

PEER-REVIEW REPORT

Name of journal: World Journal of Gastrointestinal Oncology

Manuscript NO: 40131

Title: Prognostic and predictive value of vascular endothelial growth factor receptor 1 and class III β -tubulin in long-term prognosis of non-metastatic rectal cancer

Reviewer's code: 03475590

Reviewer's country: China

Science editor: Fang-Fang Ji

Date sent for review: 2018-06-02

Date reviewed: 2018-06-09

Review time: 7 Days

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language	(High priority)	<input type="checkbox"/> Anonymous
<input checked="" type="checkbox"/> Grade C: Good	polishing	<input checked="" type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of	(General priority)	Peer-reviewer's expertise on the
<input type="checkbox"/> Grade E: Do not	language polishing	<input type="checkbox"/> Minor revision	topic of the manuscript:
publish	<input type="checkbox"/> Grade D: Rejection	<input type="checkbox"/> Major revision	<input type="checkbox"/> Advanced
		<input type="checkbox"/> Rejection	<input checked="" type="checkbox"/> General
			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

The study assess the long-term prognostic and predictive value of VEGFR1 and TUBB3 mRNA expression in non-metastatic rectal cancer and get positive results, which might serve as a potential prognostic factor. There are some questions for author: 1. Why choose



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determine the "mRNA" of VEGFR1 and TUBB3 rather than others? 2. The result indicated that the expressions of VEGFR1 and TUBB3 were positively correlated. The authors should discuss possible underlying mechanisms. 3. The results indicated that a favorable OS in both low expression of VEGFR1 and TUBB3 was noted as compared to others. The authors should discuss possible underlying mechanisms.

INITIAL REVIEW OF THE MANUSCRIPT

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- ☐ The same title
- ☐ Duplicate publication
- ☐ Plagiarism
- ☐ No

BPG Search:

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Manuscript NO: 40131

Title: Prognostic and predictive value of vascular endothelial growth factor receptor 1 and class III β -tubulin in long-term prognosis of non-metastatic rectal cancer

Reviewer's code: 03726737

Reviewer's country: South Korea

Science editor: Fang-Fang Ji

Date sent for review: 2018-06-15

Date reviewed: 2018-06-21

Review time: 5 Days

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language	(High priority)	<input checked="" type="checkbox"/> Anonymous
<input checked="" type="checkbox"/> Grade C: Good	polishing	<input type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of	(General priority)	Peer-reviewer's expertise on the
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publish	<input type="checkbox"/> Grade D: Rejection	<input type="checkbox"/> Major revision	<input type="checkbox"/> Advanced
		<input type="checkbox"/> Rejection	<input checked="" type="checkbox"/> General
			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

Overall, this study is well-evaluated the association between the expression of VEGFR1 and TUBB3 and overall survival in patients with non-metastatic rectal cancer. This research has discrimination because of using multiplex branched DNA liquid-chip

technology for the expression of VEGFR1 and TUBB3. However, this study has several weak points. 1. This study showed the correlation between the expressions of VEGFR1 and TUBB3, and those markers had positive correlation ($P = 0.006$, $r = 0.315$). Isn't it weak correlation by the Spearman's correlation test? 2. In the Discussion section, page 10, "Tsai et al. reported that the overexpression of VEGF is a significant negative predictor of early postoperative relapse in stage I-III colorectal cancer patients, leading to poor OS" had a vague expression. I think that the overexpression of VEGF is a positive predictor of early postoperative relapse, instead of negative predictor. A "negative predictor of overall survival" is a right expression, but "negative predictor of early relapse" is vague. 3. In the Discussion section, page 10, "A previous study evaluated the VEGF expression of 117 colorectal adenocarcinoma patients, and confirmed that lymph node metastasis (negative vs. positive, $P < 0.001$) and TNM stage (stage III vs. I/II, $P < 0.001$) were related to increased VEGF expression" had also a vague expression. The "positive vs. negative" is a comfortable expression than "negative vs. positive" when matched with "TNM stage (stage III vs. I/II, $P < 0.001$)".

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[] Plagiarism

[Y] No

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Manuscript NO: 40131

Title: Prognostic and predictive value of vascular endothelial growth factor receptor 1 and class III β -tubulin in long-term prognosis of non-metastatic rectal cancer

Reviewer's code: 00600507

Reviewer's country: Denmark

Science editor: Fang-Fang Ji

Date sent for review: 2018-06-15

Date reviewed: 2018-06-21

Review time: 5 Days

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			<input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

General Comments It seems like the authors do not distinguish sufficient between prognostic and predictive. When applying these definitions in the current study it is important to have in mind that 66 (88%) of the patients have been treated with 5-FU



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based chemotherapy, which will confound your prognostic data. What you have investigated in your study is mainly the predictive properties of VEGFR1 and TUBB3 in relation to 5-FU based chemotherapy, which will require that the manuscript is corrected. Below please find the general accepted definition of a prognostic and predictive biomarker: a. A prognostic biomarker is a baseline characteristic that categorizes patients by degree of risk for disease occurrence or progression of a specific aspect of a disease. A prognostic biomarker informs about the natural history of the disorder in that particular patient in the absence of a therapeutic intervention. b. A predictive biomarker is a baseline characteristic that categorizes patients by their likelihood of response to a particular treatment relative to no treatment. A predictive biomarker can be used as an enrichment strategy to identify a subpopulation likely to respond to a treatment intervention in a particular way. It may predict a favorable response or an unfavorable response.

Specific Comments **Multiplex branched DNA liquidchip (MBL) technology:** Please briefly describe how the assays was validated before applied in the current study. **Statistical analysis:** The p-values seems to be reported without adjustment for multiplicity. Please explain. **Patient characteristics:** As the cut-off's for both VEGFR1 and TUBB3 is based on the same patient population as you apply these values on there is a great risk of overfitting. The data you have generated in your study can only be regarded as hypothesis generating, which must be stated in the abstract and the main text of the manuscript. **Discussion:** Please discuss the sensitivity and specificity data for your biomarkers. For VEGFR1 the sensitivity is only 44,1% (Figure 1).

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