Editorial

Have we improved in laparoscopic resection of rectal cancer: critical reflection on the early outcomes of COLOR II study

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Jacob *et al.* reported the first series of a combination of laparoscopic colonic & rectal resections in 1991 (1). It took just over a decade of debate and several trials to prove that laparoscopic colonic surgery (LCS) unequivocally results in better short-term outcomes when compared to open colonic surgery (OCS) (2). Several randomised controlled trials (RCTs) (3-5) have demonstrated that LCS offers reduced intra-operative blood loss, length of incision, post-operative analgesia requirements as well as shorter hospital stay. In malignant resections, LCS also offers comparable clearance margins and lymph node harvest. Therefore, LCS is now a well-accepted alternative to open surgery (2). However, the debate involving the role of laparoscopic approach in rectal cancer resection continues and is far from over (6).

The CLASSIC (Conventional *vs.* Laparoscopic- Assisted Surgery in Colorectal Cancer) trial was the first RCT to include patients with rectal cancer (4). The CLASSIC trial was very successful in increasing the awareness of the morbidity associated with laparoscopic rectal cancer surgery as the laparoscopic group in the study had increased rates of positive circumferential resection margin, even though this did not reach statistical significance and it did not result in increased incidence of local recurrence on long-term follow up (7). The short-term outcomes of laparoscopic rectal surgery were probably marginally better; however, there was a clear trend towards a less favorable outcome of patients who had conversion (4). Long-term follow up demonstrated no difference between open and laparoscopic groups in the 3-year overall survival, disease-free survival or local recurrence (7). There was no difference in the quality of life. The CLASSIC trial as well as other studies demonstrated that laparoscopic rectal resection is associated with increased risk of sexual and urinary dysfunction as 41% of men in the laparoscopic rectal surgery group had sexual dysfunction after laparoscopic anterior resection in comparison with 23% in the open group as well as increased anastomotic leak (2,4,6).

However, the outcomes of the MRC CLASICC trial should be interpreted with caution as the study design had set the surgeons' learning curve at 20 laparoscopic resections which was based on the best available data at that time (8) and clearly this was an underestimation of the learning curve for laparoscopic rectal surgery (LRS) (9). The reduction in the conversion rates for every year of the study is an indication that the learning curve was functional during the trial (4). Therefore, there has been a strong need for another RCT that compares the postoperative outcomes of open and laparoscopic rectal cancer surgery beyond the initial learning curve in LRS. COLOR II study (10) was specifically designed to answer this question.

COLOR II was designed as a non-inferiority open-label randomised trial that was carried out across 30 centers and hospitals in eight countries (Belgium, Canada, Denmark, Germany, the Netherlands, Spain, South Korea, and Sweden). Inclusion criteria were patients who have a single rectal cancer within 15 cm without evidence of distant metastases. Exclusion criteria were T4 tumours, or T3 rectal cancers within 2 mm of the endopelvic fascia, as seen on pre-operative CT or MRI and T1 tumours treated with local transanal excision.

Patients were randomised in a 2:1 ratio to laparoscopic surgery or open surgery. Peri-operative care as well as the use of preoperative radiotherapy and chemo- therapy were left to the local protocols. However, COLOR II study was strict in allowing surgical teams to participate in the study as each team had to submit unedited recordings of five consecutive laparoscopic TMEs with their pathology

reports for assessment or were directly observed by one of the five governors of the study. It should be noted that quality approval within the COLOR II trial was only done at entry into the trial and unfortunately the same assessment was not done for the quality of open resections. The authors in their report acknowledged these limitations. Processing and assessment of the pathology specimens were done locally according to a pre-agreed detailed description in the study protocol. The primary outcome in the COLOR II trial is the proportion of patients with local recurrence at 3 years after index surgery; these data are not yet mature and will be reported at a later date. The current report only outlines the short-term secondary endpoints, which are the early post-operative outcomes (10).

Previous publications (2,6) have clearly demonstrated that LRS is associated with better post-operative outcomes when compared to open rectal surgery (ORS) in terms of decreased intraoperative blood loss, reduced opiates requirements, earlier return of gut function and shorter hospital stay and these findings were confirmed by COLOR II study. However, it was hoped that with the increasing expertise in laparoscopic rectal surgery other less favorable short-term outcomes in the earlier studies would improve. These include longer operating time, post-operative morbidity and mortality, increased resection margin positivity, higher rate of anastomotic leak and a trend for postoperative urinary and sexual dysfunction.

