

Dear Editor-in-Chief,

Please find attached a revised version of our review “ADJUVANT CHEMOTHERAPY FOR RESECTED COLORECTAL CANCER METASTASES: LITERATURE REVIEW AND META-ANALYSIS” (Manuscript No. 20193), which we would like to resubmit for publication.

In the following pages are our point-by-point responses to each of the comments of the reviewers: the revisions in the text are highlighter in red.

Response to reviewer 00070758's comments:

1. **COMMENT 1:** Please, organize the table contents by dates and include some authors from the last year.

RESPONSE: We organized the table contents by dates and added the following sentences: “Recently, two Japanese phase III trials (JCOG0205, ACTS-CC) showed the safety and efficacy of other oral fluoropyrimidines as adjuvant treatments for patients with resectable CRC [34, 35]. The authors demonstrated the non-inferiority of UFT/LV (tegafur-uracil/leucovorin) and S-1 (tegafur-gimeracil-oteracil) to 5-FU/LV in terms of DFS.” (page 7); “Several Japanese studies have examined the efficacy and safety of oxaliplatin-based adjuvant treatments. In a randomized, controlled phase II/III trial, Kanemitsu et al compared hepatectomy followed by m-FOLFOX-6 adjuvant chemotherapy with surgery alone, but the final results are not yet available [95]. Another two studies (a retrospective cohort study and a phase II non-controlled clinical trial) suggested that adjuvant chemotherapy after metastasectomy provides a benefit in DFS [96, 97].” (page 13); “Some recent studies have suggested the potential efficacy of other oral fluoropyrimidines also in the adjuvant setting post-metastasectomy. A phase III trial (UFT/LV trial) randomized 180 patients after metastasectomy to receive adjuvant UFT/LV chemotherapy or surgery alone. The 3-year DFS was 38.6% in UFT/LV group and 32.3% in surgery group ($p=0.003$), while a not yet significant difference in the 3-year OS was observed (82.8% vs. 81.6% respectively, $p=0.41$) [103]. N-SOG 01 was an uncontrolled single-arm study reporting the outcome of 60 patients treated with adjuvant S-1 chemotherapy after resection of CRC liver metastases: the 1-year and 3-year DFS were 68.3% and 47.4%, respectively, and 1-year and 3-year OS were 96.7% and 80% [104].” (page 14).

2. **COMMENT 2:** Instead of: The International Agency for Research on Cancer (IARC). "Colorectal Cancer Incidence,, Mortality and Prevalence Worldwide in 2012. GLOBOCAN 2012". [Online]. Available: <http://www-dep.iarc.fr>. The authors could use some most recent data as: Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA Cancer J Clin. 2015 Jan-Feb;65(1):5-29 [PMID:25559415 doi: 10.3322/caac.21254]

RESPONSE: We modified the first sentence of introduction as follows: *“Colorectal cancer (CRC) is the third most common cancer worldwide and is responsible for 8% of cancer-related deaths in men and 9% in women ^[1]”*.

Reponses to reviewer 00182114's comments:

1. **COMMENT 1:** Several reports have presented conflicting results regarding the association between resection margins and the outcome after surgery for colorectal liver metastasis. J H Angelsen et al reported resection margin below 5mm increased the risk for local recurrence and shortened the time to recurrence.(World Journal of surgical oncology 2014) Pawlik reported there was no difference in five year overall survival rate or in the rate of tumor recurrence in the liver whether the tumor free margin was 1 to 4,5 to 9, or>10mm. only patients with a positive margin had worse survival.(Ann Surg 2005). In page 6,you say “negative surgical margins remain an important determinant osurvival of patients undergoing hepatectomy”. I ask you .Please tell me the suitable negative surgical margin,1 to 4, 5 to 9,or >10mm.

REPONSE: We added the following sentences: *“Even in the era of modern chemotherapy, negative surgical margins remain an important determinant of survival for patients undergoing hepatectomy for CRC liver metastases, but most reports claim the width of a negative surgical margin does not affect outcome ^[64]. Although there is still no consensus on the definition of R1, the width of surgical margins has been gradually reduced to 0.1 mm. A recent French study showed that in multivariate analysis positive surgical margins (R1 defined as resection below 1mm) did not constitute a negative prognostic factor of survival per se, but may be related to more aggressive disease ^[65]. Conversely, other studies confirmed the role of resection margin status as an important determinant of OS. Angelsen et al reported that resection margins below 5 mm may increase the risk for local recurrence and shorten the time to recurrence ^[66]. A USA study showed a better 5-year OS in patients who underwent R0 liver resection (tumor-free margin ≥ 1 mm) compared with R1 resection (< 1 mm) ^[67]. A more recent analysis by Sadot et al compared 2368 patients who underwent R1 (0mm) or R0 hepatic resection (divided into three groups: 0.1-0.9 mm, 1-9 mm, ≥ 10 mm) for CRC liver metastases and demonstrated that all margin widths, including sub-mm, correlated with improved OS compared with R1 resection ($p=0.05$), whereas there was no significant difference in OS between 1-9 mm and ≥ 10 mm groups ^[68].”*

2. **COMMENT 2:** In page 6, the impact of the pre-operative chemotherapy on the long term outcome of radically resected metastatic CRC patients is still undefined. But chemotherapy prior to hepatic resection has been tempered by reports of steatosis, vascular injury and idiopathic noncirrhotic portal hypertension. Please tell me the comment of side effect of preoperative chemotherapy .

