Authors Response to Reviewer 00506106's Comments

This is a retrospective study, but the data and information are important to us. The paper is well written too.

- We appreciate your time for reviewing our manuscript. Thank you.

Authors Response to Reviewer 00058446's Comments

The paracrine and neuroendocrine responses caused by surgical stress could promote tumor metastasis through direct action on residual malignant cells and by suppressing natural killer (NK) cell activity. Postsurgical pain could activate the sympathetic nervous system (SNS), leading to catecholamine secretion which directly inhibits NK cells, and downregulation of immunity after surgery is known to peak at postoperative day 3. This is a very interesting issue, but the association between postoperative pain control and oncologic outcomes in resected pancreatic ductal adenocarcinoma was not evaluated clearly.

1. The definition of "good pain control group" and "poor pain control group" should be clear standard.

▶ In the current study, definition used for "good pain control group" was patients whose late pain intensity was lower than that of early pain intensity and for "poor pain control group" was patients whose late pain intensity was the same or higher than the early pain intensity. Garimella et al.[1] have suggested that satisfaction score should be considered along with pain scoring tool in order to reassess adequate pain control. Since this was a retrospective review and the medical records were not collected for the study purpose, limitations are present in making our definition of pain control group a clear standard. We have modified our definition in terminology of comments section for more clarification and included limitations of the definition in discussion as following:

(Page 14-15) **Terminology**

PD group: Patients underwent pancreaticoduodenectomy or pylorus-preserving pancreaticoduodenectomy. DP group: Patients underwent distal pancreatectomy. Good pain control group: Patients whose late pain intensity was lower than that of early pain intensity. Poor pain control group: Patients whose late pain intensity was the same or higher than the early pain intensity. Early pain intensity: Mean of all pain scores reported on POD 1, 2, and 3. Late pain intensity: Mean of pain scores reported on POD

5 and 7. Pain scores: Measurement of numerical rating scale (NRS) pain intensity score. 11-point NRS with the score ranging from 0 to 10 was used to evaluate pain intensity whenever the patients reported pain. Patients were instructed to rate 0 as "no pain at all" and 10 as "the worst possible pain".

(Page 12) In addition, our definition of pain control groups may not fully represent pain control state. There have been reports of using satisfaction score along with pain score in fully assessing adequate pain control[1,2]. In determining pain control state, we were limited to the use of NRS pain intensity. Further studies with assessment of satisfaction score and refined definitions for pain control groups should be undertaken.

2. Is the impact of postoperative pain control related with the method of pain control?

▶ It has been reported that opioids are the backbone of postoperative pain control[3]. However, more evidences support a multimodal approach[1] and evaluation of pain control method was limited due to retrospective design of current study. While the method of pain control in postoperative pain control was not the focus of this study, we have evaluated the role of IV PCA and epidural PCA in impact of postoperative pain control without significant results. Unfortunately, this result was based on limited data on disconnect timing of PCA and information on type and/or amount of pain control methods administered was also limited. Therefore, the results were not reported. In order to better answer the reviewer's comments, we believe further study with well-designed pain control protocol should be in order. We have added following sentences in discussion to address the concern.

(Page 13) The complex interaction of pain, opioids, non-opioid analgesics, and their net effect on immunosuppression, which might have impacted oncologic outcome, was not

assessed in this study. However, relationship between pain control method and postoperative pain control should be investigated further with a well-designed pain control protocol.

3. What is the major reason of poor postoperative pain control in left-sided pancreatic cancer?

▶ In our results, there were no significant differences in any clinicopathologic factors between the good pain control group and poor pain control group in left-sided pancreatic cancer. While previous studies have suggested that poor pain response can be a result of patient-specific immune state before surgery, a sign of ongoing or forthcoming complications or a contributory effect of perioperative psychological factors, we were not able to control factors related to the physical pain control due to lack of a specific pain control protocol. Therefore, we can only speculate that inadequate pain control was the major reason for poor postoperative pain control. Further study should include establishment of appropriate pain control protocol to minimize influence of inadequate pain control and evaluate whether there are other possible reasons for poor postoperative pain control in left-sided pancreatic cancer. We have addressed the reviewer's comment as following in discussion:

(Page 11) Since there were no significant differences in any clinicopathologic factors between the good pain control group and poor pain control group undergoing DP (Table 2), we can only speculate that inadequate postoperative pain control was the major reason for poor postoperative pain control in left-sided pancreatic cancer. Further study should include establishment of appropriate pain control protocol to minimize influence of inadequate pain control and evaluate whether there are other possible reasons for poor postoperative pain control in left-sided pancreatic cancer.

