Peer Review File

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Reviewer A:

A very well written manuscript.

1) There are some minor typos which need correction.
   Reply: We thank Reviewer A for this note. Please be advised that the manuscript has been fully reviewed and those typos have been corrected. The manuscript has been also proofread by an independent agency.
2) Could you please specify when you choose a PS approach versus major liver resection.
   Reply: We thank for this question. Please be advised that this study was not designed to clarify when perform parenchymal-sparing hepatectomy (PSH) versus standard major or extended hepatectomy. Both the recruitment centers (Milan and Pisa) applied a PSH approach in most of the cases. Nevertheless, we have now added a paragraph in the method section about the criteria to perform PSH.
3) Do you perform ICG clearance test preoperatively?
   Reply: We thank for this question. We do not perform the ICG-test before surgery. Thus, we cannot add those data that eventually would have been interested to consider.
4) Do you have special recommendations for surgery in patients with liver atrophy?
   Reply: According to our data, what we could suggest is to limit the use of major or extended hepatectomy in patients with post-chemotherapy liver atrophy because of the increased risk of PHLF. We thank the Reviewer A for her/him notes.

Reviewer B:

The authors presented that the parenchymal-sparing hepatectomy (PSH) for colorectal liver metastases (CLM) is a safe procedure for preoperative systemic chemotherapy-induced liver atrophy and reduced remnant liver function. PSH for CLM is already widely accepted as a safe procedure that can preserve remnant liver function without compromising curative intent.

The authors appear to insist that PSH is safer than anatomical resection for CRLM even after repeated chemotherapy (they referred #12). However, the obtained results do not support this logic. Readers think that it is impossible to do hepatectomy for CRLM without anatomical resection. If they want to insist this theory, they should show that 1) detail of surgical procedures (PSH and anatomical resection) and remnant liver volume after hepatectomy, 2) comparison between PSH and anatomical

resection, and 3) the short-term outcome after hepatectomy in pts with atrophy and without atrophy in pts undergoing PSH, and anatomical resections.

In the present form, it is unclear that whether PSH contributed to prevent PHLF or other factors were effective.

Comments to the authors

1. The authors showed that patients with a significant degree of liver atrophy did not experience a significant increase in postoperative morbidity or mortality when operated under the PSH approach. However, the detail of the surgical procedure was unclear (the number of resection places and the volume or weight of the resected specimen). If the authors are describing the relationship between volume and liver function, this is an important factor.

   Reply: We thank Reviewer B for this note. We would like to focus your attention on the fact that all the included patients had a minimum value of the future liver remnant (FLR) at 40%. This value was one of the selection criteria adopted to consider one-stage hepatectomy for CLM – meaning the removal of all the CLMs in a single stage avoiding two-stage hepatectomy with or without augmentation techniques (PVE, HVE, ALPPS). We have now remarked this point in the methods section. That 40% comes from previously publications: Makuuchi M et al. Surgery 1990; Minagawa M et al. Ann Surg 2000; Torzilli G et al. Surgery 2009; Donadon M et al. HPB (Oxford) 2017.

   Having said that, we have now added a new supplementary Figure with a dedicated legend to better detail the process of imaging analysis exactly on the issue of having the value of FLR, which of course we calculated case-by-case according to the tumors' distribution and – importantly – to the tumors' clustering aiming to define the resection areas. With that new figure, the reader can understand how from a simple 2D CT scan is it possible to develop the corresponding 3D cast of the liver and design the resection areas with having back the value of the FLR. As said before, in this study we included only patients with an anticipated FLR ≥40% as per selection criterion.

   However, please note that in the context of multiple bilateral CLMs undergoing one-stage hepatectomy is not common to have a reported series of patients with this kind of volumetric analysis. This fact represents one of the arguments in favor of our study.

Reviewer B is right. Liver volume and liver function are linked since FLR is one of the main outcome determinants after hepatectomy. However, here we have all patients with at least 40% of residual liver volume. Thus, we cannot perform an analysis on the FLR rates left in the patients because we do not have a wide distribution of FLR rates. Besides, that was not the aim of the study that was the analysis of the parenchymal liver atrophy after chemotherapy.

As requested, we have now added the numbers of resection areas in Table 2.

