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EDITORIAL – HEPATOBILIARY TUMORS

Chemotherapy-Associated Liver Injuries: Unmet Needs and New Insights for Surgical Oncologists

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Chemotherapy-associated liver injuries (CALI) were the focus of several research studies some years ago when they were associated with modern treatments for colorectal metastases and operative outcomes of liver resection.[1,2] An intensive, multidisciplinary commitment was designed to elucidate their pathogenesis, risk factors, clinical impact, diagnosis, and prevention. Then, long before reaching a full understanding, the interest in CALI rapidly decreased. The definition itself of CALI remains uncertain. While sinusoidal dilatation and nodular regenerative hyperplasia (NRH) are unequivocally associated with oxaliplatin-based chemotherapy regimens, this is not the case for steatohepatitis.[1,3] For the latter, a major, if not exclusive, impact of metabolic disorders rather than of irinotecan has been outlined.[4,5]

CALI are still part of our clinical practice. Moderate-to-severe sinusoidal dilatation is evident in more than one-third of patients undergoing liver surgery after oxaliplatin-based chemotherapy. Steatohepatitis occurs in only 10% of patients undergoing irinotecan-based chemotherapy but gains major epidemiological interest when its metabolic risk factors are considered (at least one-third of the entire U.S. population is at risk because of metabolic syndrome).[5]

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CALI DIAGNOSIS: A RIDDLE TO SOLVE

Standard imaging modalities can demonstrate steatosis, but not steatohepatitis. Liver parenchyma heterogeneity at magnetic resonance imaging (MRI) has been associated with sinusoidal dilatation, as well as splenomegaly and thrombocytopenia, but their evaluation remains uncodified.[6,7] Some authors reported a correlation between liver atrophy after chemotherapy and CALI, but data are not univocal.[8,9] The roles of both ultrasound-based and magnetic resonance-based elastography have been investigated, but neither modality can reliably discriminate steatohepatitis from simple steatosis.[10] Even liver biopsy failed to diagnose CALI other than steatosis because of heterogeneous distribution of injuries and limited tissue sample.[11] So far, we have only been able to approximately predict CALI through clinical data, i.e., chemotherapy regimen and number of administered cycles, and some liver function tests, including APRI score, ICG test, and LiMAx test.

Surgeons need a more robust assessment of CALI. While liver function tests are markedly impaired during chemotherapy and in the early postchemotherapy period, they tend to normalize within 4-6 weeks after the end of treatment. Normalization may occur later when prolonged chemotherapy is administered, but CALI last for a long time: sinusoidal dilatation and NRH require at least 9 months to disappear, while steatosis and steatohepatitis persist even later on.[12] Liver function tests are completely normal in up to one-third of patients with CALI, leading to underestimation of postoperative risk.

Clinicians have further reasons to pursue CALI diagnosis. This is mandatory to assess the effectiveness of any measure to reduce or prevent liver injuries. Second, diagnosis is needed in case of recurrent disease when patients require new chemotherapy lines and repeated surgery. CALI are crucial to predict tolerance to treatment and operative risks. Finally, the identification of CALI is needed as long as they have some oncological impact. Even if not associated with prognosis, some studies highlighted an inverse relationship between CALI and response to chemotherapy (tumor regression is less evident in patients with severe injuries).[3,13]

NEW OUTLOOKS: FUNCTIONAL IMAGING AND TEXTURE ANALYSIS

Hepatobiliary scintigraphy (HBS) with ^{99m}Tc-labeled iminodiacetate derivatives could open new perspectives. In staged procedures, HBS demonstrated accurate evaluation of liver function, outperforming volumetric assessments and liver function tests.[14,15] The hypothesis is appealing: if HBS is able to identify heterogeneous liver function it also could accurately depict the presence, distribution, and functional impact of CALI. To date, only one paper explored this topic, and the results were not completely satisfactory.[16] HBS unveiled a reduced liver function of the future liver remnant (FLR) in patients with steatosis $\geq$30% and those with NAS (Nonalcoholic fatty liver disease Activity Score) >1, but not in those with sinusoidal dilatation. HBS measures hepatocellular function and could be able to predict only hepatocyte-related diseases, but its true potentialities have not been fully explored. In the Truant et al. paper less than 5% of patients had grade 2-3 sinusoidal dilatation precluding any conclusive evaluation, and NRH, a highly relevant CALI, was not even taken into account.[7] A cohort of patients with an adequate prevalence of CALI could achieve positive data.

