

PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 35255

Title: Relationship between pancreatic cancer autophagy and perineural invasion, clinicopathological features and prognosis

Reviewer's code: 00068723

Reviewer's country: Japan

Science editor: Li-Juan Wei

Date sent for review: 2017-08-17

Date reviewed: 2017-08-18

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

COMMENTS TO AUTHORS

The authors investigated perineural invasion and autophagy of pancreatic cancer. They concluded that autophagy was related with perineural invasion, and poor prognosis. The results were rationale. But photos were not clear enough to confirm the results. LC3 immunohistochemical score should be presented in figures. Darkness and color of A and B were different. It was not appropriate to evaluate with photos with different conditions. Neural tissues of C and D were not clear. Please change the photos to those that would show perineural invasion more clearly. In D, what was the tissues that were positive? Discussion. First and second paragraphs of discussion were repeats of Introduction. Discussion. Please speculate the rationality of relationship among perineural invasion, autophagy, and poor survival in more detail.

PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 35255

Title: Relationship between pancreatic cancer autophagy and perineural invasion, clinicopathological features and prognosis

Reviewer's code: 03271124

Reviewer's country: Thailand

Science editor: Li-Juan Wei

Date sent for review: 2017-08-18

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CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input checked="" type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input type="checkbox"/> Plagiarism	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		<input checked="" type="checkbox"/> No	<input type="checkbox"/> Major revision
		BPG Search:	
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input checked="" type="checkbox"/> No	

COMMENTS TO AUTHORS

Dear Authors, This well design study demonstrated the relationship between pancreatic cancer autophagy and PNI which is one of the poor risk factor for pancreatic cancer. There are no previous reports about this topic. This is my comments. 1. There are many various poor prognostic factors for pancreatic cancer such as vascular invasion, lymph node metastasis. Why PNI are the only important factor for autophagy? 2. From the introduction part, you mentioned that "The incidence of perineural invasion (PNI) in pancreatic cancer is 80-100% and is an important factor leading to postoperative pancreatic cancer recurrence." And "Autophagy, as a mechanism of anoikis avoidance in pancreatic cancer, is closely related to the survival of pancreatic cancer cells". That's mean almost all of pancreatic cancer patients have this poor prognostic factors (PNI) and the patients who have autophagy show poor prognosis. What is the reason to find the relationship of the autophagy in pancreatic cancer to PNI? 3. In the discussion part,

you explained "This study found that high expression of LC3 was present in the cancer nests around the nerve infiltration (Fig.1 E), consistent with the discovery of Yang[8]. In histology terms, it has been suggested that high LC3 expression is related to PNI. Further analysis of immunohistochemistry showed that there was a significant positive correlation between LC3 expression and PNI in pancreatic cancer tissues. Therefore, we speculated that, in the PNI process, a high autophagy level may assist cancer cells in escaping apoptosis, avoiding the damage of adverse stress and providing energy for the invasion and metastasis of pancreatic cancer". Is there any others evidence to support this mechanism? Because you mentioned that in the aim of the study "this study focused on the relationship between pancreatic cancer cell autophagy and PNI, clinicopathological features and prognosis and provides a clinical basis for further study of the autophagy mechanisms affecting the pathogenesis of pancreatic cancer PNI." 4. From previous study show lymph node metastasis and large tumor size is the poor prognostic factor (Tarantino et al, Br J Surg 2017, Marchegiani et al. Ann Surg 2017). Do you have any comment why this factor is not the independent factor for survival in this study? 5. Is there any limitations in this study? 6. In the PNI judging part, you mentioned that "According to previous reports, a positive PNI status was determined as cancer cells being found in the perineural spaces, perineurium or nerve tract". But there is no reference. 7. In discussion part, "At present, previous pancreatic cancer studies have suggested that PNI is the main cause of abdominal pain in patients and is also one of the important causes of difficult radical operation and local recurrence of pancreatic cancer [5]". Is this reference correct?

PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 35255

Title: Relationship between pancreatic cancer autophagy and perineural invasion, clinicopathological features and prognosis

Reviewer's code: 03538158

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Science editor: Li-Juan Wei

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

COMMENTS TO AUTHORS

1. In abstract section, Is UCH a ubiquitin carboxy terminal hydrolase? 2. Authors should show the control staining and the normal pancreatic tissues stained by LC3? 3. Authors should show LC3-I and LC3-II by western blotting.

PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 35255

Title: Relationship between pancreatic cancer autophagy and perineural invasion, clinicopathological features and prognosis

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<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input type="checkbox"/> Rejection
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		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input type="checkbox"/> No	

COMMENTS TO AUTHORS

This is a retrospective study to evaluate the relationship between pancreatic cancer autophagy and perineural invasions. The authors concluded that autophagy and perineural invasions were significantly associated to pancreatic cancer progression. This was well written, but there were several points to be clarified. Major comments 1. In figure 1C, D and E, please indicate which part is the perineural invasion by using arrows. 2. As shown in Figure 2, overall survival in LC3 low expression and PNI absent patients was surprisingly high over 50%, even though both groups have stage III and IV patients. I would concern about too much censor in both groups. The authors should explain and discuss about this point. Minor comments General data 1. Please provide about the post-operative adjuvant therapy. 2. What kind of informed consent did patients provide? About surgery or participating this study? 3. Please provide the number of IRB approval. Results 1. The word, "high autophagy rate", is not defined in the materials



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and methods. Please provide its definitions. 2. In survival analysis, the risk of death was 2.78-times higher both in the LC3 high-expression group and in the PNI-positive group. Please provide how to calculate 2.78. Please re-confirm that the number is same in both situations. Discussion 1. The relationship between PNI and LC3 is the most important issue in this manuscript. Please discuss about “Chicken or Eggs” problem. Is autophagy the result of PNI? Or does PNI induce autophagy? Table 1. In table 3 and 4, please spell out B, S.E., Wals., Sig., and Exp(B) in the legend. 2. In table 5, please provide the meaning of hazard ratio in each category. For example, in sex category, male vs female or female vs male?