Date 14/05/2018

To Fang-Fang Ji

World Journal of Gastrointestinal Oncology

Re Manuscript ID: 39386

Title: **Pancreatic, periampullary and biliary cancer with liver metastases: should we consider resection in selected cases?**

Dear Fang-Fang Ji,

Thank you to the reviewers for your review and feedback on our manuscript. We have taken your comments into consideration and made necessary changes as summarised below. Please find enclosed a revised manuscript with tracked changes to indicate revisions.

With kind regards,

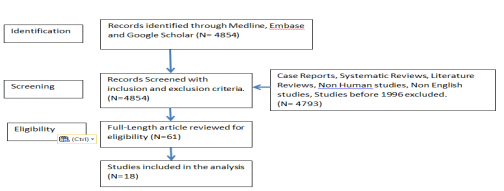
Timothy Price

Editor's feedback	Response
When you are ready to resubmit your revised paper and all required accompanying documents (listed below), you can begin the uploading process via the F6Publishing system. (1) 39386-Revised Manuscript (2) 39386-Answering Reviewers (3) 39386-Audio Core Tip (4) 39386-Biostatistics Review Certificate (5) 39386-Conflict-of-Interest Disclosure Form (6) 39386-Copyright License Agreement (7) 39386-Approved Grant Application Form(s) or Funding Agency Copy of any Approval Document(s) (8) 39386-Non-Native Speakers of English Editing Certificate (9) 39386-Video (10) 39386-Image File (11) 39386-PRISMA 2009 Checklist (12) 39386-Supplementary Material	- Our paper is a literature review. The data and studies available were too small and heterogeneous for a systematic review to be carried out We have added (1) 39386-Revised Manuscript (2) 39386-Answering Reviewers (3) 39386-Conflict-of-Interest Disclosure Form (4) 39386-Copyright License Agreement (6) have followed PRISMA 2009 Our review did not require any special grant or funding. It doesn't contain any video. We did not include biostatics as it was a literature review.
Reviewer 1, ID 03271124	
1. For the pancreatic cancer, there are a number of studies about the palliative adjuvant therapy with comparable overall survival rate with the liver resection series. This issue should be described in this review.	In few case series of liver metastasectomy, the median overall survival was comparable in the patients who under underwent liver resection to that achieved with the standard chemotherapy regimen for stage 4 PDAC without surgery. (added in discussion)
2. The manuscript contain some of the misinterpretation of the reference articles. For example, Wakai et al [70]. the study enrolled the patient with gallbladder and extra-hepatic cholangiocarcinoma who underwent hepato-	Dear Reviewer, Unfortunately we do not have enough data for gall bladder, intra hepatic and extrahepatic cholangiocarcinoma individually. We have compiled

pancreatoduodenectomy not the bile duct cancer with liver metastasis. These type of cancer have different nature from the liver metastases from bile duct cancer.	all the data together in the section of biliary tract cancer. We do agree on our study limitation.
3. The chemotherapy in the future section, is there any new modality of treatment or the new ongoing trial for the pancreatic cancer and biliary tract cancer? Currently, there are a lot of data about this topic to be discussed in this part.	Systemic Therapy in the future Recent progress in systemic therapy may play a role in increasing surgical options. In particular for pancreatic cancer response rates have increased from under 10% to now over 30% in some trials. FOLFIRINOX and gemcitabine with nab paclitaxel have substantial activity in metastatic PDAC with response rate of 31% and 23%. Furthermore, these regimens may convert a substantial number into resectable tumours. Few case series have demonstrated efficacy of these regimen in locally advanced and borderline resectable pancreatic cancer. With FOLFIRINOX, overall response rate reported range from 30 to 50%, resection rates 40-50% with 40-90% having R0 resection. In similar patient groups gemcitabine and nab paclitaxel, has a response rate of 30% with resection rate of 56% and R0 resection rate of 80%. New treatment modalities are being evaluated using genomics-driven precision medicine for advanced pancreatic ductal carcinoma. COMPASS is a prospective study which showed that patients with an 'unstable' genomic subtype responded well to m-FOLFIRINOX while tumours that displayed basal-like RNA expression signature were chemotherapy resistant. Pancreatic cancer tissues have a higher expression of CD40 as compared to adjacent normal tissues. A combination of CD40 agonist antibody with gemcitabine showed tumour regression in advanced PDAC with liver metastasis. Similarly in biliary tract cancer, gemcitabine and cisplatin is now the treatment of choice in metastatic setting with response rate of 36%. A retrospective analysis also evaluated the activity of gemcitabine-platinum-based regimen in 37 locally advanced gall bladder cancer patients showing an overall response rate (ORR) of 67.5% with 17 patients (46%) that underwent R0 resection. Unlike pancreatic cancer, clinical data have suggested an encouraging future for targeting checkpoint pathways in biliary tract tumours. A phase 1b trial using PDL1 inhibitor monotherapy for PDL1 positive advanced biliary tract cancers (BTC) demonstrated modest antitumor activity with an overall response rate of 17.4% with 4 patients having a partial response. An additional group of BTC with mismatch-repair deficiency have shown impressive durable responses with checkpoint inhibitor therapy in a phase 2 study. 4 cases of BTC had an objective response in 71% and PFS in 67% of these patients to pembrolizumab. There are clinical trials that are using combination

