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Title of the original manuscript:

Pulmonary metastasectomy for colorectal cancer: how many nodules, how many times

Answers to the comments

From Reviewer #1

**** 1. In the Introduction section: In LM, however, the role of chemotherapy has not been clearly defined yet. The above statement seems to be improper. For metastastic CRC, the role of systemic chemotherapy plus target therapy would be the first line treatment that is well established by several clinical trails. The similar misleading points was present in another one statement as follows: Since no effective chemotherapy for LM is available at present, the best way to improve treatment outcomes is to carry out PM more aggressively in patient who are most likely to benefit from PM.***

Thank you for your important comments. We agree with your opinion and what we intended to indicate was that the optimal treatment of pulmonary metastasis from CRC is still controversial because there has been no randomized controlled trial focusing on pulmonary metastasis of colorectal cancer, although the role of systemic chemotherapy plus target therapy in overall metastatic CRC has been well established by several clinical trials. In order to not mislead the readers, we decided to change several sentences that you pointed out as follows. Thank you.

From **1. Introduction**

{When used for hepatic metastases of CRC, chemotherapy in combination with surgery may prolong survival time or downsize the lesions to render them resectable for patients previously regarded inoperable[11]. In LM, however, **the role of chemotherapy has not been clearly defined yet.**}

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{When used for hepatic metastases of CRC, chemotherapy in combination with surgery may prolong survival time or downsize the lesions to render them resectable for patients

previously regarded inoperable[11]. In LM, however, **there is still controversy over the optimal management strategy.**}

From **1. Introduction**

{**Since no effective chemotherapy for LM is available at present**, the best way to improve treatment outcomes is to carry out PM more aggressively in patient who are most likely to benefit from PM.}

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{**Since chemotherapy alone is not quite reliable to control LM in many cases**, the best way to improve treatment outcomes is to carry out PM more aggressively in patient who are most likely to benefit from PM.}

**** 2. In the Preoperative imaging tests paragraph: The role of FDG PET/CT in CRC patients with LM should be included and compared to the high-resolution CT scan for the detection of LM. Additionally, the following statement: However, the optimal follow-up duration for surveillance for pulmonary metastasis has yet to be definitely determined. According to NCCN guideline 2013 Ver. 3.0, for synchronous resectable liver and/or lung metastasis, chest CT scans every 3-6 mo x 2 y, then 6-12 mo up to a total of 5 y.***

We agree with your comments and added the following sentences in the revised manuscript.

From **3.1. Preoperative imaging tests**

According to the NCCN, the Association of Coloproctology of Great Britain and Ireland, and the Danish Colorectal Cancer Group[3,27,28], the initial staging procedure should include preoperative chest computerized tomography (CT). The use of CT is justified by its higher overall sensitivity than chest X-ray and higher sensitivity for LM less than 1 cm in diameter than positron emission tomography (PET)[29,30]. **As well in terms of a PET/CT scan, there are below the level of routine chest CT detection especially for sub-centimeter lesions, a PET/CT scan is not routinely indicated a baseline for preoperative workup[3,31]. PET/CT scan is considerable only if prior anatomic imaging indicates the presence of potentially surgically curable M1 disease, with the**

purpose to evaluate for unrecognized metastatic disease that would preclude the possibility of surgical management[3].

**** 3. In the Perioperative chemotherapy paragraph: In contrast to liver metastasis, there is no evidence that adjuvant or neoadjuvant chemotherapy after PM could prolong survival of patients with LM of CRC. However, according to NCCN guideline 2013 Ver. 3.0, for synchronous resectable liver and/or lung metastasis, six month perioperative treatment preferred and adjuvant chemotherapy is preferred by FOLFOX or CapeOX regimen.***

Thank you for your important comments. We agree with your opinion about the role of adjuvant or neoadjuvant chemotherapy in patients with synchronous resectable liver and/or lung metastasis. What we intended to point out is that compared with liver metastasis, there are few data regarding the role of adjuvant or neoadjuvant chemotherapy in patients with lung metastasis only. In order to not mislead the readers, we decided to change the sentence as follows.

