Editorial Commentary

COREAN trial: long-term clinical impact of laparoscopic surgery in patients undergoing total mesorectal excision

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Comment on: Park JW, Kang SB, Hao J, *et al.* Open versus laparoscopic surgery for mid or low rectal cancer after neoadjuvant chemoradiotherapy (COREAN trial): 10-year follow-up of an open-label, non-inferiority, randomised controlled trial. Lancet Gastroenterol Hepatol 2021;6:569-77.

Received: 27 February 2022; Accepted: 10 March 2022; Published: 30 March 2022.
doi: 10.21037/dmr-22-26
View this article at: https://dx.doi.org/10.21037/dmr-22-26

In the last three decades, laparoscopic techniques have ceased to be just another surgical resource to become the approach of choice in most benign, urgent and oncological abdominal surgeries (1,2). Technological development, accompanied by new generations of surgeons who have been trained in an environment in which laparoscopic surgery is already a day-to-day tool, and robust evidence supporting an enhanced recovery has allowed the advancement of the minimally invasive technique (3). However, the implementation of new surgical approaches requires strict and audited scientific control, so that the enthusiasm for technological progress never obscures the main objective of medicine: the promotion of health.

Under this premise, it can be understood why the implementation of the laparoscopic approach in the treatment of rectal cancer lagged behind other surgical procedures. It was less than a half century ago when Heald and Ryall changed the poor prognosis of rectal cancer with the introduction of the total mesorectal excision (TME) (4). Removing all of the mesorectum containing the tumor and the lymph nodes became paramount for a good outcome and minimal recurrence within the pelvis. Combined with neoadjuvant therapy in selected patients, locoregional recurrence rates were reduced below 10% and cancer-free survival was improved by more than 70% (5). Yet the rationale for the laparoscopic approach in TME in terms of histopathological outcomes and survival needed to be corroborated in randomized controlled trials (RCT).

In a subset analysis of the CLASICC trial (6) of patients with rectal cancer, laparoscopic TME was associated with conversion and mortality rates of 34% and 5%, respectively. Moreover, the laparoscopic group presented with a nonsignificant higher positive pathological circumferential resection margin (pCRM) rate, although this did not translate into survival and recurrence differences with the open surgery group (7).

Along these lines, similar short-term data were obtained from the ACOSOG Z6051 (8) and ALaCaRT (9) randomized clinical trials. Both studies failed to demonstrate the non-inferiority of the laparoscopic approach using a new trichotomous, unvalidated, composite pathological outcome. Nevertheless, neither one of these two trials found survival differences at 2 years of follow-up (10,11). Moreover, compared to the short-term outcomes of the CLASSIC trial, a significant improvement in conversion and mortality rates (10% and <1%, respectively) in these trials was noted.

Besides the similar survival found in the CLASSIC, the ACOSOG Z6051 and the ALaCaRT trials, two other RCT deserve mention: the COREAN (12) and COLOR II (13), which also demonstrated the safety of the laparoscopic approach to the TME, with short-term clear benefits and similar mid-term locoregional and disease-free survival rates. All these combined data, together with recent meta-

analyses (14,15), provide evidence supporting the use of laparoscopy for rectal cancer resection. However, because the time to recurrence in rectal cancer may be prolonged after preoperative therapy, an extended COREAN follow-up was required (16).

Park *et al.* performed a 10-year oncological comparison between laparoscopic and open surgeries among the 340 patients that were enrolled in the COREAN trial between 2006 and 2009 (17). With a median follow-up of 143 (IQR, 122–156) months, data analysis showed similar rates of overall survival (74.1% for the open surgery group *vs.* 76.8% for the laparoscopic surgery group; P=0.44) and disease-free survival (59.3% and 64.3%; P=0.20). The local recurrence rate was less than half in the laparoscopic surgery group (8.9% and 3.4%), with a P of 0.050. Considering that the primary outcome was 3-year disease-free survival and that an adequate sample size calculation was made, with a type I error of 2.5 and a power of 85%, the data regarding local recurrence should be considered as similar in both techniques. However, it cannot be denied that a true difference that could not be statistically demonstrated might exist, and this justifies future research.