A further contribution could derive from digital images analysis and processing. They have so far persistently been proven to include invisible-to-the-human-eye texture characteristics that can be correlated with pathology data and outcomes.[17] Some evidence has been advanced for radiomic analyses in colorectal metastases, but none concerned CALI.[18] Texture information has revealed itself to be a proxy of shape, heterogeneity, and granularity of biological tissue and, consequently, potential predictor of liver parenchyma alterations. However, the close-source nature of radiomics, alongside unharmonized acquisition settings, discordant reconstruction parameters, lack of interpretability, and methodological biases result in the standard radiomic approach being scarcely flexible and robust. The direct analysis of raw data could enable clearer and more unspoiled findings. Preliminary results from our investigation show promising evidence of such correlation. Raw baseline computer tomography images were reconstructed and grey levels adjusted according to Hounsfield units scale, before extraction of volumes of interest (VOIs). VOIs consisted of standardized samples of healthy liver tissue, potentially affected by CALI. Such VOIs were unfolded to obtain a one-dimensional representation of the portion and three features entailing a homogeneity score in tissue texture, with an increasing level of detail, were explored. Two patterns per analysis can be appreciated (Fig. 1). Interestingly, the two patterns exactly correspond to patients with and without severe CALI.

COMPASS FOR SURGICAL ONCOLOGISTS

CALI have a proven negative impact on the operative outcome, increasing both major complication and liver failure rates, even in presence of apparently normal liver function.[19] Thus, surgeons must adopt a caution-driven strategy. We propose a five-step approach not to overlook any available tool and warning (Fig. 2). First, CALI should be prevented by scheduling short preoperative chemotherapy, i.e., no more than six cycles, and their negative impact should be limited by respecting an adequate chemotherapy-surgery interval, i.e., at least 4 weeks.[20,21] Do not forget that selected patients may undergo surgery without perioperative chemotherapy, as also suggested by the international guidelines.[22] No therapy for CALI is available, but some reversibility of steatosis has been obtained in living-donor liver transplantation candidates through health regimen and correction of metabolic disorders, even after a short treatment.[23] Could prehabilitation before liver resection reduce liver injuries and their negative impact on outcome?

Second, when surgery is scheduled, risk factors for CALI should be kept in mind, namely chemotherapy regimen and associated metabolic disorders. Preoperative imaging modalities should be checked for hallmarks of liver injuries, including liver atrophy after chemotherapy, parenchyma heterogeneity at MRI, and splenomegaly.[6,8,9] APRI score should be computed and additional liver function tests (e.g., ICG or LiMAx test) should be performed according to local availability. All these data taken together do not provide a conclusive diagnosis but define a risk profile for each patient.

Third, as long as CALI compromise liver function, the best way to limit their impact is parenchyma-sparing surgery. Minor hepatectomies are no more synonymous with simple resections and can be considered for complex disease presentations.[24,25] It is obvious that the higher the proportion of major hepatectomies the higher the severe