	immunotherapy or immunotherapy with chemotherapy in advanced biliary tract cancers. Like pancreatic cancer, genomic alterations in BTC may serve as biomarkers in predicting response to chemotherapy and immunotherapy.
4. The summary of the prognostic factor that affecting survival especially in the biliary and Ampullary cancer from the study of Adam et al [13], Groeschl et al [81], and lendoir et al [82] were from the all population with non-colorectal and non-neuroendocrine liver metastasis not only biliary tract and Ampullary cancer. This could mislead to the readers.	We have removed this paragraph
5. The data in the biliary tract were not sufficient to summary because of the very small population. Although the Adams et al. contained large number of the population study, the biliary tract and Ampullary cancer patients are only 28 patients. Kurosaki et al. and De Jong et al. studies are only 13 and 15 patients respectively.	We do agree and we have also mentioned this in our review. Adams et al. [13], Kurosaki et al. [47] and De Jong et al. [48] revealed that liver metastasis from duodenal- or ampullary-origin tumour was accompanied by improved survival after surgery as compared with that from pancreaticobiliary tumour with an impressive 5-year overall rate of 46%. This needs to be interpreted with caution due to small study population in each study. However this finding seems to reflect the differences in the behaviour of the primary tumour with periampullary cancers having better prognosis than pancreatic cancers.
6. What is the use of liquid biopsies and assessment of ctDNA that you state in the conclusion? This issues are not discussed in the main text.	Added in the biomarker section Recently, pharmacogenomics profiling of circulating tumour and invasive cells (CTICs) isolated from patients with PDAC was evaluated as a predictor of tumour response, progression, and resistance. As 95% of PDACs harbor KRAS mutations (mKRAS), circulating tumour DNA (ctDNA) has potential utility in this setting. Recent study demonstrated that positive ctDNA KRAS in metastatic disease has been associated with lower PFS and OS. In a study by McDuff et al., undetectable preoperative ctDNA following neoadjuvant treatment for locally advanced pancreatic cancer is associated good surgical outcome. This approach is worthy of further study also in stage 4 setting for incorporating ctDNA with the goal of improving patient selection for surgery.
Reviewer 2, ID 03647581	
1. In result section: "Pancreatic ductal […] of patients to achieve resection" these two paragraph are completely useless. This is a review about surgery for stage IV pancreaticobiliary disease, so please remove all the paragraphs concerning the evolution of treatment of PDAC.	We have removed these paragraphs as advised.
2.while searching on pubmed/embase you missed these two papers: Frigerio et al Ann Surg Oncol. 2017 Aug;24(8):2397-2403 and Lu F et al Chin J Cancer Res. 2015;27(4):358-67.	Dear reviewer, We did look into Lu F et al Chin J Cancer Res. 2015;27(4):358-67. We have mentioned all the case