References

1 Garimella V, Cellini C. Postoperative pain control. *Clinics in colon and rectal surgery* 2013; **26**: 191-196 [DOI:10.1055/s-0033-1351138]

2 Farooq F, Khan R, Ahmed A. Assessment of patient satisfaction with acute pain management service: Monitoring quality of care in clinical setting. *Indian journal of anaesthesia* 2016; **60**: 248 [DOI:10.4103/0019-5049.179450]

3 Lovich-Sapola J, Smith CE, Brandt CP. Postoperative pain control. *Surgical Clinics of North America* 2015; **95**: 301-318 [DOI:10.1016/j.suc.2014.10.002]

Authors Response to Reviewer 01191922's Comments

The study evaluated the association between postoperative pain control and oncologic outcomes in resected PDAC. The results showed that poor pain control was an independent risk factor for both DFS and OS in resected left-sided pancreatic cancer, but not in patients received PD. This is very interesting. Minor revisions are needed before publication of this well written manuscript. In univariate analysis, intraoperative transfusion, positive lymph node status, greater tumor diameter (≥3 cm), and poor pain control were identified as prognostic factors for predicting DFS in resected left-sided pancreatic cancer. For OS, longer operation time (≥300 min), positive lymph node status, greater tumor diameter (≥3 cm), multivisceral resection, not receiving adjuvant treatment, and poor pain control were significant prognostic factors in univariate analysis. The multivariable Cox proportional hazards regression model included all of the categorized patient, resection, and tumor characteristics with log-rank P-values ≤ 0.150. While Table 4 listed only significant factors including positive lymph node status, greater tumor diameter (≥3 cm), not receiving adjuvant treatment, and poor pain control.

It would be better if the authors list the Exp (?), 95% CI and p values for other significant factors in univariate analysis in Table 4.

▶ We appreciate your comment and we have modified Table 4 to include all significant factors in univariate analysis. Calculations were performed using Medcalc. Following changes were made.

(Page 7) Statistical analyses were performed using SPSS 20.0 for Windows (SPSS Inc., Chicago, IL, USA) and MedCalc 16.8.4 for Windows (MedCalc Inc., Mariakerke, Belgium)

Table 4 Univariate and multivariate Cox regression analysis of factors affecting disease-free survival and overall survival after distal pancreatectomy

	Disease-free survival	Overall survival

Variables	Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis		
	Exp (ß)	95% CI	*P*-value	Exp (ß)	95% CI	*P*-value	Exp (ß)	95% CI	*P*-value	Exp (ß)	95% CI	*P*-value
Positive lymph node status	2.183	1.162-4.101	0.011	2.259	1.150-4.437	0.018	2.105	1.094-4.053	0.020	2.501	1.218-5.134	0.012
Tumor size (≥3 cm)	1.943	0.999-3.781	0.028	2.215	1.130-4.341	0.021	2.030	1.016-4.055	0.023	2.662	1.282-5.529	0.009
No adjuvant treatment	1.742	0.800-3.794	0.094	2.468	1.196-5.093	0.015	2.205	0.981-4.955	0.017	4.649	2.124-10.172	<0.001
Poor pain control	2.934	1.158-7.430	0.001	4.157	1.938-8.915	<0.001	2.915	1.156-7.350	0.001	4.741	2.214-10.153	<0.001
Age (≥65 years)	ND			ND			1.608	0.844-3.064	0.150	1.706	0.799-3.640	0.167
Sex (Male)	0.632	0.338-1.181	0.136	0.614	0.318-1.186	0.146	ND			ND		
Operation time (≥300 min)	ND			ND			1.949	0.981-3.873	0.035	1.890	0.923-3.868	0.082
Intraoperative transfusion	2.788	0.903-8.612	0.005	1.745	0.688-4.425	0.241	2.159	0.729-6.396	0.056	1.986	0.750-5.257	0.167
Multivisceral resection	1.720	0.769-3.849	0.111	1.166	0.532-2.557	0.701	2.046	0.837-5.006	0.043	1.273	0.563-2.876	0.562

CI: Confidence interval; ND: Not determined due to lack of significance

We would like to express sincere thanks to all of the reviewers for showing interest and providing important comments that have improved our manuscript. We have done our best to respond to all comments and suggestions offered by the reviewers in order to improve the presentation of our manuscript.