



A. Spinelli<sup>1</sup> · A. D'Hoore<sup>2</sup> · Y. Panis<sup>3</sup> · W. A. Bemelman<sup>4</sup> · D. G. Jayne<sup>5</sup> · A. Fürst<sup>6</sup>

<sup>1</sup> Colorectal Surgery Unit, Humanitas Research Hospital, Rozzano, Milan, Italy; <sup>2</sup> Department of Abdominal Surgery, University Hospital Gasthuisberg, Leuven, Belgium; <sup>3</sup> Department of Colorectal Surgery, Beaujon Hospital, Assistance publique-Hôpitaux de Paris, Université Paris VII, Clichy, France; <sup>4</sup> Department of Surgery, Academic Medical Center, Amsterdam, The Netherlands; <sup>5</sup> Academic Surgical Unit, St. James's University Hospital, Leeds, UK; <sup>6</sup> Department of Surgery, Caritas-Hospital St. Josef, Regensburg, Germany

# Critical appraisal of two randomized clinical trials on pathologic outcomes

## Laparoscopic vs. open resection for rectal cancer

### Comment to

Fleshman J et al (2015) 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*. 314(13):1346–55. doi: [10.1001/jama.2015.10529](https://doi.org/10.1001/jama.2015.10529).

Stevenson AR et al (2015) Effect of Laparoscopic-Assisted Resection vs Open Resection on Pathological Outcomes in Rectal Cancer: The ALaCaRT Randomized Clinical Trial. *JAMA*. 314(13):1356–63. doi:[10.1001/jama.2015.12009](https://doi.org/10.1001/jama.2015.12009).

Two randomized controlled trials by Fleshman et al. and Stevenson et al. failed to exclude the possibility that laparoscopy was inferior to open surgery for rectal cancer. Both authors chose to pose a bold statement that their findings “do not support the (routine) use of laparoscopy in rectal cancer”, generating surprise and debate among the surgical community. Since both studies show common limitations, related to study methodology and the non-inferiority design, it may be questioned whether such bold statements are justified. Both studies were sufficiently powered such that inferiority could be excluded when the confidence intervals did not exceed the 6% and 8% margin of the comparator, respectively. Although the confidence intervals exceeded the specified margin, given that the observed differences between the two arms did fall within these

margins, the results should be considered inconclusive, i. e. it is not possible to infer that laparoscopy was inferior to open surgery from these results. As no solid rationale was provided for the margins chosen, it is unclear whether these are statistically robust or arbitrary. Furthermore, both studies chose a composite of pathological features as a primary endpoint, indicating adequate resection. Nevertheless, this is a surrogate outcome for an improved health state, rather than a direct assessment of patient health, disease state and quality of life.

In the study by Fleshman et al. a substantial proportion of patients in the laparoscopy group underwent a manually assisted or robotic procedure, possibly affecting results of the laparoscopy group.

Stevenson et al. conducted a post hoc superiority analysis, reporting that open surgery was superior; however, post hoc analyses, often being data-driven, are more likely to identify positive results than tests defined a priori. Other studies, such as the COLOR II and COREAN trials [1, 2], as well as a recent Cochrane review [3], have already been able to yield comparable, if not favorable results for laparoscopy compared to open surgery on long-term, clinically relevant endpoints. In both JAMA studies additional oncological outcomes, such as disease-free, overall survival and local recurrence, which can provide a far more clinically and patient-relevant picture of

the relative success of laparoscopic and open approaches to rectal surgery, are yet to be released. Moreover, power calculations were based on the primary endpoint, such that even longer-term outcome data will need to be interpreted with caution, since they may not be adequately powered to detect non-inferiority for any of those outcomes.

### Corresponding address

**A. Spinelli, MD, PhD**

Colorectal Surgery Unit, Humanitas Research Hospital  
 via Manzoni 56, Rozzano, Milan, Italy  
 Antonino.spinelli@humanitas.it

**Conflict of interest.** A. Spinelli, A. D'Hoore, Y. Panis, W.A. Bemelman, D.G. Jayne and A. Fürst declare that they have no competing interests.

### References

1. Bonjer J et al (2015) A randomized trial of laparoscopic versus open surgery for rectal cancer. *N Engl J Med* 372(14):1324–1332. doi:[10.1056/NEJMoa1414882](https://doi.org/10.1056/NEJMoa1414882)
2. Jeong SY et al (2014) 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* 15(7):767–774. doi:[10.1016/S1470-2045\(14\)70205-0](https://doi.org/10.1016/S1470-2045(14)70205-0)
3. Vennix S et al (2014) Laparoscopic versus open total mesorectal excision for rectal cancer. *Cochrane Database Syst Rev* 4:CD005200. doi:[10.1002/14651858.CD005200.pub3](https://doi.org/10.1002/14651858.CD005200.pub3)