	series mentioned in this review separately. We did not want to include as this was a literature review and it would have become repetitive. We have taken this article into consideration “Frigerio et al Ann Surg Oncol. 2017 Aug;24(8):2397-2403” and mentioned in our study In a recent retrospective study [43], 24 out of 535 patients achieved complete radiological response of the liver metastatic lesions post neoadjuvant chemotherapy. The chemotherapy administered consisted of single-agent gemcitabine, combination of gemcitabine and nab-paclitaxel or FOLFIRINOX regimen. However in this study, patients did not undergo liver resection. They underwent pancreatic surgery if their liver metastasis fully responded to chemotherapy.
3. Use of gemcitabine as adjuvant chemotherapy and not offering neoadjuvant chemotherapy may have impacted survival outcome". If it is an authors' opinion it should be in the discussion section, if not this needs a reference.	We have removed this from our result section and commented in our discussion.
4. Why biliary tract and ampullary cancer are considered together in the result section? These are completely different disease entities in terms of prognosis. Maybe only pancreaticobiliary carcinomas of the Ampulla of Vater are similar to cholangios. - Similarly to what I have suggested for PDAC, please remove the first three paragraphs in the Biliary tract and ampullary cancer section. These are not consistent with the aim of the paper.	We had to group biliary tract and peri ampullary cancer together due to limited evidence in literature. As advised we have removed first 3 paragraphs.
5. Is the chapter "Prognostic factors affecting survival" referring only to cholangiocarcinomas and ampullary cancer? If not, how do you can rely on data derived from a large (and old, 2006) series including PDAC, cholangios, ampullary? It is like considering apples and pears together. - The only crucial evidence is that metachronous liver resection is better thanks to patients' selection and the use of chemotherapy is even better because avoid useless resections in patients that would risk to have an early recurrence.	We do acknowledge our study limitation. Regrettably, most studies were conducted long time back and did not include chemotherapy as part of neoadjuvant strategy. Also most studies did not include details of utilized chemotherapy regimens and the combination of FOLFIRINOX and metastasectomy has yet to be evaluated.
6. The only crucial evidence is that metachronous liver resection is better thanks to patients' selection and the use of chemotherapy is even better because avoid useless resections in patients that would risk to have an early recurrence. The authors should focus on this.	Multi-institutional prospective trials are required to fully delineate the potential therapeutic utility and operative indications of liver metastasectomy in the setting of modern interdisciplinary management of hepatobiliary tract tumours. The use of neoadjuvant and adjuvant chemotherapy with FOLFIRINOX or combination of gemcitabine and nab Paclitaxel for

	pancreatic cancer and with cisplatin and gemcitabine for gall bladder, cholangiocarcinoma and ampullary cancer should be standardized to avoid confounding results. The disease free interval between PDAC diagnosis and the discovery of a metachronous liver metastases and response to the neoadjuvant treatment may also facilitate the selection of patients with more favourable tumour biology and prognosticate individual patient. Incorporation of genomic profiling in clinical practice should be carried out for improved patient stratification and treatment selection. Furthermore the use of liquid biopsies and assessment of ctDNA may have a major role here in allowing selection of patients with the lowest risk of systemic involvement being considered for surgical intervention
7. The evidence to support liver resection for biliary tract tumour is even more limited because of the rarity, heterogeneous nature of the tumours with different site of origin, the various patterns of recurrence of the disease and high mortality rate associated with procedure." What are the authors talking about? This statement needs a reference.	Have changed to The evidence to support liver resection for biliary tract tumour is even more limited due to the paucity of cases of surgical treatment of biliary carcinoma, the diversity of surgical procedures and the surgical outcomes of the procedure have not been adequately analysed. In all the studies, there was no defined control group and lack of standard chemotherapy may have impacted long term outcome.
Reviewer 3, ID 01191922	
1. The Result Section is tedious and doesn't focus on the key topics. Some paragraphs should be placed in the Introduction and Discussion Sections.	The result section has been modified.
Reviewer 4, ID 00043819	
1. Flow-chart of the literature review should be added	
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3. The possible role of neoadjuvant therapy in metachronous metastases should be discussed.	The use of neoadjuvant and adjuvant chemotherapy with FOLFIRINOX or combination of gemcitabine and nab Paclitaxel for pancreatic cancer and with cisplatin and gemcitabine for gall bladder, cholangiocarcinoma and ampullary cancer with synchronous or metachronous liver metastases should be standardized to avoid confounding results. The disease free interval between primary tumour diagnosis and the discovery of a metachronous liver

	metastases and response to the neoadjuvant treatment may also facilitate the selection of patients with more favourable tumour biology and prognosticate individual patient.

