	**Baseline estimate**	**Data source**	**Relative effect estimate**	**Data source**	**Baseline estimate**	**Relative effect estimate**	**Combined**	**Data source**
	high and low based on IQR (£56–£91)	cost						
Cost of colonoscopy	£622, triangular distribution with high and low based on IQR (£370–£868)	National reference cost for HRG F35 (an endoscopic or intermediate procedure for the large intestine)	-	-	-	-	-	-
Cost of surgery for hernia	£1689, triangular distribution with high and low based on IQR (£1306–£2234)	National reference cost for HRG F72 (abdominal hernia procedures for age<70)	-	-	-	-	-	-
Cost of non-operative management following recurrence	£1216	Use of drugs from personal communications with a MacMillan Cancer Nurse; costs of drugs were from the *British National Formulary* (March 2005).	-	-	-	-	-	-
Utility values associated with	Time spent disease-free = 1;	Norum (1997)[22]	-	-	Disease-free = 100; disease-free after	-	-	Petrou (1997)[23]

[22] Norum J, Vonen B, Olsen JA, Revhaug A. (1997) Adjuvant chemotherapy (5-fluorouracil and levamisole) in Dukes' B and C colorectal carcinoma. A cost-effectiveness analysis. *Annals of Oncology* 8(1): 65–70. This is a published Norwegian study of 95 patients with Dukes' B and C colorectal cancer who underwent adjuvant chemotherapy after surgical resection. A median quality of life value of 0.83 (0–1 scale) was reported in all patients and measures.

	Base case				Sensitivity analysis			
Parameter	**Baseline estimate**	**Data source**	**Relative effect estimate**	**Data source**	**Baseline estimate**	**Relative effect estimate**	**Combined**	**Data source**
various health states -free	death = 0; all other states = 0.83				successfully treated recurrence = 100; death = 0; initial operation = 95; recur = 95; non-operative management (progressive disease) = 57.5; non-operative management (terminal disease) = 10			
					Disease-free = 0.92; disease-free after successfully treated recurrence = 0.92; initial operation = 0.92; recurrence = 0.92; non-operative management (on palliative chemotherapy) = 0.24; non-operative management (on adjuvant chemotherapy) = 0.70	-	-	Pandor (2005)[24]

IQR, interquartile range; LS, laparoscopic surgery; OS, open surgery; QALY, quality-adjusted life years; WMD, weighted mean difference.

[23] Petrou S, Campbell N (1997) Stabilisation in colorectal cancer. *International Journal of Palliative Nursing* 3(5):275–80.
[24] Pandor, A, Eggington, S, Paisley, S et al. (2005). *The use of oxaliplatin and capecitabine for the adjuvant treatment of colon cancer* [document on the Internet]. National Institute for Health and Clinical Excellence. Available at: www.nice.org.uk/pdf/Assessment_Report_(CiC_removed).pdf