Original article

Long-term follow-up of the Medical Research Council CLASICC trial of conventional *versus* laparoscopically assisted resection in colorectal cancer

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Background: Laparoscopic resection is used widely in the management of colorectal cancer; however, the data on long-term outcomes, particularly those related to rectal cancer, are limited. The results of long-term follow-up of the UK Medical Research Council trial of laparoscopically assisted *versus* open surgery for colorectal cancer are presented.

Methods: A total of 794 patients from 27 UK centres were randomized to laparoscopic or open surgery in a 2 : 1 ratio between 1996 and 2002. Long-term follow-up data were analysed to determine differences in survival outcomes and recurrences for intention-to-treat and actual treatment groups.

Results: Median follow-up of all patients was 62·9 (interquartile range 22·9 – 92·8) months. There were no statistically significant differences between open and laparoscopic groups in overall survival (78·3 (95 per cent confidence interval (c.i.) 65·8 to 106·6) *versus* 82·7 (69·1 to 94·8) months respectively; $P = 0·780$) and disease-free survival (DFS) (89·5 (67·1 to 121·7) *versus* 77·0 (63·3 to 94·0) months; $P = 0·589$). In colonic cancer intraoperative conversions to open surgery were associated with worse overall survival (hazard ratio (HR) 2·28, 95 per cent c.i. 1·47 to 3·53; $P < 0·001$) and DFS (HR 2·20, 1·31 to 3·67; $P = 0·007$). In terms of recurrence, no significant differences were observed by randomized procedure. However, at 10 years, right colonic cancers showed an increased propensity for local recurrence compared with left colonic cancers: 14·7 *versus* 5·2 per cent (difference 9·5 (95 per cent c.i. 2·3 to 16·6) per cent; $P = 0·019$).

Conclusion: Long-term results continue to support the use of laparoscopic surgery for both colonic and rectal cancer.

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Introduction

The Medical Research Council Conventional *versus* Laparoscopic-Assisted Surgery In Colorectal Cancer (MRC CLASICC) trial was designed to determine the long-term oncological safety and efficacy of laparoscopically assisted surgery in comparison with conventional open surgery for the treatment of colorectal cancer. Earlier diagnosis of colorectal cancer, and changes in surgical technique, chemotherapy and radiotherapy, have led to substantially improved survival over recent years.

Surgical resection of colorectal cancer remains the only curative modality. The laparoscopic approach is now increasingly being used for colorectal cancer, and the UK National Institute for Health and Clinical Excellence guidance was updated in 2006 to recommend laparoscopic resection in patients in whom both open and laparoscopic approaches were deemed suitable[1]. CLASICC, along with similar trials, was instrumental in promoting the uptake of laparoscopic surgery, demonstrating improved short-term outcomes including reduced hospital stay, fewer wound complications and expedited return to normal function[2–4].

Adequacy of technique was initially a criticism of laparoscopically assisted surgery; however, studies showing comparable outcomes in terms of resection margins and lymph node harvest have suggested equal short-term

oncological efficacy[4,5]. Studies examining long-term follow-up, including CLASICC 3- and 5-year analyses, have generally shown comparable outcomes between open and laparoscopic surgery in terms of disease-free survival (DFS) and overall survival[3,6–8].

CLASICC differed from other similar trials conducted at the time, with the inclusion of both colonic and rectal tumours, and also the requirement for central pathological review of all resection specimens. This paper reports long-term follow-up data from CLASICC, now exceeding 10 years, and provides further insight into the long-term outcomes and comparability of open *versus* laparoscopically assisted resection.

Methods

CLASICC is a multicentre randomized controlled open parallel-group trial. A total of 794 patients (413 with colonic and 381 with rectal cancer) were randomized on a 2 : 1 basis to either laparoscopically assisted (526) or open (268) surgery between July 1996 and July 2002. Patients were recruited from 27 UK centres and operated on by 32 individual surgeons. This update reports the longer-term outcomes of the trial, and includes the key secondary endpoints overall survival, DFS, and locoregional, wound/port-site and distant recurrences. The methodological details have been reported previously[2,6,7].

