Editorial Commentary

The future of minimally invasive liver resection for hepatocellular carcinoma BCLC stage 0–A

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Minimally invasive liver resection is moving toward the gold standard treatment for liver cancer due to its short-term clinical advantages when compared to the traditional open operation. The advent of robotic surgical system which enables surgeons to undertake liver resections that were technically difficult/impossible laparoscopically further advances forward the minimally invasive field. Solid long-term oncological outcome data, however, are lacking since most of the published studies are retrospective series with short-term follow-up. Recognizing this defect in the literature, Zhu *et al.* sought to provide more substantial evidence via a propensity score matched study aimed at evaluating minimally invasive hepatectomy outcomes for Barcelona Clinic Liver Cancer (BCLC) stage 0–A hepatocellular carcinoma (HCC) (1). A total of 1,104 consecutive patients underwent liver resection for HCC, of which 369 patients had tumors within BCLC stage 0–A. Upon 1:1:1 [robotic assisted laparoscopic (RALR):laparoscopic (LLR):open liver resections (OLR)] propensity score matching, 169 patients were enrolled in the study, with 56 patients in each group. The patients were responsible for the decision of surgical approach at their index operation. Baseline characteristics between groups represented a good balance and were statistically similar.

Intraoperatively, five patients in the RALR group required conversion to open for uncontrollable bleeding (n=3), intraoperative tumor rupture (n=1), and failure to progress in a timely manner (n=1). An additional seven patients in the LLR group required conversion for uncontrollable bleeding (n=2), difficulty in dissecting tumor from vasculature (n=2), and failure to progress in a timely manner (n=3). The minimally invasive groups experienced significantly longer operative duration, including pringle maneuver duration (220 *vs.* 215 *vs.* 155 minutes, P<0.001), however, R0 resection margin was achieved comparably (98.2% *vs.* 96.4% *vs.* 100%, P=0.361), and no intraoperative death occurred across all groups.

Post-operatively, patients from the minimally invasive groups showed shorter length of stay compared to the OLR group (6 *vs.* 8 *vs.* 12 days, P<0.001), which is consistent with our current knowledge of minimally invasive liver resection (2). Notably, while there was no difference in complication rate (12.5% *vs.* 17.9% *vs.* 23.2%, P=0.334), the OLR group had a higher rate of textbook outcomes of liver surgery (TOLS) compared to the minimally invasive groups (80.4% *vs.* 80.4% *vs.* 94.6%, P=0.049). This is rather an

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interesting finding since minimally invasive liver resection is generally associated with significantly lower complication rates when compared to open, besides its much shorter hospital stay (3). Unfortunately, the discrepancy between similar complication rates but superior TOLS in the OLR group was not further elaborated in the manuscript.

During the risk factor analysis, four independent factors negatively correlated with 5-year overall survival, including tumor diameter >5 cm, clinically significant portal hypertension, alpha fetoprotein (AFP) level >400 ng/mL and advanced Edmondson-Steiner grading (III or IV). However, clinically significant portal hypertension was the only risk factor found to significantly influence 5-year disease free survival (DFS) in the study. Recurrence in the OLR group occurred more frequently as multiple tumors and at more advanced stages than the minimally invasive groups (52.2% BCLC stage B *vs.* 18.5% *vs.* 22.2%, P=0.032). However, overall survival was comparable across the board (74.4% *vs.* 76.8% *vs.* 78.6%, P=0.90). The authors proposed that the less inhibitory effect on the immune system of the body associated with minimally invasive approach might play a role in tumor recurrence. Furthermore, in animal study, carbon dioxide pneumoperitoneum can better protect the function of peritoneal mononuclear macrophages, so that the cell- mediated immune response of the body can be better preserved. These important findings and concepts may become more relevant in the future as we discover similar findings with minimally invasive treatment in other cancers.

Although this study is not a randomized control trial, it offers a higher level of evidence through prospective propensity matched groups as opposed to a meta-analysis of retrospective studies for the implementation of minimally invasive approaches to BCLC stage 0–A HCC tumors. The inclusion of the robotic platform in this study provides new insights beyond the current European Society of Medical Oncology (ESMO) Clinical Practice Guidelines, which only include laparoscopic and open approaches (4,5). This study, which was conducted at a major Asian liver center, not surprisingly, reported a significant percentage of hepatitis B virus (HBV)-related HCC. This provided monocentric data and demonstrated a possible generalization of the results to Asian population, where HBV is most endemic. Throughout the world, however, leading causes of HCC vary such as alcohol and nonalcoholic fatty liver disease (NAFLD). Populations with more prevalent rates of these etiologies are important to developing appropriate clinical guidelines in the future. To this point, another recent Asian study evaluated NAFLD *vs.* HBV associated HCC found that more advanced BCLC stage (B/C/D) but less major vascular invasion was seen in the NALFD group (6). Therefore, long-term oncologic follow-up, as shown in this study, is important to elucidate differences in ultimate outcomes between the various etiologies of HCC.

Concerning the tumor recurrence, the OLR group showed more advanced tumor stage and increased multiplicity at the time of detection. Overall, however, the groups were similar and comparable for the disease-free five-year survival. The lack of difference between the groups raises a question again about the etiologic nature of HCC in these patients. Further descriptive information including the HBV cure rate, length of detectable viral load, and HBV recurrence rate could be important to clarify this data.

The authors emphasize the significance of their institutional experience with the minimally invasive techniques, including the robotic technique used in this study. The authors deserve a full commendation for mastering the robotic approach in a setting/country where robotic surgical system is seen as an expensive tool, not readily available to all patients. This study asserts that each participating member had completed their minimally invasive (laparoscopic and robotic) learning curves prior to conducting the study. This is a very important point to consider when integrating study outcomes into a clinical guideline. A study involving complex hepatobiliary resections must be conducted at institutions with experienced minimally invasive surgeons in order to reduce potential bias in technical operative proficiency (7). As exposure to the robotic platform is increasingly integrated into the residency and fellowship programs, trainees will begin their minimally invasive learning curve much earlier, which eventually will bring more experienced minimally invasive and robotic surgeons to the forefront of Surgical Oncology (8-10). Finally, it is essential to ensure comparable long-term oncological outcomes with all minimally invasive techniques using the conventional open operation as the reference point, as shown in this important study by Zhu *et al.*

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