Randomized clinical trial

Randomized clinical trial comparing laparoscopic and open surgery in patients with rectal cancer

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Background: **The laparoscopic treatment of rectal cancer is controversial. This study compared surgical outcomes after laparoscopic and open approaches for mid and low rectal cancers.**
Methods: **Some 204 patients with mid and low rectal adenocarcinomas were allocated randomly to open (103) or laparoscopic (101) surgery. The surgical team was the same for both procedures. Most patients had stage II or III disease, and received neoadjuvant therapy with oral capecitabine and 50–54 Gy external beam radiotherapy.**
Results: **Sphincter-preserving surgery was performed in 78·6 and 76·2 per cent of patients in the open and laparoscopic groups respectively. Blood loss was significantly greater for open surgery ($P < 0.001$) and operating time was significantly greater for laparoscopic surgery ($P = 0.020$), and return to diet and hospital stay were longer for open surgery. Complication rates, and involvement of circumferential and radial margins were similar for both procedures, but the number of isolated lymph nodes was greater in the laparoscopic group (mean 13·63 *versus* 11·57; $P = 0.026$). There were no differences in local recurrence, disease-free or overall survival.**
Conclusion: **Laparoscopic surgery for rectal cancer has a similar complication rate to open surgery, with less blood loss, rapid intestinal recovery, shorter hospital stay, and no compromise of oncological outcomes. Registration number: NCT00782457 (http://www.clinicaltrials.gov).**

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Introduction

Multicentre studies and meta-analyses comparing laparoscopic with open surgical treatment of colonic cancer have demonstrated short-term advantages for the laparoscopic approach, including less postoperative pain, rapid recovery of intestinal function and short length of hospital stay, but similar long-term oncological outcomes and survival[1–4]. However, less is known about the role of laparoscopy in rectal cancer surgery, where outcomes are more closely linked to the surgical technique for several reasons. First, the anatomical position of the rectum makes access more difficult; second, total mesorectal excision (TME) is important for reducing local recurrence and improving survival; and, finally, preservation of the autonomic nerves and sphincter apparatus are important to maintain bladder, sexual function and continence, which represent important aspects of quality of life after surgery[5]. Although there is some evidence for the safety and efficacy of the laparoscopic approach in rectal cancer surgery, there is still controversy because most studies were not randomized[6–11], and the few prospective randomized studies had only short-term follow-up[1,12,13].

The aim of this study was to compare the outcome of laparoscopic and open surgery for mid and low rectal cancer. The primary endpoints were number of lymph nodes isolated, circumferential margin involvement, rate of complications and length of hospital stay. Secondary endpoints were local recurrence and survival.

Methods

Between January 2002 and February 2007 a randomized prospective study was performed to compare laparoscopic and open surgery in patients with mid and low rectal adenocarcinoma. Patients with locally advanced disease (T4) or familial adenomatous polyposis, and those who underwent emergency surgery were excluded. The study was approved by the hospital ethics committee.

Consenting patients were allocated to laparoscopic or open surgery by computer-generated randomization with the surgical approach concealed in a sealed envelope until the day of operation.

All patients underwent physical examination, total colonoscopy plus biopsy, rigid sigmoidoscopy, anorectal ultrasonography, thoracic and abdominal computed tomography (CT) and pelvic nuclear magnetic imaging; patients without a complete colonoscopy had a barium enema. The anaesthetist assessed all patients before operation and assigned an American Society of Anesthesiologists grade.

Patients with stage II or III adenocarcinoma according to the International Union Against Cancer/American Joint Committee on Cancer colorectal cancer staging system[14] received neoadjuvant treatment with chemotherapy and radiation therapy as follows: three-field pelvic radiation therapy with 50–54 Gy, 5 days a week, 1·8 Gy/day, together with oral capecitabine at a dose of 1000–1500 mg per m^2 per day for the whole duration of radiotherapy. The operation was carried out 6–8 weeks after the end of the neoadjuvant treatment. Patients with resectable distant metastases were operated on electively after recovering from rectal surgery. Patients with stage III or IV disease received adjuvant chemotherapy.