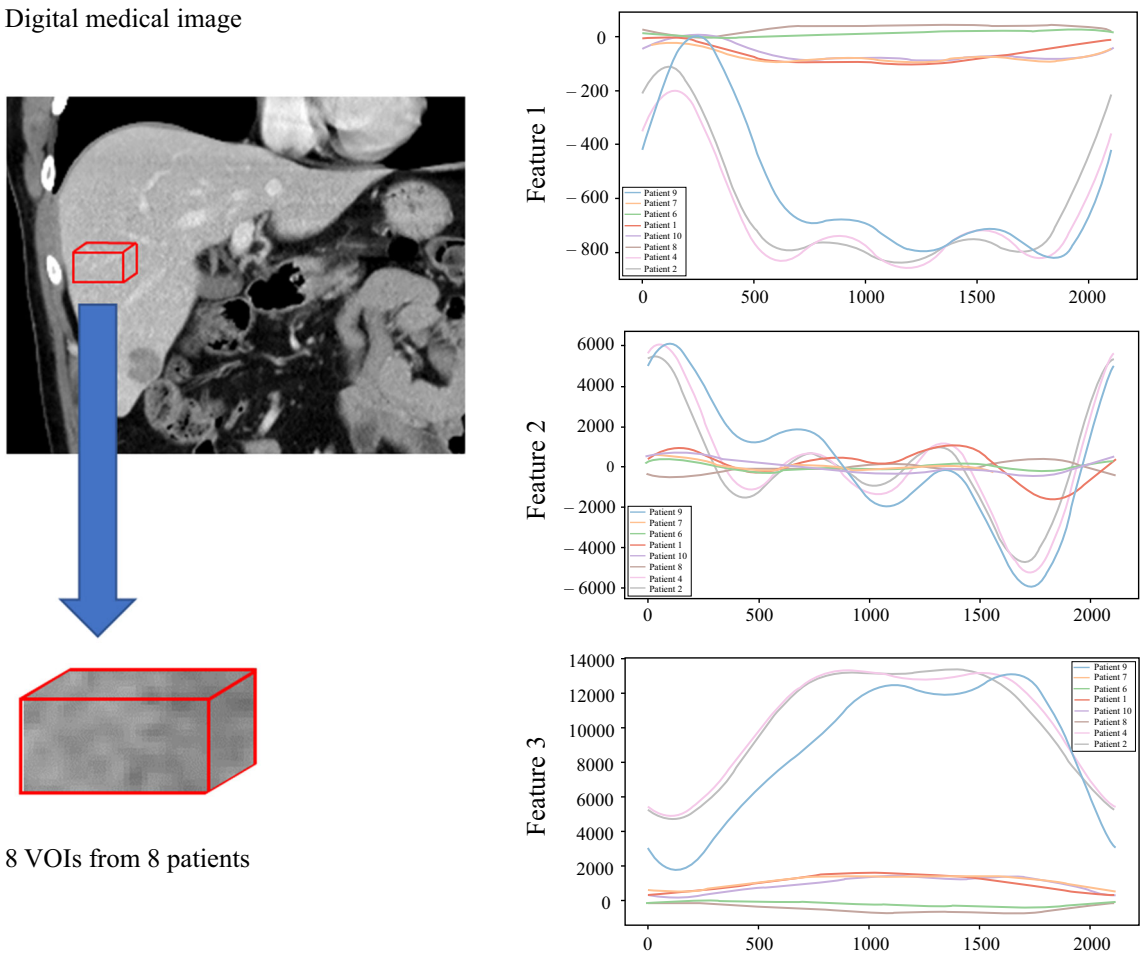

FIG. 1 Texture analysis of CT scan of eight patients undergoing liver resection for colorectal metastases after preoperative chemotherapy. Raw images were reconstructed, and grey levels were adjusted according to the Hounsfield units scale before volumes of interest (VOIs) extraction. VOIs consisted of standardized samples of healthy liver tissue, potentially affected by CALI. Such VOIs were then analyzed, and three functional features were computed as follows: feature #1: volumes were unfolded to obtain a one-dimensional representation of the portion; feature #2: volumes were then derived, applying a Sobel filter to the three directions, and unfolded to create a one-dimensional metrics of neighbor grey level first-order variability; feature #3: Laplacian of Gaussian filter was performed on volumes such that, after unfolding, one-dimensional second-order variability measure among neighborhoods of grey level was built for each patient's study. Patients with CALI (#2, 4, and 9) and without CALI (#1, 6, 7, 8, and 10) have a different pattern of all features

morbidity and postoperative liver failure rates, but this correlation is much more evident in patients with CALI than in patients without it (Fig. 3).[7,8,12,16,19] In patients without CALI, the postoperative liver failure rate was almost stable through series suggesting an adequate policy for patients' selection and an effective modulation of liver volume. This was not the case for patients with CALI that have a nonnegligible risk of liver failure, even after preoperative portal vein occlusion.

Fourth, if major hepatectomy is needed and CALI are suspected, a cutoff value of FLR volume higher than the one adopted for the patients with healthy liver parenchyma should be considered. In the presence of sinusoidal injury or NASH, the postoperative liver failure rate is more than 15% when the surgeons adopt a minimum value of FLR of 25%, and is between 10 and 15% when they rise the threshold to 30%.[7,16,26–29] Even if these data did not correspond to an increased mortality rate (0% in most series), they suggest the need for an extension of the indications to preoperative portal vein occlusion. Robust evidence is still to provide. Ferrero et al. reported no liver failure in patients with FLR > 35%.[29] We adopt a higher cutoff value, i.e., 40%, in agreement with the Eastern centers.[30] Additional features could be considered, such as the postchemotherapy liver atrophy, and the remnant growth rate after portal vein occlusion, but they are not yet part of current clinical practice.[8,31] A more sophisticated approach could modulate the cutoff value of FLR volume according to the results of liver function tests. Even if appealing, this approach has been poorly explored. Takamoto et al. proposed an FLR volume >60% in patients with ICG test ≥10.[30] Such a high threshold could be difficult to conciliate with modern