2. Liver atrophy after systemic chemotherapy was reported previously as the risk factor of post-hepatectomy liver failure, and the authors described that the only predictive factor of postoperative liver atrophy was the pre-chemotherapy total liver volume (TLV). TLV varies individually depending on body size. It is difficult to compare only absolute values. A comparison with standard liver volume or something is necessary.

   Reply: We thank the reviewer for this observation. And you are right. With this paper we cannot conclude anything in terms of absolute values of TLV that, you are right, depends on factors among which the BMI or BSA values. We are aware of different formulas (among which the one from JN Vauthey is one of the most used) to calculate the liver volume but in this study, we applied the standard volumetric analyses of the liver volumetry performed with the CT scan. We have now added a comment on this point in the discussion section. Certainly, a given specific value of TLV pre or post chemotherapy does not indicate much. With this study we would like to focus the readers' attention on three main points: 1. CT volumetry of the liver is important, and a starting low value of TLV may anticipate a greater risk of post-chemotherapy liver atrophy; 2. The phenomenon of post-chemotherapy liver atrophy exists and should be considered – again the performance of the CT volumetry is important; 3. PSH rather than more demolitive surgery might be considered in those cases.

3. In the Abstract, some words were ambiguous and unclear, for example, "whether PSH can protect(?) against such risk(?)", "risk factors for PHLF were assessed (Is this necessary for this paper?)", "major complications occurred (Clavien-Dindo?)", "TLV 1387ml (not logical as described in comments #2), …The abstract is very important and should be logically perfect to insist their conclusions.

Reply: We thank for these observations. Please be advised that we have now modified accordingly.

While the analyses of complications and PHLF is not truly necessary for this paper, we believe that having an idea of those factors in this specific patient's cohort is helpful. Those data might be used for a rapid comparison with readers' own data. Finally, the value of TLV 1387 is what comes from the statistical analysis. Certainly, there is no meaning in speaking about a single absolute value of TLV as you have written above. Please consider all my arguments listed in the previous points. As requested, that part has been now removed from the abstract, while it is still present – with those limitations – in the results section.

Reviewer C:

Summary:

In their manuscript the authors evaluate the influence of post-chemotherapy liver atrophy on outcome after parenchymal sparing hepatectomy (PSH). Chemotherapy associated liver injury remains one of the main risk factors for postoperative complications and liver failure after liver surgery. Hepatic atrophy has been shown to be able to predict posthepatectomy liver failure (PHLF). PSH has been evaluated as an alternative to non-parenchymal sparing or anatomical resection, with an argument being made for improved salvageability after PSH. There is limited data on the effect of post-chemotherapy liver atrophy on outcome after PSH. However, due to many major and minor issues this manuscript lacks novelty and does not significantly advance the literature.

Major issues:

1. One of the main findings of this study is a supposed benefit for outcome after liver resection when using a PSH approach in patients with liver atrophy after chemotherapy. However, due to this study being severely underpowered it is difficult to make this statement. The authors mention themselves that PHLF showed a tendency to be higher in patients with liver atrophy. I agree that with adequate sample size this analysis would probably show significant results. With PHLF arguably being the most relevant factor for postoperative mortality in patients it is debatable if PSH really did improve outcome in these patients.

Reply: We thank for these comments. PHLF is a rare event, which also depends on the definition adopted. There are published series with less that 2% of PHLF events, and other with PHLF events up to 20%. In this study, we adopted the ISGLS definition that is the one usually adopted around. We had 2.4% of PHLF

in patients without liver atrophy versus 15.2% of PHLF in those patients with liver atrophy. While this difference is not statistically significant, we believe that a 6-fold increase of PHLF in patients with liver atrophy is clinically significant and worthy to be reported and further investigated. Of note, those two groups (no liver atrophy vs. yes liver atrophy) were statistically similar for baseline and surgical data. While the occurrence of PHLF is multifactorial, certainly the residual liver in terms of volume and quality plays a very important role. Yes, we cannot draw definitive conclusions, but it is reasonable to state that the performance of major or extended hepatectomy in patients with liver atrophy would be risky and, consistently, is wise to preserve more residual liver volume by performing PSH, when technically indicated. This message is consistent with previous literature on the risk of performing major or extended hepatectomy in patients with liver atrophy after systemic chemotherapy for colorectal liver metastases (Yamashita S, et al. J Hepatol 2017; Omichi K et al. J Gastrointest Surg 2018).