Surgical technique

All operations were performed by the same surgical team (J.L., Q.H. and G.V.), which had experience in open TME and advanced laparoscopic colorectal surgery. All patients had bowel preparation with polyethylene glycol, low molecular weight heparin, and amoxicillin–clavulanic acid or metronidazole plus gentamicin in patients who were allergic to β-lactam antibiotics.

All patients underwent TME with preservation of the hypogastric nerves. An abdominoperineal excision (APE) was performed when the tumour infiltrated the anal canal or it was not possible to obtain a distal margin of more than 1 cm. For anterior resection, stapled side-to-end colorectal or handsewn coloanal anastomoses were constructed. An ileostomy was fashioned at the surgeon's discretion, mainly in patients who had undergone neoadjuvant treatment, when the procedure was challenging and in all patients with a coloanal anastomosis.

Patients undergoing open surgery were placed in the Lloyd-Davis position, and the abdominal and pelvic cavity was accessed via a midline laparotomy extending from above the umbilicus to the pubis. Patients having laparoscopic surgery were placed in the Lloyd-Davis position with forced Trendelenburg (30°). The surgeon stood to the patient's right, the first assistant to the left and the second assistant between the patient's legs. The monitor was placed at the patient's feet on the left. A pneumoperitoneum was created with a pressure of 12–15 mmHg and the following ports were inserted: one supraumbilical (11 mm), two in the right iliac fossa (5 and 12 mm) and one in the left iliac fossa (5 mm). When necessary a fifth (10-mm) port was inserted in the suprapubic region to separate at the cul-de-sac of Douglas and occasionally an accessory port in the right upper quadrant for splenic flexure mobilization.

Patients undergoing anterior resection received a small mini-incision, usually horizontal, for removal of the specimen and placement of the staple-gun head. For patients having APE or coloanal anastomoses the specimen was removed through the perineum with no need for an abdominal incision.

Treatment of the perineal wound in all patients receiving APE was with postoperative lavage using two tubes placed in the pelvis through the abdominal wall. One of these was used to instil saline at a rate of 42 ml/h for 24–48 h, and the other for drainage. Once the lavage had been completed, one of the tubes could be withdrawn or left for drainage[15].

Patients started oral intake on the first or second day after operation and the urinary catheter was removed. Use of nasogastric tubes was avoided. The drain was removed when less than 100 ml/day was produced. Mobilization was encouraged on the first day after surgery. Patients were discharged from hospital after removal of the drain when they were able to tolerate a normal diet, had evidence of intestinal transit, had no evidence of complications and had social support.

Pathological analysis

All specimens were analysed by the same experienced pathologist, who assessed involvement of the circumferential margin (distance of 1 mm or less from the tumour to the mesorectal fascia), involvement of the distal margin (tumour reaching the distal section) and number of isolated lymph nodes.

Follow-up

Postoperative complications were regarded as those occurring during admission or leading to readmission in the first 30 days after surgery. A clinical anastomotic leak was considered present when dehiscence was detected by digital examination or endoscopy and the patient had peritonitis, leakage of gas, faecal drainage or pelvic abscess.

All patients were followed up as outpatients every 3 months for the first 2 years and every 6 months thereafter. On each visit they had a physical examination, general blood tests and determination of the carcinoembryonic antigen level. Every 6 months they alternated between thoracic and abdominal CT or abdominal ultrasonography and chest radiography. A complete colonoscopy was performed yearly.

Local recurrence was defined as reappearance of tumour in the surgical field. Both local recurrence and distant metastases were confirmed by histological examination.

Study endpoints

The primary endpoints were number of lymph nodes isolated, circumferential margin involvement, rate of complications and length of hospital stay. Secondary endpoints were local recurrence, disease-free and overall survival.

Statistical analysis

The sample size was calculated based on the number of lymph nodes isolated. Isolation of a mean of 12·0 lymph nodes per specimen is deemed appropriate, and there are considered to be no differences in the radicality of the technique when there is a difference of 2·0 in the number of lymph nodes isolated. The size of each group calculated for two samples, using a bilateral test with an α error of 0·05, a β error of 0·20 and a s.d. of 5, was 97·5 patients.

