Editorial

Laparoscopic hepatectomy for hepatocellular carcinoma: are oncologic outcomes truly superior to an open approach?

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Provenance: This is an invited Editorial commissioned by Editor-in-Chief Yilei Mao (Department of Liver Surgery, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing, China).

Comment on: Cheung TT, Dai WC, Tsang SH, *et al.* Pure Laparoscopic Hepatectomy Versus Open Hepatectomy for Hepatocellular Carcinoma in 110 Patients With Liver Cirrhosis: A Propensity Analysis at a Single Center. Ann Surg 2016;264:612-20.

Submitted Feb 25, 2017. Accepted for publication Mar 03, 2017.
doi: 10.21037/hbsn.2017.03.09
View this article at: http://dx.doi.org/10.21037/hbsn.2017.03.09

Despite decades of research and an emerging understanding of the molecular biology of disease, the prognosis for patients diagnosed with hepatocellular carcinoma (HCC) remains poor. Epidemiologic surveys continue to show a rising incidence of disease and therapeutic options remain largely ineffective. Surgical extirpation, whether by hepatectomy or transplant, remains the favored option in a curative paradigm of disease management. It is with great interest, therefore, that we read the work of Cheung and colleagues in the *Annals of Surgery* evaluating the role of laparoscopic hepatectomy in HCC (1). This study was performed by retrospectively evaluating outcomes for patients presenting to a single high-volume institution in Hong Kong. Importantly, these authors have demonstrated a prior aptitude for laparoscopic hepatectomy by publishing their early experience in a subset of this same cohort of patients (2). This initial manuscript aimed to demonstrate safety in patients with cirrhosis by documenting short-term outcomes for both the early laparoscopic cohort and a case-matched cohort of patients having undergone open hepatectomy (ratio approximately 1:2). This initial work also attempted to comment on the oncologic adequacy of a laparoscopic resection in a secondary analysis. As the authors make clear in their response to discussants during the Annual Meeting of the American Surgical Association, a comment on survival was likely premature and biased by patient selection in their early case-matched report.

Accepting the safety of laparoscopic hepatectomy in patients with early cirrhosis, as shown by their initial report, this manuscript details an updated experience with cases of increasing technical complexity. Further, the statistical methods used in this paper are more nuanced than those used prior. Rather than relying on simple case-matching to eliminate selection bias, the laparoscopic data are now compared to an open cohort by propensity matching (3:1 ratio). Key findings include improved perioperative outcomes in the laparoscopic cohort (reduction in blood loss, operative time, and hospital length of stay) and favorable overall survival. Survival data are compelling enough to lead the authors to conclude "a potential oncological benefit of the laparoscopic approach over the open approach." This last conclusion is striking and has led many liver surgeons to critically examine this study in the context of the statistical methods used and other available evidence.

The use of laparoscopy by general surgeons in hepatobiliary procedures is a lens through which both the opportunities and challenges of this new tool can be viewed. The opportunity is reflected by the rise of the safe, minimally invasive cholecystectomy. The challenge and application of this technique for other hepatobiliary procedures, is in part what this manuscript is designed to address. Importantly,

we do suggest that the laparoscope, like the Kelly clamp or the ultrasonic surgical aspirator, is a tool to be used in the right hands and for the right patients. As with any tool, patient safety is paramount. One notable finding that can be drawn from this manuscript is a re-examination of perioperative outcomes and the safety of the laparoscopic approach in more complex hepatobiliary procedures. In total, ten patients who underwent major hepatectomy were included in these data. The surgeons are to be commended for excellent perioperative outcomes with the only surgical complications noted in the laparoscopic group being wound infection (n=4). We suspect that the current success in the laparoscopic cohort is grounded in a team of surgeons performing beyond their learning curve and highly selective patient evaluations. Given the data available in this report, it is notable that only 8% (110 of 1,358 patients) of operations were selected for a laparoscopic approach over the course of this study period.

This preoperative patient selection certainly accounts for some degree of bias in the retrospective evaluation of both perioperative surgical outcomes and patient survival. At its core, therefore, this manuscript is about accurate interpretation of preoperative selection bias. What is the best method to account for, or compensate against, this bias and how should the conclusions drawn from this methodology be broadly interpreted? The authors utilized propensity matching to evaluate outcomes between the laparoscopic cohort and a, roughly, contemporary group having undergone an open procedure. In general, propensity matching can be an effective tool to partially account for selection bias in a retrospective study analysis. In a simplified view, this method is an automated way to match cases in which a conditional probability is calculated for each potential confounding variable and a total score is derived. Case-matching is subsequently completed by identifying "nearest neighbor" scores and a control data set is built. Critically, even this highly nuanced method of case matching cannot eliminate bias and is not a substitute for pretreatment randomization. Perhaps the most critical disadvantage of propensity score matching is that this model can only account for potential confounding variables that are identified and measured in a data set. It is therefore unreasonable to expect that this method could exhaustively account for bias likely present during the preoperative evaluation of patients with HCC and chronic liver disease by a multidisciplinary team of highly experienced surgeons, interventional radiologists, hepatologists and oncologists. In fact, these hidden biases remain unknown and likely impacted the findings reported.