Statistical analysis

Survival and recurrence data were compared using Kaplan–Meier and cumulative incidence function curves respectively. Survival data were tested using log rank and Wilcoxon rank-sum tests. Data were adjusted for stratification factors, and age, sex and tumour node metastasis (TNM) stage of disease using Cox proportional hazards regression models. Stratification factors used in randomization included tumour site, presence of liver metastases, neoadjuvant radiotherapy and surgeon. Sensitivity analyses were performed to assess the impact of exclusions for DFS on overall survival, in addition to the effect of conversions on the results. In the cumulative recurrence incidence analyses, absence of recurrence at death was considered to be a competing-risk event and was not censored.

All hypothesis tests were performed using intention-to-treat and actual treatment populations: open, laparoscopic and laparoscopic converted to open. All statistical tests were at the 1 per cent significance level throughout (two-tailed), and were performed using SAS® version 9.2 (SAS Institute, Cary, North Carolina, USA).

Results

A CONSORT diagram summarizing the allocation of patients during the study is shown in *Fig. 1*. Median (interquartile range) follow-up of all patients was 62·9 (22·9 – 92·8) months and that for patients alive at the time of analysis was 91·8 (74·2 – 112·1) months. Baseline patient characteristics and reasons for intraoperative conversion have been reported previously[2].

Overall survival

Median overall survival was 80·7 (95 per cent confidence interval (c.i.) 70·6 to 91·8) months, with a total of 428 deaths (144 in open group and 284 in laparoscopic group). There were no significance differences in overall survival between the open and laparoscopic groups: median 78·3 (65·8 to 106·6) and 82·7 (69·1 to 94·8) months respectively (log rank statistic = 0·08, $P = 0·780$).

Median overall survival for patients with colonic cancer was 85·1 (72·7 to 105·7) months, with no difference between open and laparoscopic groups: 105·7 (72·9 to –) and 81·9 (61·0 to 103·3) months respectively (log rank statistic = 0·87, $P = 0·352$) (*Fig. 2a*).

Median overall survival for patients with rectal cancer was 73·6 (64·3 to 89·5) months, with no difference by group: 65·8 (49·0 to 83·8) and 82·7 (67·3 to 97·6) months in open and laparoscopic groups respectively (log rank statistic = 2·11, $P = 0·147$) (*Fig. 2b*). Median overall survival in patients with rectal cancer undergoing anterior resection (AR) or abdominoperineal resection (APR) was 82·7 (67·3 to 105·6) and 61·5 (44·8 to 81·7) months respectively. There was no difference in overall survival by randomization group among patients with rectal cancer undergoing either AR (log rank statistic = 1·23, $P = 0·268$) or APR (log rank statistic = 0·71, $P = 0·400$). A trend towards improved overall survival in patients with rectal cancer was observed for laparoscopic surgery; however, this was significant only in terms of early survival (Wilcoxon statistic = 9·90, $P = 0·007$).

No significant differences in overall survival between randomized procedures were apparent when analysed by TNM stage; however, a non-significant trend towards improved overall survival was observed following open surgery in patients with TNM stage III colonic cancers. Median overall survival in patients with TNM stage III colonic cancer was 79·0 (32·3 to –) months in the open group compared with 34·9 (22·3 to 60·3) months in the laparoscopic group (log rank statistic = 4·68, $P = 0·031$).

Median overall survival in patients who underwent intraoperative conversion to open surgery was significantly worse: 59·2 (38·8 to 73·5) months compared with 78·4

