therapy anyway. The argument that randomization would address this issue may not hold if the study population is a biased one.

A recurrence rate of 49% in the active care group is high by any standards.[3] Again, one wonders whether or not the population studied is representative of the general population.

Withdrawals in each group were high (56 total), 22 with disease recurrence and 34 with comorbid conditions. Other reasons for withdrawal were loss to follow-up, patient preference, protocol violation and pregnancy. Although the sample size calculation had factored a high dropout rate, this in itself is a cause for worry, and again, may reflect a patient population with severe disease.

Rutgeerts score is not a formally validated score. The strength of the study is that it is a randomized controlled trial, which has never been done before. The design and analysis is robust, with mITT and per protocol analysis reported adequately. The study is based on the fact that mucosal healing has been shown to result in more clinical remission, less hospital admissions and less bowel resections. Thus, mucosal healing was used as the end-point. Since evidence suggests that anti-tumour necrosis factor (TNF) therapy reduces endoscopic and clinical recurrence in postoperative patients, the study investigated if stepping up therapy when mucosal recurrence occurs will lead to long-term healing. However, universal, immediate postoperative treatment with anti-TNF agents is expensive, has its own complications and will over-treat some patients. This study provides some rationale for using such therapy in high-risk patients.

The study is a pragmatic, real-life therapeutic strategy trial; and this is one of its major strengths. The sample size was calculated with an anticipated dropout rate of 31%.

However, more questions remain to be answered. Can we extrapolate these results to patients where mucosal recurrence cannot be seen? Are there other reliable ways to detect recurrence when the anastomosis is not within the reach of a colonoscope? Faecal markers, capsule endoscopy and cross-sectional imaging may be of value.[4]

With all its drawbacks, this study provides level 1 evidence for aggressive immunosuppressive therapy in high-risk postoperative patients.

REFERENCES

1 Bernell O, Lapidus A, Hellers G. Risk factors for surgery and postoperative recurrence in Crohn's disease. *Ann Surg* 2000;**231:**38–45.
2 Rutgeerts P, Geboes K, Vantrappen G, Beyls J, Kerremans R, Hiele M. Predictability of the postoperative course of Crohn's disease. *Gastroenterology* 1990;**99:**956–63.
3 Regueiro M, Kip KE, Baidoo L, Swoger JM, Schraut W. Postoperative therapy with infliximab prevents long-term Crohn's disease recurrence. *Clin Gastroenterol Hepatol* 2014;**12:**1494–502.e1.
4 Ananthakrishnan AN. Surgery for Crohn's disease: Look harder, act faster. *Lancet* 2015;**385:**1370–1.

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Rectal cancer: Time to change?

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SUMMARY

There has been an increase in laparoscopic surgery for colorectal cancers in the past decade owing to favourable short-term as well as oncological outcomes. The COLOR II trial aimed to compare laparoscopic and open surgery for rectal cancers in terms of locoregional recurrence, disease-free survival (DFS) and overall survival (OS). It was a non-inferiority, open-label, multicentre, randomized controlled trial conducted at 30 centres in 8 countries. Patients with solitary adenocarcinoma of the rectum within 15 cm from the anal verge without distant metastasis were included. The localization of the tumour was categorized as upper rectum (distal border of tumour, 10–15 cm from the anal verge), middle rectum (5–10 cm from the anal verge), and lower rectum (<5 cm from the anal verge). Patients with T4 or T3 tumours within 2 mm of the endopelvic fascia, as determined on imaging, were excluded.

Randomization was stratified according to the hospital, tumour location and use of preoperative radiotherapy. Patients were assigned in a ratio of 2:1 to undergo either laparoscopy or open surgery according to a list of randomization numbers with treatment assignments. A total of 1103 patients were randomized, among them 739 were assigned to laparoscopic surgery and 364 to open surgery. For various reasons 40 patients in the laparoscopic group and 19 patients in the open group were excluded. In the laparoscopic group, 699 patients were included in the analysis; however, 7 patients had open surgery. Of 349 patients in the open surgery group, 5 had laparoscopy. Both groups did not differ in baseline characteristics. Multidisciplinary cancer boards at the participating hospitals determined the use of neoadjuvant therapy. Stringent quality assessment of the surgical technique—by using unedited videos, and pathology reports—was done by the study management committee. The presence of tumour cells within 2 mm from the lateral surface of the mesorectum was considered as a positive circumferential resection margin. In this trial the primary end-point was locoregional recurrence 3 years after the index surgery and the secondary end-points were DFS and OS. The follow-up protocol was annual clinical examination 5 years after surgery and CT or MRI scan of the pelvis, abdomen and chest 3 years after surgery. Appropriate statistical analyses were done.

