



Long term outcome of laparoscopic liver resection for HCC—is the jury still out?

Daniel Seehofer, Robert Sucher

Department of Visceral, Transplantation, Thoracic and Vascular Surgery, University Hospital Leipzig, Leipzig, Germany

Correspondence to: Prof. Dr. Daniel Seehofer. Department of Visceral, Transplantation, Thoracic and Vascular Surgery, University Hospital Leipzig, Liebigstr. 20, Leipzig D-04103, Germany. Email: daniel.seehofer@medizin.uni-leipzig.de.

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After relatively slow implementation in the initial phase, the application of laparoscopic liver resection (LLR) is sharply increasing worldwide within the last years. As for every newly evolving technique, the analysis of long-term outcome and tumor recurrence after LLR is an important issue, before general implementation of this technique. Specifically, in HCC patients, the outcome after liver resection is affected by several factors. The three most important determinants of survival are: (I) severe perioperative complications causing mortality; (II) liver cirrhosis eventually leading to non-tumor related liver failure and deaths; and (III) tumor related factors and the risk of tumor recurrence. Beyond that, also patient age and comorbidities are important cause variables. Especially in evolving techniques, the stage of learning curve and the individual experience of the surgeon are further potential determinants, which need to be considered.

In a recent study (1), Tsai and colleagues retrospectively analyzed the short and long term results of 313 HCC patients, who underwent either LLR (n=150) or OLR (n=163). Overall LLR was confirmed to be associated with a significantly shorter operation time (175±85 *vs.* 202±59 min, P=0.001), shorter length of hospital stay (7±4 *vs.* 11±7 d, P<0.001), less blood loss (363±579 *vs.* 839±866 mL; P<0.001) and a lower postoperative morbidity (9.8% *vs.* 18.1%, P=0.034). However, although in the analysis entire cohort the long-term survival after LLR was significantly better than after OLR, the stage specific survival for the TNM stages I to III did not differ between LLR and

OLR. Interestingly, the recurrence free survival showed no differences between the study groups, neither in the overall study population nor in the stage specific subgroups. From the present literature including the recent manuscript by Tsai *et al.*, the appraisal of LLR based on the data available requires distinct assessment of short and long-term results, due to differences in scientific evidence.

Short-term results of laparoscopic liver surgery

The short term advantages of LLR compared to OLR have been sufficiently proven in the last few years, although only one high quality randomized controlled trial has been completed so far. This trial indicated better short-term results after LLR. Namely, a reduced rate and severity of complications and a shorter postoperative hospital stay was observed after LLR (2). Another well-designed randomized controlled trial on open or laparoscopic left lateral sectionectomy could not be completed due to low recruitment (3), since patients and surgeons began to favor LLR during the study time span and therefore completion of the OLR group was not feasible any more. This shows that scientific evidence might be overtaken by clinical reality. A similar phenomenon was observed in the early phase of many minimal invasive procedures. In consequence, this might slow down further generation of scientific evidence, which than has to be created by alternative means as discussed below.

Besides randomized controlled trials, numerous

retrospective analyzes have been published, some with high numbers of patients, often applying propensity score matching. Almost all analyses confirm the short term advantages of LLR which have been properly summarized in a recent meta-analysis (4). The proven benefits include a shorter length of hospital stay, a lower complication rate, and a lower rate of superficial and deep wound infections. The reported benefits are evident in the clinical practice, and therefore LLR is evolving as a clinical standard in addition to OLR. This development is reasonable and supported by several consensus conferences (5).

In patients with liver cirrhosis, careful patient selection including assessment of liver function (6) is most important. Together with adequate surgical technique, it helps to achieve a low postoperative complication rate and thereby to avoid liver failure. This brings about LLR with its theoretical benefits in patients with liver cirrhosis. These include minimal destruction of the body wall and portal collaterals and a reduced inflammatory response (7). For those surgeons, who already perform laparoscopic liver surgery, the short-term advantages for a laparoscopic approach in HCC patients with cirrhosis are self-evident. This is also supported by several retrospective analyses and subsequent meta-analyses (8). Specifically in cirrhotic patients, the risk of postoperative decompensation by infectious complications, ascites production and/or liver failure is significantly reduced after LLR compared to OLR (8). However, despite a reduced complication rate in many and a reduced in-hospital mortality in few studies, an improved long-term survival has been shown only in one propensity score analysis so far (9). All other studies revealed a similar survival after LLR and OLR for HCC (4).

Oncological outcome after laparoscopic liver surgery

Most analyses reveal similar long-term results after LLR and OLR. However, this is supported by one randomized trial only (2) and therefore still requires a detailed and critical reflection.

