

Should All Colon Cancer Patients Undergo Laparoscopic Colectomy? The Evidence from the Randomized Clinical Trials

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Abstract: Although more than 20 years have elapsed since the performance of the first laparoscopic colectomy, the scientific community is still divided between the overoptimistic enthusiasm of surgeons who would apply this procedure to all colon cancers and those who would favor a more prudent and selective approach.

In the last years the issue was further complicated by the results of a randomized clinical trial which repeatedly claimed better oncologic results in patients undergoing laparoscopic colectomy as compared with those receiving the traditional open procedure.

This short review focuses on the distinct randomized clinical trials comparing the two procedures, the published meta-analyses obtained thereof, in order to comment on the reliability of the studies claiming the evidence of an oncologic benefit with the laparoscopic approach.

There is a scientific evidence that in the patients' population eligible for randomization in the published randomized clinical trials the oncologic results appear quite similar.

Nothing can be stated for the vast patients' population which did not meet the inclusion criteria in the trial and was therefore excluded.

The actual difficulty to generalise the results of randomized clinical trials to all the colon cancer patients suggests a cautious approach to the problem and emphasizes the need of a full explanation to the patients about the limits of the currently available scientific evidence.

In the meantime the short-term benefits of the laparoscopic approach have to be weighed against the recent results of the enhanced recovery programmes.

Keywords: Colon cancer, laparoscopic colectomy, conventional open colectomy.

The possibility that minimally invasive surgery could be applied to patients with colon cancer was first considered about 20 years ago [1].

In the following years laparoscopic colectomy for benign surgical diseases gained a growing acceptance because of worldwide recognized short-term clinical benefits [2] including less pain and wound complications from smaller incisions, decreased narcotic use leading to faster return of intestinal motility and more rapid mobilization of patients, and finally, to a shorter hospital stay and a quicker return to normal activities.

However, two facts have limited the acceptance of laparoscopic colectomy in patients with cancer in contrast to its wide consensus on this procedure for benign diseases.

First, the primary expectation of patients undergoing an oncologic treatment mainly focuses on the ability of the procedure to totally eradicate the tumor and to provide them

with the best possible cure (rather than on some short-term postoperative clinical benefits).

As a matter of fact a recent *ad hoc* investigation from Austria [3] in 167 patients candidate to colorectal surgery showed that a complete cure of the disease was regarded of highest importance and, in a list of 15 preoperative expectations, "to be able to travel as soon as possible", "a quick return to work" "a small incision" and "a nice scar" ranked 11th, 12th, 13th, and 14th, respectively.

Secondly, there was some concern by the surgeons about whether an adequate intra-abdominal exploration for cancer can be undertaken laparoscopically and a curative removal can be feasible with a minimally invasive technique, especially in tumors with an ill-defined T3-T4 stage, with the same radicality achieved with the open resection. For instance, it was reported [4] that resection of colon extended to neighbouring structures and organs was inappropriately performed in about half of patients because the infiltration/adhesion was found at the subsequent pathologic examination to be inflammatory rather than neoplastic. This occurred despite a careful palpation and manipulation during the open procedure and it is reasonable to expect this diffi-

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culty is magnified with the laparoscopic approach. In fact in a recent review of the CLASICC randomized clinical trial, the extent of tumor spread from the muscularis propria was found to be an independent statistically significant predictor for conversion to an open colectomy [5].

Nowadays, however, we have the data of 4 major randomized clinical trials [6-11], and one small single centre trial [12] and meta-analysis [13] and two systematic reviews [14, 15] comparing the two procedures in colon cancer patients.

All these investigations not only have definitely settled that oncologic outcome is not compromised by the laparoscopic colectomy but the Barcelona trial [6,7] also claims a better cancer-related survival with laparoscopic colectomy than with open colectomy.

The last paper from the Barcelona group [7] concluded that laparoscopic colectomy was more effective than open colectomy because of a better cancer-related survival despite a non-significant difference in the overall survival. The benefit was only due to the significant difference in survival of patients with Stage III tumors.

These papers by Lacey *et al.* [6,7] were widely criticised in literature.

For instance Evrard *et al.* [16] wrote in a letter to the journal that “a superiority trial would have been more suitable and that the equivalence difference of 15% is much too high. A 5% equivalence region would have been more appropriate, but would have required many more patients. Despite this, if a 15% difference in cancer-related survival were indeed judged as an equivalence region, then we would conclude that the two treatment groups are equivalent and not significantly different as the authors suggest, since 5-year rates read from the graph are estimated as 75% for open colectomy and 90% for laparoscopy-assisted colectomy”.

Similarly, Koretz [17] argued that “if there is an advantage in avoiding one cause of death, but total mortality is unaffected, it follows that there must be a corresponding disadvantage in some other form of mortality (in this case, the non-cancer mortality in the 2 groups was 9% versus 5%)”.

From the clinical point of view we have the following comments concerning the Barcelona study:

- Loco-regional relapse rate in open colectomy was very high (14% versus 7% in laparoscopic colectomy) whereas in the conventional surgical literature it is in the range of 2-4% [18].
- Stage III means patients with lymph nodes metastases, but this stage pools 3 different sub-groups : Stage A (T1-2 N1) and Stage B (T3-4 N1) and Stage C (any T N2) and since in the Barcelona study Stage III included only 37 and 36 patients in laparoscopic colectomy and open colectomy arms, respectively, a small imbalance in the distribution of cases may be important for the final outcome. In fact, according to the new revised TNM classification stages III A, B, C have different 5-yr survivals: 67-74%, 43-58%, 13-31%, respectively, in a recent study including about

100000 patients [19]. Moreover the assessment of the stage is a postoperative attribute.