COLOR II study confirms that LRS was associated with less blood loss, reduced use of epidural analgesia, earlier restoration of bowel function, and shorter hospital stay when compared to open rectal surgery (ORS). These findings are similar to those in other trials (2,6). Despite the extensive laparoscopic experience of the surgical teams involved in the study laparoscopic procedures took longer than open [LRS: 240 mins (184-300 mins) *vs.* ORS: 188 mins (150-240 mins); P<0.0001].

There were similar oncological outcomes in terms of the resected surgical specimens. Macroscopically, completeness of the resection was not different between laparoscopic & open groups (LRS: 88% *vs.* ORS: 92% respectively; P=0.250). Positive circumferential resection margin (<2 mm) was noted in 10% of LRS as well as 10% OSR (P=0.850). Median tumour distance to distal resection margin did not differ significantly between the groups [LSR: 3.0 cm (2.0-4.8 cm) *vs.* OSR: 3.0 cm (1.8-5.0 cm); P=0.676]. However, the proportion of patients with low rectal cancers with positive CRM was significantly lower in the laparoscopic surgery group than in the open surgery group (P=0.014), which could be attributed to the better visibility offered by the laparoscopic approach. The median number of lymph nodes harvested after surgery was not significantly different in the two groups.

Compared to the CLASSIC trial, there has been a definite improvement in conversion rate from 29% in the CLASSIC trial to 17% in COLOR II study. This probably does not only reflect the increasing experience with LRS, but it could also be related to the availability of improved equipment such as better optics with high definition video, better quality energy devices and more reliable instruments. However, conversion rate for standard LRS reported in COLOR II study remains higher than that reported for robotic rectal surgery (RRS), which is 1-7% (11). As the surgical teams in COLOR II study have extensive experience in LRS, this conversion rate should be attributed to other factors such as the limitation of the current generation of laparoscopic instruments, which is in part addressed by the increased dexterity available with the robotic system.

The proportion of patients who needed re-intervention within 28 days after surgery was similar in the two groups. However, LRS continues to be associated with increased anastomotic leak rate, which was 13% in the laparoscopic group and 10% in the open surgery group (P=0.462). The authors acknowledge that this anastomotic leak rates have not improved in comparison those reported in the CLASSIC trail (LRS: 7% and ORS: 10%) (4). Morbidity was similar in both groups, (LSR: 40% *vs.* OSR: 37%, respectively; P=0.424). Also, mortality within 28 days after surgery was similar (LSR: 1% *vs.* OSR: 2%; P=0.409).

Urinary continence and sexual function were not reported in the current publication. These adverse events were recorded in the COLOR II trial 1 year after the index surgery and will be reported later with the long-term outcomes (10).

The authors indicate that '*the short-term outcomes of the COLOR II trial show that the radicality of laparoscopic resection (as assessed by pathology report) in patients with rectal cancer is no different to that of open surgery, and that laparoscopic surgery was associated with similar rates of intra-operative complications, morbidity, and mortality*' (10). This in part implies that LRS is not superior to the open approach and there is no clear reduction in morbidity or mortality for patients with rectal cancer subjected to surgical resection when the laparoscopic approach is used.

The currently published report on COLOR II study (10) did not address 2 major points, namely the outcomes in the converted group of patients and the cost-effectiveness of LRS. One of the main concerns from the CLASSIC trial was

the clear trend towards a less favorable outcome in patients who had conversion. In the published COLOR II report, there was no separate sub-analysis of the outcomes of the converted group to ascertain if, with increasing experience, timely conversion would not result in poorer outcomes.

The second issue that was not addressed is cost-effectiveness analysis of LRS *vs.* ORS. Currently most, if not all, health care systems across the world are under undue financial pressure and therefore cost-effectiveness analysis comparing the costs of LRS *vs.* OSR per each country would have been useful. Previous analysis of the cost of laparoscopic colorectal surgery over time, projected that the results of future economic evaluations will unequivocally show that laparoscopic colorectal surgery would be cheaper than open surgery when practiced in Western health care systems where postoperative care cost is high (12). The reduction in hospital stay following laparoscopic colorectal surgery reduces the overall cost of the procedure. However, in Asian health care systems, operative costs overshadow the cost savings gained by reduced hospital stay. However, this previous analysis included both colonic and rectal resections. Providing detailed cost-effectiveness analysis for LRS *vs.* ORS were going to be an invaluable addition to the current literature. As the main savings associated with LRS comes from reduced post-operative stay, the reported reduction in COLOR II study in the LRS group by 1 day is unlikely to result in cost-effective savings.