Data were processed with the software package SPSS® version 13.0 for Windows® (SPSS, Chicago, Illinois, USA). Comparisons of two means were made with the combined Student t test or Behrens–Fisher test, depending on whether there was homogeneity of variances or not between the two samples, or with the non-parametric Mann–Whitney test when the data were clearly distributed in an abnormal fashion even after performing log transformation. To study the relationship between qualitative variables and compare ratios in independent samples a contingency table analysis was performed using Pearson's χ^2 test and subsequent residuals analysis, or Fisher's exact test.

Survival rates were calculated using the Kaplan–Meier estimation method and survival curves were compared with the log rank test. Survival data are summarized as mean rates with 95 per cent confidence intervals. Likewise

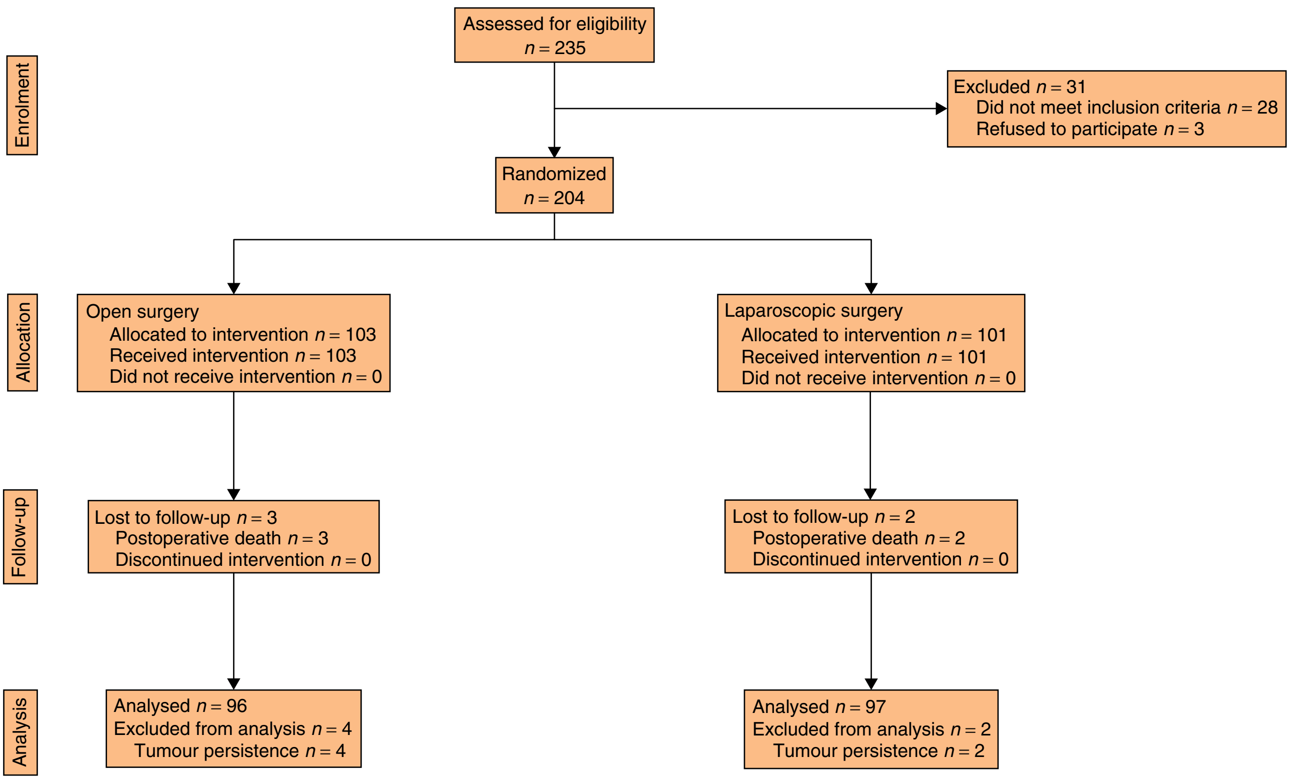


Fig. 1 Study flow diagram. Patients who died after surgery and those whose surgery was not curative were excluded from follow-up but were included in the short-term analyses

a survival analysis was carried out for the disease-free interval, where the event of interest was not death but the appearance of recurrence and/or metastases, local recurrence, hepatic metastases and pulmonary metastases.

