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Research Article

Robotic Surgery for the Treatment of Chronic Pancreatitis. Pain Control, Narcotic Use Reduction and Re-Intervention Rate. Ten Years Follow-Up Retrospective Study

Eduardo Fernandes*, Valentina Valle, Gabriela Aguiluz Cornejo, Roberto Bustos, Roberto Mangano, Pier Cristoforo Giulianotti

University of Illinois at Chicago College of Medicine Chicago, IL United States

ABSTRACT

Introduction: Surgical treatment of chronic pancreatitis is reserved to patients with intractable pain, pancreatic duct obstruction or suspicion of malignancy. Robotic surgery in this context has proven to be a safe and feasible.

The aim of this study was to evaluate the effect of robotic assisted surgery in the context of chronic pancreatitis with regards to pain control, narcotic usage and need for re-intervention.

Methods: A retrospective analysis of a prospectively collected divisional database at the University of Illinois Hospital & Health Sciences System was carried out.

The primary endpoint was: 1) Evaluation of pre and post-operative pain and narcotic usage. The secondary endpoints were: 1) 10-year overall survival; and 2) 'Event Free Survival' (EFS).

Results: 37 patients entered the study. The procedures performed were: pancreatic head resection (7), total pancreatectomy (1), hepatico-jejunostomy (6), longitudinal Roux-en-Y pancreato-jejunostomy (4), pancreato-gastrostomy (14) and thoracoscopic splanchnicectomy (7).

The mean pre and post-operative pain scores were 6.5 and 4.5 respectively ($p<0.05$, paired Student t-test). Rates of narcotics use pre and post-surgery were 74% and 50% of patients respectively.

Re-intervention rates were: 57% for splanchnicectomies, 16% for hepatico-jejunostomies, 35% for pancreato-gastrostomies, 1% for pancreatic resections and 25% for Puestow procedures. Splanchnicectomy group was the one to experience the shortest EFS compared to other groups (log-rank test, $p<0.05$).

Conclusions: Robotic surgical treatment is an effective mean to symptoms control in chronic pancreatitis.

Amongst the procedures taken into consideration, pancreatic resection, hepatico-jejunostomies and Puestow procedures appear to have the longest lasting beneficial effects.

Keywords: Chronic pancreatitis; Robotic surgery; Minimally invasive surgery; Laparoscopic surgery

INTRODUCTION

Chronic pancreatitis is an invalidating condition which often presents in a highly morbid population [1-5]. It is characterized by an irreversible damage to the pancreas, with histology features of chronic inflammation, fibrosis and destruction of both exocrine and endocrine tissue [6,7]. Several etiological hypotheses have been proposed [8-10]: 1) Toxic-metabolic, from direct injury of alcohol, lipids, medications or toxins to pancreatic cells; 2) Ductal obstruction, from intraductal plugging of ducts from stones, tumor or congenital abnormalities such as pancreas divisum; 3) Autoimmune, from oxidative stress of autoantibodies activation; and 4) Genetic, from coding abnormalities of certain genes such as CFTR, SPINK-1 and PRSS [11,12].

***Correspondence to**: Eduardo Fernandes, University of Illinois at Chicago College of Medicine Chicago, IL United States, E-mail: e.fernandes76@icloud.com

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Whatever the etiology, the chronic inflammatory status leads to a vicious circle of deposition of collagen, fibrosis, further ductal obstruction and repeated episodes of pancreatitis [13].

Historically, surgery for this condition was limited to the treatment of complications (chronic pseudocysts, PD derivation, suspicion of malignancy) [14].

With the expansion of robotic minimally invasive surgery, surgical options have re-gained popularity and have been more frequently employed [15-17]. As one of the first institutions to offer this approach [18], we present a series of 37 patients who underwent minimally invasive/robotic surgical treatment for chronic pancreatitis and provide long term follow-up results.

