Peer Review File

Article Information: https://dx.doi.org/10.21037/jgo-21-514

Reviewer A

General comments
This manuscript investigated the efficacy of HAI for CRLM with KRAS mutation.
This topic is important because the effect of systemic chemotherapy for CRM with KRAS mutation is limited.
Although KRAS mutation negatively affected tumor response to HAI, those findings showed a benefit from the treatment. The response rate was superior to systemic chemotherapy alone which previously described.

Detailed comments

Materials and Methods
1. The primary endpoint and secondary endpoints are usually defined in the prospective trial.
Reply: Seeing as this is an observational study, perhaps a more correct verbiage would be “primary outcome variable” and “secondary outcome variable”.
Changes in text: This change has been made in Materials and Methods, lines 98 and 100.

Results
2. The patient’s number and characteristics should be described in Materials and Methods section in the retrospective study.
Reply: This change has been made.
Changes in text: See addition to Materials and Methods, lines 125-128.

3. Please describe the detailed information of prior regimes. The prior regimens were failed in all patients?
Reply: We have now added data on prior systemic chemotherapy regimens and a direct comparison of nr of prior chemotherapy cycles administered (Median 6 vs 7.5 cycles, p=0.76.) Prior regimens did not all fail. The decision to move forward with HAI therapy was made on an individual basis by a multi-disciplinary tumor board. Patients could have anything from favorable response to overall disease progression on prior chemotherapy, this did not determine eligibility for HAI pump placement.
Changes in text: See addition to Table 1 and Results, Lines 152-157.

4. How about the differences of prior regimes numbers? The prior regimens may influence the efficacy of HAI.
Reply: We have now added data to compare the total number of prior systemic chemotherapy delivered before HAI pump chemotherapy. There was no difference in the number of chemotherapy cycles administered between groups (p=0.76)

Changes in text: See addition to Results, lines 152-153.

5. Please define the evaluation of complication in Materials and Methods section.
Reply: Post-operative complications were classified according to the Clavien-Dindo classification system for surgical complications. We have added a definition for long-term HAI related complications.
Changes in text: See addition to Materials and Methods, lines 131-132.

6. Please describe the detailed information of complications.
Reply: See existing paragraph in Results; "Complications", lines 159-168.
Changes in text: No changes in the text were made.

7. How about other hematological and non-hematological toxicity related HAI?
Reply: See existing paragraph in Results; "Complications", lines 159-168. There were no other hematological or other toxic adverse events related to pump chemotherapy.
Changes in text: No changes in the text were made.

8. Please described median survival time.
Reply: Median Overall Survival = 23.7 months (95%CI 14.3-33.1) for the whole cohort. KRAS-mut = 23.7 (95%CI 2.8-44.6). KRAS-wt = NR
Changes in text: This has been added to Results – Tumor response and survival, lines 180-183.

Discussion
9. Please describe the comment of the hepatic progression free survival (20.5m in KRAS-mut vs 12.7m in wild, p=0.63).
Reply: There was not a statistically significant difference in hepatic progression free survival between the two groups. No conclusions can be made based on these findings.
Changes in text: See addition to discussion section, lines 223-225.

Figure and Table
Figure 1.
10. Why the authors did not show the Waterfall plot of progressive disease?
Reply: Including the three patients who progressed while on HAI treatment would distort the waterfall plot as one of these patients had tumor burden progression of +257%. We have therefore elected to keep the asterix but instead detailing in the Figure legend the amount of tumor burden increase each of the three patients had.
Changes in text: See new figure legend for Figure 1.

11. Please describe the main results of this study in Table.
Reply: We have now added Table 2 which summarizes main outcomes.
Changes in text: Table 2, see in text citation, line 174.

Reviewer B

I read with great interest this original article from Yokoyama and colleagues, reporting KRAS mutation effects and outcomes of unresectable patients treated with HAI. I have several concerns before potential publication. My main point is the use of WHO and not RECIST criteria to evaluate tumor response. It makes it difficult to compare with previous studies. RECIST criteria should be used. The chemotherapy systemic drug should also be given. Please also consider the following comments.