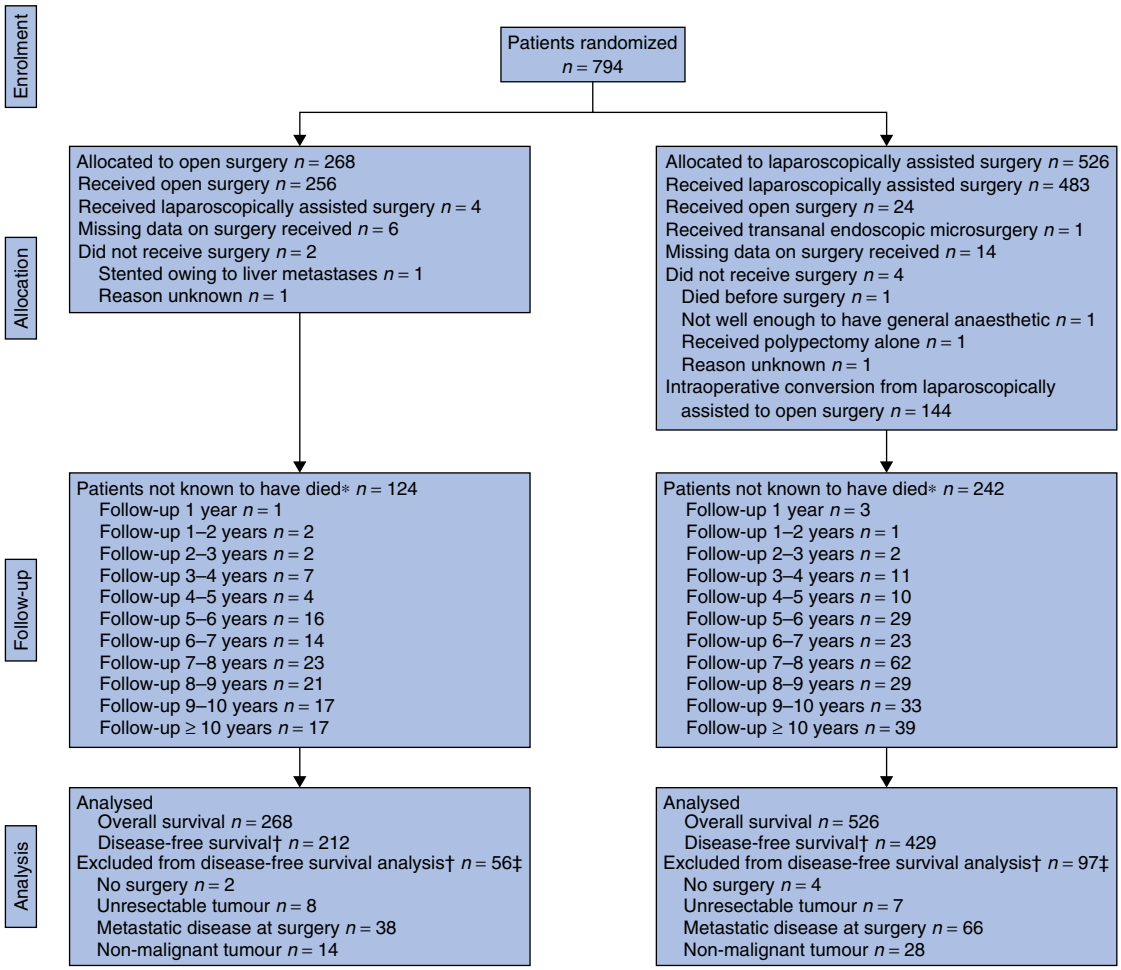


Fig. 1 CONSORT diagram showing allocation of patients in the long-term follow-up analysis. *The last patient was randomized in July 2002; therefore, all patients could have had at least 9 years of follow-up. †Numbers of patients included and excluded in analyses of disease-free survival also apply to analyses of local, distant and wound/port-site recurrence. ‡More than one reason may be given per patient

(66·1 to 106) months for open surgery and 94·8 (81·9 to 150·9) months for successful laparoscopically assisted surgery (log rank statistic = 13·58, $P = 0·001$). The difference remained following adjustment for stratification factors, age, sex and TNM stage ($P < 0·001$). This effect of conversion was statistically significant in colonic cancer (log rank statistic = 12·67, $P = 0·002$) (hazard ratio (HR) 2·28, 95 per cent c.i. 1·47 to 3·53; $P < 0·001$), but a non-statistically significant trend in rectal cancer (log rank statistic = 6·88, $P = 0·032$).

Sensitivity analysis of data for surgeons with a lower-than-average conversion rate showed that overall survival remained significantly worse in the converted group (log rank statistic = 9·23, $P = 0·001$), indicating that surgical experience is unlikely to influence outcome. This was maintained in patients with colonic cancer (log rank statistic = 9·84, $P = 0·007$), but sensitivity analysis for rectal cancer indicated no difference in overall survival by actual procedure (log rank statistic = 3·83, $P = 0·147$).

