PEER-REVIEW REPORT

Name of journal: World Journal of Clinical Oncology
Manuscript NO: 31675
Title: Recurrence-free survival as a putative surrogate for overall survival in phase III trials of curative-intent treatment of colorectal liver metastases: Systematic review
Reviewer's code: 03253495
Reviewer's country: Italy
Science editor: Fang-Fang Ji
Date sent for review: 2017-01-13
Date reviewed: 2017-01-13

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	Google Search:	[Y] Accept
[Y] Grade B: Very good	[Y] Grade B: Minor language polishing	[ ] The same title	[ ] High priority for publication
[ ] 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	[ ] Major revision
		BPG Search:	
		[ ] The same title	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

The review is OK for me.

PEER-REVIEW REPORT

Name of journal: World Journal of Clinical Oncology
Manuscript NO: 31675
Title: Recurrence-free survival as a putative surrogate for overall survival in phase III trials of curative-intent treatment of colorectal liver metastases: Systematic review
Reviewer's code: 03259512
Reviewer's country: Bosnia and Herzegovina
Science editor: Fang-Fang Ji
Date sent for review: 2017-03-10
Date reviewed: 2017-03-14

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

COMMENTS TO AUTHORS

The authors conducted systematic review and tested the hypothesis that if gains in progression free survival (PFS) predicted gains in overall survival (OS), trials of new drugs in the setting of CRLM could use RFS as a surrogate endpoint, and thus expedite drug development.   The paper is well written, properly designed, and comprehensive. Abstract : authors wrote "5 phase III trials (1,162 patients) were included for analyses…". However, later on page 9 authors wrote: "A total of 1,182 patients were included in this pooled analysis" ;   please clarify the differences.   Original studies were not properly described in the Results section, although the information was presented in the tables. The difference between original studies (the 5 included trials) has to be presented in more details in the text (the use of chemotherapy drugs, gender differences, follow-up periods, etc.)   Some mistprints found : page 12 "metanalysis…", page 24 "elegible…"

PEER-REVIEW REPORT

Name of journal: World Journal of Clinical Oncology
Manuscript NO: 31675
Title: Recurrence-free survival as a putative surrogate for overall survival in phase III trials of curative-intent treatment of colorectal liver metastases: Systematic review
Reviewer's code: 03094792
Reviewer's country: Spain
Science editor: Fang-Fang Ji
Date sent for review: 2017-03-10
Date reviewed: 2017-03-18

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	[ ] The same title	[ ] High priority for
[Y] Grade C: Good	polishing	[ ] Duplicate publication	publication
[ ] Grade D: Fair	[ ] Grade C: A great deal of	[ ] Plagiarism	[ ] Rejection
[ ] Grade E: Poor	language polishing	[Y] No	[Y] Minor revision
	[ ] Grade D: Rejected	BPG Search:	[ ] Major revision
		[ ] The same title	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

It is not clear that you understand by "recurrence" or if all the essays by you analyzed contemplate the term in a similar way. It should be clear whether the term refers exclusively to the local recurrence of the excised metastasis. As it is a metastatic disease, the probability of relapse to other levels is comparatively higher than if we are referring to the local control of a primary tumor. For that reason it is logical that there is a parallelism between PFS and OS and in fact this is proven but it does not have to be so between RFS and OS. It is not clear that patients were excluded due to extrahepatic disease: "Studies were excluded when extra-hepatic disease was present in more than 5%". It should be specified.

PEER-REVIEW REPORT

Name of journal: World Journal of Clinical Oncology
Manuscript NO: 31675
Title: Recurrence-free survival as a putative surrogate for overall survival in phase III trials of curative-intent treatment of colorectal liver metastases: Systematic review
Reviewer's code: 02510166
Reviewer's country: Martinique
Science editor: Fang-Fang Ji
Date sent for review: 2017-03-10
Date reviewed: 2017-03-19

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

COMMENTS TO AUTHORS

The manuscript addresses the important issue of costs of clinical trials. There are minor language syntax errors and non-English expressions, "they imply in a time and resource-consuming methodology", "furthermore when", "follow up is required what adds", etc. Professional editing is advised. Major remark regarding the methods: Conventional regression models make a fundamental assumption that the independent variable ("X-axis") is measured without error. This is not the case in the present study. Table 4 shows that the RFS hazard ratios have large confidence intervals, i.e. considerable errors. The regression should take into account the X-variable errors. Minor remarks: Figure 3 might be misleading. It would be more appropriate to show the horizontal and the vertical confidence bars associated with each of the data points. A graph with the confidence bars would show that a zero-slope regression (i.e. no correlation between RFS and OS) is also compatible with the data. Note that the regression's p-value is attributable to the single extreme outlier. Overall remark: The

manuscript should acknowledge that the predictive value of RFS is questionable, that further studies are required.

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COMMENTS TO AUTHORS

This article investigated RFS as a putative surrogate of OS and found that RFS could work as a putative surrogate of OS in this population avoiding bigger, longer and more resource-consuming trials. The OS could be assumed based on RFS and our model could be useful to better estimate sample size calculations of phase III trials of CRLM aiming for OS. Their research is meaningful to clinical practice. However, there are some sentences to be corrected such as in Introduction the sentence 'furthermore when the primary endpoint include overall survival (OS) of slow progressive malignancies' is confusing. There is no explanation about how the authors get formula: OS HR= (0.93 x RFS HR) + 0.14. As this is a meta-analysis, there should be description about whether the authors adopted fixed model or randomized model.