The reviewers recommend updating your manuscript according to the Guidelines and Requirements for Manuscript Revision and the Format for Manuscript Revision for your specific manuscript type: 'Systematic Review'.

Dear Editor,

This is a literature review. We have included the following documents as advised. We have added Revised Manuscript, Answering Reviewers, Conflict-of-Interest Disclosure Form, Copyright License Agreement and have followed PRISMA 2009 checklist. Our review did not require any special grant or funding. It doesn't contain any video. We did not include biostatics as it was a literature review.

Reviewer 1, ID 03271124

1.For the pancreatic cancer, there are a number of studies about the palliative adjuvant therapy with comparable overall survival rate with the liver resection series. This issue should be described in this review.

In few case series of liver metastasectomy, the median overall survival was comparable in the patients who under underwent liver resection to that achieved with the standard chemotherapy regimen for stage 4 PDAC without surgery. (added in discussion)

Refer page 10, paragraph 3, comment CR6

2.The manuscript contain some of the misinterpretation of the reference articles. For example, Wakai et al [70]. the study enrolled the patient with gallbladder and extra-hepatic cholangiocarcinoma who underwent hepato-pancreatoduodenectomy not the bile duct cancer with liver metastasis. These type of cancer have different nature from the liver metastases from bile duct cancer.

Unfortunately we do not have enough data for gall bladder, intra hepatic and extrahepatic cholangiocarcinoma individually. We have compiled all the data together in the section of biliary tract cancer. We do agree on our study limitation.

3. The chemotherapy in the future section, is there any new modality of treatment or the new ongoing trial for the pancreatic cancer and biliary tract cancer? Currently, there are a lot of data about this topic to be discussed in this part.

Systemic Therapy in the future

Recent progress in systemic therapy may play a role in increasing surgical options. In particular for pancreatic cancer response rates have increased from under 10% to now over 30% in some trials.

FOLFIRINOX and gemcitabine with nab paclitaxel have substantial activity in metastatic PDAC with response rate of 31% and 23%. Furthermore, these regimens may convert a substantial number into resectable tumours. Few case series have demonstrated efficacy of these regimen in locally advanced and borderline resectable pancreatic cancer. With FOLFIRINOX, overall response rate reported range from 30 to 50%, resection rates 40-50% with 40-90% having R0 resection. In similar patient groups gemcitabine and nab paclitaxel, has a response rate of 30% with resection rate of 56% and R0 resection rate of 80%.

New treatment modalities are being evaluated using genomics-driven precision medicine for advanced pancreatic ductal carcinoma. COMPASS is a prospective study which showed that patients with an 'unstable' genomic subtype responded well to m-FOLFIRINOX while tumours that displayed basal-like RNA expression signature were chemotherapy resistant.

Pancreatic cancer tissues have a higher expression of CD40 as compared to adjacent normal tissues. A combination of CD40 agonist antibody with gemcitabine showed tumour regression in advanced PDAC with liver metastasis.

Similarly in biliary tract cancer, gemcitabine and cisplatin is now the treatment of choice in metastatic setting with response rate of 36%. A retrospective analysis also evaluated the activity of gemcitabine-platinum-based regimen in 37 locally advanced gall bladder cancer patients showing an overall response rate (ORR) of 67.5% with 17 patients (46%) that underwent R0 resection.

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There are clinical trials that are using combination immunotherapy or immunotherapy with chemotherapy in advanced biliary tract cancers.

Like pancreatic cancer, genomic alterations in BTC may serve as biomarkers in predicting response to chemotherapy and immunotherapy.

Refer page 8, paragraph 3, comment CR4

4. The summary of the prognostic factor that affecting survival especially in the biliary and Ampullary cancer from the study of Adam et al [13], Groeschl et al [81], and lendoir et al [82] were from the all population with non-colorectal and non-neuroendocrine liver metastasis not only biliary tract and Ampullary cancer. This could mislead to the readers.

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Refer page 10, paragraph 1, comment CR9

6. What is the use of liquid biopsies and assessment of ctDNA that you state in the conclusion? This issues are not discussed in the main text.

Added in the biomarker section

Recently, pharmacogenomics profiling of circulating tumour and invasive cells (CTICs) isolated from patients with PDAC was evaluated as a predictor of tumour response, progression, and resistance.