MATERIALS AND METHODS

The original data presented in this study are based upon a retrospective analysis of a prospectively collected divisional database at the University of Illinois Hospital & Health Sciences System, approved by the Institutional Review Board. The analysis has been performed on a sample of 37 patients with a diagnosis of chronic pancreatitis who underwent a minimally invasive robotic or laparoscopic surgical procedures. The main indication for pancreatic resection or pancreatic duct drainage was intractable pain. Drainages procedures were considered in case of enlarged pancreatic ducts, (especially is greater than 5 mm), whereas patients with suspicion of malignancy within a severe chronic pancreatitis processes were offered resections. Patients with poor functional status, no suspicion of malignancy and no duct dilatation were offered a thoracic splancnicectomy. All procedures were performed in a robotically except for the splancnicectomis, which were performed purely laparoscopically. The time frame selected has been from 2006 to 2016 with a follow-up of up to 120 months. All the procedures included have been performed by the same team (University of Illinois Hospital & Health Sciences System).

Patients who underwent pseudocysto-gastrostomies were excluded from the study as this condition most often reflects the sequelae of acute pancreatitis.

The primary end points were: 1) Post-operative morbidity and mortality, measured according to Clavien-Dindo classification; 2) Evaluation of pre and post-operative pain assessed on 0 to 10 visual analogue scale; [2] at 6 weeks follow up, and 3) Pre and post-operative use of narcotic medications at the same time follow-up. Secondary endpoints were: 1) 10-year overall survival, and (EFS), defined as the time elapsed from the initial surgery to the occurrence of an additional procedure (endoscopic or surgical) required to address patients' symptoms. Categorical variables were analyzed with 2 × 2 tables and chi-square test. Means of continuous variables normally distributed were compared with Student t-test. Survival curves were calculated with Kaplan-Mayer method and groups compared with the log-rank test. IBM SPSS Statistics for Macintosh, Version 25.0 (IBM Corp. Released 2017. Armonk, NY) was used for statistical computation.

RESULTS

55 patients were extracted from the database. 18 had received surgical interventions not related to chronic pancreatitis and were excluded from the study.

37 patients were enrolled in the analysis.

There were 20 males and 17 females with a mean age of 47 (range 19-82). The median BMI was 23.3 (range 16-59). The most frequent etiology was alcoholic pancreatitis (54%), followed by biliary (29.7%), idiopathic (13.5%) and hereditary (2.7%) pancreatitis. Patient's characteristics are reported in Table 1.

Table 1: Patient's characteristics.

N of patients	**37**
Gender	20 (55%)
Male	17 (45%)
Female	
Mean age	47 (19-82)
Median BMI	23.3 (16-59)
Etiology	20 (54%)
Alcohol	11 (29.7)
Biliary	5 (13.5)
Idiopathic	1 (2.7%)

The total number of procedures was 39, as some patients underwent more than one procedure simultaneously (i.e. pancreato-gastrostomy and hepatico-jejunostomy).

We performed 14 pancreato-gastrostomies (derivation of Pancreatic Duct (PD) through the stomach, with techniques previously described [19]), 6 hepatico-jejunostomies, 7 Pancreato-Duodenectomies (PD), 1 total pancreatectomy, 4 Puestow procedures and 7 thoracoscopic splanchnicectomies.

Post-operative complications according to Clavien-Dindo classification of grade 3 or higher were recorded in 3 patients. One patient suffered from a retroperitoneal hematoma, one patient formed a grade A Post-Operative Pancreatic Fistulas (POPF) and one patient suffered from portal vein thrombosis and hepatico-jejunostomy anastomotic leak, likely secondary to bowel edema. There were no peri-operative mortalities.

The overall mean pain scores before and after surgery at 6-week follow-up were 6.5 and 4.5 ($p<0.05$).

Table 2 reports the percentage of patients with pain reduction by intervention group. The hepatico-jejunostomy group and the splanchnicectomy group did not reach statistically significant

reduction, whereas the pancreato-gastrostomy, any type of pancreatic resection and the Puestow procedures did.