Several aspects of the COREAN trial can be criticized. First, despite the randomization, pathological responses (expressed within the ypT, ypN and TRG classifications) were higher in the laparoscopic group. However, after stratified multivariable analysis for these variables, similar survival and recurrence outcomes were maintained between groups. Second, unlike in the COLOR II trial (10) which included over a thousand patients from thirty international hospitals, the COREAN trial was composed by a smaller population from three tertiary referral South Korean hospitals. This population may be different from those other parts of the world; for example, the median of the body-mass index, a well-known factor for increased procedural difficulty, of the patients included was lower than 25 kg/m^2, which is lower than in other trials (13). Besides, only highly skilled surgeons participated, after conducting the required minimum number of surgeries, and qualified for the trial through live demonstrations and assessment of an unedited video by the trial steering committee. This limitation in the external validity of an RCT is well known, since strict eligibility criteria usually lead to trial populations that differ from patients seen in routine clinical practice.

Although every RCT has its limitations, the COREAN trial is the first to investigate the long-term survival outcomes of laparoscopic TME. Such collection and analysis of 10-year follow-up data gives provides the scientific community with very valuable information about its safety. One may criticize the lack of standardized assessment of the quality of the laparoscopic approach in this trial, allowing that some patients might have undergone surgery during the learning curve of the surgeons. This fact may lead to an underestimation of the value of the minimally invasive approach. Therefore, more research is needed to determine whether the oncological outcomes of laparoscopy are really similar to those of open surgery, or if, on the contrary, this technique performed in centers of excellence by experienced surgeons may be oncologically superior—in addition to providing an enhanced recovery and lower rate of incisional hernias and small bowel obstruction. The fact that some works have found improved disease-free survival rates in advanced stages, justified by less surgical aggression, is worth mentioning (13,18).

Park *et al.* (17) also highlight the importance of appropriate patient selection for the laparoscopic approach. Even though they included locally advanced rectal cancer after neoadjuvant chemoradiotherapy, they excluded T4 tumors because of the risk of suboptimal resection. In the COLOR II trial, pT4 tumors were also excluded from the final analysis, although they had been previously randomized (13). Despite randomization, more node-positive and pT4 tumors were identified in the pathological specimens of the laparoscopic group in the ALaCaRT trial, which may have influenced the unfavorable results of this group (9). Without underestimating or limiting the indications for the laparoscopic approach, this measure should be taken into account as an extension of the fundamental bioethical principles: "first do no harm". We must never lose sight of the fact that the optimal TME, regardless of the approach we use, will depend on the surgeon's skills but also on the patient's anatomy (narrow pelvis, obesity) and the characteristics of the tumor (T4, post-chemoradiotherapy fibrosis).

Along with the results of COREAN trial, the long-term outcomes of the COLOR II, ACOSOG Z6051 and ALaCaRT trials will offer further clarity regarding the long-term oncological safety of laparoscopic resection for rectal cancer. Nevertheless, it should be borne in mind that, at present, the dichotomy between open surgery and laparoscopic surgery has been dissolved by the minimally invasive alternatives that have been established during the last decade. Cohort series have demonstrated the potential benefits of transanal total mesorectal excision (TaTME) technique for low and mid rectal cancer, including better specimen quality with better radicality and less morbidity