As 95% of PDACs harbor KRAS mutations (mKRAS), circulating tumour DNA (ctDNA) has potential utility in this setting. Recent study demonstrated that positive ctDNA KRAS in metastatic disease has been associated with lower PFS and OS.

In a study by McDuff et al., undetectable preoperative ctDNA following neoadjuvant treatment for locally advanced pancreatic cancer is associated good surgical outcome. This approach is worthy of further study also in stage 4 setting for incorporating ctDNA with the goal of improving patient selection for surgery.

Refer page 9, paragraphs 5-7, comment CR5

Reviewer 2, ID 03647581

1. In result section: "Pancreatic ductal […] of patients to achieve resection" these two paragraph are completely useless. This is a review about surgery for stage IV pancreaticobiliary disease, so please remove all the paragraphs concerning the evolution of treatment of PDAC.

We have removed these paragraphs as advised.

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We did look into Lu F et al Chin J Cancer Res. 2015;27(4):358-67. We have mentioned all the case series mentioned in this review separately. We did not want to include as this was a literature review and it would have become repetitive.

We have taken this article into consideration “Frigerio et al Ann Surg Oncol. 2017 Aug;24(8):2397-2403” and mentioned in our study

In a recent retrospective study [43], 24 out of 535 patients achieved complete radiological response of the liver metastatic lesions post neoadjuvant chemotherapy. The chemotherapy administered consisted of single-agent gemcitabine, combination of gemcitabine and nab-paclitaxel or FOLFIRINOX regimen.

However in this study, patients did not undergo liver resection. They underwent pancreatic surgery if their liver metastasis fully responded to chemotherapy.

Refer page 5, paragraph 1, comment CR3

3. Use of gemcitabine as adjuvant chemotherapy and not offering neoadjuvant chemotherapy may have impacted survival outcome". If it is an authors' opinion it should be in the discussion section, if not this needs a reference.

We have removed this from our result section and commented in our discussion.

4. Why biliary tract and ampullary cancer are considered together in the result section? These are completely different disease entities in terms of prognosis. Maybe only pancreaticobiliary carcinomas of the Ampulla of Vater are similar to cholangios. - Similarly to what I have suggested for PDAC, please remove the first three paragraphs in the Biliary tract and ampullary cancer section. These are not consistent with the aim of the paper.

We had to group biliary tract and peri ampullary cancer together due to limited evidence in literature.

As advised we have removed first 3 paragraphs.

5. Is the chapter "Prognostic factors affecting survival" referring only to cholangiocarcinomas and ampullary cancer? If not, how do you can rely on data derived from a large (and old, 2006) series including PDAC, cholangios, ampullary? It is like considering apples and pears together. - The only crucial evidence is that metachronous liver resection is better thanks to patients' selection and the use of chemotherapy is even better because avoid useless resections in patients that would risk to have an early recurrence.

We do acknowledge our study limitation.

Regrettably, most studies were conducted long time back and did not include chemotherapy as part of neoadjuvant strategy. Also most studies did not include details of utilized chemotherapy regimens and the combination of FOLFIRINOX and metastasectomy has yet to be evaluated.

Refer page 10, paragraph 4, comment CR7

6. The only crucial evidence is that metachronous liver resection is better thanks to patients' selection and the use of chemotherapy is even better because avoid useless resections in patients that would risk to have an early recurrence. The authors should focus on this.

Multi-institutional prospective trials are required to fully delineate the potential therapeutic utility and operative indications of liver metastasectomy in the setting of modern interdisciplinary management of hepatobiliary tract tumours. The use of neoadjuvant and adjuvant chemotherapy with FOLFIRINOX or combination of gemcitabine and nab Paclitaxel for pancreatic cancer and with cisplatin and gemcitabine for gall bladder, cholangiocarcinoma and ampullary cancer should be standardized to avoid confounding results.

The disease free interval between PDAC diagnosis and the discovery of a metachronous liver metastases and response to the neoadjuvant treatment may also facilitate the selection of patients with more favourable tumour biology and prognosticate individual patient. Incorporation of genomic profiling in clinical practice should be carried out for improved patient stratification and treatment selection. Furthermore the use of liquid biopsies and assessment of ctDNA may have a major role here in allowing selection of patients with the lowest risk of systemic involvement being considered for surgical intervention.

