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EDITORIAL

Oncologic results of conventional laparoscopic TME: is the intramesorectal plane really acceptable?

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After two decades of conventional laparoscopic surgery for rectal cancer, during which a plethora of promising results were reported and expected, the simultaneous publication of the two most recent multicenter randomized controlled trials (RCT) in *JAMA* (i.e. ACOSOG Z6051 and ALaCaRT trials) started a debate regarding its oncological safety [1, 2]. These studies presented some similarities, such as a shared main outcome defined by the achievement of a composite pathologic endpoint including free margins (radial and distal − 1 mm) and appropriateness of mesorectal excision (i.e. obtaining an intact mesorectum with defects no deeper than 5 mm) [1, 2]. Remarkably, the oncologic non-inferiority for laparoscopy compared with open surgery was not established [1, 2]. As they were not identical studies, it is crucial to mention that method of grading the mesorectal quality adopted in each was apparently different (Table 1). ALaCaRT trial used the Dutch Colorectal Cancer Group (DCCG) classification, as the vast majority of contemporary literature, and *complete* resections (with mesorectal defects up to 5-mm) were considered successful and were included alone in the composite main outcome. However, researchers from the ACOSOG Z6051 trial selected a different grading system. They considered *complete* specimens those with a smooth surface of mesorectal fascia with all fat contained in the enveloping and *nearly complete* specimens those with a mesorectal envelope that was intact except for defects of no more than 5 mm. Interestingly, only their *complete* resections (no defects in the mesorectum) were initially considered appropriate. However, after a modification in the protocol during the study their own definition of *nearly complete* specimens (defects up to 5 mm) was also considered adequate [1]. Therefore, their endpoint became the same as *complete* resections as defined by DCCG and in the ALaCaRT trial.

More than a year later, the first meta-analysis based on RCTs compared the postoperative pathologic outcomes of open and laparoscopic rectal resections [3]. Obtaining a *complete* resection as defined by the DCCG was established as an endpoint, and surgeons using laparoscopy showed a significantly higher risk for not achieving it (i.e., 13.2% lap vs.10.4% open—RR 1.31; 95% CI 1.05–1.64) [3]. Additionally, the result was confirmed by performing a sensitivity analysis with only the four major multicenter RCTs (i.e. the ACOSOG, ALaCaRT, COLOR II and COREAN trials). Moreover, the meta-analysis considered the ACOSOG Z6051 trial *nearly complete* resections as *complete* for the scope of the analysis allowing a uniform comparison between studies according to the DCCG classification.

It was one of the ACOSOG authors who wrote the invited commentary accompanying the meta-analysis [4]. There, the meta-analysis findings were criticized because the DCCG *nearly complete* mesorectal quality had not been considered oncologically adequate. The argument was based on the findings of the earliest DCCG study published in 2002 which included only 180 patients, in which no differences were found between *complete* and *nearly complete* mesorectal grades outcome at 2-year follow-up [5]. The commentary motivated up to four (to date) groups to publish a re-meta-analysis of the previous one [6–9]. Disregarding some differences in study designs they all shared the common feature that DCCG *nearly complete* resections were pooled together with the *complete* as "complete" [6, 7] or "acceptable" [8] mesorectal quality, or plane of the mesorectal excision [9]. When considering successful the *nearly complete* resections, they all showed no significant differences in the mesorectal quality achieved by laparoscopic and open approaches [6–9].

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Table 1 Macroscopic quality of mesorectum gradings according to Dutch Colorectal Cancer Group (DCCG) [5] and ACOSOG Z6051 trial [1] protocol

DCCG 2002 [5]	ACOSOG Z6051 2015 [1]
Complete (mesorectal plane) Intact mesorectum with only minor irregularities of a smooth mesorectal surface No defect is deeper than 5 mm No coning toward the distal margin of the specimen Smooth circumferential resection margin on slicing	**Complete** Rectal resection specimen that has an intact mesorectum and covering peritoneal envelope all the way to the level of rectal transection with no coning in of the mesorectum above the point of transection The surface of the peritoneal covering should be smooth and shiny with no defects exposing the underlying fat **Nearly complete** Rectal resection specimen where the mesentery is all present, without coning or missing fat A < 5 mm deep defect may be present in the envelope covering the mesenteric fat caused either by a wayward incision or traction injury during extraction of the TME specimen through a small extraction site
Nearly complete (intramesorectal plane) Moderate bulk to the mesorectum, but irregularity of the mesorectal surface Moderate coning of the specimen is allowed At no site is the muscularis propria visible, with the exception of the insertion of the elevator muscles	**Incomplete** Rest of specimens[a]
Incomplete (muscularis propria plane) Little bulk to mesorectum with defects down onto muscularis propria and/or very irregular circumferential resection margin	