The conversion rate from laparoscopic surgery to open surgery was 16%. In the laparoscopic surgery group, the operating time was 52 minutes longer, the short-term outcomes such as bowel function returned one day earlier in the laparoscopic group and the hospital

stay was one day shorter than that in the open surgery group. There were no significant differences in the rates of anastomotic leak, complication or death. The groups did not differ with respect to the macroscopic completeness of mesorectum, involved circumferential resection margins or distal resection margins. They observed, at the end of 3 years, 5% locoregional recurrence in both the groups. In the intention-to-treat analysis, the rate of locoregional recurrence of upper rectal cancers was 3.5% in the laparoscopic surgery group and 2.9% in the open surgery group (difference 0.6%). In patients with middle rectal cancers, locoregional recurrence rates were 6.5% and 2.4%, respectively (difference 4.1%). In patients with lower rectal cancers the rates were 4.4% and 11.7%, respectively (difference 7.3%). In the per protocol analysis, the locoregional recurrence rate in patients with upper rectal cancers was 3% in the laparoscopic surgery group and 3.9% in the open surgery group (difference –0.9%). In patients with middle rectal cancers locoregional recurrence rates were 5.7% and 4.1%, respectively (difference 1.6%). While in patients with lower rectal cancers the rates were 3.8% and 12.7%, respectively (difference –8.9%). At 3 years, the DFS was 74.8% in the laparoscopic surgery group and 70.8% in the open surgery group (difference 4%). Though in stage I and II rectal cancers the DFS rates were similar in the two groups, in patients with stage III disease the laparoscopic surgery group had better DFS rates (64.9% *v*. 52%). The OS rates were almost similar in both the groups (86.7% in the laparoscopic group *v*. 83.6% in the open surgery). This was similar even according to the disease stage in the two groups. At 3 years, 19.1% of patients in the laparoscopic surgery group and 22.1% of those in the open surgery group had distant metastasis. In conclusion, long-term outcomes of the COLOR II trial indicate that laparoscopic surgery is as safe and effective as open surgery in patients with rectal cancers without invasion of adjacent tissues.

COMMENT

This study is relevant because it is a multicentre, randomized controlled trial, which is well designed and has a 3-year follow-up giving reliable information about recurrence. The authors included T1, T2 and a few T3 rectal cancers, which is more specific when compared with previous trials in colorectal cancers. The COREAN trial[1] was conducted in almost similar patients, but in fewer numbers. The randomization of patients in the ratio of 2:1 was pragmatic for accrual. The authors considered either CT or MRI scan for radiological staging of the disease, though uniform high resolution MRI scan would have been better.[2] The committee followed stringent quality control and decision-making criteria regarding neoadjuvant therapy. However, this was done by the local multidisciplinary cancer boards based on local facilities. Rectal cancer management is multimodal with neoadjuvant chemoradiotherapy as an important component.[3] In our opinion, in the era of advanced information technology, a single panel making these decisions would have been better. Since one-third of the study population received neoadjuvant therapy, a single tumour board taking the decisions on neoadjuvant therapy would have led to more consistent decisions and strengthened this trial.

All the centres in the trial performed both laparoscopic and open procedures and followed adequate standards of total mesorectal excision (TME). This was confirmed by the committee assessing sample videos from each centre. The lower circumferential resection margin (CRM) and locoregional recurrence rates were achieved because of standard surgical approaches, but the assessment of pathological specimens by different pathologists underscores the need for uniformity of pathological staging. The short-term outcomes such as return of bowel function and hospital stay were low as expected in the laparoscopic surgery group, probably because of this inherent property of minimal access surgery. A 16% conversion rate was higher compared to the COREAN trial. This might be due to few centres and more experienced surgeons in the COREAN trial. Although both intention-to-treat and per protocol analyses were done, the higher rate of conversion (112 patients) means that this might have influenced outcome. A detailed analysis of the reasons for conversion might have given a clearer picture and helped to formulate a protocol in the future. Better locoregional recurrence when compared with the CLASSIC trial[4] in both the groups might be due to more specific inclusion and exclusion criteria. At the same time taking a 2 mm CRM will add more strength to the results achieved. Comparison of the involved CRM and locoregional recurrence does not show a uniform correlation. The level of cancer versus local recurrence seems to be similar in different groups, but because of good vision in the lower pelvis in the laparoscopic method low CRM positivity in lower rectal cancer was observed when compared with the open surgery group. In middle rectal cancers, a higher local recurrence in the laparoscopic surgery group in contrast to open surgery cannot be explained. The DFS was not significantly different in both the groups. The stage-specific analysis of DFS shows that in stage 3 disease a higher percentage of patients had better results in the laparoscopic group. It is possible that in the future transanal procedures in combination with the abdominal operation may have a bigger impact on results. In conclusion, the results of this well-designed trial can be used to justify laparoscopic resection for T1, T2 and T3 rectal cancer with a CRM >2 mm.

REFERENCES

1 Kang SB, Park JW, Jeong SY, Nam BH, Choi HS, Kim DW, *et al.* Open versus laparoscopic surgery for mid or low rectal cancer after neoadjuvant chemoradiotherapy (COREAN trial): Short-term outcomes of an open-label randomised controlled trial. *Lancet Oncol* 2010;**11:**637–45.

2 Bipat S, Niekel MC, Comans EF, Nio CY, Bemelman WA, Verhoef C, *et al.* Imaging modalities for the staging of patients with colorectal cancer. *Neth J Med* 2012;**70:**26–34.

3 Huebner M, Wolff BG, Smyrk TC, Aakre J, Larson DW. Partial pathologic response and nodal status as most significant prognostic factors for advanced rectal cancer treated with preoperative chemoradiotherapy. *World J Surg* 2012;**36:**675–83.

4 Guillou PJ, Quirke P, Thorpe H, Walker J, Jayne DG, Smith AM, *et al.*; MRC CLASICC trial group. Short-term endpoints of conventional versus laparoscopic-assisted surgery in patients with colorectal cancer (MRC CLASICC trial): Multicentre, randomised controlled trial. *Lancet* 2005;**365:**1718–26.

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