Disease-free survival

A total of 641 patients (212 open group and 429 laparoscopic group; 315 with colonic and 326 with rectal cancer) were included in the analyses of DFS and time to local, distant and wound/port-site recurrence.

The median DFS for all patients was 79·6 (70·3 to 92·8) months, with no difference between open and laparoscopic groups: 89·5 (67·1 to 121·7) and 77·0 (63·3

to 94·0) months respectively (log rank statistic = 0·29, $P = 0·589$).

Median DFS for patients with colonic cancer was 94·8 (74·2 to 108·7) months, with no differences by randomization group: 106·6 (72·7 to –) and 86·6 (67·3 to 108·7) months for open and laparoscopic groups respectively (log rank statistic = 0·60, $P = 0·438$). However, DFS varied according to tumour site; left-sided and sigmoid colonic resections performed markedly better than right-sided resections (HR 0·68, 95 per cent c.i. 0·48 to 0·97; $P = 0·031$).

Median DFS for patients with rectal cancer was 70·6 (55·0 to 85·5) months, with no differences between open and laparoscopic groups: 67·1 (49·0 to 121·7) and 70·8 (52·1 to 90·0) months respectively (log rank statistic = 0·01, $P = 0·925$). After adjustment for stratification factors, age, sex and TNM stage, APR was associated with worse DFS than AR (HR 1·82, 1·20 to 2·76; $P = 0·005$). No difference in DFS by randomized procedure was identified for AR (log rank statistic = 0·11, $P = 0·739$) or APR (log rank statistic = 0·79, $P = 0·373$).

DFS was significantly different by actual treatment received, following adjustment for stratification factors, age, sex and TNM stage (laparoscopic *versus* open: HR 0·92, 0·71 to 1·20; conversion *versus* open: HR 1·56, 1·13 to 2·15; $P = 0·003$); patients who had a laparoscopic procedure converted to open surgery had worse DFS than patients who had a planned open operation. When analysed by site, DFS was significantly worse in patients with colonic cancer whose operation was converted (HR 2·20, 1·31 to 3·67; $P = 0·007$), but not for those with rectal cancer ($P = 0·025$), after adjustment for stratification factors, age, sex and TNM stage.

Sensitivity analysis of data for surgeons with a lower-than-average conversion rate showed a trend towards worse DFS in patients whose procedure was converted (log rank statistic = 7·91, $P = 0·019$); this remained apparent in the subgroup with colonic cancer (log rank statistic = 3·99, $P = 0·136$), but not among those with rectal cancer (log rank statistic = 1·77, $P = 0·412$).

Overall, no differences were noted between randomization groups for any stage of colonic or rectal cancer, and the trend in overall survival favouring open surgery for TNM stage III colonic cancers was not maintained in DFS (log rank statistic = 1·86, $P = 0·173$).