Major comments

1. Please precise in the abstract the chemotherapy HAI drug received.
   Reply: This has been added.
   Changes in text: See abstract, line 31

2. Who define resectability of hepatic lesions ? A surgeon ? A multidisciplinary team ?
   Reply: All patients are discussed at a multidisciplinary tumor board that includes surgical oncologists, a radiologist, pathologist and medical oncologists.
   Changes in text: This has been added into Materials and Methods, lines 97-98.

3. Why eight lesions for resectability ? Please give a reference or explain local practice.
   Reply: Cases were reviewed at multi-disciplinary tumor board for determination of resectability. Patients were determined to be anatomically unresectable if resection could not be performed with preservation of at least two contiguous segments or biologically unresectable if there were more than eight bilobar lesions present. A similar definition of biological unresectability has been utilized before. See the following reference:

   1. D'Angelica MI, Correa-Gallego C, Paty PB, et al. Phase II trial of hepatic artery infusional and systemic chemotherapy for patients with unresectable hepatic metastases from colorectal cancer: conversion to resection and long-term outcomes. Ann Surg. 2015;261(2):353-360. doi:10.1097/SLA.0000000000000614

   Changes in text: Resectability criteria was clarified with minor changes to text in Methods, lines 97-100.

4. Why didn't you use RECIST1.1 criteria for ORR? RECIST criteria are now very common and much more used than WHO criteria. RECIST criteria for evaluation of tumor response would be much interesting.
   Reply: While RECIST criteria are widely used to evaluate tumor response, the WHO criteria has been utilized extensively to measure liver tumor response in this setting, most notably by the HAI research group out of Memorial Sloan Kettering Cancer Center. See the following articles.

   1. Pak, Linda M et al. "Prospective phase II trial of combination hepatic artery infusion and systemic chemotherapy for unresectable colorectal liver metastases: Long term results and curative potential." Journal of surgical oncology vol. 117,4 (2018): 634-643. doi:10.1002/jso.24898
   2. D'Angelica, Michael I et al. "Phase II trial of hepatic artery infusional and systemic chemotherapy for patients with unresectable hepatic metastases from

colorectal cancer: conversion to resection and long-term outcomes." Annals of surgery vol. 261,2 (2015): 353-60. doi:10.1097/SLA.0000000000000614

3. Kemeny, Nancy E et al. "Conversion to resectability using hepatic artery infusion plus systemic chemotherapy for the treatment of unresectable liver metastases from colorectal carcinoma." Journal of clinical oncology : official journal of the American Society of Clinical Oncology vol. 27,21 (2009): 3465-71. doi:10.1200/JCO.2008.20.1301

4. Kemeny, Nancy E et al. Hepatic Arterial Infusion Versus Systemic Therapy for Hepatic Metastases From Colorectal Cancer: A Randomized Trial of Efficacy, Quality of Life, and Molecular Markers (CALGB 9481). Journal of Clinical Oncology 2006 24:9, 1395-1403

5. Gallagher DJ, Capanu M, Raggio G, Kemeny N. Hepatic arterial infusion plus systemic irinotecan in patients with unresectable hepatic metastases from colorectal cancer previously treated with systemic oxaliplatin: a retrospective analysis. Ann Oncol. 2007 Dec;18(12

Changes in text: None were made.

5. Please also give progression-free survival as secondary endpoint.
   Reply: This has been added to secondary endpoints.
   Changes in text: See addition to Materials and Methods, line 104.

6. Please discuss KRAS prognosis effect among CRC patients, outside HAI chemotherapy.
   Reply: This is discussed in Background, lines 73-75 as well as in Discussion, lines 194-196 with relevant literature cited.
   Changes in text: No changes were made

7. What drug was received as systemic chemotherapy?
   Reply: Information on prior and concomitant systemic chemotherapy has now been added.
   Changes in text: See addition to Materials and Methods, lines 120-122 for concomitant chemotherapy. See Results, lines 152-157 for prior chemotherapy.

