

July 23, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 4018 -edited.doc).

**Title:** Laparoscopic versus Open Distal Pancreatectomy for Solid Pseudopapillary Tumor of the Pancreas

**Author:** Ren-Chao Zhang, Jia-Fei Yan , Xiao-Wu Xu, Ke Chen, Harsha Ajoodhea, Yi-Ping Mou

**Name of Journal:** *World Journal of Gastroenterology*

**ESPS Manuscript NO:** 4018

The manuscript has been improved according to the suggestions of reviewers:

1.Format has been updated.

2. Revision has been made according to the suggestions of the reviewer

(1) **Reviewer1:**

The Authors compare outcome of patients with a rare disease, solid pseudopapillary tumors of the pancreas, who underwent laparoscopic pancreatectomy vs an historical group of patients who had undergone open pancreatectomy. Surgery included distal pancreatectomy with or without splenectomy and central pancreatectomy. Laparoscopic distal pancreatectomy resulted in faster postoperative stay whereas mortality, morbidity and long-term results were similar in both groups. Moreover, there was no difference in both early and late results after open or laparoscopic central pancreatectomy. The topic is interesting, and despite the rarity of this disease, the study includes a large series of patients. However, there are some limitations in the manuscript.

1) The main problem is the retrospective nature of the study that includes two different periods of time, and two types of operation: so, it is difficult to compare patients operated with different techniques and surgeons' preferences.

**Answer:** In our study, all operations were performed by four experienced surgeons using

our institution's standardized technique. We revised the manuscript that the study was just limited to patients underwent distal pancreatectomy for the better comparability.

2) The number of patients operated with central pancreatectomy (n=8) is too small to draw any conclusion. I think the study should be limited to patients operated only with distal pancreatectomy (n= 29).

**Answer:** According to the suggestion, we revised the manuscript that the study was just limited to patients underwent distal pancreatectomy. Moreover, one patient with liver metastasis and colon cancer was excluded from the study for the better comparability between laparoscopic and open groups.

3) Long term functional results were evaluated only by simple clinical examination. However, more specific laboratory investigations could better evaluate exocrine (i.e., fecal elastase or chymotrypsin) and endocrine (oral glucose tolerance test) before and after operation.

**Answer:** This is where we felt pity. In this retrospective study, most of the cases had not received the tests of pancreatic exocrine (i.e., fecal elastase or chymotrypsin) and endocrine (oral glucose tolerance test) before the operation. It was hard to make conclusion from these tests. Therefore, we selected the fasting blood glucose level (normal range  $\leq 110$  mg/dL) for evaluating pancreatic endocrine function and the clinical evaluation including diarrhea, weight loss, and fatty stools for assessing the pancreatic exocrine function. Recently, our center became to use fecal elastase and oral glucose tolerance test to evaluate pancreatic exocrine and endocrine function. I believe that we will get more accurate result some years later.

4) It is unclear which operation (laparoscopic or open pancreatectomy) was performed for the patient who had a recurrent tumor and for the patient with liver metastasis and colon cancer. Did they receive chemotherapy?

**Answer:** The patient experienced recurrence underwent open distal pancreatectomy. She refused the chemotherapy. She was treated by traditional Chinese medicine.

The patient with liver metastasis and colon cancer was treated by open distal

pancreatectomy , liver nodule biopsy and liver nodules anhydrous alcohol injection, partial resection of sigmoid colon and descending colon. She received postoperative adjuvant chemotherapy with 5-fluorouracil、 mitomycin C、 calcium leucovorin for 3 times and transarterial chemoinfusion for 4 times.

**(2) Reviewer 2:**

**Major comments:** #1. Pancreatic SPT has already been reported in several journals, and the features of pancreatic SPT in diagnostic imaging and pathology are well known. Although the authors reported short-and long-term outcomes of laparoscopic versus open surgery for SPT arising from the distal pancreas, the clinical background and exclusion criteria of patients in this study are hard to understand. The authors should clarify the exclusion criteria. Did the authors select patients determined by only arising portion of SPT as exclusion criteria?