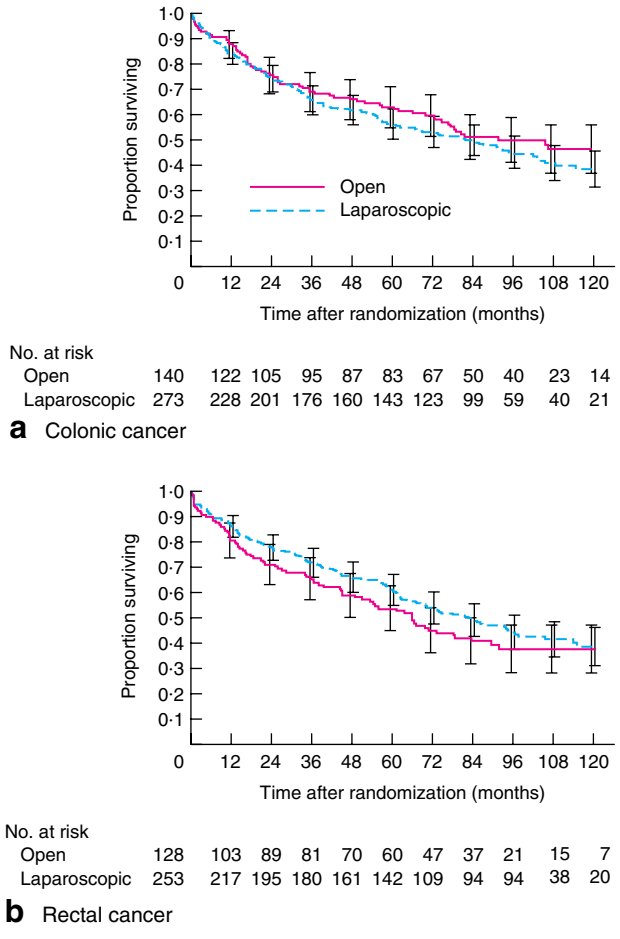
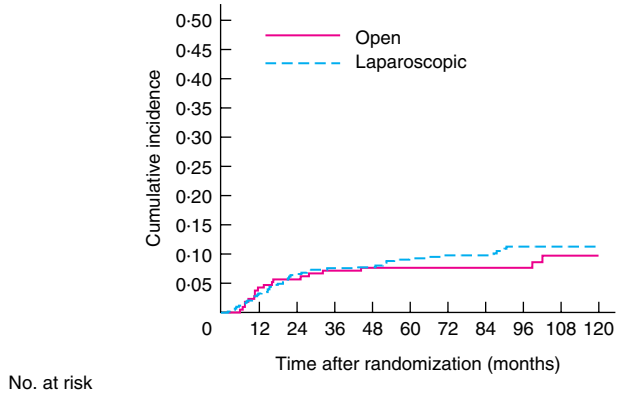


Fig. 2 Overall survival by randomized procedure for **a** colonic and **b** rectal cancer. Error bars represent 95 per cent confidence intervals

Local recurrence

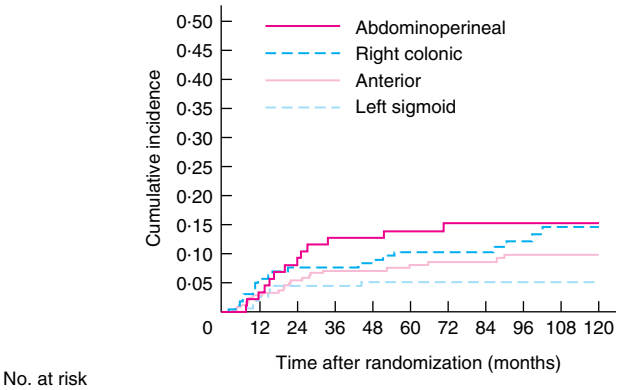
A total of 65 patients experienced at least one local recurrence. At 10 years, the local recurrence rate for all patients was 10·9 (95 per cent c.i. 8·3 to 13·5) per cent. There were no differences by randomized procedure for local recurrences at any site (*Fig. 3a*). However, right colonic cancers were associated with a trend towards increased local recurrence compared with left-sided and sigmoid cancers (log rank statistic = 5·52, $P = 0·019$) (*Fig. 3b*). The 10-year local recurrence rate for patients with left-sided and sigmoid cancers was 5·2 per cent compared with 14·7 per cent for those with right colonic cancers (difference 9·5 (95 per cent c.i. 2·3 to 16·6) per cent). No significant differences were observed between AR and APR (log rank statistic = 3·11, $P = 0·078$); the 10-year rates were 9·9 and 15·3 per cent respectively (difference 5·4 (−3·3 to 14·0) per cent) (*Fig. 3b*). Overall, no differences in local recurrence were observed by actual procedure. No differences in local recurrence by randomized procedure were noted for any stage of disease.



