Peer Review File

Article Information: http://dx.doi.org/10.21037/jgo-20-507

Review Comments

1. Please address why the average time from TARE to resection was 235 days in more detail. Is this purely due increased time to induce hypertrophy or were there other factors?

Response:

We thank the reviewer for this comment. The mean time from TARE to resection predominantly reflects the 'biologic test of time' observations in this cohort of patients who were unresectable at initial presentation by multidisciplinary consensus.

Changes in text:

None

2. How was it decided if PVE was attempted first as opposed to TARE? Only 4 were treated with PVE prior to TARE. Although you mention high mortality associated with ALPPS, PVE is generally considered safe with mortality approaching 0% (Abulkhir A, Limongelli P, Healey A J. et al.Preoperative portal vein embolization for major liver resection: a meta-analysis. Ann Surg. 2008;247(1):49–57) and TACE in combination with PVE has been used successfully in HCC. Please also discuss rationale for not using TARE with PVE in all cases as it seems that the time required for adequate FLR is significantly longer when treated with neoadjuvant TARE alone.

Response:

We thank the reviewer for this comment. Our typical practice is that patients will receive PVE if they have well consolidated metastatic disease with favorable biology, a narrow systemic therapy window, and minor needs for FLR growth. TARE was used to salvage suboptimal PVE results in a small subset of patients.

The mortality of PVE we mentioned is not related to the procedure, but of the reported post hepatectomy liver failure ('Discussion' lines 218-219).

We agree that TACE and PVE is an effective strategy for HCC. We prefer radioembolization due to the established evidence for superior time to progression over TACE. Furthermore, we report on the use of neoadjuvant TARE in other malignancies.

Changes in text:

We have made a minor change in the mechanics of 'Discussion' line 217 to clarify procedural morbidity/mortality is associated with ALPPS rather than both ALPPS and PVE. The sentence now reads:

"PVE and ALPPS have been utilized in patients with inadequate FLR but are associated with a risk of tumor progression and significant morbidity/mortality, respectively (15,16,44–48)"

3. Do you have any data on patients who were treated with neoadjuvant TARE with plans for resection but ultimately progressed prior to resection? This would be interesting in the context of the longer time to resection and discussion of this approach allowing for better understanding of tumor biology. Although this approach is widely appreciated in HCC, only 34% of this cohort had HCC.

Response:

We thank the reviewer for this comment. We agree with this comment however, the scope of this study was not an intention to treat (ITT) for hepatectomy but rather an analysis of outcomes in patients who received hepatectomy ('Discussion' lines 286-288). Tumor progression rates are well recognized after PVE and are not an uncommon limitation to subsequent resection. The response rates of TARE (given the extensive pathologic response we report) compared with tumor non-treatment in PVE has driven our adoption of TARE as a neoadjuvant without ITT data.

Changes in text:

None

4. Please provided more information regarding patients with cirrhosis including stage of disease and how many had evidence of portal hypertension. Also, HCC is quite uncommon in the absence of cirrhosis, however in your series of the 9 patients with HCC only 4 had cirrhosis according to table 1. Is this correct? Please either explain or correct.

Response:

We thank the reviewer for this comment. Due to the retrospective nature of this study, pre-operative testing was variable among patients. Of the patients who underwent percutaneous liver biopsy prior to intervention (n= 5), four had findings of cirrhosis and/or mild portal hypertension. Many patients in this highly selected cohort had HCC in the setting of a non-cirrhotic liver. Patients that had HCC in the setting of

significant liver disease would have likely been listed for transplant if eligible or undergone interventions to downstage to transplant.

Changes in text:

We have clarified these findings in the 'Results' (lines 160-163) and added the following text:

"Five patients underwent percutaneous liver biopsy prior to intervention. Of these, four patients with hepatocellular carcinoma demonstrated signs of cirrhosis and/or mild portal hypertension and one patient with cholangiocarcinoma demonstrated steatosis and minimal portal fibrosis (Table 1)."

We have also updated Table 1 to reflect that one patient was found to have steatosis and minimal fibrosis at biopsy. Please note that there was a typographical error in the original text of Table 1 for number of patients with liver disease. Five patients total were found to have liver disease (one with both steatosis and minimal fibrosis).

5. Consider discussing PVE poses higher risk to patients with cirrhosis and portal hypertension as opposed to TARE as a possible advantage of neoadjuvant TARE.

Response:

We thank the reviewer for this comment. This is definitely a consideration however, we do not have the institutional experience to confirm this as many of our patients with HCC in the setting of significant portal hypertension are offered liver transplantation and do not undergo partial hepatectomy. There is a risk for portal hypertension after lobar TARE as well, only the effects are more gradual allowing the liver more time to hypertrophy which may benefit patients with cirrhosis.

Changes in text:

None

6. Consider adding a survival curve to better demonstrate patient outcomes after resection.

Response:

We thank the reviewer for this comment. A survival curve was not included in the results to emphasize the primary endpoint of post-hepatectomy liver failure. Given the

small sample size, survival analysis is highly susceptible to outliers in this heterogeneous cohort (e.g. patients with neuroendocrine tumor).

Changes in text:

None

7. Provide more detail on the patients with "steatosis" and "fibrosis" described in table 1. How was this assessed (biopsy vs imaging) and what stage.

Response:

We thank the reviewer for this comment. We have added additional details in the results section and further revised Table 1, as noted in item #4.

Changes in text:

See item #4.