[a]DCCG incomplete and nearly complete resections are included together at ACOSOG. There is no way to assess how many patients are in each group using the published data [1]

To this day only three large studies have addressed the relationship between mesorectal quality grading and long-term oncologic outcome. One of the main papers on the subject was published by Quirke et al. in 2009 and included 1156 patients from a phase 3 trial [9]. In univariate analysis the plane of surgery was strongly associated with the 3-year local recurrence rate—4% for *complete*, 7% for *nearly complete*, and 13% for *incomplete* resections, ($p = 0.0039$). A 3-tiered system was also used in their multivariate analysis showing that that the plane of the surgery was independently and significantly associated with the risk of local recurrence. While a direct comparison between *complete* and *nearly complete* resections was not done the local recurrence free survival curves nearly overlapped. Nevertheless, the authors noted that local recurrence was almost abolished in patients who received short-course preoperative radiotherapy and in whom mesorectal plane surgery was achieved (1% at 3 years) [10]. To specifically address the issue of weather *nearly compete* should be grouped with *complete* or with *incomplete* Leonard et al. examined the results of a nationwide database including 1382 patients. They found that when they grouped *nearly complete* and *incomplete* resections and compared them to the *complete* resections there was a significant increased risk of distant metastasis and a decreased survival in the former group. However, when grouping *complete* and *nearly complete* as the most recent meta-analysis are doing [6–9] the plane of surgery lost its prognostic significance. Following these results, they concluded that intramesorectal resections (i.e., *nearly complete*) should not be combined with the *complete* for analysis [11]. More recently, Kitz et al. when examining the data of 1152 patients from a phase 3 trial found at univariate analysis that the 3-tiered mesorectal grade system was significantly associated with disease-free survival, incidence of distant metastasis and local recurrence. While there was no significant difference between *complete* and *nearly complete* in any of the oncologic outcomes only the comparison between *complete* vs *incomplete* was an independent risk factor for local recurrence [3.72 (95% CI 1.59–8.71; *p* 0.002)] [12].

Therefore, according to the current evidence and taking the more conservative approach until more data is available, we believe that it is not safe to consider *nearly complete* resections optimal for treating patients with rectal cancer as this would lead to considering intramesorectal dissection an acceptable technique which the above mentioned data do not support.

Moreover, all four recent meta-analysis [6–9] did not recognize that the mesorectal grading that the ACOSOG

reported was different from the DCCG. In fact, DCCG *nearly complete* resections cannot be extracted from the trial's data for the purpose of a meta-analysis according to the published data (see Table 1).

Briefly, the quality of the surgical specimen provided by conventional laparoscopy, i.e. by obtaining a *complete* mesorectum or by a composite outcome also associating free circumferential and distal margins, might not be as good as those provided by open rectal resection [1–3]. However, the oncologic inadequacy of the surgical specimen related to conventional laparoscopy should be accompanied by an effect on local recurrence and disease-free survival rates to be considered clinically relevant. This is not the actual scenario, since the mid-term (2-year follow-up) results of the ACOSOG Z6051 and ALaCaRT trials so far did not prove so [13, 14].

In conclusion, it is clear that the use of minimally invasive surgery for rectal cancer is here to stay and is aimed at improving patient outcomes. The fact that laparoscopic surgery failed the non-inferiority test against open surgery should be an incentive to improvement and a sign that conventional laparoscopic procedure may not be the last step in the evolution of rectal cancer surgery. However, the results of the ROLARR trial do not seem to suggest that robotic approach offers any advantage over laparoscopy in achieving *complete* resection (77% in the laparoscopic group vs 76% in the robotic group, respectively). While the results of minimally invasive surgery for rectal cancer have perhaps not met our highest expectations we can foresee a future with more emphasis on training and with minimally invasive less operator-dependent techniques.

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Compliance with ethical standards

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