Results

Some 103 patients were randomized to open surgery and 101 to a laparoscopic procedure (*Fig. 1*). There were no significant differences in baseline characteristics between the two groups (*Table 1*). The operative results are summarized in (*Table 2*). The rate of sphincter-preserving surgery was 77·5 per cent overall, and was similar in the two groups. A defunctioning ileostomy was created in 60·8 per cent of patients who had sphincter-preserving surgery, again with no differences between groups. Blood loss was statistically significantly greater during open surgery ($P < 0{\cdot}001$), but the difference between groups was not clinically important (approximately 100 ml). Mean operating time was 21 min longer for laparoscopic than open surgery. Return to oral diet and length of hospital stay were longer by a mean of 1 day in the open group, but these differences were not significant, perhaps indicating a type II error.

Eight operations (7·9 per cent) in the laparoscopic group were converted to an open procedure, because the distal section of the TME could not be completed in two patients, and owing to difficulty in mobilizing the splenic flexure (two), bleeding of the presacral bed (one), an ectopic kidney (one), ischaemia of the descending colon (one) and ureteral injury (one). These patients remained in the laparoscopic group for analysis of the results.

Complications occurred in 34 patients (33·0 per cent) after open surgery and 34 (33·7 per cent) in the laparoscopic group (*Table 3*). Eighteen patients underwent reoperation, eight (7·9 per cent) in the laparoscopic and ten (9·7 per cent) in the open group. Reasons for reoperation in the laparoscopic group were dehiscence (two patients;

Table 1 Patient characteristics

	Open ($n = 103$)	Laparoscopic ($n = 101$)	P†
Age (years)*	66·0(9·9)	67·8(12·9)	0·311‡
Sex ratio (M : F)	64 : 39	62 : 39	0·608
ASA grade			0·982
I	32 (31·1)	32 (31·7)	
II	35 (34·0)	35 (34·7)	
III	31 (30·1)	28 (27·7)	
IV	5 (4·9)	6 (5·9)	
Tumour location (cm from anal margin)*	6·24(2·91)	5·49(3·04)	0·105‡
Previous abdominal surgery	32 (31·1)	28 (27·7)	0·316
Preoperative stage			0·344
I	15 (14·6)	11 (10·9)	
II	39 (37·9)	35 (34·7)	
III	44 (42·7)	45 (44·6)	
IV	5 (4·9)	10 (9·9)	
Neoadjuvant therapy	77 (74·8)	73 (72·3)	0·551

Values in parentheses are percentages unless indicated otherwise; *values are mean(s.d.). ASA, American Society of Anesthesiologists. †χ^2 test unless indicated otherwise; ‡t test.

Table 2 Peroperative data

	Open ($n = 103$)	Laparoscopic ($n = 101$)	P‡
Surgical procedure			0·643
Abdominoperineal excision	22 (21·4)	24 (23·8)	
Anterior resection	81 (78·6)	77 (76·2)	
Anastomosis†			0·812
Stapled	67 (83)	65 (84)	
Handsewn	14 (17)	12 (16)	
Ileostomy†	48 (59)	48 (62)	0·775
Blood loss (ml)*	234·2(174·3)	127·8(113·3)	< 0·001§
Anterior resection	199·5(153·3)	109·6(117·3)	0·001§
Abdominoperineal excision	346·9(195·3)	187·5(74·9)	0·006§
Operating time (min)*	172·9(59·4)	193·7(45·1)	0·020§
Anterior resection	166·6(57·2)	195·1(43·9)	0·004§
Abdominoperineal excision	193·1(63·9)	189·2(49·8)	0·841§
Time to oral diet (days)*	3·6(3·4)	2·8(4·4)	0·198§
Length of hospital stay (days)*	9·9(6·8)	8·2(7·3)	0·106§

Values in parentheses are percentages unless indicated otherwise; *values are mean(s.d.). †Calculated from anterior resections. ‡χ^2 test unless indicated otherwise; §t test.