The findings in the COLOR II study answered an important question that was raised after the CLASSIC trial: can increased experience in LRS address the limitations of the laparoscopic approach seen in the CLASSIC trial. COLOR II study indicates that LRS could offer better short-term outcomes but with no reduction in morbidity or morality. Given that ORS is well known to be associated with inherent morbidity and mortality it was assumed that the reduction in the trauma of access could help to provide better outcomes. However, it is difficult to support this hypothesis from the current evidence.

This is in an agreement with the findings in two systematic reviews on the outcomes of minimally invasive approach in rectal cancer recently published by our group. A systematic review that included all the published studies on laparoscopic rectal cancer surgery over the last 20 tears failed to show clear evidence of improvement in the early post-operative outcomes over time. The fact that despite 20 years of practice of LRS there has been no clear trend of improvement in the rate of postoperative complications indicate that other factors, apart from the learning curve, could be involved such as limitations of the current laparoscopic instrumentation, possibly exceptionally long learning curve or it could be that rectal resection is associated with inherent morbidity regardless of the approach used (13). Also a systematic review on the studies reporting the use of the robotic approach to resection of rectal cancer failed to show clear significant reduction in early post-operative complications when compared with standard laparoscopic surgery with only potentially better short-term outcomes when applied in selected patients such as obesity, male sex, preoperative radiotherapy, and tumors in the lower two-thirds of the rectum (11).

The findings in the currently available literature indicate the need for a different approach in resection of rectal cancer, as it is unlikely that further experience in laparoscopic rectal surgery will result in improved short-term outcomes. The challenges in LRS could be possibly addressed by development of specifically designed laparoscopic instruments to tackle the limitation of the current instruments which is usually manifested by difficulty in obtaining adequate retraction and tissue tension to help precise dissection in the confines of the pelvis. This is in part has been addressed by robotic surgery. However, there are still several well-known limitations with the currently available laparoscopic staplers especially when used low down in the male pelvis (14).

It is more likely that we need to adopt a novel approach to surgical resection of rectal cancer as the available evidence suggests that it is unlikely that further experience with the currently available minimally invasive approaches would result in better outcomes compared to ORS. There is an increasing interest in rectum-preservation strategies for patients with early rectal cancer. Currently, two CRTs are examining rectum-preserving strategies in early rectal cancer. The CARTS study [chemoradiation therapy for rectal cancer in the distal rectum followed by organ-sparing transanal endoscopic microsurgery (TEMS)] has been designed to assess the adequacy of TEMS following pre-operative radiotherapy. Patients with a clinical T1-3 N0 M0 rectal adenocarcinoma below 10 cm from the anal verge will receive neoadjuvant chemoradiation therapy followed by TEMS 8-10 weeks later. The UK-TREC trial (TEM and Radiotherapy in Early Rectal Cancer) is offered for patients with early rectal cancer (T1-2N0) where patients are randomised between radical TME surgery and short-course preoperative radiotherapy with delayed local excision at 8-10 weeks. If local recurrence rate in these studies were found to be acceptable or comparable to standard TME

surgery then TEMS might become the standard treatment of rectal cancer in the future.

There is also some growing interest in these rectum-preserving techniques even for some locally advanced rectal cancer given the encouraging long-term results of patients with complete pathological response after chemoradiotherapy. These patients could be offered 'close follow up' if they were found to be stage 0 rectal cancer following neoadjuvant chemoradiation (15). Alternatively, tumours that either do not disappear or "regrow" during the first 12-month follow up period are referred to surgery, either TEMS or TME (16).

There are also several emerging reports on 'bottom to top' approach for resection of rectal cancer in an attempt to address the difficulties faced during LRS in terms of tumour localization, achieving adequate distal resection margin and to deal with the difficulty in firing the stapler distal to the tumour (17).

In conclusion, it is evident that the quest for the optimal approach for surgical resection of rectal cancer is far from over. COLOR II study, as well as other studies, indicates that further experience in LRS is doubtful to offer significantly better short-term outcomes when compared with ORS. Therefore, it is very likely that we will see increasing reports on various novel approaches for resection of rectal cancer.

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