



Resections for colorectal liver metastasis: the breakthrough of laparoscopic surgery?

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Liver resection is still considered the treatment of choice for colorectal liver metastasis (CRLMs) with 5-year survival rates of 40–58% when associated with modern regimes of chemotherapy. Traditionally, liver resections have been performed through open surgical access. In the last two decades, laparoscopic liver surgery (LLS) has been gaining acceptance with many studies confirming its feasibility, safety and oncological efficiency. Improvement in outcomes have partially been explained by the advantages of minor surgical trauma when maintaining the integrity of the abdominal wall and by reducing intraabdominal scarring. Moreover, a number of techniques have been developed and implemented to ensure that parenchymal-preserving resections can be safely performed in any segment with comparable results to those seen in open surgery (1,2). The feasibility of such oncological resections in the context of a minimally invasive approach has certainly led to many specific advantages especially when dealing with CRLMs, encouraging the feasibility of repeated hepatectomies (3). This is obviously a huge advantage in metastatic colorectal cancer, nowadays considered as a chronic systemic disease, with high incidence of recurrence. Hence, creating optimal conditions for reinterventions is paramount and should be a mainstay of the surgical approach to CRLMs.

The Southampton Consensus Guidelines for Laparoscopic Liver Surgery has confirmed that laparoscopy is a valid approach to treat CRLMs in any location of the

liver. In addition, its advantage in repeat hepatectomies was shown (4). The focus has then moved towards long-term oncologic outcome.

The impact of repeat resections facilitated by the adoption of a minimally invasive approach on oncological long-term outcomes has not yet been fully assessed. Interestingly, a recent multicenter study has shown a similar disease-free survival (DFS) but a better overall survival (OS) in patients treated laparoscopically when compared to those treated with open surgery in case of positive resection margins (5). The only difference between the two groups was a higher incidence of redo surgery in patients undergoing LLS. More data, from large cohorts and longer follow ups on this topic are seriously needed.

The first randomized controlled trial (OSLO-COMET) has now been published. It showed that patients undergoing parenchymal-sparing laparoscopic liver resection for CRLMs had a similar median OS and recurrence-free survival to open liver resection (6). The second trial (LapOpHuva) has demonstrated similar oncologic outcomes, with no difference in 5-year DFS or OS between the minimally invasive and the open arm (7). Due to the long recruitment period of 11 years, long-term results were readily available.

Syn *et al.* published a systematic review on laparoscopic and open surgery for CRLMs focusing on OS (8). Strict in- and exclusion criteria selected relatively high-quality

studies including the two RCTs. In the pooled cohort with 3,148 patients, LLS was associated with a lower hazard of death (hazard ratio: 0.853, 95% CI: 0.754–0.965, $P=0.0114$). Moreover, the authors also estimate a fraction of patients that can be cured or are long-term survivors, defined as no recurrence during a follow >10 years. The cure rates were 47.4% and 18.0% in the laparoscopic and open group, respectively, and the mean survival time was longer in the laparoscopic group. In a subgroup of patients with synchronous resections of the primary tumor and CRLMs no survival advantage of the laparoscopic approach was found although the authors state that the analysis is underpowered. Similarly, in the two RCTs analyzed separately, there was no survival difference. The conclusive statement of the authors is that there is a survival benefit in favor of LLS and that laparoscopy is at least not inferior to the open approach.

This is the first high-quality meta-analysis providing encouraging findings of better survival following LLS and there is currently no superior data synthesis akin to this report. A recent meta-analysis published by Ciria *et al.*, including only the OSLO-COMET trial, has shown better short-term results after LLS but no oncological advantages (9).

We support the cautious conclusion on superior survival after LLS as most of the included studies only report 3-year survival. But in line with the plurality of other reports on perioperative outcomes, confirming the superiority for LLS, this surely will further promote the already widespread use of the approach.

But cautiously we remind the reader that patient selection is an issue in propensity-score matched studies as it is in RCTs and hence may only conditionally be applied to the general population. We also believe that RCTs powered to detect a survival benefit may not be conducted due to the high number of patients needed to detect a survival difference.

Generally, the approach to surgical research is profoundly different from other medical fields. No strict regulations apply to testing and implementation of surgical techniques unlike for example the introduction of new pharmaceutical drugs. New drugs regularly must pass through multiple phases, from exploration to safety, benefit and comparison to the standard treatment before regulatory approval and widespread clinical use. In surgery, studies usually follow the clinical use. Therefore, the introduction of surgical techniques poses considerable methodological challenges and motivation to conduct high-quality RCTs may be low.

With the results from this and other high-quality data from meta-analyses, an evidence-based shift towards LLS as standard of care has started. More data from multicenter RCTs, the ORANGE II Plus trial comparing laparoscopic versus open hemihepatectomies (NCT00874224) and the ORANGE Segments trial comparing resections in the posterosuperior segments (4a, 7, 8) for the two approaches (NCT03270917) is expected.

We believe that a careful implementation, no matter how revolutionary a novel technique appears at first sight, is mandatory and doesn't hinder a steady progress. Multicenter randomized controlled trials should be conducted and international registries be initiated simultaneously. Analysis and reports from such collaborations should then be pooled in meta-analysis to help in the evaluation of the current practice and guide future research.

However, already now, there are good reasons to assume that LLS will become a standard approach for the treatment of CRLMs and may become a strong alternative to open liver surgery.

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Footnote

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