Table 3 Postoperative complications

	Open ($n = 103$)	Laparoscopic ($n = 101$)	P‡
Any complications	34 (33·0)	34 (33·7)	0·956
Surgical complications	30 (29·1)	31 (30·7)	0·946
Anastomotic leakage*	10 (12)	5 (6)	0·237
Urinary retention	5 (4·9)	7 (6·9)	0·747§
Perineal infection†	7 (32)	6 (25)	0·510
Ileus	8 (7·8)	6 (5·9)	0·522
Surgical wound infection	2 (1·9)	0 (0)	0·243§
Abscess	2 (1·9)	3 (3·0)	1·000§
Obstruction	2 (1·9)	2 (1·9)	1·000§
Haemoperitoneum	1 (1·0)	1 (1·0)	1·000§
Colovaginal fistula	0 (0)	2 (1·9)	0·497§
Ileostomy prolapse	0 (0)	1 (1·0)	1·000§
Urinary fistula	0 (0)	1 (1·0)	1·000§
Death	3 (2·9)	2 (1·9)	0·680§
Non-surgical complications	6 (5·8)	7 (6·9)	0·807
Urinary infection	5 (4·9)	6 (5·9)	0·759
Respiratory	4 (3·9)	1 (1·0)	0·365§
Sepsis	1 (1·0)	3 (3·0)	0·621§

Values in parentheses are percentages. *Calculated from anterior resections; †calculated from abdominoperineal excisions. ‡χ^2 test unless indicated otherwise; §Fisher's exact test.

Table 4 Anatomical and pathological characteristics

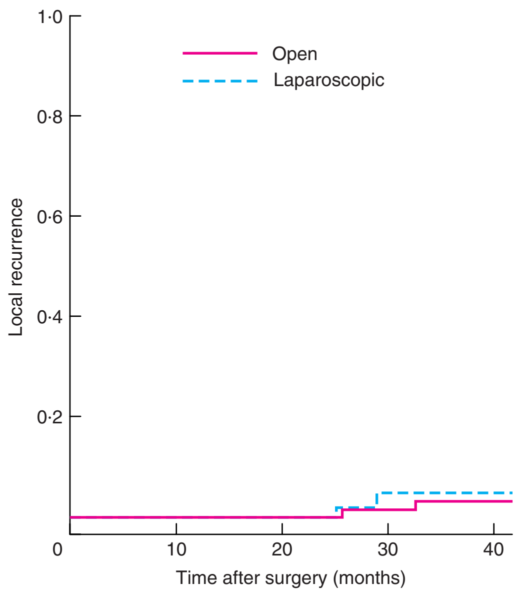
	Open (n = 103)	Laparoscopic (n = 101)	P
No. of lymph nodes isolated*	11·57(5·10)	13·63(6·26)	0·026†
Circumferential margin involved	3 (2·9)	4 (4·0)	0·422‡
Distal margin involved	0	0	—

Values in parentheses are percentages unless indicated otherwise; *values are mean(s.d.). †t test; ‡Fisher's exact test.

Table 5 Local recurrence, and disease-free and overall survival

	Open	Laparoscopic	P*
Local recurrence (%)			0·781
2 years	1·5 (0–4·4)	2·0 (0–5·9)	
5 years	5·3 (0–11·2)	4·8 (0–11·5)	
Disease-free survival (%)			0·895
2 years	88·7 (81·5–96·0)	89·8 (82·9–96·7)	
5 years	81·0 (71·4–90·6)	84·8 (75·4–94·2)	
Overall survival (%)			0·980
2 years	89·2 (82·5–95·9)	91·1 (84·6–97·6)	
5 years	75·3 (63·3–87·3)	72·1 (54·1–90·1)	

