Author’s response to reviews

Title: Comparison of Sequential, Delayed and Simultaneous Resection Strategies for Synchronous Colorectal Liver Metastases

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Dear editor,

We thank you and the reviewer for your helpful comments about our manuscript titled "Compare of Sequential, Delayed and Simultaneous Resection Strategies for Synchronous Colorectal Liver Metastases" (BSUR-D-19-00609). Following these comments, we have thoroughly revised the manuscript and we now resubmit it for your consideration. We have marked all changes in the revised manuscript, and we reply point by point to the reviewer comments as below. We hope that the revision is acceptable, and we look forward to hearing from you soon.

Sincerely,

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We would like to express our sincere thanks to you and the reviewers for your constructive and positive comments.

Response to Nobuhisa Akamatsu (Reviewer 1) comments:

(1) Authors should clarify their institutional policy for the treatment selection, sequential resection (SeR), delayed resection (DeR) and simultaneous resection (SiR), with respect to the number or the distribution of CRLM.

Authors: Thank you for your considerable comment. Based on the primary tumour location and tumour disease burden of liver metastases, the treatment selection was made. Simultaneous resection was performed in patients in whom 1) the primary tumour was located in the right colon regardless of the tumour disease burden of liver metastases through one incision; 2) the tumour disease burden was not heavy, and the tumour number was less than two, if the primary tumour was located in the left colon or rectum (Page 6, line 3).

(2) How did authors distinguish CRLM cases technically resectable and technically unresectable at the time of first visit? If the study included these as a whole, they should be investigated separately.

Authors: Thank you for your considerable comment. Patients with disease considered resectable were assigned to undergo hepatic resection with curative intent and the aim of achieving complete resection (R0) while preserving as much normal, functional liver parenchyma (with adequate vascular inflow, outflow, and biliary drainage) as possible. The normal liver parenchyma remnant volume was $\geq 30\%$ (Annals of Oncology 27: 1386–1422, 2016) (Page 6, line 20). The presence of extrahepatic tumours was not considered a contraindication to hepatic resection if the lesions were limited and resectable.
In our center, the resectable condition was not an independent risk factor for CRLM, there was no significant difference in long term survival outcome for resectable and unresectable patients initially (HR 1.211, 95% CI 0.934-1.570, p=0.149) (Eur J Surg Oncol. 2019 Nov;45(11):2070-2077). Therefore, the present study included these as a whole.

(3) Please provide the hitopahologic information for the cohort.

Authors: We have added the differentiation of metastases in detail in the revised manuscript (Table 2).

(4) Please present the tumour markers.

Authors: We have added the CEA level at initial diagnosis in the revised manuscript (Table 1).

(5) Please demonstrate the kind of complication and the Clavien degree.

Authors: We have added the details of complication in the supplementary table 1 and Clavien degree in the revised Table 2.

Response to Elena Arabadzhieva, M.D., Ph.D. (reviewer 2) comments:

(1) The study is retrospective with relatively small sample size. Because of that, I am not sure that this paper itself adds anything new to the current status of literature.

Authors: Thank you for your considerable comment. Although the present study was retrospective with relatively small sample size, it was well designed and written. Moreover, it was inspiring and cheerful that interval chemotherapy should be recommended for staged resection to improve the overall survival. Therefore, it is hoped that the present study could provide some treatment selections and clues to more readers.

(2) The article is well written, despite of several language errors.

Authors: Thank you for your considerable comment. This manuscript has been edited by the editors at SNAS (Editing Certificate).
Response to Andy Petroianu, M.D., Ph.D. (Reviewer 3) comments:

(1) Colon cancers are metastatics, but their metastasis are not metastatics.

Authors: Thank you for your considerable comment. This topic is still in debate, however, recent studies support that hilar lymph node could be remetastasis from liver, therefore, liver metastasis are not metastatics (Updates Surg (2014) 66:239–245).

(2) After removal of primary cancer no new metastasis will occur, but some of metastasis are still very little to be detected. It is well established that metastasis may occur any time after primary tumour resection, even after 10 or 15 years, but most of metastasis are detected during the early six months postoperative period.

Authors: As you mentioned, there are more than 50% colorectal cancer patients could suffer from liver metastases (Eur J Cancer 2006;42:2212-222; World J Gastroenterol. 2007;13:3806–15;). Among of them, 15%-35% patients happened to liver metastases after primary tumour were resected (BMC Surg.2010;10:27; J Clin Oncol, 1997,15:938-946).

(3) Removal of the known liver metastasis in one or two stages does not warrant that new metastasis will not occur in the liver or in other organs and lymph nodes.

