Rectal cancer surgery: can a clinical trial be conducted today?

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The article entitled "A Multicenter Matched Comparison of Transanal and Robotic Total Mesorectal Excision for Mid and Low-rectal Adenocarcinoma", published by Lee *et al.* (1), could, in our view, be the reference as to answer the question "what is the best surgery for low-rectal carcinoma?"

Indeed, this series has included a large number of low rectal carcinoma patients (n=730) operated by skillful surgeons in high-volume centers. They were matched to create two balanced cohorts [226 TaTME (Trans-anal Total Mesorectal Excision) and 370 R-TME (robotic TME)] to compare the quality of surgical resection using with the two techniques.

Despite these favorable arguments, the conclusion made by the authors was incredibly poor "High-quality TME for patients with rectal adenocarcinoma of the mid and low rectum can be equally achieved by trans-anal or robotic approaches in skilled hands ….", as if the prognostic factor represented by the surgeon was a new parameter (2).

This article raises the fundamental question of conducting clinical trials in surgery, and more specifically the choice of the trial objective and the inclusion criteria to propose. Evidence-based medicine has difficulties to give an answer to the question of the best technique for rectal cancer surgery. Five phase III trials (3-7) could not conclude on the best approach between laparotomy and laparoscopy, neither could one phase III trial show a difference between the robotic and laparoscopic approaches (8). Main reasons were that the patients' inclusions were large, the learning curves of the techniques often not reached or the primary objective not appropriate.

The publication of Lee *et al.* tried to avoid these pitfalls: 5 high-volume centers included consecutive patients during a short period [2011–2017]; patients included were "standard" rectal cancer patients, the surgical techniques used were standardized techniques; and the primary objective was composite [quality of the mesorectum resection, circumferential resection margin (CRM) and distal margin (DM)]. To increase the homogeneity of the overall cohort, the two populations were matched. The proportion of patients who achieved a high-quality resection was similar in the two groups (TaTME 93.1% and R-TME 93.2%, P=0.819). The authors performed subgroups analyses, but could not find any significant difference. They concluded that surgeons do not need to abandon one approach in favor of the alternate if their outcomes are in line with the published data. Regarding surgeons who perform open techniques and wish to adopt minimally-invasive surgical technique, the choice remains open.

What then could be the next step? Would there be a trial able to discriminate between the four major surgical techniques (open approach, laparoscopy, robotic approach and TaTME) for rectal cancer surgery?

This question is essential, both for our junior surgeons and our senior colleagues who are willing to improve their technique.

Three areas of discussions must be considered:

- Randomization: evidence-based medicine classically requests prospective randomized trials. In the surgical field, randomization is a challenge because only few surgeons are equally-skilled in two (or more) techniques at the same time for a given study, especially when the surgical difficulty increases, or during the acquisition of a new technique, which requires practice (9). Indeed, most publications

consider the learning curve for RTME or TaTME with a cut-off of at least 50 or 70 patients. In the Lee *et al.* article, among the five high-specialized centers who participated in the study, only one uses the two techniques at the same level of efficiency. It was obviously not possible for four participating teams to conduct a randomized trial!

- ❖ Inclusions criteria: the inclusion of all rectal cancer patients in a prospective trial induces mixing of easy and difficult surgical patients, which may then level off the global results. This notion of surgical difficulties is well known by all surgeons, and is now well documented in prospective trials. In the ROLARR trial (8) or in the prospective TaTME database, surgical difficulty was found as a significant parameter in the multivariate analyses (high BMI, low anastomoses, big tumors and narrow pelvis). We have recently proposed a MRI-based score to predict surgical difficulty in patients with rectal cancer (10). This predictive score could be used to select high-risk patients in order to emphasize differences between the surgical techniques.
- ❖ Objectives: to be practical, trial results must be as close as possible to real clinical practice. Oncological results as well as functional results include too many variables which alter the real contribution of the surgical procedure *per se*. For example, the conversion rate is closely linked to the surgeon's learning curve. The most appropriate way to evaluate and compare these techniques may be associating markers of surgery quality, e.g., TME grading and CRM, and post-operative morbidity in a composite endpoint.

In order to overcome these pitfalls, we have initiated a prospective observational case-matched multicenter trial designed to study TME with low anterior resection in four cohorts of high-risk patients with mid-to-low, non-metastatic rectal cancer: open laparotomy, laparoscopy, robot-assisted surgery, or trans-anal surgery. All surgeries will be performed by surgeons experienced in at least one of the techniques. Oncologic, morbidity and functional outcomes will be assessed in a composite primary outcome, with success defined as CRM ≥1 mm, TME grade III, and minimal postoperative morbidity (absence of Clavien-Dindo grade III–IV complications within 30 days after surgery). The ambition of this wide European trial is to include 1,300 patients over a 2-year period in 30 high-volume centers. This trial was called RESET (rectal surgical evaluation trial), a pun to reset our surgical knowledge in the treatment of rectal carcinoma.

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