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EDITORIAL – HEPATOBILIARY TUMORS

Utilization of Multiorgan Radiomics to Predict Future Liver Remnant Hypertrophy After Portal Vein Embolization: Another Tool for the Toolbox?

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Indications for hepatic resection have continued to expand with improvements in understanding of intrahepatic anatomy, advancement in surgical technology and technique, as well as improvement in anesthetic techniques and postoperative care. Partial hepatectomy often is considered for patients with primary malignancies (such as hepatocellular carcinoma and intrahepatic and perihilar cholangiocarcinoma) as well as secondary malignancies (such as colorectal liver metastases (CRCLM) and metastatic neuroendocrine tumor). While parenchymal-sparing operative strategies are prioritized when appropriate and feasible, major hepatic resections are still often required to treat these conditions.

When selecting appropriate patients for major liver resection, technical factors to consider include the ability to achieve an R0 resection margin while (1) the ability to preserve at least two contiguous liver segments, (2) the ability to maintain adequate vascular inflow, preserve at least one of the three hepatic veins, and biliary drainage (whether natively, or with a Roux en Y hepaticojejunostomy), and (3) the ability to preserve an adequate standardized future liver remnant (sFLR) volume in order to mitigate the complications of posthepatectomy liver failure and postoperative mortality due to liver failure.[1] We know from previous studies that for patients with normal liver function, an sFLR of at least 20% is required to mitigate posthepatectomy liver failure.[2] Similarly, for patients who have been treated previously with long-course chemotherapy for CRCLM, an sFLR of at least 30% is required to avoid posthepatectomy liver failure.[3] This need for a higher sFLR in these patients is to account for some of the adverse effects that chemotherapeutic agents, such as oxaliplatin (sinusoidal obstruction syndrome) and irinotecan (chemotherapy-associated steatohepatitis), can have on the liver. Last, for patients with underlying cirrhosis and preserved liver function, an sFLR cutoff of 40% is generally accepted as the minimum sFLR value with some authors advocating for an even higher residual volume.[4,5]

Particularly in cases when a right hepatectomy or an extended right hepatectomy is required, many patients fail to meet these sFLR minimum cutoff values. In such cases, volume augmentation procedures are available to induce hypertrophy of the sFLR. Portal vein embolization (PVE) has long been established as the principle option for inducing hypertrophy of the sFLR. As most of the blood flow into the liver occurs through the portal venous system, occlusion of the portal vein into one side requires that blood to flow into the contralateral side of the liver (the sFLR) and to meet this increased demand placed on it, it hypertrophies in response to this increased portal flow.[6]

Hepatic vein embolization (HVE) has emerged recently as an added measure to ensure even greater hypertrophy of the sFLR. After observing that hepatic vein stenosis after dual graft living donor liver transplantation led to accelerated atrophy of the right liver with further contralateral hypertrophy in a state of portal flow deprivation, Hwang et al. hypothesized that subsequent right-sided HVE would lead to even greater hypertrophy in patients who had undergone right-sided PVE already in preparation for a right hepatectomy.[7] In their exploratory series, patients had a mean sFLR of 34.8% before PVE, 39.7% 2 weeks after PVE, and 44.2%

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2 weeks after HVE. Deal et al. found in an animal model that hypertrophy of the sFLR inversely correlated with the degree of portal vein neo-collaterization between the portal vein-supplied and the portally deprived liver lobes, meaning that increased collateralization meant a stunted hypertrophy effect. Interruption of this collateralization could lead to more rapid hypertrophy of the sFLR.[8] This may explain why parenchymal transection during associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) leads to rapid hypertrophy that often outperforms PVE alone; however, the high risk of morbidity and mortality has led many centers to abandon this procedure. In another animal model, Schadde et al. demonstrated that performance of simultaneous PVE and HVE led to abrogation of these porto–portal collaterals without the need for operative transection, offering an explanation for why occlusion of the hepatic vein leads to further hypertrophy of the liver.[9] Safety of simultaneous PVE and HVE (known as liver venous deprivation [LVD]) is currently being investigated by the phase II DRAGON 1 trial,[10] which has closed for accrual and results are forthcoming, as well as the subsequent DRAGON 2 trial, which is a phase 3 trial randomizing patients to PVE versus LVD.[11] However, results from exploratory and retrospective studies have been promising.[12]

Despite using these advanced techniques, some patients will fail to achieve sufficient hypertrophy of the sFLR required to proceed with a major hepatectomy while mitigating the risk of posthepatectomy liver failure. Reasons for failure of response were discussed in a systematic review by van Lienden et al. Previous chemotherapy seemed to have no influence on the hypertrophy response; however, patients with preexisting chronic liver disease (cirrhosis or fibrosis) demonstrated less hypertrophy response than patients with a normal liver.[13] Options for managing these patients include performing HVE if one has not yet been performed. In cases where an extended right hepatectomy will need to be performed, performing segment 4 PVE leads to further hypertrophy of the left lateral section.[14] Finally, if all else fails, the concept of salvage ALPPS procedure after inadequate hypertrophy was discussed by Enne et al. in their investigation of the International ALPPS registry.[15] In this study, 20 patients completed both stages of the ALPPS procedure with a median sFLR increase of 88% (23–115%) between the two stages. However, as stated previously, many centers have abandoned this procedure due to the high morbidity and mortality.

