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Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
https://www.wjgnet.com

PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology
Manuscript NO: 34905
Title: Impact of homogeneous pathologic response to preoperative chemotherapy in patients with multiple colorectal liver metastases
Reviewer's code: 02537773
Reviewer's country: Germany
Science editor: Ze-Mao Gong
Date sent for review: 2017-06-22
Date reviewed: 2017-06-25

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] Grade A: Excellent	[Y] Grade A: Priority publishing	Google Search:	[ ] Accept
[ ] Grade B: Very good	[ ] Grade B: Minor language polishing	[ ] The same title	[ ] High priority for publication
[Y] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] Duplicate publication	[ ] Rejection
[ ] Grade D: Fair	[ ] Grade D: Rejected	[ ] Plagiarism	[ ] Minor revision
[ ] Grade E: Poor		[Y] No	[Y] Major revision
		BPG Search:	
		[ ] The same title	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

Overall it's a valuable study with clinically relevant questions. However, there are several major limitations that hamper the definite conclusions in the present form. 1) It's a retrospective study and a large number of factors that are present in personalized everyday patients care are not taken to account 2) The molecular tumor biology is not taken to account (MSI; BRAF; KRAS; number of therapies etc.). 3) Location of the primary tumor is not taken into account. 4) The number of the patients is way too small to address those concerns. To my point of view, the study can still address the differences of homogeneous vs. heterogeneous response- but I doulbt that this study would allow a strong conclusion to PRPC and its values in clinical settings. Several points would be valuable to address in revision: 1) Were the pathologist blinded for the results of the second pathologist? 2) What is the homogeneity/heterogeneity within the single metastasis? 3) What are the differences in BRAF/KRAS mutation status?

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Location of primary tumor? 4) Were the primary tumors resected, and if yes at what time point? 5) What is the correlations between RTG and MD Anderson classification? Could the authors present the data more clearly as simple number presentation as in Table 2. 6) Why P value </= 0.1 is consider as significant risk factor? Please, comment. 7) Ethical statement is missing in methods. Where the study was performed? 8) Figure legends would benefit from more detailed information. 9) The authors do not provide information to resection status? All tumors R0- which is actually the most important factor for curative resection?! 10) It would be great if the authors would include a separate table (or integrate in Table 2) showing/comparing the homogenous and heterogeneous cohorts including all the characteristics and subgroup comparison. 11) The authors use strictly pathological characterization, however, the information to global tumor cancer is missing, as well as radiological classification. No information is provided if patients had stable disease or progressive disease during the observation time. What was the correlation between radiological staging and pathological score? 12) The litigations part need to be expended based on the comments above.

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology
Manuscript NO: 34905
Title: Impact of homogeneous pathologic response to preoperative chemotherapy in patients with multiple colorectal liver metastases
Reviewer's code: 00009760
Reviewer's country: Australia
Science editor: Ze-Mao Gong
Date sent for review: 2017-06-22
Date reviewed: 2017-06-25

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] Grade A: Excellent	[Y] Grade A: Priority publishing	Google Search:	[Y] Accept
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[ ] Grade D: Fair	[ ] Grade D: Rejected	[ ] Plagiarism	[ ] Minor revision
[ ] Grade E: Poor		[Y] No	[ ] Major revision
		BPG Search:	
		[ ] The same title	
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		[Y] No	

COMMENTS TO AUTHORS

This is a useful paper for me. Preoperative chemotherapy, limited response and not prognostic.

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Fax: +1-925-223-8243
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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology
Manuscript NO: 34905
Title: Impact of homogeneous pathologic response to preoperative chemotherapy in patients with multiple colorectal liver metastases
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Reviewer's country: Japan
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CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	Google Search:	[ ] Accept
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COMMENTS TO AUTHORS

The authors evaluated the association between pathologic response of preoperative chemotherapy (PRCP) and survival in patients with colorectal liver metastases using major two classifications, and concluded that homogenous PRCP does not associate with overall survival. I have several concerns about this study. 1. Study population This study includes patients who underwent PRCP and surgery for with at least two liver metastases. However, there is no information about the presence of the other metastases such as lung metastasis or peritoneal dissemination, and please write the criteria of the induction of PRCP in your institute? Besides, it is also important whether these patients underwent the resection of primary tumor or not, because several studies report that it affects to the survival. 2. Evaluated criteria When did you measure these criteria, particularly tumor size? Is it before or after chemotherapy? 3. Endpoints Please write the definition of overall survival. 4. Results 4-1) It is better to change mean follow up to

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median follow up. 4-2) This study includes both synchronous and metachronous metastases together, but the survival is worse in metachronous metastases than that of synchronous metastases. Therefore, subgroup analysis is needed although it does not affect to homogeneity in logistic regression model in this study. 4-3) How did you select the factors to put in logistic regression model? The use of FOLFOX/FOLFIRI should be included. Are there any reason to select the cut-off of 3cm for tumor size and 9 for the number of chemo cycles? Did you put continuous value or dichotomized value in this analysis? The HR of colon cancer and rectal cancer should be opposite but it does not. Please check again. 4-4) In table 2, how did you calculate the rate of site of metastases? It is strange the sum is 100%. And in preoperative chemotherapy section of table 2, FOLFIRI should be combined with Campto or FOLFIRI with or without cetuximab. 4-5) The number of the metastases may affect the homogeneity, because theoretically the more the site to evaluate, the more the chance of heterogeneity increases. (Besides, the more the site of metastases increases the OS gets worse.) 4-6) Please show the statistical power to conclude your results.

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology
Manuscript NO: 34905
Title: Impact of homogeneous pathologic response to preoperative chemotherapy in patients with multiple colorectal liver metastases
Reviewer's code: 03476083
Reviewer's country: France
Science editor: Ze-Mao Gong
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CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
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		[ ] Duplicate publication	
		[ ] Plagiarism	
		[ ] No	

COMMENTS TO AUTHORS

The authors review a cohort of 73 patients undergoing liver resection for colorectal liver metastases after systemic chemotherapy in order to assess the impact of homogeneity of pathological response to chemotherapy on survival and routine management of patients. The pathological response was homogeneous in only one half of patients. Heterogeneity of pathological response did not influence overall survival The authors conclude that pathological response to chemotherapy is not a powerful prognostic factor and do not influence treatment or management in patients with advanced resectable liver metastases. Overall this is a concise and well written manuscript. However a number of issues must be addressed. 1) The definition of heterogeneity of pathological response is not clear and should be clarified. In particular, what is the definition of heterogeneity of pathological response according different histological classifications? 2) The authors claim that that the pathological response did not influence survival and MDT decision in

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routine practice. The data presented did not provide adequate evidence to support this statement. No conclusion can be made from a single centre study about the impact of pathological response on management of patients. The authors did not take into account pathological response but it could be different in another centre. Furthermore the authors have shown that heterogeneity of pathological response had no impact on survival but they can conclude that pathological response is not a prognosis factor. In other word heterogeneous response does not mean absence of response. The authors can made only conclusion about the impact of heterogeneity of pathological response. 3) What is the impact of heterogeneity of pathological response on disease free survival ? 4) The impact of heterogeneity on survival and disease free survival should be analysed in the entire cohort using univariate logistic regression analysis. 5) Abbreviation MDT should be defined