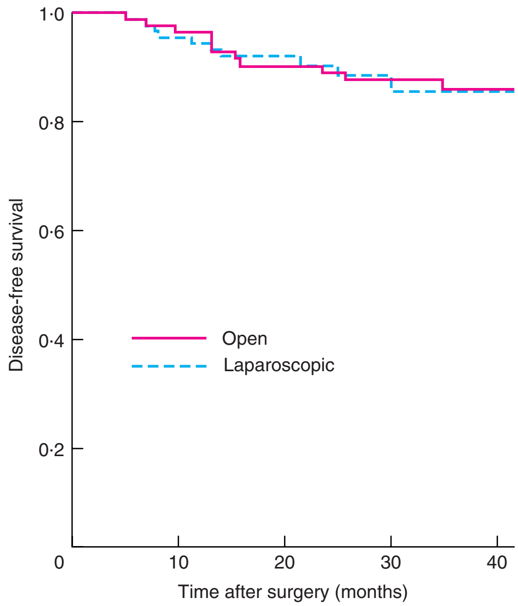
Values are mean (95 per cent confidence interval). *Log rank test.



No. at risk					
Open	96	89	78	62	43
Laparoscopic	97	88	75	60	40

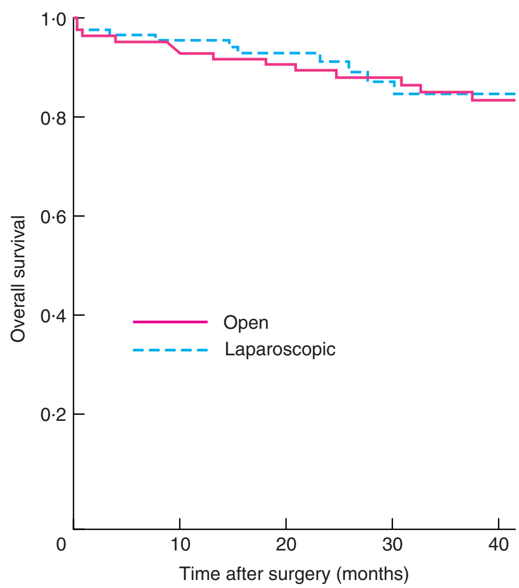
Fig. 2 Kaplan–Meier survival curves comparing local recurrence in open and laparoscopic groups

colostomy was performed in one and ileostomy in the other), obstruction at the ileostomy (two), haemoperitoneum (one), ileostomy prolapse (one), colovaginal fistula (one) and urinary fistula (one). Reasons for reoperation in the open group were dehiscence (seven patients; ileostomy was performed in three, colostomy in two, and lavage of the



No. at risk					
Open	96	81	71	51	37
Laparoscopic	97	79	68	48	33

Fig. 3 Kaplan–Meier survival curves comparing disease-free survival in open and laparoscopic groups



No. at risk					
Open	96	89	80	64	45
Laparoscopic	97	88	78	63	43

Fig. 4 Kaplan–Meier survival curves comparing overall survival in open and laparoscopic groups

cavity and drainage in two), intestinal obstructions owing to adhesions (two) and haemoperitoneum (one).

There were three deaths (2·9 per cent) in open group, one each from dehiscence, septic shock and respiratory infection. Two deaths (1·9 per cent) in the laparoscopic groups were due to dehiscence and septic shock owing to *Staphylococcus aureus*.

Anatomical and pathological examination of the specimen showed similar involvement of the circumferential and radial margins in the two groups, but the number of lymph nodes isolated was greater in laparoscopic group (*Table 4*).

Mean(s.d.) follow-up was 34·1(20·0) months for the open and 32·8(18·9) months for the laparoscopic group. There were no differences in rates of local recurrence, disease-free survival or overall survival (*Table 5*, *Figs 2–4*). No recurrence was observed at the trocars or surgical wound. Six patients in the open group developed hepatic metastases and nine pulmonary metastases, compared with five and six respectively in the laparoscopic group ($P = 0{\cdot}960$ and $P = 0{\cdot}842$ respectively).

Discussion

In this study the complication rate after laparoscopic surgery for rectal cancer was similar to that of open surgery, but there was less blood loss, more rapid recovery of intestinal transit and a shorter hospital stay. Local recurrence rates were similar and there was no difference in disease-free or overall survival.