Authors: Although it has been reported that the recurrence rate is almost 60% (Ann Surg. 2009, 250 : 440-448), hepatic resection is still recommended to resectable CRLM patients. The effective local treatment could offer them a long-term survival, such as repeat hepatic resection (Ann Surg Oncol. 2015;22: 2761–71) and radiofrequency ablation (World J Surg. 2013;37:1340–7) . Therefore, it still should perform hepatic resection for these patients regardless the recurrence rate. Furthermore, the candidate should be strictly selected.

(4) Some protocols indicate only colectomy even when metastasis are detected in only one liver segment. The patients are followed for 6 months and then new imaging propedeutics are performed. If metastasis are present in only one liver lobe, without other metastasis, partial hepatectomy is indicated. Otherwise, in presence of multiple metastasis are spread in the liver or other organs, the patient is submitted only to chemotherapy.
Authors: Up to now, hepatic resection is still golden treatment for CRLM. The 5-year overall survival rate could be 45% (Oncologist. 2012;17(10):1225-39). For synchronous CRLM patients, preoperative chemotherapy could offer the opportunities to observe how liver metastasis to evolve. If the disease obviously progressed, it could be not a candidate for hepatic resection. It is accordance with your idea to wait and see.

(5) My suggestion to the authors is: to verify the presence of new liver metastasis six months after the first surgical procedure with or without simultaneous hepatectomy during the first surgical procedure. A comparison of these two groups will be very useful.

Authors: Thank you for this fantastic idea. The present study aimed to compare perioperative safety and long-term survival of patients with synchronous colorectal liver metastases receiving sequential resection (SeR), delayed resection (DeR) and simultaneous resection (SiR). It would be designed and performed as your suggestion.

Response to Silvio Nadalin, MD, Prof. (Reviewer 4) comments:

(1) The 3 groups are not comparable, you should identify similar groups in a sort of matched pair analysis.

Authors: Thank you for your considerable comment. Propensity score matching analysis could reduce differences between groups. It is a pity that the sample size of each group in this study was relatively small. This limitation has been pointed in the discussion. After propensity score matching, the sample size of each group will become smaller, affecting the reliability of the results. Moreover, although several factors among the three groups were not comparable, these differences have been adjusted using multivariable analysis.

(2) Sometimes the sy. CRLM are diagnose few weeks/months after diagnosis of primary CRC. Which is the max time frame you considered to include CRLM after the diagnosis of primary CRC?

Authors: According to the synchronous liver metastases international consensus (Cancer treatment reviews 2015, 41(9):729-741), synchronous liver metastases is defined as liver metastases detected at or before diagnosis of the primary tumour. All patients included in the study met this criterion. Those liver metastases detected within 12 months after diagnosis or surgery of the primary was defined as early metachronous metastases, which was not discussed in this study. (Page5, line 5)
When “liver first” was performed at your center.

Authors: “Liver first” strategy was selectively used in patients with heavy tumour burden or with tumours located in the rectum requiring preoperative radiochemotherapy (Page 7, line 15). The number of patients who underwent “liver first” strategy was added in the results part (Page 10, line 20).

What about technical aspects? standard liver resection? any augmentation procedures? i.e. PVE or ALPPS? Laparoscopic vs open?

Authors: The liver resection was performed in an open procedure (Page 7, line 8). Portal vein ligation (PVL) was applied in patients requiring right hepatectomy or more extent resection with insufficient remnant liver volume (Page 7, line 17). Only 4 patients underwent PVL procedure and no ALPPS was in the whole group (Page10, line 22).

Regarding CTx treatment: any side effects? (e.g. NAFLD after CTx?). How many patients got molecular target therapy (e.g. anti EGFR or similar). What about side effects at this regard?

Authors: Thank you for your considerable comment. The proportion of patients receiving initial chemotherapy with molecular targeted agents was shown in Table 2 and Results 2 (Page 10, line 8). The interval chemotherapy regimen was usually the same as the initial effective chemotherapy and molecular targeted agents, except for bevacizumab (anti VEGF agent) which may be stopped for the second stage of surgery in parts of patients.

Because our center is a regional center, some patients were treated in the Department of Medical Oncology or in other centres, so complete, detailed records of specific adverse events or chemotherapy-induced liver injury pathological scores cannot be obtained. In addition, this study is a retrospective study, so no chemotherapy-induced liver injury pathological score was collected prospectively (Page 17, line 3). Therefore, we did not illustrate these data in this study. It would be designed and performed as your suggestion in the future.