Editorial

Do we really need a standardized approach to spontaneously ruptured hepatocellular carcinoma?

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Hepatocellular carcinoma (HCC) is one of the leading causes of cancer-related death in Asian and African countries due to a high prevalence of chronic hepatitis B infections (1,2). The vast majority of current studies focus on the treatment of HCC itself rather than complications from HCC. A potentially life-threatening complication of HCC is spontaneous rupture, and its prevalence has been reportedly to be 5–15% of all HCC cases (1). This is the third leading cause of HCC-related death after tumor progression and liver failure, and there is a high mortality associated with rupture (3,4).

Because spontaneous rupture of HCC (RHCC) occurs infrequently, the optimal approach is unclear and specific management is not included in treatment algorithms. In general, trans-arterial embolization (TAE), hepatectomy, and two-stage hepatectomy following TAE are the main treatment options, and often, TAE has been a preferred treatment. Because RHCC was thought to disseminate cancer and increase the risk of HCC recurrence, providers may hesitate to offer invasive surgical approaches when rupture occurs.

In a recently published study, Wang *et al.* retrospectively evaluated the prognosis of RHCC by each treatment modality. In their cohort of 366 patients with HCC, 5.1% had RHCC, with a median follow-up of 12 months (1). The majority of patients had underlying hepatitis B. The in-hospital mortality was 0.9%, and the median survival was 17 months. Multivariate Cox analysis showed that age, Child-Pugh classification, tumor diameter, microvascular invasion, hemoglobin, and alpha-feto protein were associated with overall survival.

It would be difficult to create a randomized prospective controlled study to explore the optimal management for RHCC due to the emergent nature of this problem. From a logistical and ethical standpoint, subjects could not be adequately consented and enrolled in such a short time and often while they are in extremis. Wang *et al.* attempted to address this issue using propensity score matching in which statistical methods are used to address the differences based on defined observable characteristics (1). After propensity score matching, TAE, followed by two-stage hepatectomy, was shown to provide better survival (1,5). It was suggested that TAE should generally be attempted to control bleeding, but surgical resection can be considered if embolization fails.

Like many studies on HCC treatment, the authors accounted for many characteristics including demographics, laboratory studies, tumor size, cirrhosis, TNM stage, and

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Child's class. However, ruptured HCC has an extremely variable presentation. Not every patient ruptures their HCC in the exact same way. Some of this has to do with tumor location and appearance and not just size. A 5 cm that is mostly exophytic in the inferior border of the liver may rupture with massive hemoperitoneum, while a 5 cm at the dome of the liver that is tamponaded by the diaphragm and the rest of the liver may just have a small amount of blood around the rupture site. Other comorbidities such as cardiovascular and pulmonary disease may also affect how a patient responds to bleeding and hemodynamic instability.

Arterial embolization does lead to partial tumor necrosis and cessation of bleeding but this alone is rarely definitive treatment for long-term control of HCC. Because tumor necrosis is generally incomplete there is eventually regrowth and recurrence of HCC. Those patients who do not undergo a subsequent therapy may have been too sick or may have refused to have further treatment. We cannot expect that single treatment with arterial embolization would have comparable long-term survival to other more definitive modalities. The patients in this study who only received TAE were likely the sickest in ways that were not captured by the propensity-score matching.

It is unclear how patients were selected for one-stage hepatectomy. This may have included patients who had massive bleeding and either TAE was not available or surgery was selected to offer better control. It is also possible that this group included patients with minimal bleeding, hemodynamic stability and more favorable tumor location for expedited resection. While we can surmise that these patients survived the emergency department resuscitation and anesthesia induction, it is unclear whether patients had their surgery emergently in the middle of the night or if they were not bleeding very much and essentially had a semi-elective liver resection during the daylight hours. There is likely a mixture of both types of cases in the study. This study did show an increased risk of death that was 1.5 times that of those receiving TAE and two-stage hepatectomy. However, one wonders if there is a subset of relatively stable patients with only a minimal amount of bleeding who would fare just as well with a one-stage approach. Indeed, this is the suggested approach based on their treatment algorithm.

While every hepatobiliary surgeon is aware of these options of TAE, one-stage and two-stage hepatectomy, the approach that is selected may have more to do with rate of bleeding, tumor location, hemodynamic instability, availability of resources and potentially the time of the day that the patient presented. Performing TAE first provides time for the surgeon to risk stratify the patient and assess the situation. Patients with multiple comorbidities may be high-risk candidates for surgery and may choose not to pursue aggressive management. Embolization in resource-constrained areas may also allow time for transfer to a tertiary center which may be better equipped to perform liver resections. Finally, for those patients with more significant underlying chronic liver disease, embolization and a period of stabilization may allow for better patient selection and improved outcome after liver resection. At the very least, evidence of significant decompensation may prompt the surgeon to hold off on immediate liver resection and perhaps pursue other therapies after some recovery of liver function.

This study by Wang *et al.* involved a rather homogenous population in which 85% of cases were hepatitis B related and about 80% had cirrhosis (1). Our previously published study suggested that non-cirrhotic patients were more likely to present with rupture and larger tumor size (6). We postulated that patients with cirrhosis were more likely to have chronic disease management and surveillance for HCC. This is indeed similar in this study before propensity score matching. Patients who present with rupture are likely those who have evaded chronic liver disease management and surveillance for HCC.

One wonders if this study would be applicable in other populations with a much lower predominance of hepatitis B and a higher proportion of metabolic dysfunction-associated steatotic liver disease (MASLD). Non-cirrhotic MASLD is a risk factor for HCC development, but the current American Association for the Study of Liver Disease guidance on HCC does not suggest routine HCC surveillance on this population as the incidence is less than 0.2% per year (7). However, a subset of MASLD patients will develop HCC, and will be less likely to have HCC found with surveillance (8). They also present with larger tumor size (9), which is a risk factor for rupture. Patients with MASLD also have a high association with cardiovascular comorbidities and their response to bleeding and hemodynamic changes potentially be worse. With the epidemic of MASLD, we will need studies to identify those at the highest risk for HCC who should undergo surveillance to minimize the consequences of late presentation with tumor rupture.

Finally, this study also reports median overall survival and disease-free survival but there is no mention of subsequent therapies for recurrence. Despite previous beliefs, this study did not find an increased tumor spread or recurrence due

to rupture, given that there was no worsening of disease-free survival after the rupture (1). However, it is possible that overall long-term survival may be more impacted by subsequent locoregional or systemic therapy.

Rupture is a devastating and potentially fatal complication of HCC. A thoughtful approach is required by a team of surgeons, oncologists, hepatologists and interventional radiologists. Unlike other presentations of HCC, RHCC also requires critical care management. In the real world, optimal management may not be easily defined by a standardized algorithm and may also depend on patient stability and available resources. Certain stable patients with minimal bleeding and good liver function may potentially be candidates for liver resection similar to other patients who undergo elective liver resection. However, TAE is an excellent temporizing measure for less stable patients, with the goal of two-stage hepatectomy in better surgical candidates in order to afford the best longer term survival.

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