Editorial

How can we predict hepatic insufficiency after resection of colorectal liver metastases?

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We read with highest interest the paper recently published in the *Journal of Hepatology* entitled "*Hepatic atrophy following preoperative chemotherapy predicts hepatic insufficiency after resection of colorectal liver metastases (CLM)*" written by Yamashita *et al.* from the MD Anderson Cancer Center (1). They reported with clear and definite clinical data from very large cohort (n=459) that hepatic atrophy ≥10% evaluated by multidetector row enhanced computed tomography (CT) following preoperative chemotherapy can predict postoperative hepatic insufficiency (PHI) after resection of CLM. We honor their major and long-lasting contributions to the prediction or prevention of PHI after resection for CLM (2-5). Not only is PHI a major cause of postoperative mortality after the resection of CLM, but postoperative morbidities including PHI have negative impacts on patients' survival after resection of CLM (6-8). While their work is clear and definite, I think there are several points that should be discussed. We would like to address those points in this "Editorial", and discuss how we can predict PHI after the resection of CLM.

First, we should consider what hepatic atrophy itself following chemotherapy means. The authors explained that hepatic atrophy may be a surrogate for chemotherapy-related collapse of hepatocyte plates (centrilobular atrophy) in association with extensive chemotherapy. In their paper, they referred to two papers that addressed this point; however, neither report mentioned the mechanism or meaning of centrilobular atrophy caused by extensive chemotherapy (9,10). Of course, the hepatic volume itself does not directly correlate with hepatic function. In this paper, both standardized future liver remnant (sFLR) ≤30% and hepatic atrophy ≥10% which signifies the volume change following preoperative chemotherapy are independent predictors for PHI. However, the odds ratio for PHI of hepatic atrophy ≥10% is 43.5, and this value is far higher than that of sFLR ≤30% (odds ratio, 4.03). I wonder if the hepatic atrophy is a surrogate for the degree of hepatic injury caused by chemotherapy and susceptibility for iatrogenic invasiveness. In addition, the small liver volume brought about as a result of liver injury following preoperative chemotherapy leads to negative effects in the postoperative course. The molecular mechanism of hepatic atrophy caused by chemotherapy should be evaluated by histopathological examinations or murine models (11). Another concern of mine is the kinetic change of liver volume following preoperative chemotherapy in patients with hepatic atrophy ≥10%. When hepatic atrophy starts, and when it recovers? Does the cessation of chemotherapy immediately lead to the recovery of hepatic volume? If we consider hepatic atrophy ≥10% as a new marker of risk for PHI after the resection of CLM, which degree of recovery from hepatic atrophy enables us to safely perform surgery for CLM? This is an important problem that we should attempt to solve.

The evidence-based clinical practice guidelines for hepatocellular carcinoma (HCC) include the following. The Japan society of Hepatology 2013 update (3rd JSH-HCC Guidelines) mentioned that the 15-min retention rate of indocyanine green (ICGR15) is useful for assessing liver function before surgery (Grade B) (12). Of course, CLM is different from HCC. However, the background liver in CLM is sometimes damaged by preoperative chemotherapy,

and that in HCC is also damaged by hepatitis. These are similar situations; therefore, ICG 15R is also useful for assessing liver function before resections of CLM. ICG clearance is a simple test assessing hepatic blood flow, hepatocellular uptake, and biliary excretion, hence assessing dynamic hepatic function. Krieger *et al.* reported the usefulness of the value of ICG clearance to assess impaired liver function or to estimate the postoperative risk of morbidity after the resection of CLM (13). On the other hand, Wakiya *et al.* reported that ICGR15 does not correlate with the degree of sinusoidal injury or steatohepatitis after chemotherapy in patients with resections of CLM (14). Tani *et al.* reported that hepatic atrophy ≥10% is independently associated with ICGR15 >15% after chemotherapy, and there is a tendency toward correlation between the kinetic changes in total liver volume (TLV) and ICGR15 during chemotherapy (r=–0.33, P=0.080) (5). These results mean that the degree of hepatic atrophy is correlated with the ICGR15 value, which signifies an impaired hepatic functional reserve. According to Makuuchi's criterion, the maximum range of resections of the liver is determined by the ICGR15 value (15). Many liver surgeons follow this criterion; therefore, the correlation between the degree of hepatic atrophy and the change in the ICGR15 values should be examined in more detail. On the other hand, we reported the significance of the "future remnant function" using the 99mTc-garactosyl human serum albumin (GSA) scintigraphy SPECT-CT fusion system (16,17). The future remnant function is a more accurate marker for PHI after major hepatectomies compared to the conventional future remnant volume. In any case, the key factors for predicting PHI are the examinations for how much liver is remnant, and how well the remnant liver functions.