as result of avoiding extraction wounds and more sphincter preserving procedures, without compromising oncological outcomes (19). The COLOR III trial, currently running, is an international randomized trial that will evaluate the TaTME technique compared to conventional laparoscopic rectal resection for patients with mid and low rectal cancer. Moreover, robotic surgery technology has rapidly gained ground: with three-dimensional views, endowristed instrumentation and a stable camera platform, this is a very attractive option to handle the difficult approach to a narrow pelvis in an obese male patient. Provisional results from the multi-national ROLARR trial found no difference in pCRM positive rate or postoperative complications, with a lower rate of conversion in men and obese patients undergoing robotic resection, suggesting a benefit for the robotic TME in this patient cohort (20). Overall, and while we await future trials on TaTME and robotics, we advocate that minimally invasive techniques and centralized care should be considered the contemporary standard approach to rectal cancer.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Digestive Medicine Research*. The article did not undergo external peer review.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure forms (available at https://dmr.amegroups.com/article/view/10.21037/dmr-22-26/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Mandalà V. editor. The Role of Laparoscopy in Emergency Abdominal Surgery. Milano: Springer, 2012.
2. Angst E, Hiatt JR, Gloor B, et al. Laparoscopic surgery for cancer: a systematic review and a way forward. J Am Coll Surg 2010;211:412-23.
3. Fuchs KH. Minimally invasive surgery. Endoscopy 2002;34:154-9.
4. Heald RJ, Ryall RD. Recurrence and survival after total mesorectal excision for rectal cancer. Lancet 1986;1:1479-82.
5. Kapiteijn E, Marijnen CA, Nagtegaal ID, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. N Engl J Med 2001;345:638-46.
6. Jayne DG, Guillou PJ, Thorpe H, et al. Randomized trial of laparoscopic-assisted resection of colorectal carcinoma: 3-year results of the UK MRC CLASICC Trial Group. J Clin Oncol 2007;25:3061-8.
7. Green BL, Marshall HC, Collinson F, et al. Long-term follow-up of the Medical Research Council CLASICC trial of conventional versus laparoscopically assisted resection in colorectal cancer. Br J Surg 2013;100:75-82.
8. Fleshman J, Branda M, Sargent DJ, et al. Effect of Laparoscopic-Assisted Resection vs Open Resection of Stage II or III Rectal Cancer on Pathologic Outcomes: The ACOSOG Z6051 Randomized Clinical Trial. JAMA 2015;314:1346-55.
9. Stevenson AR, Solomon MJ, Lumley JW, et al. Effect of Laparoscopic-Assisted Resection vs Open Resection on Pathological Outcomes in Rectal Cancer: The ALaCaRT Randomized Clinical Trial. JAMA 2015;314:1356-63.
10. Fleshman J, Branda ME, Sargent DJ, et al. Disease-free Survival and Local Recurrence for Laparoscopic Resection Compared With Open Resection of Stage II to III Rectal Cancer: Follow-up Results of the ACOSOG Z6051 Randomized Controlled Trial. Ann Surg 2019;269:589-95.
11. Stevenson ARL, Solomon MJ, Brown CSB, et al. Disease-free Survival and Local Recurrence After Laparoscopic-assisted Resection or Open Resection for Rectal Cancer: The Australasian Laparoscopic Cancer of the Rectum Randomized Clinical Trial. Ann Surg 2019;269:596-602.
12. Jeong SY, Park JW, Nam BH, et al. Open versus laparoscopic surgery for mid-rectal or low-rectal cancer

after neoadjuvant chemoradiotherapy (COREAN trial): survival outcomes of an open-label, non-inferiority, randomised controlled trial. Lancet Oncol 2014;15:767-74. Erratum in: Lancet Oncol 2016;17:e270.
13. Bonjer HJ, Deijen CL, Abis GA, et al. A randomized trial of laparoscopic versus open surgery for rectal cancer. N Engl J Med 2015;372:1324-32.
14. Conticchio M, Papagni V, Notarnicola M, et al. Laparoscopic vs. open mesorectal excision for rectal cancer: Are these approaches still comparable? A systematic review and meta-analysis. PLoS One 2020;15:e0235887.
15. Acuna SA, Chesney TR, Ramjist JK, et al. Laparoscopic Versus Open Resection for Rectal Cancer: A Noninferiority Meta-analysis of Quality of Surgical Resection Outcomes. Ann Surg 2019;269:849-55.
16. Yeo SG, Kim MJ, Kim DY, et al. Patterns of failure in patients with locally advanced rectal cancer receiving pre-operative or post-operative chemoradiotherapy. Radiat Oncol 2013;8:114.
17. Park JW, Kang SB, Hao J, et al. Open versus laparoscopic surgery for mid or low rectal cancer after neoadjuvant chemoradiotherapy (COREAN trial): 10-year follow-up of an open-label, non-inferiority, randomised controlled trial. Lancet Gastroenterol Hepatol 2021;6:569-77.
18. Lacy AM, García-Valdecasas JC, Delgado S, et al. Laparoscopy-assisted colectomy versus open colectomy for treatment of non-metastatic colon cancer: a randomised trial. Lancet 2002;359:2224-9.
19. de Lacy FB, Roodbeen SX, Ríos J, et al. Three-year outcome after transanal versus laparoscopic total mesorectal excision in locally advanced rectal cancer: a multicenter comparative analysis. BMC Cancer 2020;20:677.
20. Jayne D, Pigazzi A, Marshall H, et al. Effect of Robotic-Assisted vs Conventional Laparoscopic Surgery on Risk of Conversion to Open Laparotomy Among Patients Undergoing Resection for Rectal Cancer: The ROLARR Randomized Clinical Trial. JAMA 2017;318:1569-80.

doi: 10.21037/dmr-22-26
Cite this article as: Domínguez-Garijo P, de Lacy FB, Lacy AM. COREAN trial: long-term clinical impact of laparoscopic surgery in patients undergoing total mesorectal excision. Dig Med Res 2022;5:1.