Editorial

Laparoscopic surgery for colorectal liver metastases: moving forward while keeping feet on the ground

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The laparoscopic approach to the surgical treatment of colorectal liver metastases (CRLMs) is supported nowadays by high evidence (1). In the hand of expert surgeons, patients undergoing laparoscopic liver surgery (LLS) for CLRMs benefit from a number of advantages, including a shorter postoperative in-hospital stay, less pain, fewer complications and a faster recovery (1). More importantly, all these profits are achieved while preserving the oncological outcomes, which are not-inferior to those achieved by open procedures (1). Recently published long-term results of randomized trials have shown similar patient survival after laparoscopic and open surgery for CRLM (2).

As surgeons with a great interest in the LLS since its beginning, we were excited to read in Annals of Surgery the recent meta-analysis by Syn *et al.* (3). These colleagues computed the results from randomized trials and studies using propensity-score matching (PSM), which compared open and laparoscopic surgery for CRLMs. They found a survival advantage for patients undergoing LLS, a result which indeed surprises the surgical community, engaged until today to prove the non-inferiority of the laparoscopic approach.

Several hypotheses are postulated to explain the improved survival following LLS (3). These include the reduced postoperative morbidity and the shorter recovery, which both lead to an earlier resume of chemotherapy (4,5). LLS is also claimed to be performed by more experienced surgeons and more frequently with a parenchymal-sparing approach, which reduces the risk of postoperative liver failure and eases repeat liver resections. Finally, LLS may preserves immune-surveillance by reducing the surgical stress and, compared to open surgery, may lead to an inferior inflammatory boost (6,7), which has been shown to promote metastatic growth. However these data are still controversial and more studies are needed to clarify the role of inflammation in open and laparoscopic surgery of CRLM. Many of these assumptions are sharable, although some (i.e., surgeon experience and the parenchymal-preserving approach) represent a potential confounding factor rather than a real advantage within this comparison.

Nonetheless, even the most avid supporters of LLS should doubt that the findings by Syn *et al.* could be the result of a patient selection bias, despite the very complex methodology used for this meta-analysis.

Notably, in this work the survival advantage favouring LLS is sustained only by PSM studies (see subgroup analysis). Propensity score balances groups for known confounders, and the authors assume that all potential confounders were balanced in all the studies, with no need of further adjustment. At regard, it is worthy to note that the included thirteen PSM studies controlled for a median number of 9 confounders, varying from 4 to 18 variables. This means that study were indeed heterogeneous for the matching criteria. In addition, survival of patients undergoing surgery for CRLMS depends on a number of prognostic factors which include the number of metastases (8), nodal status (8), differentiation (8) and site

of the primary tumour (9), and the response to neoadjuvant chemotherapy (10). Even though all PSM studies matched patients according to the number of metastases, only seven, six and five of the included studies matched patients for site, nodal status and differentiation of the primary tumour, respectively. No study took into account the response to the neoadjuvant chemotherapy, in patients who received it. These prognostic factors, especially the last one, could be to some extent determinant of the patient selection for one or the other treatment.

As meta-analysis can detect statistical significant differences while single studies cannot, similarly meta-analysis can amplify bias of single studies bringing them to a significance level. To stay in line with a famous saying about meta-analysis (i.e., "comparing apples and oranges"), in this case the risk is to merge many apples, each one with a small bite, and to obtain a bigger apple with a big hole inside.

In the recent years big steps forward have been made in the surgical literature to understand the real role of LLS in patients with liver disease. First level evidence has come up for CLRMs, supporting the use of LLS, and, step-by-step, we should continue on this way, waiting for the long-term results of the OSLO-COMET and further coming-up randomized trials. These studies will need to confirm the findings by Syn *et al*., that, in the meanwhile, should be accompanied by a wise caution, since big numbers and complex methodology cannot always go beyond the limits of limited-quality data.

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