No. at risk

Open	212	180	162	147	133	122	99	77	53	31	19
Laparoscopic	429	373	330	300	275	239	192	161	90	62	32

a Randomized procedure



No. at risk

Abdominoperineal	87	74	59	51	44	41	32	26	11	8	5
Right colonic	157	132	116	103	95	85	75	61	41	30	19
Anterior	239	211	192	177	161	136	106	91	54	37	19
Left sigmoid	158	136	125	116	108	99	78	60	37	18	8

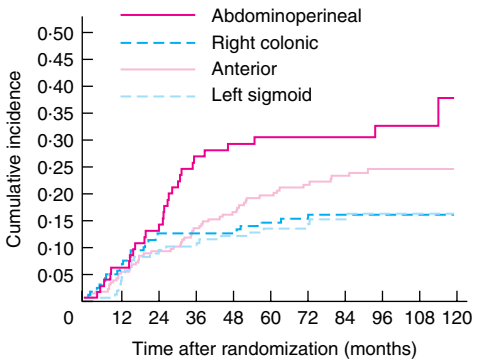
b Site of operation

Fig. 3 Cumulative incidence of local recurrence for all patients by **a** randomized procedure and **b** resection type

Distant recurrence

Overall 129 patients experienced at least one distant recurrence, 40 in the open and 89 in the laparoscopic group, giving a 10-year distant recurrence rate of 21·8 (18·3 to 25·3) per cent. There were no differences in distant recurrences between open and laparoscopic groups (log rank statistic = 0·29, $P = 0·588$); the 10-year rates were 19·8 and 22·7 per cent respectively (difference 2·9 (−4·2 to 10·0) per cent).

No differences in distant recurrence were found between randomization groups for colonic or rectal cancer (log rank statistic = 0·002, $P = 0·965$ and log rank statistic = 0·228, $P = 0·633$ respectively). No differences in distant recurrence by site of operation were observed for patients with colonic cancer (log rank statistic = 0·07,



No. at risk

Abdominoperineal	87	73	59	45	38	36	29	24	10	7	5
Right colonic	157	132	114	104	98	89	78	63	45	33	22
Anterior	239	206	187	169	151	126	101	84	54	38	19
Left sigmoid	158	134	121	113	106	97	77	58	35	17	7

Fig. 4 Cumulative incidence of distant recurrence by resection type for all patients

$P = 0·795$). However, among patients with rectal cancer there was a trend towards increased distant recurrence in those undergoing APR compared with AR (log rank statistic = 5·50, $P = 0·019$); the 10-year rates were 37·7 and 24·3 per cent respectively (difference 13·3 (−1·3 to 27·9) per cent). Patients with rectal cancer remained at a higher risk of distant recurrence than those with colonic cancer (log rank statistic = 16·10, $P = 0·001$) (*Fig. 4*).

Over the duration of the study, distant recurrence rates did not differ significantly by actual treatment received (log rank statistic 0·21, $P = 0·899$); the 10-year rates for patients who had an open, laparoscopic and converted procedure were 20·1, 22·6 and 22·5 per cent respectively. No differences in distant recurrence by randomized procedure were noted for any stage of disease.

Wound/port-site recurrences

Twelve patients (1·9 per cent of the DFS population) experienced at least one wound or port-site recurrence: two in the open and ten in the laparoscopic group. No significant differences in time to wound/port-site recurrences were observed by randomization group or actual procedure for either colonic or rectal cancer. A significant increase in wound/port-site recurrences was seen with increasing TNM stage (log rank statistic = 14·81, $P = 0·002$).

Discussion

Laparoscopically assisted surgery has been established previously as a recognized option for the surgical management

of colorectal cancer. Evidence from randomized clinical trials, including CLASICC, has consistently shown comparable outcomes between open and laparoscopically assisted surgery in terms of overall survival and DFS[6,7]. Reassuringly, pathological data from CLASICC, showing non-significantly raised circumferential resection margin positivity rates with laparoscopically assisted AR compared with open AR[2], did not translate into survival differences at either 3- or 5-year follow-up[6,7]. The present long-term follow-up of CLASICC has further demonstrated that laparoscopically assisted surgery is oncologically safe, and a suitable alternative to open surgery in the treatment of colorectal cancer, reporting no differences in long-term overall survival and DFS. There were no significant differences in local recurrence rates between randomized groups, and in particular the rectal cancer subgroups, a finding supported by recent meta-analyses[9,10].

In terms of survival, patients with colonic cancer appeared to do better than those with rectal cancer, a finding at odds with trends reported at the time of data collection in the general UK surgical population. However, CLASICC has demonstrated that survival of patients with rectal cancer is equivalent to that of the general UK surgical population, and improved survival in patients with colonic cancer in CLASICC is most likely explained by selection in terms of higher social class and lower stage of disease[11].

