Editorial

Expanding the role of laparoscopic hepatectomy for hepatocellular carcinoma in patients with portal hypertension

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Hepatocellular carcinoma (HCC) in the setting of cirrhosis represents a uniquely challenging clinical problem. While orthotopic liver transplantation (OLT) offers the potential for radical resection and treatment of the underlying cirrhosis, the limited availability of organs means that an exceedingly small (single digit) percentage of HCC patients undergo OLT (1). Surgical resection follows closely behind OLT with respect to intention to treat 5-year survival, but may have higher perioperative risk in cirrhotics and has higher recurrence over time. Behind OLT and resection follow a spectrum of locoregional therapies (ablation, stereotactic radiation, chemo/radioembolization, etc.) with progressively lower local control rates (and therefore curative potential) but a correspondingly lower risk of precipitating hepatic decompensation. Matching the treatment to the tumor and the underlying liver is a significant challenge. In this context, the Barcelona Clinic Liver Cancer (BCLC) group offers guidance on the treatment of HCC. These guidelines, which are widely cited and incorporated to some degree or other by a number of Western liver societies, advise that patients with single tumors less than 3 centimeters in diameter and clinically significant portal hypertension or hyperbilirubinemia are candidates for radiofrequency/microwave ablation or liver transplantation but not for liver resection (2). This recommendation stems from concern that liver resection in the setting of cirrhosis and portal hypertension may increase the risk of surgical complications and post-operative liver failure. However, as liver surgeons gain experience, it is slowly becoming apparent that laparoscopic liver resection (LLR) for selected patients with portal hypertension can be performed with reasonable safety (3-6). Thus, the BCLC guidelines are criticized for being too restrictive as they exclude many patients who may benefit from curative resection.

LLR has rapidly become an integral component of the modern hepatobiliary surgery skillset. There are numerous benefits to LLR including shorter duration of hospitalization, reduced intra-operative blood loss, post-operative pain, and overall cost (7-10). Further, oncologic outcomes appear equivalent between laparoscopic and open hepatectomy (11-15). Even though much of the experience in LLR has been in non-cirrhotic patients, there are a few small series that demonstrate the safety of LLR in selected patients with cirrhosis. Despite the relative paucity of data, we and many other laparoscopic liver surgeons feel that the benefits of LLR are amplified in cirrhotic patients. As experience grows, it is becoming increasingly apparent that with careful patient selection and adjustment of technique, LLR is likely safer than open surgery in patients with cirrhosis (16). While the mechanisms underlying this are not completely clear, reduced trauma to the peritoneum and uninvolved parenchyma, less hepatic mobilization, reduced fluid requirements, and less bleeding due to pneumoperitoneum are thought to play a role. The net effect of preserving collateral blood flow, minimizing lymphatic disruption, and reducing trauma to the peritoneal surface is decreased formation of ascites, reduced risk of

post-operative liver insufficiency, and overall reduction in morbidity (17,18). The benefits are such that patients who are not candidates for open surgery may, in some cases, be safely offered laparoscopic resection. Thus, laparoscopic resection in cirrhotic patients may be a crucial component of expanding criteria for resection beyond the BCLC guidelines.

In a recent study, Lim *et al.* conducted a prospective single-center trial comparing patients with and without portal hypertension who underwent LLR for HCC (19). The researchers identified 45 consecutive patients who underwent LLR for HCC between 2014 and 2017, of which 27 (60%) had no clinically significant portal hypertension and 18 (40%) did have clinically significant portal hypertension as defined by a hepatic venous pressure gradient greater than or equal to 10 mmHg (uniformly measured prospectively). They found that the groups were similar in the extent of resection, transfusion, and duration of pedicle clamping. Ninety-day mortality and severe morbidity rates were zero. Moderate morbidity was higher in the clinically significant portal hypertension group, but the groups did not differ in the rate of unresolved liver decompensation. Intensive care unit and hospital duration of stay was longer in the clinically significant portal hypertension group. There were no differences in overall survival and recurrence-free survival between the groups. The authors go on to conclude that LLR is safe in BCLC stage 0-A patients with clinically significant portal hypertension.

This is an impressive series and the authors should be commended on their work. This contribution adds to a relatively small body of literature and helps to confirm what a number of liver surgeons have felt for some time, though previously with little evidence. We and others believe that LLR is safer than open resection in cirrhotic patients and actually enables resection for a subset of patients who may not be candidates for open surgery (16,20,21).

There are, however, a number of areas that remain unclear. Many studies focus on portal hypertension as strictly defined by a hepatic venous pressure gradient greater than or equal to 10 mmHg. However, hepatic venous pressure gradient measurement is cumbersome and expensive and is not routinely performed by most centers. Identifying clinical surrogates that correlate with the degree of portal hypertension would be far more useful in practice. In this study, the median platelet count in both the portal hypertension and non-portal hypertension groups is greater than 100,000. We are given the median and the range but we do not know how many patients in each group had a platelet count above or below 100,000. This leads us to wonder to what degree a platelet count of less than 100,000 is predictive of portal hypertension (and perioperative outcomes) and raises the question of whether these patients have portal hypertension that is not reflected in their platelet count. Ideally, future studies will identify clinical surrogates that accurately reflect the degree of portal hypertension and use these to assess the safety of liver resection.

There is an important group of patients that remains invisible to us in this study—those who were not considered for laparoscopic resection and went on to other therapies. How many patients had technically resectable tumors but had an elevated hepatic venous pressure gradient or other factors that excluded them from resection? While it is becoming clear that resection will benefit an expanding pool of patients, there is clearly some threshold at which point even in experienced hands the risks of LLR exceed the potential cancer survival benefit. Understanding this unstated denominator would help greatly in developing guidelines to determine which among these patients should or should not undergo resection and re-establish boundaries to guide resection.

Finally, we must figure out how to put these findings into action. Studies such as this one are helping to establish the safety of LLR in cirrhotics. Translating this recommendation into practice, however, is a challenging proposition. While laparoscopic resection in the expert hands of a few very experienced centers appears safe (and the authors of this study are renowned for their ability and experience in LLR), the number of liver surgeons and centers that can replicate these results may be small. As we re-evaluate the recommendations and assess the safety of resection in such a complex and fragile patient population we must proceed carefully with an emphasis on developing guidelines that can be widely implemented by the majority of liver surgery centers. To help guide this, subsequent studies need to focus on identifying clinical surrogates that can assess the degree of portal hypertension and establish new guardrails.

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