**Answer:** For the better comparability, we revised the manuscript that the study was just limited to patients underwent distal pancreatectomy. Of the 55 patients, we retrieved 29 patients underwent distal pancreatectomy. 1 patient with liver metastasis and colon cancer was excluded from the study. 28 patients were included in this study. These changes have been made in the revised manuscript.

#2. Was the lymph node dissection performed to the all patients in this study? Although the authors describe that all patients had negative surgical margin at final pathology, are there no infiltration to the adjacent organs?

**Answer:** All patients underwent lymph node dissection. Even the incidence of lymph node metastasis in SPT is rare, but some studies showed lymph node metastasis in SPT and indicated a relationship between lymph node positivity and recurrence [1、 2 ]. Therefore, we routinely performed lymph node dissection in SPT. No tumor was found infiltration to the adjacent organs. The detail of pathological result has been added into the revised manuscript.

[1] Kang CM, Kim KS, Choi JS, Kim H, Lee WJ, Kim BR. Solid pseudopapillary tumor of the pancreas suggesting malignant potential. *Pancreas*. 2006; 32: 276–280.

[2] Adamthwaite JA, Verbeke CS, Stringer MD, Guillou PJ, Menon KV. Solid

pseudopapillary tumour of the pancreas: diverse presentation, outcome and histology. JOP. 2006;7: 635–642.

#3. Did the authors include one patient with SPT who had metastasis at the initial operation in this study? Did the authors indicate that “1 case of liver metastasis(Page8, Line2)” and “A 16 year-old female (Page8, Line27)” are same patient? If so, (perhaps this patient may have no recurrence in this study period), is there the necessity of including this patient to compare the outcome of laparoscopic versus open surgery for SPT?

**Answer:** “1 case of liver metastasis” and “A 16 year-old female” is the same patient. According to the suggestion and carefully consideration, this patient with liver metastasis and colon cancer was excluded from the study for the better comparability between laparoscopic and open groups. These changes have been made in the revised manuscript.

#4. In Discussion section, the authors specifically described the needle biopsy of the pancreatic SPT. In this study, the authors describe that 18 patients underwent laparoscopic pancreatectomy without biopsy. Nevertheless, there is the possibility of the tumor cell spread; needle biopsy was often performed to the patients. How many patients received preoperative needle biopsy in this study? Is there the necessity of needle biopsy in these patients?

**Answer:** In our study, no patient received preoperative needle biopsy. Owing to the availability of high-resolution medical imaging , we believe that needle biopsy is not necessary for these patients.

#5. The authors describe about the perineural invasion of SPT in Result section (Page8, line2) and the recurrence of SPT in Discussion section(Page11, line23-30). Did the authors examine the pathological malignant features of SPT reported in the previous studies[1]? According to the WHO, criteria that could distinguish potentially malignant tumors, classified as SPT carcinomas, included the following: (1) perineural invasion, (2) angioinvasion, (3) deep invasion into the surrounding tissue, and (4) distant metastasis. Were the tumors classified as SPT carcinomas included in this study? [1] Kim CW, Han DJ, Kim J, Kim YH, Park JB, Kim SC. Solid pseudopapillary tumor of the pancreas: can

malignancy be predicted? Surgery. 2011 May; 149(5):625-34.

**Answer:** We reexamined pathological diagnosis of all patients of SPT and added the detail into the revised manuscript. All patients had negative surgical margin at final pathology. An average number of 5.3 lymph nodes were resected without metastases. There was no significant differences in number of harvested lymph nodes (4.6 vs 6.4,  $p = 0.549$ ) between the LDP and ODP group. 7 (25%) patients' pathological findings consist with malignant features of SPT. The malignant features included local invasion of peripancreatic tissue (6 patients), perineural invasion (2 patients), no liver metastasis, invasion of adjacent organs and angioinvasion. There were no significant differences in pathologic characteristics between the 2 groups. The tumors classified as SPT carcinomas were included in this study.