On multivariable analysis, there was a statistically significant difference in DFS when right-sided cancers were compared with left-sided and sigmoid colonic cancers, with a non-statistically significant trend towards increased local recurrence in patients with cancers of the right colon. Recent evidence suggests that complete mesocolic excision (CME) with central vessel ligation (CVL) may improve oncological outcomes following right-sided resections[12,13]. Although equivalence in terms of resection has been suggested[14], there are no randomized data comparing laparoscopic and open surgery from which to draw any firm conclusions. It should be noted, however, that neither CME nor CVL was practised in the laparoscopic arm of CLASICC.

The present study has confirmed the observation that rectal cancers, in particular those subjected to APR, are at a higher risk of distant recurrence than colonic cancers. The local recurrence rates were similar in both the open and laparoscopic groups for AR and APR. CLASICC was undertaken before popularization of the extralevator APR (EL-APR) technique[15], and it is interesting to speculate what impact the EL-APR might have on local recurrence rates following APR (15·3 per cent at 10 years with APR in CLASICC compared with 7–10 per cent reported with EL-APR)[16,17].

Higher local recurrence rates may also reflect the lower use of radiotherapy during the trial period compared with current practice. Further recent advances in this field include the introduction of robotic-assisted surgery. Early data from non-randomized sources suggest that robotic assistance may help to reduce the conversion rates in laparoscopic surgery[18,19]. Other potential advantages include better autonomic nerve preservation, which may impact on the previously high rates of postoperative sexual and urinary dysfunction following total mesorectal excision[20,21].

There remains conflicting evidence regarding the impact of conversion on postoperative outcomes, with a number of studies suggesting that conversion does not influence survival adversely[22,23]. In contrast, CLASICC previously reported worse outcomes associated with conversion, although this was statistically significant only in terms of overall survival[6,7]. In the present analysis of long-term follow-up data, only patients with colonic cancer appeared to suffer adverse survival following conversion, which was associated with a statistically significant reduction in both overall survival and DFS following adjustment for key prognostic factors. The finding of poor DFS after conversion in patients with colonic cancer suggests that the disease process itself adversely influenced survival rather than conversion *per se*. As advanced cancer is the most commonly cited reason for conversion, this would appear to be the most likely explanation[24]. The DFS data showed gradually worsening survival in patients whose procedures had been converted compared with those who had a planned open procedure. This suggests a long-term process, that is advanced cancer pathology affecting survival. The more rapid initial decline seen in overall survival is explained by the presence of factors such as increased stress owing to a prolonged operation, in addition to adverse prognostic factors including, but not limited to, surgical experience, and inherent patient factors such as advanced disease, obesity and anatomical variation. These are likely to increase early morbidity and adversely affect recovery, thus primarily affecting overall survival.

Neither overall survival nor DFS appeared to be influenced adversely by intraoperative conversion in patients with rectal cancer. The reason for this is unclear, and the limited patient numbers preclude further subgroup analysis.

Interestingly, there was a trend towards improved early survival associated with laparoscopic surgery in patients with rectal cancer. Although this has not been reported elsewhere, it may be due to improved functional recovery resulting from the minimally invasive nature of the surgery[2,4,25]. This finding in particular should encourage

surgeons to use laparoscopic surgery in patients with rectal cancer.

Overall, there were no statistically significant differences in overall survival or DFS between surgical techniques when analysed by TNM stage. A trend favouring survival following laparoscopic resection of stage III colonic cancer has been reported previously[26], although these findings have since been explained as an outlier effect owing to underpowered subgroup analysis. The long-term follow-up of CLASICC has shown a converse trend, favouring open surgery in patients with stage III colonic cancer. Although this appears to suggest worse oncological outcomes associated with laparoscopic surgery, the numbers at risk are small and no confirmatory reports have been found. Any real effect therefore remains speculative, and it is evident that caution should be employed pending further research in this group of patients.

The long duration of follow-up examined here provides evidence to support the use of laparoscopically assisted surgery for colonic and rectal cancer. Laparoscopic surgery should be the treatment of choice, enabling patients to benefit from earlier functional recovery with no detriment to long-term survival outcomes.

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