Given the hypothesis that the laparoscopic approach provides an oncologic benefit in HCC, it is important to evaluate the manuscript critically for evidence that hidden biases remain unaccounted for. Tables 2,3 provide insightful data to examine, as does the discussion transcript from the Annual Meeting of the American Surgical Association (1). First, the type of resection, and presumably the location of the tumor, is a bias that remains evident, with over 80% of subjects in the laparoscopic cohort undergoing either left lateral sectionectomy or wedge resection. It seems reasonable, when evaluating oncologic outcomes, to reserve final judgment until an analysis that accounts for the operative procedure and anatomic location of the tumor can be completed. Second, the clinicopathologic factors of disease that included number of tumor nodules, bilobar disease, cirrhosis, and margin status, while not reaching statistical significance, all favor improved outcomes for patients in the laparoscopic group. Lastly, as it relates to long-term survival, the more complex operations were completed more recently in the laparoscopic cohort compared with the open cohort (as evident in disparities in the median follow-up time). Given the methods used to analyze oncologic outcomes, the relatively short period of follow-up for these more complex patients may bias the reported actuarial survival estimate.

There are several other minor considerations that we commend the authors for addressing in the discussion. These include a potential difference between margin positivity and true margin width, the suggestion in the manuscript that a laparoscopic approach may be suitable for patients with Child's B cirrhosis, and the provocative hypothesis that a "no touch" technique may contribute to the differences observed in oncologic outcomes. While the authors demonstrated similar rates of R1 resections in both groups, a recent meta-analysis demonstrated that laparoscopy results in significantly wider tumor margins (3). This is of significant clinical interest as patients with chronic liver disease and a marginal functional liver remnant cannot be universally offered a major hepatectomy with wider margins due to the slightly increased risk of postoperative liver failure. Additionally, despite intending to include Child-Pugh A and early B patients in the study (as indicated in the methods section), the final data includes only patients with class A. Lastly, in this study, around 25% of patients, though suspected to have cirrhosis, did not meet histologic criteria on final pathological examination. This finding could potentially affect the results of the study,

as recent data suggest that cirrhosis was associated with poorer prognosis, in part due to higher hepatocarcinogenic potential among these patients (4). Taken together, findings from this work confirm prior data demonstrating the safety of laparoscopy in patients with Child-Pugh class A associated HCC.

We urge caution to readers who may interpret these data as support for the hypothesis that oncologic outcomes are improved with laparoscopy. While these data do again demonstrate the safety of a laparoscopic approach to HCC (even in patients with comorbid cirrhosis), the study is not powered for, nor does it actually demonstrate improved oncologic outcomes for the laparoscopic cohort when examined critically. We agree with the authors that a true randomized trial in this setting is unlikely to be accomplished, but further studies to more adequately match cohorts and attain equivalent long-term follow up is likely warranted before a minimally invasive approach is accepted as oncologically superior.

Acknowledgements

None.

Cite this article as: Moris D, Burkhart RA, Beal EW, Pawlik TM. Laparoscopic hepatectomy for hepatocellular carcinoma: are oncologic outcomes truly superior to an open approach? HepatoBiliary Surg Nutr 2017;6(3):200-202. doi: 10.21037/hbsn.2017.03.09

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Cheung TT, Dai WC, Tsang SH, et al. Pure Laparoscopic Hepatectomy Versus Open Hepatectomy for Hepatocellular Carcinoma in 110 Patients With Liver Cirrhosis: A Propensity Analysis at a Single Center. Ann Surg 2016;264:612-20.
2. Cheung TT, Poon RT, Yuen WK, et al. Long-term survival analysis of pure laparoscopic versus open hepatectomy for hepatocellular carcinoma in patients with cirrhosis: a single-center experience. Ann Surg 2013;257:506-11.
3. Twaij A, Pucher PH, Sodergren MH, et al. Laparoscopic vs open approach to resection of hepatocellular carcinoma in patients with known cirrhosis: systematic review and meta-analysis. World World J Gastroenterol 2014;20:8274-81.
4. Sasaki K, Shindoh J, Margonis GA, et al. Effect of Background Liver Cirrhosis on Outcomes of Hepatectomy for Hepatocellular Carcinoma. JAMA Surg 2017;152:e165059.

