Editorial

Is laparoscopic liver resection for hepatocellular carcinoma in patients with well-preserved liver cirrhosis superior to conventional open liver resection?

Toru Beppu[1,2], Hiromitsu Hayashi[2], Tastunori Miyata[2], Nobutaka Sato[1,2], Yasushi Yoshida[1,2]

[1]Department of Surgery, Yamaga City Medical Center, Kumamoto, Japan; [2]Department of Gastroenterological Surgery, Graduate School of Life Sciences, Kumamoto University, Kumamoto, Japan

Correspondence to: Toru Beppu, MD, PhD, FACS. Department of Surgery, Yamaga City Medical Center, Kumamoto, 511 Yamaga, Kumamoto 861-0593, Japan. Email: tbeppu@yamaga-mc.jp.

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Laparoscopic liver resection (LLR) has become the standard treatment for various tumors of the liver including hepatocellular carcinoma (HCC) (1-3). LLR for liver tumors are considered to possess several perioperative advantages compared with conventional open liver resection (OLR). The Oslo-CoMet is the only randomized-controlled trial (RCT) to provide solid evidence that LLR is safer, less invasive, and cost-effective compared with OLR in patients with colorectal liver metastases (4). Unfortunately, there are no RCTs comparing LLR and OLR in patients with HCC. Numerous original studies, reviews, and meta-analyses comparing LLR with OLR for HCC harbor evident selection biases in the size, number, and location of the tumor, because LLR was performed in cases that tended to be less challenging, especially in the learning phase of this new approach. Importantly, several studies including HCC patients utilized propensity score matching (PSM) to minimalize such selection biases (5) and demonstrated that LLR was associated with slightly longer surgical times, reduced intraoperative blood loss and transfusion rates, shorter hospital stays, lower morbidity, and similar mortality compared with OLR (6-13). From an oncological viewpoint, LLR can provide long-term outcomes comparable with OLR with no specific recurrence patterns. Although several reports compared LLR and OLR specifically in patients with HCC and liver cirrhosis (14-17), the definition of liver cirrhosis varied among the studies.

We congratulate Dr. Wu and colleagues for their recently published study entitled "Perioperative and long-term outcomes of laparoscopic versus open liver resection for hepatocellular carcinoma with well-preserved liver function and cirrhotic background: a propensity score matching study" in Surgical Endoscopy (18). In this unique study, the authors compared LLR with OLR for patients with limited HCC and well-preserved liver cirrhosis and used one-to-one PSM to minimalize the confounding factors. The background variables were well investigated and well matched after PSM, including baseline characteristics, preoperative laboratory and intraoperative data, and pathological tumor characteristics in both groups. The authors compared surgical outcomes and long-term prognosis in patients who underwent LLR and OLR. The primary endpoint was to determine the risk factors for post-hepatectomy liver failure (PHLF) proposed by the International Study Group of Liver Surgery (ISGLS) (19). ISGLS grades B and C PHLF were reported to be an accurate predictor of postoperative mortality in a recent international multicenter study (20). In their study, Wu *et al.* indeed found that the frequency of grade B PHLF was significantly higher in the OLR group than the LLR group. Factors that might have contributed to this outcome can be categorized as patient-, surgery-, and background liver function-related (21). Among the surgery-related factors are small liver remnant, massive intraoperative bleeding, transfusion of red cell concentrates, and postoperative major complications. Conversely, the lower rate of morbidity was

a major cause of the lower PHLF rate. The study included several resection approaches; however, minor resection was the most frequent method in both the LLR (73.3%) and the OLR (82.6%) groups.

We would like to ask Wu and colleagues to elucidate their finding of OLR as the only independent risk factor for PHLF (odds ratio, 2.539, 95% confidence interval: 1.127-7.851, P=0.014). The article was unclear on assignment of the study patients to undergo LLR or OLR. Certainly, the authors stated that the choice between LLR and OLR in all cases was determined by comprehensive assessment by surgeons with informed consent from the patients (18). PSM is quite difficult to achieve if the target patient selection to undergo LLR or OLR is completely separated. Although the background factors were well-matched between the two groups; efforts to match factors that determine surgical difficulty were not insufficient (22,23). Unresolved selection bias such as frailty and sarcopenia might exist which can influence the PHLF rate between the two groups (24,25).

Additionally, the definition of well-preserved liver function and cirrhotic background is critical. The inclusion criteria used in this study (18) were: (I) histopathological diagnosis of HCC and a background of cirrhosis; and (II) well-preserved liver function defined as Child-Pugh class A with less than 10% retention rate of indocyanine green (ICG) retention at 15 min and adequate future liver remnant (FLR) at >40% of total liver volume. Patients with pathological cirrhosis are well known to occasionally exhibit abnormal ICG retention rates at 15 min (26). In our experience, only 7 of 34 (20.6%) HCC patients with histologically confirmed liver cirrhosis who underwent LLR showed normal ICG retention rates at 15 min (8). This criterion should be considered as another limitation that could have contributed to the selection of patients with severe cirrhosis in the current study. We propose that patients considered for LLR should be selected carefully with adaptation on the laparoscopic technique.

The authors also found that the morbidity in the LLR group was significantly lower than that in the OLR group (7.0% *vs.* 19.8%, P=0.014) and was accompanied with a lower rate of ascites (0% *vs.* 7.0%, P=0.029). The median hospital stay was significantly shorter in the LLR group (8 *vs.* 13 days, P=0.018). These advantages can be explained by the hemostatic effect of pneumoperitoneum, better magnification, and application of newly developed devices for parenchymal transection. Conversely, the amount of blood loss and the rate of blood transfusion were comparable between the two groups. These results are different that those reported in previous comparative studies of cirrhotic HCC patients undergoing LLR or OLR (14-17), in which the conversion rate was relatively high at 9.3%. Albeit slightly higher in the LLR group compared to the OLR group, the survival curves were not significantly different between the two groups. Similar, comparable survival rates were reported previously (6-15,17). However, one pivotal study of cirrhotic patients demonstrated that LLR was associated with a significantly higher median overall survival (136 *vs.* 120 months for OLR) and greater 5-year overall survival (83.7% *vs.* 67.4% for OLR) (P<0.033) (16). This survival advantage was detected only in patients with stage II HCC (P=0.045). This difference was suggested to be due to less blood loss and less tissue manipulation, defined as “no-touch isolation”, in LLR compared to OLR.

In recent years, LLR has become an especially useful tool for patients with advanced liver cirrhosis. To minimize the incision wound can preserve portosystemic collaterals and lymphatic circulation. Additionally, refractory ascites can be controlled by avoiding liver mobilization. Conversely, high-pressure pneumoperitoneum can lead to a decrease in the portal vein flow in the cirrhotic liver. The study by Wu *et al.* included only HCC patients with well-preserved liver function and a cirrhotic background; therefore, their findings are less impactful compared to other studies investigating patients with more advanced cirrhosis (14-17). Therefore, further prospective studies are critical to investigate the utility of LLR and its potential superiority to OLR based on to the extent of liver cirrhosis.

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