#6. Did the SPT with 57-year-old female with recurrence have the pathological malignant features as a solid pseudopapillary carcinoma? Was she one of the five cases with perineural invasions? Please describe the pathological result of this patient.

**Answer:** A 57-year-old female patient's pathology report revealed SPT with peripancreatic tissue invasion and perineural invasion. These findings were consistent with malignant features as a solid pseudopapillary carcinoma.

**Minor comments:** #1. LDP (Page4, line18)" is an abbreviated word. The authors should clarify the phrase "LDP" in the first enrollment of the literature.

**Answer:** We added "**laparoscopic distal pancreatectomy**" to clarify the phrase "LDP".

#2. What type of operating method was performed in patient experienced recurrence (Page8, line25)? LDP or ODP? Was the peritoneal recurrence site of this tumor resected by open tumorectomy(Page8, line26)? The authors should clarify the operating method.

**Answer:** The patient experienced recurrence underwent **ODP**. The peritoneal recurrence site of this tumor was resected by **open tumorectomy**. The details of the operating method have been added into the revised manuscript.

#3. Was the 16-year female treated by ODP (Page8, line30)? The authors should clarify the operating method.

**Answer:** The 16-year female was treated by **ODP**.

(3) **Reviewer 1:** They would describe in which patients performed and why, pancreaticojejunostomy(PJ) vs pancreaticogastrostomy(PG)?

**Answer:** According to the suggestion, we revised the manuscript that the study was just limited to patients underwent distal pancreatectomy.

Of the 8 patients undergoing central pancreatectomy, 1 patient underwent laparoscopic central pancreatectomy with PG; the other 7 patients underwent laparoscopic or open central pancreatectomy with PJ. In our center, PJ or PG was executed on the surgeons' preferences and the informed consent from the patients.

Nowadays, a randomized controlled trial of comparing the perioperative outcome of pancreaticoduodenectomy with PG vs PJ showed there was non-significantly lower pancreatic fistula rate with PG (PG vs PJ, 14 vs 24 %,  $p=0.352$ ) [1]. A shorter operation time (404 vs 443 min,  $p=0.005$ ) and reduced hospital stay for PG (15 vs 17 days,  $p=0.155$ ). Delayed gastric emptying (DGE; PG vs PJ, 27 vs 17 %,  $p=0.246$ ) and intraluminal bleeding (PG vs PJ, 7 vs 2 %,  $p=0.364$ ) were more frequent with PG [1]. Pancreaticojejunostomy allows better pancreatic exocrine function preservation than pancreaticogastrostomy after pancreaticoduodenectomy [2]. Both of them have advantages and disadvantages. In China, many people have gastritis and gastric ulcer. So we tend to prefer PJ to accomplish the pancreaticojejunal reconstruction.

1. Wellner UF, Sick O, Olschewski M, et al. Randomized controlled single-center trial comparing pancreaticogastrostomy versus pancreaticojejunostomy after partial pancreaticoduodenectomy. *J Gastrointest Surg.* 2012;16:1686-1695.

2. Rault A, SaCunha A, Klopfenstein D et al . Pancreaticojejunal anastomosis is preferable to pancreaticogastrostomy after pancreaticoduodenectomy for long-term outcomes of pancreatic exocrine function. *J Am Coll Surg.* 2005; 201:239-244.

3.References and typesetting were corrected.

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

Ren-Chao Zhang, MD

Department of General Surgery,

Sir Run Run Shaw Hospital

3 East Qingchun Road, Hangzhou 310016,

China

E-mail: areenn@163.com

Yi-Ping Mou, MD, FACS

Department of General Surgery,

Sir Run Run Shaw Hospital

3 East Qingchun Road, Hangzhou 310016,

China

Telephone +86-571-86006952

Fax +86-571-86044817

E-mail: mouyp@srrsh.com