Trends and Outcomes of Pancreaticoduodenectomy for Periampullary Tumors: Results of a 25 Years Single Center Study on 1000 Consecutive Cases

Dear (Editor-in-Chief**):**

Thanks for your help and advices. Please, find the revised manuscript entitled: " Trends and Outcomes of Pancreaticoduodenectomy for Periampullary Tumors: Results of a 25 Years Single Center Study on 1000 Consecutive Cases" Manuscript NO: 34673 to be published in World Journal of Gastroenterology. The concerns of the reviewers were fully addressed in the sent response and appropriate revisions were carried out. Accept my best personal regards for your great effort. Many thanks for all reviewers for their help and great effort.

Reviewers' comments:

Recension of manuscript No. 34673: „Trends and Outcomes of Pancreaticoduodenectomy for Periampullary Tumors: Results of a 25 Years Single Center Study on 1000 Consecutive Cases written by Ayman El Nakeeb et al. “, which will be published in World Journal of Gastroenterology.

The structure of manuscript is in keeping with the common required criteria. The topic of the work is very actual. Pancreaticoduodenectomy is a complex abdominal procedure, the hospital mortality rate has decreased to less than 5% however the rate of postoperative morbidities remains high, from 40 to 50%. Pancreatic reconstruction following pancreaticoduodenectomy is still debatable. The research work follows several aims and interesting parametric studies. Work is clearly legible, brings summarizes new knowledge. The results are documented in graphs that present the review of the obtained data. The citations are well-chosen and relevant and their format respects usual standards. The

conclusion summarizes the author ś results. Summarizing, I recommend that the manuscript can be published.

Reviewer 2

The new visions that the manuscript offers to readers: - This study provides comparisons for early, middle and late periods of PD by means of mortality and morbidity. It is observed that although pancreatic reconstruction following PD is still debatable, there was a significant improvement of median survival and the overall survival among the periods.

The weaknesses or deficiencies in the manuscript:

- The manuscript is highly repetitive and should be shortened at least %10.

ok

The following paragraphs were removed

Now the hospital mortality rate has decreased to less than 5% however the rate of postoperative morbidities remains high, from 40 to 50% (5-8, 9-11).

However, prophylactic measures must be done to decrease POPF and to improve the surgical outcomes.

Uncinate process carcinoma should not be a contraindication for PD.

In the first ten years (1993-2002) the total number was 300 cases underwent PD (30 cases / year). In the next ten years (2003-2012) the total number was 442 cases underwent PD (44.2 cases /year). In the last 4 years (2013-2017) the total number was 258 cases underwent PD (51.6 cases /year) as noticed in other high volume center (6,7).

LPD is one of the most complex operations in laparoscopic field. However, partly due to its complications and steep learning curve, this procedure remains limited to a few selected high volume centers (32-33).

Ideally, the pancreatic anastomosis after PD should decrease the risk of POPF and its severity if developed and also, preserve the morphology and functions of pancreas.

In the first ten years we performed simple loop PJ but the incidence and severity of POPF were high so we shifted to perform PG and the short term outcome including POPF improved markedly. In the second ten years, the majority of cases reconstructed by PG so short term outcomes were improved and lower rate of POPF was noticed, but the long-term outcomes regarding the pancreatic function and nutrition were not appropriate. In the last five years, a re-shift to PJ (simple loop or isolated loop) was done to improve long term outcomes.

. In high risk patients of pancreatic fistula (presence of two or more risk factors) PG is preferred. In low and moderate risk patients (presence of one risk factors) of pancreatic fistula, PJ is more preferred.

Increased frequency of PD and evolution of operative technique in our center lead to decrease the rate of postoperative complications after PD and consequently decreased postoperative hospital stay.

Delay gastric emptying was the most common complication after PD (18%). It is secondary to POPF, abdominal collection or biliary leakage in 15.2%. Primary DGE was presented in 2.8% of cases and not associated with any complications. The cause of primary DGE may be antroduodenal ischemia, diabetes, peripancreatic inflammation, or aggressive lymphadenectomy. These patients usually improved with total parenteral nutrition, without any further treatments (34).

In our series, female gender, patients not developed major complications, ampullary tumour, negative safety margin, negative lymph nodes, chemoradiotherapy and period of the study were all favorable prognostic variables in univariate and multivariate analysis. The improvements of interventional radiology in managing postoperative complications after PD avoids a re-explorations. There were 70 patients who underwent ultrasound guided tubal drainage.

- **In the figures and tables the integrity of the text should be more concise and clear.**

ok

- The language of the manuscript needs minor revisions

ok

Reviewer 3

In this manuscript, the authors try to evaluate the evolution, trends in surgical approaches and reconstruction techniques. They reviewed the data of all patients who underwent pancreaticoduodenectomy (PD) during 1993 to 2017. In the results, they concluded that the frequency of is increased. The median operative time and postoperative hospital stay time were decreased. The hospital mortality was also declined. The postoperative complications is significantly decreased. They also found that the median survival and the overall survival was improvement. The results sound interesting, but the reviewers still have the following concerns:

1) The data were categorized into three periods, would you please explain why you need to categorized the data to three periods?

Many points still debatable as regards PD included selection of patients, pancreatic reconstruction, and factors that improve survival rate so the aim of this study is to evaluate the mile stones, trends in surgical approaches and reconstruction techniques, and important lessons learned from performing 1000 consecutive PD for periampullary tumors in Gastrointestinal Surgery Center –over a period of 25 years.

For the trend analysis, the study was divided into three periods. The study spans a period during which significant management changes occurred, which allows for a meaningful analysis of trends in outcomes. There are many modifications that will be noticed when categorized the data to three periods. Over the study period and with accumulating experience, evolution of the surgical approach and techniques occurred.

Dissection technique:

Approach:

Meso-pancreatectomy:

Division of the pancreatic neck:

Reconstruction: In the beginning of our series, we performed simple loop pancreatico-jejunostomy (PJ) for the reconstruction of the pancreatic stump. However, a high rate of pancreatic fistula was noticed. A shift of the reconstruction plan occurred to pancreatico-gastrostomy (PG). Short term outcomes were improved and lower rate of pancreatic fistula was noticed, but the long-term outcomes regarding the digestive and nutritional conditions were not appropriate.

With accumulating experience and refinement of the surgical technique, a re-shift to PJ (simple loop or isolated loop), with improved long term outcomes (18,19).

Recently, we adopted a tailored approach for the management of pancreatic stump management. In high risk patients of pancreatic fistula, , PG is preferred. In low and moderate risk patients of pancreatic fistula, PJ is more preferred.

2) In the manuscript, there were 20 surgeons conducted the surgery, how they carried out the same quality monitoring?

All surgeons participated in the study are expertise hepatobilliary and pancreatic surgeons. When PD was performed by Junior surgeon, there is a protocol for regulation of work in our institute including, the junior surgeon must assists in more than 100 PD and must be assisted by seniors in all steps of procedure.

3) In this manuscript , there were so many spell mistakes, and it is hard to understand, the language need to be polished.

ok