The authors identified two predictors of hepatic atrophy ≥10% following preoperative chemotherapy: preoperative chemotherapy ≥7 cycles (odds ratio, 2.07) and no use of bevacizmab (odds ratio, 1.87). Karoui *et al.* reported that prolonged neoadjuvant systemic chemotherapy alters liver parenchyma and increases morbidity after major resections of CLM (10). They reported that the morbidity rate increases to 45.4% in patients with 6–9 cycles of preoperative chemotherapy compared to 19% in patients with ≤5 cycles. The use of oxaliplatin leads to sinusoidal obstruction syndrome (SOS) and irinotecan leads to steatohepatitis (3). These pathological images are quite different. The presence of oxaliplatin is higher in patients with hepatic atrophy ≥10% (P=0.093), but this difference is not statistically significant. Tani *et al.* reported that steatosis is significantly frequent in patients in whom TLV increases more than 10% (P<0.001). According to these results, hepatic atrophy ≥10% would be major problem in patients using oxaliplatin. Bevacizmab has been reported to have protective effects against SOS caused by oxaliplatin in patients with CLM (18,19); therefore, it is natural that no use of bevacizmab is a predictor of hepatic atrophy ≥10%. Among surgeons dealing with CLM, it is commonly held that prolonged preoperative chemotherapy is a cause of morbidity and the use of bevacizmab has positive effects to prevent SOS in patients with oxaliplatin; therefore, these results have no impacts on the daily clinical practice of physicians dealing with CLM.

The authors defined PHI as a postoperative peak total bilirubin level in serum (T-bil) greater than 7 mg/dL. As is well-known, there is an international definition of posthepatectomy liver failure (PHLF) from the International Study Group of Liver Surgery (ISGLS) (20). The ISGLS definition is based on an increased international normalized ratio (INR) and hyperbilirubinemia on or after postoperative day 5. These criteria include protein synthesis in the liver and bilirubin metabolism; therefore, using these criteria is preferable to performing the evaluation based on T-bil only. However, Skrzypczyk *et al.* reported that the ISGLS definition was less discriminatory than a peak T-bil greater than 7 mg/dL for identifying patients at risk of major posthepatectomy complications or death among 680 hepatectomies (21). According to this result, the authors adopted "T-bil >7 mg/dL" as a limit for diagnosing PHI. Of course, the T-bil value of "7 mg/dL" itself of T-bil in serum has no meaning in clinical practice, and the ISGLS definition also has a severity grading system that considers the impact on patients' clinical management (20). Grade B PHLF refers to PHLF resulting in a deviation from the regular clinical management but that is manageable without invasive treatment (20). Therefore, we think that defining PHI in this paper as "Grade B PHLF" would be better than defining it as peak T-bil >7 mg/dL.

The authors identified four predictors of PHI: sFLR ≤30% (odds ratio, 4.03), aspartate aminotransferase (AST)-to-platelet ratio index (APRI) >0.17 (odds ratio 5.27), major hepatic resection (odds ratio, 5.78), and hepatic atrophy ≥10% (odds ratio, 43.5). According to the odds ratio, hepatic atrophy ≥10% following preoperative chemotherapy should be a strong predictor of PHI. Based on the experiences of resections of CLM, PHI occurs in patients with a small remnant liver volume after major hepatic resection; however, APRI is not very common in the daily

clinical practice of liver surgeons. Wai *et al.* firstly reported the significance of APRI as a simple noninvasive index of fibrosis in patients with chronic hepatitis C (22). Several years later, Soubrane *et al.* reported that a high APRI score is the most reliable indicators for predicting SOS severity (23). A high value of AST corresponds to hepatocyte destructions caused by preoperative chemotherapy, and a low platelet count corresponds to hypersplenism with portal hypertension caused by SOS. To broadly use APRI in assessing liver injury or surgical indications following chemotherapy, the kinetic change of APRI during chemotherapy should also be examined.

We honor again their major and long-lasting contributions of these authors to the prediction or prevention of PHI after resections for CLM, including this wonderful paper. Hepatic atrophy following preoperative chemotherapy in patients with CLM is itself a very interesting phenomenon. In addition, ROC analysis revealed that the degree of atrophy significantly predicted PHI (AUC, 0.933; P<0.001), and the best cut off value of the degree of atrophy for predicting PHI was 10% (sensitivity, 0.885; specificity, 0.855). As the authors mentioned in this paper, the error in volume assessment performed using modern CT techniques of TLV should be very low compared to the error assessing the volume of remnant liver in living donor transplantation (24). This assessment is simple and quick. We should assess the shrunken liver following preoperative chemotherapy and understand the meaning of hepatic atrophy. Based on the recent progress in chemotherapy for CLM, the indication or the ideal timing of resections of CLM will likely be changing day by day. To utilize this outstanding work in the daily practice of treating CLM, further basic study for hepatic atrophy following chemotherapy should be needed, and kinetic changes in TLV during chemotherapy should be revealed.

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Footnote

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