2. To truly make the statement that outcome in patients with post-chemo liver atrophy is improved due to PSH this study would need a non-PSH comparison group. The authors mention that other studies exploring post-chemotherapy liver atrophy also did not include a comparison group. However, while it is true that the study by Yamashita et al. (J Hepatol, 02/2017), referenced by the authors, did not include a comparative group, their aim was not to compare surgical approaches or demonstrate safety of a type of procedure. Yamashita et al. demonstrated in a large patient cohort that PSH correlates with postoperative hepatic insufficiency. While it is possible to compare findings with historical data it is difficult to compare two different surgical approaches based on different publications from varying centers. There are too many variables that cannot be accounted for unless in a direct comparison. With the available literature, it is debatable whether there is enough novelty in a study design focusing solely on the influence of post-chemotherapy liver atrophy on the postoperative outcome in patients after PSH.

Reply: We thank for the opportunity to clarify some points. From the clinical standpoint, the presence of post-chemotherapy liver atrophy in patients awaiting hepatectomy for CLM is a sign of chemotherapy-associated liver injury and should be considered a kind of alert in candidates to major or extended hepatectomy. This is the conclusion from previous studies (Yamashita S, et al. J Hepatol 2017; Omichi K et al. J Gastrointest Surg 2018) that, as said, did not include comparison groups. We are in the same situation. Conversely to them, we looked at PSH rather than to major or extended hepatectomy. And we found no increased risk of complications even in case of liver atrophy. Our conclusion, supported by our data with all the stated study limitations, is that in case of diagnosed liver atrophy because of extensive systemic chemotherapy PSH should be preferred to major hepatectomy. We do not want to draw definitive conclusions on this argument, which deserves further studies.

Reviewer C is right. "There are too many variables that cannot be accounted for unless in a direct comparison". Only a randomized clinical trial (RCT) would solve this problem, but as usually the performance of RCT requires much more resources not easily available. Retrospective studies, with all the stated methods limitations, may indicate the road, may give a clue, may support a thesis that requires many others studies – ideally also RCT – to be confirmed.

3. There are multiple instances where the authors speak of a difference, even though this can't be proven statistically. For example, on page 6 when taking about oncomarkers, the authors write "However, none of these differences reached statistical significance." This simply does not make sense scientifically and needs to be changed as well.

Reply: We thank for that observation. That part of the paper has been consistently changed. Now, it should be more readable.

4. It is unclear to me how the authors arrived at the parameters which were included in their multivariable models for prediction of liver atrophy and postoperative complications. Can the authors include all available variables and calculate univariate analysis, followed by multivariable analysis for the parameters proving to be predictive? Also, I would suggest including a cutoff for cycles of chemotherapy. As there are only a few patients with 3 or 4 cycles, this would better represent this high-risk group. Bilobar metastases should also be introduced as a parameter.

Reply: We thank for the opportunity to improve our manuscript. We have now added two new paragraphs in the methods section named "Selection of predictors". There, you can find the list of variables we selected for the univariate and multivariate analyses of post-chemotherapy liver atrophy development as well ass of postoperative complications. As a matter of fact, we selected and included only the variables clinically available in the preoperative setting and deemed to potentially impact post-operative morbidity and predict the postoperative course. We hope that now the statistical methods herein applied will appear clearer.

Minor issues:
1. The authors mention that this study is a prospective study, however as they also mention it is actually an observational retrospective study. This is not the same type of study design and should be appropriately mentioned in the manuscript. While an observational study has certain prospective aspects in regards to data collection, there are major differences in patient selection. An observational study does not necessarily include patients consecutively like a prospective study. Can the authors explain how these patients were selected, whether or not they were consecutive or non-consecutive? If they were non-consecutive this also raises the question of sampling bias, please discuss.

Reply: We are sorry for this little confusion. This study is a retrospective study on a consecutive cohort of CLM patients operated in two institutions. We have now modified accordingly in the text as well as we have now added more information about the selection process.

2. There are multiple minor errors, for example on page six postop morbidity graded using the criteria put forth by Dindo et al is categorized as Clavien-Dindo 1-3 and Clavien-Dindo 3a-4 which is not correct. Only in table 2 itself are the categories classified as 1-2 and ≥3 as it should be.

Reply: We thank for that note. Please be advised that now everything has been corrected.

We thank Reviewer C for the opportunity to revise our manuscript. We hope that she/he will now find it valuable for publication.