From **3.3. Perioperative chemotherapy**

{In contrast to liver metastasis, **there is no evidence that adjuvant or neoadjuvant chemotherapy after PM could prolong survival of patients with LM of CRC**.}

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{In contrast to liver metastasis, **few data is available comparing survival between patients undergoing PM with and without adjuvant or neoadjuvant chemotherapy for LM only.**}

**** 4. In the Disease-free interval paragraph: Onaitis et al. reported that a DFI of less than 1 year was an independent predictor of recurrence. The above sentence should be corrected to Onaitis et al. reported that a DFI of less than 1 year was an independent predictor of recurrence after PM.***

Thank you for your meticulous review. We agree that this is a very important point. We changed the sentence as you suggested.

From *Disease-free interval*

{Onaitis et al. reported that a DFI of less than 1 year was an independent predictor of recurrence.}

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{Onaitis et al. reported that a DFI of less than 1 year was an independent predictor of recurrence **after PM.**}

**** 5. In the Distribution of metastasis paragraph: Riquet et al. reported that 5-year survival rates of patients undergoing complete bilateral metastasectomies tended to be even better than those observed in cases of complete unilateral metastasectomy (68% vs. 35.5%; p = 0.09)[66]. The above sentence should be corrected to "Riquet et al. reported that 5-year survival rates of patients undergoing complete bilateral metastasectomies tended to be comparable to those observed in cases of complete unilateral metastasectomy (68% vs. 35.5%; p = 0.09)[66]." as P value is more than 0.05.***

Thank you for your meticulous review. We agree with your opinion and changed the sentence as you suggested.

From *Distribution of metastasis*

{Riquet et al. reported that 5-year survival rates of patients undergoing complete bilateral metastasectomies tended to be **even better than** those observed in cases of complete unilateral metastasectomy (68% vs. 35.5%; p = 0.09)[66].}

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{Riquet et al. reported that 5-year survival rates of patients undergoing complete bilateral metastasectomies tended to be **comparable to** those observed in cases of complete unilateral metastasectomy (68% vs. 35.5%; p = 0.09)[66].}

**** 6. The differences between synchronous and metachronous lung metastasis should be addressed in the manuscript.***

Thank you for your important comment. We agree with your opinion and added the sentences as follows.

From *Disease-free interval*

At the extreme end of a short DFI is synchronous LM. **Although it has been recommended that patients with resectable synchronous LM can be resected synchronously or using a staged approach, survival after PM for synchronous LM are reported to be poorer than for metachronous LM[3].** Onaitis et al. reported that a DFI of less than 1 year was an independent predictor of recurrence after PM[56]. They also showed that none of the patients with 3 or more lesions and a DFI of less than 1 year were cured by surgery, suggesting that medical management alone should be considered for these patients.

**** Minor Essential Revisions: 1. Some typos and grammar error should be improved by English-writing expert. 2. Some reference number is missing in the manuscript. For example, Onaitis et al. reported that a DFI of less than 1 year was an independent predictor of recurrence.***

Thank you for your meticulous review. Since you pointed out, we got our manuscript improved by an English-writing expert and we believe that this revised manuscript has been much improved. We also checked if there is another missing reference number in the manuscript and corrected them.

From Reviewer #2

**** Overall the manuscript is well written, however, there are many grammatical and tying errors. Below are some I have picked up, but I do recommend to have this paper undergo English Editing prior to be considered for publication. Page 4, line 3 (first line of 2nd paragraph): Why PM should NOT be offered for a solitary, slowly growing etc etc LM? Is it a typing error to say PM should be offered? Page 5, 2nd paragraph line 3, NCCN as follow --> NCCN as the following? Page 16, 2nd paragraph line 2, have bee --> have been Page 16, 2nd paragraph line 3, may have --> may had***

Thank you for your kind comments. Since you pointed out, we got our manuscript improved by an English-writing expert and we believe that this revised manuscript has been much improved. Thank you.