In recent years the most significant progress in the treatment of rectal cancer has been the development of standardized TME[5] and neoadjuvant treatment. Both have led to a reduction in local recurrence, an increase in conservative sphincter-preserving surgery[5,16,17] and, in some studies, an improvement in survival[17]. Laparoscopic surgery for colonic cancer has led to a major improvement for patients[1–4]. Patients with rectal cancer were excluded from some of these multicentre studies[2,3] owing to the complexity of rectal surgery. One difficulty lies in mechanical distal dissection of the low-lying rectum when a coloanal anastomosis is required. In addition, the autonomic nerves must be identified and preserved while complying with the oncological principles of adequate margins (circumferential and distal) and proximal ligation vessels. All these aspects mean that the use of laparoscopic surgery for rectal cancer is controversial, there being no consensus on the advantages of this approach.

Laparoscopic surgery for rectal cancer, like open surgery, is complex and is associated with a considerably higher rate of complications than colonic surgery, especially if the surgeon does not have sufficient experience in open TME and advanced laparoscopic surgery. A similar incidence of complications has been reported for both open and laparoscopic techniques[1,9–13], and no differences in complications have been found in meta-analyses[18,19]. The complication that most affects prognosis is anastomotic leakage, which on most occasions is related to surgical technique because the linear staplers used for distal dissection of the rectum are not ideal and it is not uncommon for technically incorrect dissections to be made (zig zags, ischaemic ends, non-airtight stapling, etc.) The consequences of anastomotic leakage can be reduced, but not eliminated, by performing an ileostomy in patients with complex or low-lying anastomoses, those who have had neoadjuvant treatment and in men.

The duration of operation is longer for laparoscopy in most publications. In the present study the operating time was longer for laparoscopic surgery when anterior resection was performed but similar for APE. This is because the time spent on APE in open surgery is longer as a laparotomy has to be performed and closed, as well as closure of the perineal wound. Despite the longer operating time, most studies report a shorter hospital stay for patients having laparoscopy. In this study the length of stay was short in both groups, especially the laparoscopic group, without significant differences.

One of the most important prognostic factors in TME is involvement of the circumferential and distal margins, which leads to an increase in local recurrence and a reduction in survival. Several studies and meta-analyses of laparoscopic *versus* open surgery have shown that laparoscopic TME is an oncologically correct technique, and that the rate of distal and circumferential margin involvement and the number of isolated lymph nodes are similar with both techniques[9,19–21]. On the other hand, the conventional *versus* laparoscopic-assisted surgery in patients with colorectal cancer (CLASICC) trial[22] initially reported greater circumferential margin involvement in rectal cancer treated via a laparoscopy (although the difference was not significant) and at the time recommended caution when treating rectal cancer using the laparoscopic approach. However, after 3 years' follow-up the long-term results showed that this greater circumferential margin involvement did not lead to a greater incidence of local recurrence[1]. The number of isolated lymph nodes was higher in the laparoscopic group in the present study, probably because the laparoscopic approach allows better dissection and accuracy, owing to the better vision, amplification and exposure of structures, especially in narrow pelvises, and less manipulation of the mesorectum during dissection[8,11]. For the same reasons, blood loss tends to be smaller than for open surgery, which leads to a reduction in infectious complications and may reduce tumour recurrence[23,24].

The rate of conversion to open surgery varies enormously, from 5 to 20 per cent, depending fundamentally on the experience of the surgical team and patient selection. Conversions are associated with a poorer prognosis[11]. The incidence of conversion was low in the present study. Among other reasons, this may be explained by the exclusion of patients with tumours invading neighbouring structures.

A long-term analysis of outcome with assessment of local recurrence and survival is necessary for establishing the value of laparoscopic surgery in the treatment of rectal cancer. None of the short-term advantages would be important if the incidence of local recurrence and survival were compromised. Survival and local recurrence in this study, with a mean follow-up of over 30 months, were similar with both surgical techniques and comparable with previous findings[9–13,18,19,25]. Therefore, if the correctness of TME is reflected by the rate of local recurrence, laparoscopic TME is as efficient as open TME. The high incidence of local recurrence after both open and laparoscopic surgery reported by some authors[20,21] is probably due to the small series, the selection of patients (inclusion of tumours affecting adjacent organs) and high rates of conversion to open surgery. Further studies with more patients and longer follow-up are now needed to confirm the present results.

Acknowledgements

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