The patients who fail to respond to PVE or LVD fortunately represent a small minority. In a 23-year analysis of 431 patients undergoing PVE before liver resection, Alvarez et al. found that 96% of patients achieved sufficient increase in their sFLR after PVE alone that would allow them to proceed safely with a major hepatectomy.[16] In this same study, however, 34% of patients did not undergo hepatectomy after PVE. The most common reason for failure to proceed to surgery after PVE was disease progression (67%), and this was most frequently observed in patients with biliary malignancies. Of note, 5% of patients in this study also failed to proceed to curative resection because of PVE-related complications. Therefore, whereas drop out after PVE is not uncommon, the reasons for that are rarely because of a lack of hypertrophy in the sFLR but most commonly because of disease progression.

Currently, there is no established way of being able to predict who will be responders to volume augmentation and who will not. While relatively few patients will fail to achieve an adequate hypertrophy response in their sFLR, *a priori* identification of nonresponders to PVE or LVD theoretically could prove beneficial and spare futile attempts at PVE and subsequent surgery, allowing them to explore other potentially life-prolonging therapies, such as chemotherapy or liver-directed therapy. Radiomics involves the extraction of a large number of features from imaging studies through the use of data-characterization algorithms to help uncover patterns and characteristics not otherwise seen on review of imaging. These radiomic features may follow distinctive patterns that can be useful for predicting, for example, prognosis, or response to a particular treatment. This is an exciting new area of investigation that has expanded to several different areas.

In the article in this issue of *Annals of Surgical Oncology*, Gerwing et al. sought to evaluate the feasibility of radiomic features extracted from baseline abdominal CT scans to predict which patients will undergo adequate hypertrophy response in their sFLR after PVE.[17] The authors built a cohort of 53 patients who underwent PVE, including 19 patients who also had a simultaneous HVE, nine patients who underwent a segment IV PVE, as well as four patients who had segment IV PVE and HVE. Baseline CT scans of the abdomen with IV contrast were reviewed. The liver, spleen, and bone marrow were chosen as factors that may influence liver hypertrophy. The authors point out that known molecular factors regulated by the spleen affect liver cirrhosis and the potential for liver regeneration, leading to the hypothesis that splenic imaging parameters may support the prediction of liver-associated disease. Bone marrow imaging data also were included, because stem cells and bone marrow-derived liver sinusoidal endothelial cells contribute to liver regeneration, and bone marrow suppression can hinder adequate liver regeneration. Therefore, liver, splenic, and bone marrow-specific radiomic features from CT data were extracted. Ultimately, three independent, radiomic features were found to differentiate well between the responders and the nonresponders:

- *Maximum probability of the liver*: The occurrence of the most predominant pair of neighboring intensity values

in the baseline CT data related to the segmented liver volume;
- *Skewness of the spleen*: The asymmetry of the distribution of values about the mean value in baseline CT data related to the segmented spleen volume;
- *Total energy of the bone*: The magnitude of voxel values scaled by the volume of the voxel in baseline CT data related to the segmented first lumbar vertebra bone marrow.

They defined adequate hypertrophy as an increase in the FLR by ≥ 1.33. Based on this definition, 66% of patients achieved adequate hypertrophy (i.e., FLR ≥ 1.33), whereas 34% of the cohort did not achieve adequate hypertrophy and therefore were characterized as nonresponders. When assessing the predictive value of the three radiomic features by using ROC analysis, the model was able to discriminate between responders and nonresponders to PVE or LVD with an AUC of 0.875.

It is worth noting that the number of nonresponders to PVE or LVD in this study is high: 34% of patients failed to achieve an adequate hypertrophy response compared with other studies that report a nonresponder rate as low as 2% to 4%.[16,18] In reviewing the technique described for PVE and LVD, this appears to be consistent with what is practiced at other centers.[19] In the absence of variability in technique and failure of the embolization procedures, this large discrepancy in nonresponder rate must be a result in how a responder versus a nonresponder is defined. As mentioned above, the authors in this study define a responder as someone who has an increase in their FLR by ≥ 1.33 and a nonresponder who fails to meet this threshold growth in their sFLR. Many centers, including ours, rely on calculation of the kinetic growth rate (KGR), defined as the degree of hypertrophy of the sFLR per week since PVE or LVD. When using KGR as the standard of an adequate responder, Shindoh et al. have reported that when patients have a KGR ≥2% per week, then there were no cases of posthepatectomy liver failure and no cases of death from liver failure in a cohort of 107 patients undergoing hepatectomy for CRCLM.[20] Therefore, the definition of responder versus nonresponder used in the manuscript may be too restrictive as there are likely several patients defined as nonresponders in this study who likely had a KGR >2% per week and therefore could have safely undergone a hepatectomy.

It is important to point out this distinction in how responders versus nonresponders to PVE or LVD is defined, because this study heavily relies on it. Changing the definition of a responder from a nonresponder may change the radiomic differences between the groups, as well as the ROC analysis. If for example the authors instead grouped the cohort according to KGR (i.e., <2% per week for nonresponders vs. ≥2% per week for responders), we are left wondering whether other features would have been observed or whether the three radiomic features outlined in the manuscript would still hold up. This does bring into question the applicability of the results of this study widely, especially with differing definitions of responders and nonresponders to PVE and LVD, and when the nonresponder rate, when using KGR, is actually quite low.

Regardless of these differences in the determination of responders versus nonresponders after PVE or LVD, this study presents an interesting application of radiomics that demonstrate how exciting this field of study is and gives a glimpse into potential future applications. We therefore applaud the authors for their work and look forward to other investigations on the application of radiomics.

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