RESPONSE: We added the following sentence: *“It is noteworthy that pre-operative chemotherapy can induce regimen-specific liver damage, increasing the risk of mortality after liver resection. A*

retrospective study by Vauthey et al evaluated the postoperative outcome of 406 patients after metastasectomy with or without pre-operative chemotherapy (5-FU/LV alone, oxaliplatin+5-FU/LV, or irinotecan+5-FU/LV). In pre-operative chemotherapy group, oxaliplatin was associated with sinusoidal injury and irinotecan with steatohepatitis, but only irinotecan-based regimes also increased the 90-day mortality rate compared with surgery alone [79]. These data were confirmed by Pawlik et al, who found regimen-specific hepatic injury in about 20-30% of their patients treated with pre-operative chemotherapy [80].”

3. **COMMENT 3:** Now portal vein embolization and associating liver partition with portal vein ligation for staged hepatectomy (ALPPS) are sometimes used in otherwise suitable candidates in whom the predicted liver remnant is too small. Please write portal embolization and ALPPS in this review.

RESPONSE: We added the following sentences:” New surgical techniques have recently been considered to treat patients with a small future liver remnant. Portal vein embolization and two-stage hepatectomy is based on hypertrophy of the future liver remnant caused by contra-lateral portal vein occlusion. The functional reserve of the liver grows within 2-4 weeks and the patients may be subjected to subsequent metastasectomy [81, 82]. Instead, associating liver partition and portal vein occlusion for staged hepatectomy (ALPPS) combined portal vein ligation with in situ parenchymal transaction, reducing the risk of tumor progression during the period of liver regeneration and increasing the resectability rate [83]. A multicenter Italian study showed no significant difference in feasibility between these two surgical techniques, but the overall complication rate was higher in the ALPPS group [84]. Consequently, ALPPS should be proposed with caution in patients with CRC liver metastases and small functional liver reserve.”

4. **COMMENT 4:** Radiofrequency ablation (RFA) or cryosurgery is sometimes applied following macroscopically incomplete resection of CRC liver metastasis. Please write RFA and cryosurgery in this review.

RESPONSE: We added the following sentences: “In addition to surgical techniques, ablative therapies (such as radiofrequency ablation (RFA), cryosurgery or microwave) can be used as potentially curative treatments for CRC liver metastases. In several studies, the 5-year OS ranged between 20-30% in patients with advanced CRC who underwent RFA [85, 86]. Pawlik et al’s study was the first to evaluate the outcome of a large series of patients treated with combined hepatic resection and RFA [87]. More recently, Eltawin et al estimated the recurrence rate of 174 patients with CRC liver metastases (24 undergoing liver resection with RFA and 150 undergoing surgery alone). The median OS were 38 vs. 52 months and the median RFS were 7.4 and 13 months, without statistically significant differences ($p=0.95$ and $p=0.08$, respectively) [88]. These studies suggested that RFA combined with liver resection may enhance long-term survival in a select group of patients.

To date, no randomized trials have compared RFA and surgery. A recent Cochrane review included 18 studies comparing RFA and any other treatment (10 observational, 7 clinical controlled trials and 1 randomized clinical trial) [89]. These data did not allow any definitive conclusion to be reached and are insufficient to recommend RFA as a radical treatment for CRC liver metastases.

Cryotherapy (in which liquid nitrogen or argon gas is delivered to the liver tumor) is another local ablative technique used to treat patients unsuitable for liver resection, alone or in combination with surgery. A retrospective USA study analyzed 158 patients with CRC liver metastases treated with surgery and/or ablation treatment. The ablation techniques were performed by radiofrequency ablation, cryotherapy and microwave ablation (total: 315 treated tumors). The local recurrence rate in the cryotherapy group was statistically significantly higher than in the RFA group both in univariate and multivariate analysis ($p=0.03$ and $p=0.018$, respectively) [90]. "

Reponses to reviewer 00070934's comments:

1. **COMMENT 1:** Authors showed that HAI with systemic chemotherapy was superior to systemic chemotherapy only in OS, DFS, and PFS. But, authors gave up the notice of HAI superiority because OS was not significantly difference in only reference 96.

RESPONSE: No significant difference in median OS was observed also in reference no. 92. However, we added the following sentence: "*To date, the use of HAI in the adjuvant setting has not demonstrated a significant difference in term of OS, also due to the increasing efficacy of the new systemic chemotherapy regimens. HAI, however, could be employed only to achieve a better DFS.*"

We hope that the revisions in the manuscript and our accompanying responses will be sufficient to make our manuscript suitable for publication in ***World Journal of Gastroenterology***.

Best regards

Giovanni Brandi