Refer page 11, paragraphs 3-4, comment CR10

7. The evidence to support liver resection for biliary tract tumour is even more limited because of the rarity, heterogeneous nature of the tumours with different site of origin, the various patterns of recurrence of the disease and high mortality rate associated with procedure." What are the authors talking about? This statement needs a reference.

Have changed to

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Refer page 10, paragraph 7, comment CR8

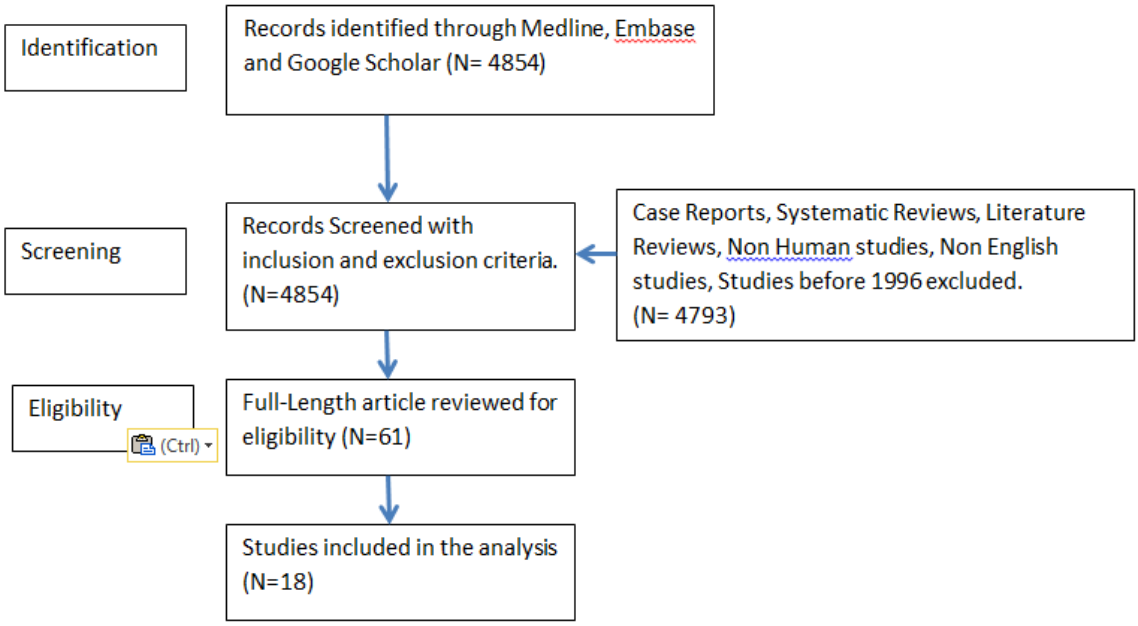
Reviewer 3, ID 01191922

1.The Result Section is tedious and doesn’t focus on the key topics. Some paragraphs should be placed in the Introduction and Discussion Sections.

The result section has been modified.

Reviewer 4, ID 00043819

1.Flow-chart of the literature review should be added



2. The extension of hepatic resection for synchronous metastases and the site of primary pancreatic cancer (head vs tail) should be considered when planning the surgical treatment

For patients with synchronous liver metastasis, most common type of pancreatic resection was pancreatoduodenectomy (n=125) followed by distal pancreatectomy (n=75) and total pancreatectomy (n=27) and most common type of liver resection performed were atypical resection (n=61), wedge resection (n=32) and segmentectomy (n=25) with hepatectomy (n=5) being less common.

Refer page 4, paragraph 5, comment CR2

3. The possible role of neoadjuvant therapy in metachronous metastases should be discussed.

The use of neoadjuvant and adjuvant chemotherapy with FOLFIRINOX or combination of gemcitabine and nab Paclitaxel for pancreatic cancer and with cisplatin and gemcitabine for gall bladder, cholangiocarcinoma and ampullary cancer in setting of synchronous or metachronous liver metastases should be standardized to avoid confounding results.

The disease free interval between primary tumour diagnosis and the discovery of a metachronous liver metastases and response to the neoadjuvant treatment may also facilitate the selection of patients with more favourable tumour biology and prognosticate individual patient.

Refer page 11, paragraphs 3-4, comment CR11