Editorial

Complete mesocolic excision with central vascular ligation: is this the approach to improve colon cancer surgery oncological outcomes?

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The concept of total mesorectal excision (TME) as proposed by Heald *et al*. (1) in the early 80's resulted in significantly better oncological outcomes in rectal cancer surgery (1-3). TME also raised the issue of better outcomes in colon cancer surgery, which, until then, was not standardized and the reports in the literature displayed a great deal of heterogeneity and high recurrence rates (4-7). In 2009 and in parallel to the TME concept, came the first report and description of the complete mesocolic excision (CME) with central vascular ligation (CVL) from the Erlangen group of Hohenberger (8), with quite impressive oncological outcomes and an overall 5-year survival reaching up to 70% for stage III colon cancer patients. They also showed that it is a safe and feasible technique which bears at least the same morbidity and mortality as the "so called" standard technique (8).

CME with CVL consists of two main components. Firstly, it aims at the preservation of intact fasciae of the mesocolon between which relevant lymph nodes are contained. Secondly, the vessels that supply the tumor colon site must be ligated at their origin, namely (I) at the level of the superior mesenteric vein for right sided lesions, and (II) at the level of the take-off of the inferior mesenteric artery for left sided lesions. In this way the nerves of the celiac plexus, which run along the superior mesenteric artery, and the hypogastric plexus, which runs on the aorta, respectively, are protected, and the removal of the complete mesocolon and the maximum lymph node yield is achieved.

The concept of CME with CVL has been strongly criticized. At the beginning the criticism was on the novelty of the technique. Many supported that it is a concept already implemented by the majority of colorectal surgeons, in particular for tumors of the left colon (9,10). In addition, the issue of reproducibility of the technique due to the high level of expertise necessary was raised. Many experienced and skillful colorectal surgeons claimed that some steps of the CME with CVL, as described by Hohenberger *et al*. (8), were very technically demanding, some were unnecessary, and because of that the technique was rendered very difficult to teach and to reproduce (11-14). Furthermore, reports from Japan also demonstrated that perhaps the main element of the technique is the CVL, because they showed similar results not by removing longer specimens but by removing more radically the supplying vessels (15).

The establishment of CME with CVL in the mind of many, at first skeptical, colorectal surgeons came when the leading group of pathologists from Leeds, which is involved in almost all the techniques used by pathologists to assess and measure surgical quality in rectal surgery, published the first morphometric criteria of macroscopical and microscopical assessment of colon cancers specimen (16). In this way, the superiority of the CME with CVL, as far as the quality of the surgical specimen is concerned, was proven (16).

Thereafter, reports by many groups followed comparing the CME with CVL with retrospective cohorts of conventional colectomies and contemporarily the first reports concerning laparoscopic CME appeared in the literature (12,17-30). The results from all these studies were rather conflicting, probably due to the fact that conventional colectomy is not at all standardized and that surgeons

participating in the studies may not have any specific CME training offered by an established training course.

One of the first reports, which compared the standardized CME with CVL with a cohort of conventional colectomy in a defined population after the special training of the surgeons on CME with CVL, came from a group in Denmark (31). The authors studied all patients who underwent elective colectomy for colon cancer from the Danish Colorectal Cancer Group national registry for a specific region from June 2008 until December 2011. The CME with CVL group consisted of patients operated in a specific hospital at which a previous special training program on CME with CVL was implemented and surgeons were trained. The conventional colectomy group consisted of patients operated in three other hospitals of the same region. The medical records from all patients were cross-checked by the participating surgeons ensuring the highest possible validity of data analyzed.

The authors found that the implementation of CME with CVL is a significant independent predictive factor for higher disease-free survival for all patients, irrespective of the stage of the disease. As expected they also showed a significantly higher lymph node yield for the CME with CVL group as well as a significantly higher rate of mesocolic-graded resections. They also report a higher number of invaded lymph nodes in the CME with CVL group. On the contrary, they showed that overall survival was not effected by CME with CVL. The authors speculate that this is probably due to advances in surgery of the metastatic disease and chemotherapy and to the short period of follow-up.