Stage specific analysis is an important issue for the evaluation of LLR, since otherwise long term data are not comparable or even misleading. This is clearly demonstrated in the paper of Tsai and colleagues (1), since in the overall cohort, a significantly improved survival after LLR with a P value of 0.002 is suggested. However, the stage specific analysis discloses the effect of different tumor stages in the LLR group, with a significantly higher

number of stage I tumors (52% *vs.* 26 %) and a significantly lower proportion of stage III and IV tumors (15% *vs.* 43%). In the stage specific subgroup analysis, no differences of overall and recurrence free survival can be documented any more. However, from the scientific point of view, one could argue, that there are still some imbalances. For example in stage I tumors, the groups are well balanced for the confounders presence of cirrhosis (57% *vs.* 59%) and Child-Pugh B stage of cirrhosis (9.5% *vs.* 8.8%), which both are important determinants of long-term survival. However, after propensity matching the tumor size was still significantly larger in the OLR than in the LLR group (4.7 *vs.* 3.1 cm, $P=0.025$). Unfortunately, no data on vascular invasion are available. Due to the retrospective nature of this and most other studies, it remains unclear, if the lower number of major resections in the LLR-group (21% *vs.* 13 %) is arisen because of tumor size and/or location or if it is an indication of lower surgical radicality? In the light of general evaluation of LLR also the results in stage II patients could be exemplary discussed. In this subgroup, the disease free survival rate was similar after LLR and OLR. However, in the OLR group only 60% of patients had liver cirrhosis (*vs.* 78% in the LLR group) and no patient had Child B cirrhosis, whereas 8% in the LLR did so. Again, the rate of major resections was higher in the OLR group (34% *vs.* 24%), probably based on these differences in liver damage. Nevertheless the rate of complications (24% *vs.* 14%) and severe complications (Clavien-Dindo 3–4; 16% *vs.* 2%) was significantly higher in the OLR group. However, overall survival was again without significant differences.

The only study, which has shown a better overall survival and a better disease free survival rate after LLR for HCC in cirrhosis was published by Cheung and colleagues (9). This properly matched propensity score analysis on a homogenous cohort of cirrhotic patients (110 patients after LLR *vs.* 330 after OLR) constitutes the largest single center series so far.

Only one randomized controlled trial has been published so far (10), however with 25 patients in each group only. Patients after LLR revealed a shorter duration of hospital stay and a comparable overall complication rate. Blood loss transfusion rate and R0 resection rate were similar in LLR and OLR. One-year and 3-year disease free survival (DFS) rates in this trial were similar between LLR and OLR ($P=0.09$) after median follow-up of 34 months, however this relatively short follow up might be too short for patients with early HCC and the long term outcome has to be awaited. However, all analysis revealed at least similar

recurrence rates and long-term survival after LLR and in the literature there is no indication for inferior results for any tumor entity after LLR.

HCC in cirrhosis: status quo and unmet needs

The question of long-term outcome of HCC patients after LLR is difficult to answer by retrospective analyses and by using more or less historical control groups for several reasons:

- (I) The median survival of HCC patients has improved within the last decades due to new drugs for the treatment of HCC as well as viral hepatitis and refinement of interventional therapy (11). Due to this, a more or less historical control group might be expected to have a “naturally” impaired long term survival.
- (II) By introduction of LLR an extension of indications for liver resection in cirrhotic patients in terms of liver function is seen in many centers (12). Even selected patients with Child B cirrhosis are considered for LLR nowadays (13).
- (III) Especially in the early phase of the learning curve, patients without cirrhosis might be considered for OLR rather than LLR.
- (IV) With an increasing patient number differences in perioperative morbidity and even mortality should have an effect on long term outcome.
- (V) The relatively long learning curve of LLR (14) might result in slightly inferior results concerning surgical radicality, mainly in difficult tumor locations. Therefore, the true effect of LLR on long-term outcome might only be seen after completion of the learning curve and acquisition of considerable experience with LLR.
- (VI) The overall survival “after” liver resection is among others influenced by secondary liver transplantation, therefore data on transplant frequency in different groups are essential.

Owing to resulting crucial differences in the study population of OLR and LLR, the net effect of all these factors is difficult to estimate. The resulting disparity of study groups may only be overcome with a high patient number, and appropriate inclusion criteria. For the given reasons, further analyses should clearly address patients with HCC in cirrhosis separately, since this subgroup is supposed to have the highest benefit provided by the laparoscopic approach. Matching of cohorts should also focus on liver

function, since otherwise patients with LLR might have more advanced cirrhosis. This should automatically bring about a matching of major/minor resections.

In the future, also data after the learning curve might become more and more important, since results of LLR resection might further improve afterwards. Moreover, data on stage specific outcome and secondary liver transplantation are also mandatory. In general, the initiation of randomized controlled trials using long-term survival as primary endpoint is even at that point difficult, since the data discussed above are very suggestive of a significantly lower perioperative complication rate after LLR. However, systematic acquisition of data on LLR, e.g. by surgical registries as initiated in Japan recently (15) may additionally help to unravel the impact of LLR on long-term outcome.

At present, very few data from European and US-centers are available due to the lower incidence of HCC. Especially from a Western perspective on HCC, a separate analysis of patients with and without severe parenchymal damage (NASH) or cirrhosis would be of paramount interest. However, the short-term benefit of LLR is so evident in cirrhotic patients, that some of the patients might not undergo surgery by OLR due to the risk of perioperative morbidity and mortality. However, detailed analysis of long term results of these patients are still mandatory, since alternative, interventional treatment modalities are available.

At present, the conclusion of Tsai and colleagues (1), that “LLR for HCC is a safe and feasible procedure that does not compromise long-term oncological outcomes” is still not sufficiently proven by the current scientific evidence. However, so far the use of LLR for HCC patients is still preferable due to the improved short term results, proven in many trials. The authors are convinced, that with progress in the learning curve and comparison with well-balanced control groups in a higher number of patients, the better postoperative outcome will translate into a better long term survival in the future

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