Viewpoint

Same soup different taste—how to best manage the future liver remnant—a surgical perspective

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A small but measurable percentage of major hepatic resection patients will experience major morbidity or mortality due post-hepatectomy liver failure after major liver resection. Pre-operative optimization, in particular pre-operative induction of liver growth to increase the future liver remnant (FLR) volume, has become frequently used in patients considered to be high risk. However, this process of hepatic augmentation remains incompletely understood, particularly in humans. Recent advances in techniques for FLR management have resulted in dramatic expansion of the liver surgeon's armamentarium. Patients who were considered clearly unresectable 20 years ago are now routinely offered curative-intent resection (1,2). Although extended hepatectomy procedures with small pre-operatively measured FLR remain higher risk than standard hepatic resections, the general trend in liver surgery has been toward ever-expanding opportunities for curative surgical management, facilitated by improved FLR augmentation techniques. In spite of this, mortality of major and extended hepatectomy continues to decrease over time (3).

Kim *et al.* (4) have provided an articulate summary of the current state of the art of the procedures which have enabled advances in FLR management such as portal vein embolization (PVE), associating liver partition and portal vein ligation for staged hepatectomy (ALPPS), combination of PVE with transarterial embolization (TAE-PVE), liver venous deprivation (LVD), and radiation lobectomy (RL). Against this backdrop, there remains a small proportion of patients who either do not adequately hypertrophy or experience post-hepatectomy liver failure even in the setting of seemingly-adequate FLR volume. This fact highlights a gap in the clinical understanding of the meaning of adequacy as it pertains to the FLR and represents the greatest opportunity for future improvements in the surgical management of hepatic neoplasms.

As illustrated in the article by Kim *et al.* (4), technical variability and differences in reporting have made a clear comparison of FLR management methods challenging. An example of this is the criticism of the LIGRO trial for procedural inconsistencies resulting in limited ability to make direct comparisons between disparate techniques (5). The mortality after hepatectomy for these complex patients requiring manipulation of the FLR is typically around 10% (5), compared to around 2% in more routine liver surgery. However, despite this risk, the opportunity to offer resection to such patients (until recently often not considered candidates for surgery at all) mean these procedures are here to stay.

The layers of bias in studies comparing FLR management techniques are particularly complex. This is due to the fact that the optimal management strategy depends not only on the FLR itself, but also on underlying hepatic disease, hepatic anatomy, tumor biology, patient condition, and clinical considerations which may have nothing to do with the liver. Surgical management of hepatic tumors is typically dictated by tumor location (central *vs.* peripheral) and relationship to vasculobiliary pedicles and draining veins. These considerations can determine for example whether

minimally-invasive surgery (MIS) would be a management option and can also dictate whether PVE would be an appropriate choice. For example, if left lobe clearance via an MIS parenchymal sparing approach, followed by PVE and then right hepatectomy is an option for a patient with neuroendocrine metastasis, that may be preferable over ALPPS. However, if clearance of the left liver requires a laparotomy, an ALPPS may be less morbid overall. If a patient with a large HCC in the setting of underlying liver disease requires a right hepatectomy, PVE and transarterial radioembolization (TARE) may both give adequate hypertrophy, though on a very different timetable. For a patient with a very high AFP, the clinician may choose TARE in order to let the tumor biology declare itself.

The presence of underlying liver disease is critically important as a confounder when comparing FLR-management strategies. The pre-existing liver disease may critically disrupt hepatic regeneration and ultimately determine the time to full functional maturation of the FLR. This points towards the critical dilemma that volume does not equal function (6). The elephant in the room is that efforts at comparison of FLR management approaches are so focused on assessment of hypertrophy that the distinction between size and function is being ignored. Predictive modeling that aims for an integrative approach to assess function and volume remains in its infancy (7). It almost seems naïve that surgeons remain reliant on assessment of size rather than function.

In summary, it is clear that advances in FLR management have had a significant impact on the field of hepatic surgery in recent years, and this has dramatically expanded the population of patients who are potential candidates for curative-intent surgical resection. However, the bespoke nature of hepatic surgery and the myriad underlying drivers of clinical decision-making including baseline liver function, anatomic, biologic, conditional, and patient-related factors make it unlikely that any one technique will be the panacea which will be uniformly applicable. Liver surgeons and proceduralists will need to be prepared to leverage all of these options in order to deliver the best care plan which is truly optimized for each patient. Future efforts should focus on understanding the relationship between and relative importance of volumetric hypertrophy and functional augmentation. This means going beyond metrics such as Childs-Pugh, volumetric analysis, and indocyanine green clearance as isolated means to assess hepatic performance and will require a focus on integrative models. The alphabet soup is here to stay, and physicians performing procedures in patients with marginal FLR will need to retain a versatile palette of taste for it.

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Footnote

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