- Adjuvant chemotherapy, which is a main determinant of the oncologic outcome, was not examined as prognostic factor in the univariate and multivariate analysis and it was given to 86% of II-III Stage laparoscopic colectomy patients *versus* 70% of open colectomy ones (p=0.02).
- Median number of lymph nodes per specimen was <12, hence the true tumor Stage is uncertain since a number of at least 12 lymph nodes is recommended in the American Guidelines [20,21].

Lacy *et al.* [7] emphasized that the minimal manipulation of the tumor-bearing colon by means of the laparoscopic dissection could lead to minimal cells mobilization, and hence to a lower metastatic spread. However Tsavellas *et al.* [22] did an extensive review of 29 papers on about 1000 patients and could not find a definite association between circulating tumor cells and oncologic outcome. Furthermore, a randomized clinical trial [23] comparing the so-called “no touch isolation technique” with conventional operation in 237 colon cancer patients failed to show any benefit for the procedure with minimal manipulation. Again, Slanetz *et al.* [24] showed on 1863 patients that early ligation of regional mesenteric vessels (prior to the mobilization of the primary colorectal tumor) to prevent the cancer cells dissemination through the venous and the lymphatic pathways, did not affect the 5- and 10-year disease-free survival as compared with late ligation after the tumor was mobilized.

We now have the recent data from the 3-year overall and disease-free survival (1076 patients) of the COLOR randomized clinical trial [25] and from a meta-analysis pooling the Barcelona randomized clinical trial, the COST randomized clinical trial, the COLOR randomized clinical trial and the CLASICC randomized clinical trial (1540 patients) [13]. In both cases similar overall and disease-free survival figures were reported in the two arms, laparoscopic colectomy and open colectomy, even when the analysis was performed by stage.

Hence we could summarize that we have a scientific evidence that the oncologic results from laparoscopic colectomy and open colectomy are quite similar whereas the short-term and long-term surgical outcomes are still controversial.

While it is usually reported that postoperative stay is shorter after laparoscopic colectomy, it is impressive that a recent multicentre randomized clinical trial in a moderate-risk population failed to show any advantage for the minimally invasive approach in terms of overall, general or local morbidity, on the contrary the reoperation rate for postoperative small bowel obstruction was significantly higher in patients undergoing the laparoscopic procedure [26]. No significant differences were found between laparoscopic and open surgery in the occurrence of incisional hernias or the number of reoperations for adhesions according to a recent Cochrane revision [27].

Does this mean that all colon cancer patients are optimally served through a laparoscopic approach?

We agree with the opinion of those who state that we are still not fully ripe for such decision, basically for two main reasons:

- criteria for ineligibility in the different randomized clinical trials included: elderly subjects, patients with an absolute contraindication to long-term pneumoperitoneum, with body mass index $>32 \text{ kg/m}^2$, with severe medical illness and those requiring emergency operation, patients with previous colon surgery or diffuse abdominal adhesions and those with obstructing or perforated or advanced local (T4) or systemic (Stage IV) lesions or big lesions and lesions invading the surrounding structures as well as those with primary tumor located in the transverse to descending colon. Some of these features are easily identified preoperatively, other are only recognised during the surgical exploration.

Hence data from randomized clinical trials can be applied but to a quite selected series of colon cancer patients in the routine practice.

- Furthermore the growing interest for the fast-track surgery appears to erode the advantage of laparoscopic colectomy as regards the short-term benefit. There are few randomized clinical trials exploring the difference between fast-track surgery and laparoscopic colectomy plus fast-track: Basse *et al.* [28] in a blind randomized clinical trial on 60 elderly patients found that functional recovery after colonic resection was rapid with a multimodal rehabilitation regimen and without differences between open and laparoscopic operation, while King *et al.* [29] in 62 patients reported that combined hospital, convalescent and readmission stay was 37 per cent shorter with laparoscopic colectomy. It has to be pointed out that in the setting of a long-established and efficient enhanced-recovery protocol [27] no further improvement in short-term outcome was seen by adding laparoscopy (median postoperative length of stay of 2 days in both groups). The second study [28] had longer hospitalizations, and here a reduction in postoperative stay was seen in the laparoscopic colectomy group as compared with the group undergoing open surgery (3.5 vs 6 days, respectively).

Finally, a word of caution has been expressed concerning the oncologic quality of laparoscopic colectomy in these randomized clinical trials since the number of lymph nodes was a bit lower the value recommended by the international guidelines as appropriate for an adequate staging and a radical surgical procedure [20,21].

In conclusion there is a scientific evidence that in a selected patients' population the laparoscopic and the open procedures are somewhat equivalent as regards surgical and oncologic outcome.

Surgeons are obviously free to expand the indications for laparoscopic colectomy also to the patients' population excluded from randomized clinical trials but they should be aware that they cannot claim for the same clinical outcomes achieved by open surgery and should provide their patients with such information.

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