8. Please precise the number of HAI chemo stopped for pump dysfunction (infection, biliary obstruction etc).
   Reply: HAI pump related complications are specified in Results – Complications, lines 158-167. Two patients with biliary complications (One patient with a biloma and one patient with strictures) required discontinuing HAI chemotherapy, both after 6 cycles of treatment due to biliary complications.
   Changes in text: See addition to Results, lines 167-168.

9. Please discuss this very important ORR compared to previous studies of pretreated CRLM patients receiving HAI chemo?
   Reply: This is discussed in Discussion, lines 199-201.
   Changes in text: No changes in text were made.

10. Did you observe hepatitis or liver dysfunction?
    Reply: No hepatitis was observed in the cohort. Liver dysfunction in relation to biliary strictures was seen two patients that improved with adequate decompression of the biliary system.
    Changes in text: No changes were made.

11. Please precise the type of KRAS mutation observed.
    Reply: Of 11 patients with KRAS mutation, majority had codon 12 mutations (three had a G12D, one patient G12C, four G12V). Two patients had codon 13 mutation (G13) and one patient A146T.
    Changes in text: See addition to Materials and Methods, lines 127-129.

12. Please discuss oxaliplatine vs floxuridine HAI chemotherapy.
    Reply: We believe the difference in Oxaliplatin and Floxuridine HAI chemotherapy are beyond the scope of this study. While oxaliplatin has been utilized by some, reported outcomes have been mixed and mostly inferior to those described with Floxuridine use. This is however not the focus of this manuscript.
    Changes in text: No changes were made.

13. Please precise whether patients had previously received 5-FU among previous treatments.
    Reply: Information on previously administered systemic chemotherapy has been added to Results, lines 151-156.
    Changes in text: see Results, lines 152-157.

14. On figure 1 there are only 21 patients. please also include the 4 others.
    Reply: 1/25 patients was excluded from the analysis as they had a BRAF mutation as is stated in Materials and Methods. The three patients that are depicted by the Asterix in the waterfall plot had tumor burden increase during treatment. One of these patients had a tumor burden increase of 257%, including this patient would distort the waterfall plot. We have elected to keep the figure unchanged but include a detailed explanation of the Asterix in the Figure legend.
    Changes in text: See new Figure 1 legend.

15. Please precise what kind of extrahepatic disease was observed. Were there any exclusion criteria for extrahepatic disease?
    Reply: This is specified in Materials and Methods, lines 108-110. Only patients with isolated lung or portal lymph nodes disease were considered for HAI pump placement. Patients with other sites of disease or those with aforenoted disease sites but with progression on prior systemic therapy were excluded.
    Changes in text: None were made

Minor comments

16. “Overall decrease in liver tumor burden was 63.5% (median, Range -257 – 100%)”. I do

not get the range -257.
Reply: This range starts at "-257%" which signifies a negative response to 257%. Meaning tumor burden increased 257% while on HAI therapy.
Changes in text: none

17. p=0.05 is not statistically significant, strictly speaking.
Reply: We do not specifically state that the finding is statistically significant.
Changes in text: None

18. "recent evidence has shown superior survival data with HAI therapy compared with chemotherapy alone" : please precise for CRLM patients.
Reply: This suggestion has been added.
Changes in text: See addition to Background, line 69.

19. Line 72 : please precise these numbers refer to no pretreated patients.
Reply: This line refers to the results from a 2009 study by Kemeny et al where 53% of the cohort had prior chemotherapy (pretreated), their findings were an overall 47% conversion to resection. Therefore, this sentence does not just refer to chemo-naïve patients.
Changes in text: No changes were made.

20. Why only symptomatic or right colon for concomitant surgery? Why not left colon? Please give a reference.
Reply: The perceived recovery time and complication rate (mainly anastomotic leak) are traditionally higher following left colon and rectal resections. The institutional preference has been to leave these tumors if asymptomatic as to not risk delaying systemic chemotherapy/HAI chemotherapy infusion.
Changes in text: None were made.

21. figure 2 is blurry and difficult to read.
Reply: This has been fixed
Changes in text: See new Figure 2.