Despite the fact that this study is very well designed and uses a quite meticulous statistical methodology using complex multivariable modeling and propensity score matching to reduce the bias due to confounding factors, it has some methodological flaws many of which could be anticipated. First of all, a very important issue that appears is the quality of the pathology reports. The surgeons performing CME with CVL were trained but similar training is required for the pathologists who grade the macroscopic and microscopic quality of the resected specimens for both groups in order for the pathological data to be equally valid. The pathologist for this kind of study is even more important than the surgeon because he is the one who searches for and determines the biomarkers that are important for the final oncological outcome both prognostic and predictive. If the quality of the pathology is poor or even worse, has a huge variability then the dataset for analysis is biased by definition.

Secondly, a methodological flaw is that the authors chose to exclude R2 resections. This creates bias in favor of the standard colectomy group, because, since all operations were performed on an intention-to-treat basis, a R2 resection in the standard group may be a technical disadvantage of the technique itself as compared to the CME with CVL group where a R2 resection is a real limit of oncological radicality. R2 resections and the exact site of positive margin should have been included in detail in order to identify any advantage in resectability of the CME with CVL over the standard technique.

Thirdly, the variability in the type, the time-intervals and the duration of follow-up among the participating centers is a potential source of bias affecting the timing of identification of possible recurrences. This is discussed also by the authors in the discussion section of the manuscript.

Fourthly, the dataset of the study itself and the type of analysis bear some possible sources of bias the majority of which are also discussed and accounted for in the final analysis. Pathological features of the tumors resected in the CME with CVL group displayed some differences that could have confounded the data in favor of the conventional colectomy group such as higher serosal invasion rates, higher rates of extramural venous invasion and higher rates of signet-ring cell and undifferentiated carcinomas. All these confounders were picked up by the authors and by the use of propensity score matching their effect on the outcomes was correctly adjusted.

Also, a matter for discussion and overall criticism for CME with CVL is the lack of effect in stage III patients in whom theoretically the maximum effect is anticipated. This comparative study is the only that identified a positive effect in this subgroup despite the almost equally use of adjuvant therapy in both groups. In parallel, the importance of accurate staging is stressed because the effect of false down-staging could be an important source of bias. In the same sense, the quality of the pathology handling of the specimen during lymph node identification (especially identification and status of apical lymph nodes) is of utmost importance for the determination of all relevant lymph node status and the correct staging. In their study, the methylene-blue injection technique was used by the pathologists in the middle of the study period only in the CME with CVL group and this fact might be an important source of bias. They conclude that patients' staging has a very low chance of being inaccurate because data do not differ from that of the whole country.

An additional argument that is discussed is the effect of CME with CVL on stage II patients. In this dataset, a significantly higher proportion of stage II patients received adjuvant chemotherapy possibly due to worse pathological features of the tumors (serosal invasion, extramural venous invasion) and this is the fact that one could attribute the positive effect of CME with CVL. The authors put these variables in the modeling for the multivariable analysis and none of them proved to be an independent prognostic factor causing bias.

In our opinion, the most important omission in the analysis of the data is the absence of a subgroup analysis on the basis of tumor location. This is of great importance given the fact that conventional colectomy has a great variability in the definition of the term and this becomes more complicated when the tumor site changes from left to right. In detail, left-sided conventional resections are closer and sometimes coincide with the concept of CME with CVL. On the other hand, right-sided and transverse tumors constitute a different group of tumors, and the CME with CVL technique differs hugely from the conventional one. In this sense, tumor site may be a significant confounder when all cases are being analyzed together and the only way to account for this is the subgroup analysis of the data based on tumor location. CME with CVL is expected to have a greater effect for tumors located in the right and transverse colon. A hint towards the above is given by the authors when discussing the lower rate of laparoscopy in the CME with CVL group and attribute it to the fact that right-sided and lesions of the transverse colon are not preferred to be operated laparoscopically due to limitations of the approach to the radicality of the technique.

In conclusion, the study, despite several methological limitations, points towards the correct direction. The setup of a randomized study that compares the conventional to the CME with CVL colectomies for colon cancer seems impossible, and this is because conventional colectomy cannot be standardized at all. Therefore, large series of patients been prospectively subjected to CME with CVL must be accumulated and be compared to conventional surgery cases deriving form large archive data-bases. A prerequisite for more reliable and less biased results and conclusions are the adequate training of both surgical teams and pathologists, and the subgroup analysis that must take into account several parameters, such as tumor location, type of surgical approach, quality of surgery, histo-pathological characteristics including stage of the disease and adjuvant treatment.

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