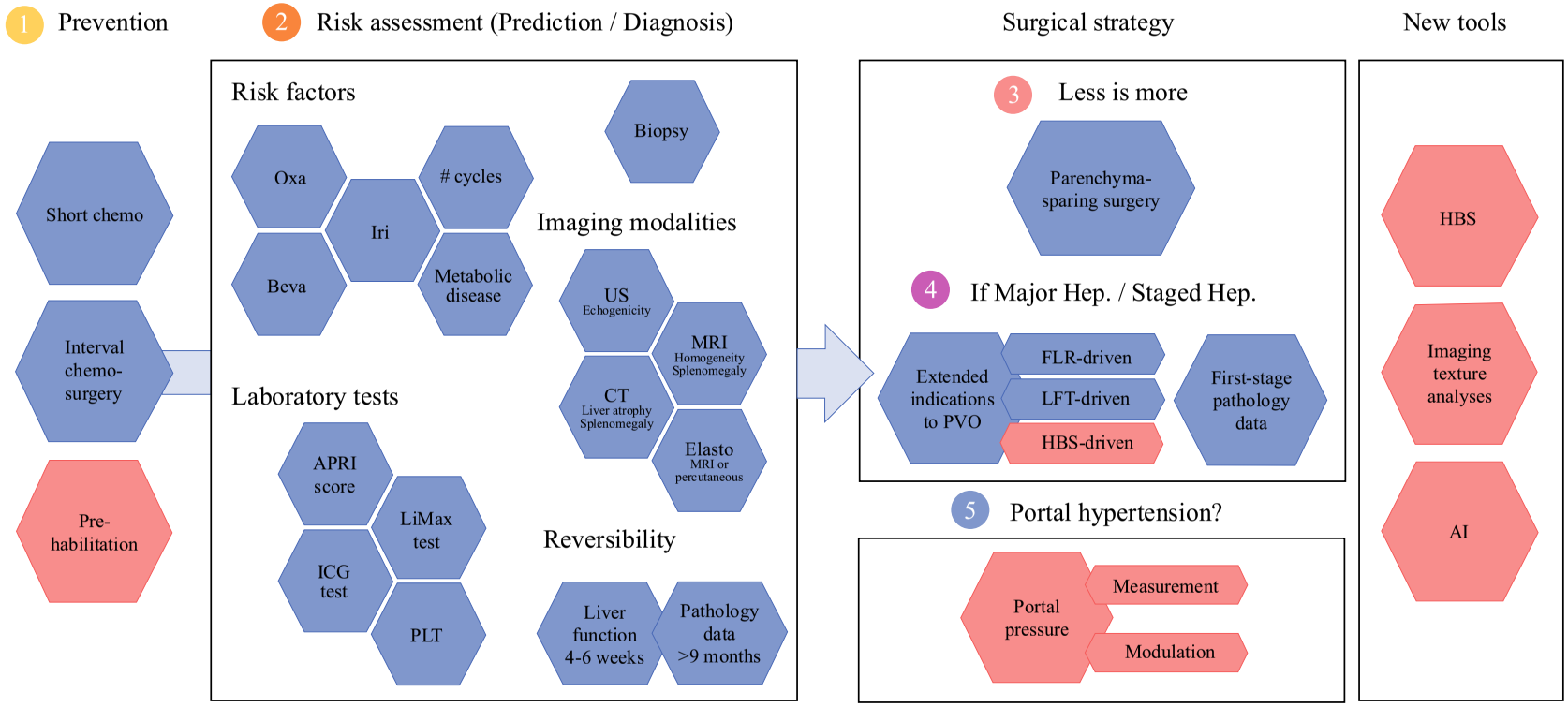

FIG. 2 A vademecum for surgeons to manage patients scheduled for liver resection after preoperative chemotherapy. Available and future tools to assess the presence of CALI and strategies to prevent the negative impact of liver injuries on postoperative outcomes. Red boxes include options still to explore. *Oxa* oxaliplatin; *Iri* irinotecan; *Beva* bevacizumab; *PLT* platelet count; *PVO* portal vein occlusion; *FLR* future liver remnant volume; *LFT* liver function tests; *HBS* hepatobiliary scintigraphy; *AI* artificial intelligence

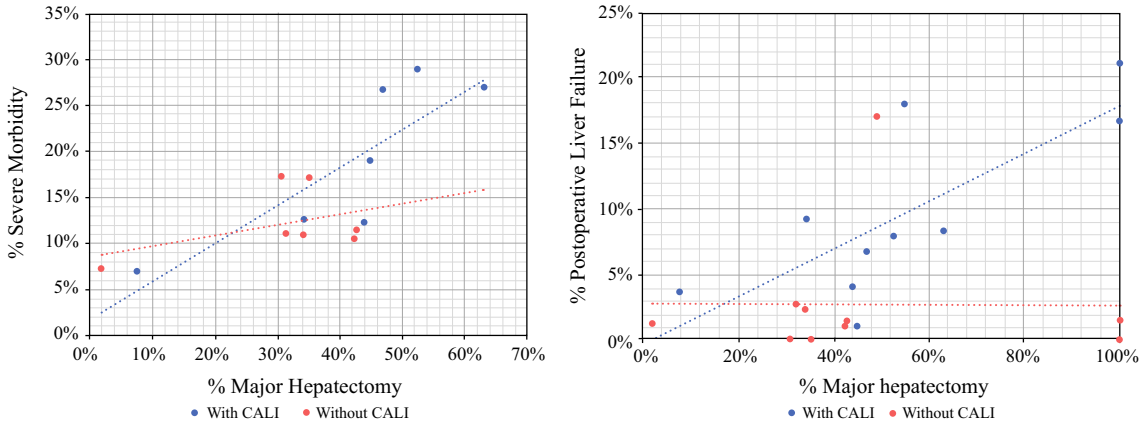

FIG. 3 Correlation between the proportion of major hepatectomies and the severe morbidity (**a**) and postoperative liver failure rate (**b**) in the published series. Data were extracted from the following studies: Nakano et al., *Ann Surg*. 2008;247:118-24; Soubrane et al., *Ann Surg*. 2010;251:454-60; Wicherts et al., *Ann Surg Oncol*. 2011;18:659-69; Viganò et al., *Ann Surg Oncol*. 2015;22:4149-57; Viganò et al., *J Hepatol*. 2017;67:84-91; Zhao et al., *Br J Surg*. 2017;104:990-1002; Shindoh et al., *Ann Surg Oncol*. 2019;26:4100-7; Truant et al., *Ann Surg Oncol*. 2021;28:1959-69; Viganò et al., submitted data.

aggressive surgical indications, especially when staged procedures are scheduled. Obviously, if a staged hepatectomy is planned, the evaluation of CALI on the specimen of the first hepatectomy should drive decisions concerning the second-stage procedure. The association between the CALI, FLR value and outcomes in patients undergoing staged procedures remains unexplored.

Fifth, sinusoidal injuries, namely severe NRH, may lead to portal hypertension.[7] If suspected, preoperative assessment of hepatic venous pressure gradient could be considered, as well as intraoperative measurement of portal pressure and portal flow modulation.

TOWARD A PRECISION SURGERY

So far, surgeons are aware that liver function, histology, and volume express different nuances that have to be separately weighted, and then combined together and with the other patients' characteristics to obtain the whole picture, to accurately predict outcomes, and to design the most adequate approach. In this sense, HBS and texture analyses could consistently be two major breakthroughs. HBS unveils any functional heterogeneity of liver parenchyma and provides a functional volumetry of the FLR that could further refine indications to preoperative portal vein occlusion. On the other hand, image mining and analysis enables the performance of a "virtual biopsy" of the liver that could lead to a reliable CALI diagnosis. Furthermore, radiomic features could be *per se* biomarkers of liver function and predictors of postoperative outcome, as anticipated by some preliminary studies.[32,33] The next step forward, worth mentioning, is the exploration of artificial intelligence protocols. They could combine clinical, laboratory, volumetric, and imaging data into a single predictive model that can provide a patient-tailored surgical strategy. These are consistently the basis for a precision medicine approach. Premises are enough to fuel a renewed interest in CALI research.

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