Table 2: Pre and post-operative pain reduction by group of intervention (paired Student t-test).

Procedure	Mean pain score before surgery	Mean pain score after surgery	p value (paired sample t-test)	% of patients with pain reduction
Hepatico-jejunostomy (6)	5.5	4	> 0.05	50% (3)
Pancreato-gastrostomy (14)	7.2	5	< 0.05	50% (7)
Pancreato-duodenectomy/total pancreatectomy (8)	5	2.8	< 0.05	62% (5)
Puestow procedure (4)	7	3.7	< 0.05	75 % (3)
Splanchnicectomy (7)	6.4	5.8	> 0.05	28% (2)

With regards to narcotic usage, prior to any surgical intervention 78% of patients were taking opiate medications daily versus 40% post operatively ($p<0.05$).

Table 3 reports the impact of each procedure on the use of narcotics. Regular daily narcotic medication intake was evaluated before and after each surgical procedure. The impact of surgery on narcotics intake was measured as percentage of patients on narcotics before and after surgery, with details reported for each procedure group.

Table 3: Pre and post-operative percentage of patients on narcotic medications

Procedure	% of pts on narcotics before surgery	% of pts on narcotics after surgery	reduction (N of patients)	p value (chi square)
Hepatico-jejunostomy (6)	50% (3)	33% (2)	1	>0.05
Pancreato-gastrostomy (14)	85% (12)	50% (7)	5	<0.05
Pancreato-duodenectomy (7)	71% (5)	14.2 (1)	4	<0.05
Total pancreatectomy (1)	100%	100%	0	N/A
Puestow procedure (4)	100% (4)	25% (1)	3	< 0.05
Splanchnicectomy (7)	100%	85%	1	> 0.05

The pancreatic resection, pancreato-gastrostomy and Puestow procedure groups achieved a significant reduction of narcotic usage ($p<0.05$). Hepatico-jejunostomy and splanchnicectomy groups did not.

The additional interventions carried out after the primary surgery were as follows: The Puestow procedure and the hepatico-jejunostomy groups required one additional intervention each. In the hepatico-jejunostomy group, one patient developed cholangitis 10 years after the initial procedure.

He underwent double balloon diagnostic Endoscopic Retrograde Cholangio-Pancreatography (ERCP) which showed a patent hepatico-jejunostomy anastomosis. No intervention was taken. Patients in the pancreato-gastrostomy group required 5 additional interventions at different times up from the initial procedure (Figure 1).

The procedures required were ERCP for PD re-stenting (4 patients) and splanchnicectomy to optimize pain control (1 patient). Re-interventions are showed in Table 2.

A patient in the pancreatectomy group developed pancreatitis of the pancreatic stump and required ERCP/EUS to evaluate the pancreato-gastrostomy anastomosis.

Within the splanchnicectomy group, one patient required a distal pancreatectomy, two an ERCP and stenting of the PD and another one went on to have a total pancreatectomy (Table 4).

The estimated median EFS was 76 months. The hepatico-jejunostomy, pancreatic resection Puestow and pancreato-gastrostomy procedures had similar EFS. Only the splanchnicectomy group compared to the rest of the procedures had a significantly lower EFS (17 months, $p<0.05$).

Table 4: Subsequent interventions.

Initial procedure	Second intervention
Pancreato-gastrostomies (14)	4 ERCPs for PD stricture (3 at the site of anastomosis, 1 at different site) 1 splanchnicectomy
Hepatico- Junostomies (6)	1 double balloon ERCP for cholangitis
Pancreato-duodenectomy/Total pancreatectomy (8)	1 EUS/ERCP Pancreato-gastrostomy/stump pancreatitis
Puestow procedure (4)	1 ERCP (for cholangitis)
Splanchnicectomy (7)	1 distal pancreatectomy 2 ERCP stent 1 total pancreatectomy

The overall 5-year survival of the study group was 77%. The estimated median survival was 94 months. The causes of deaths are reported in Table 5. Two patients died of ischemic stroke, one of hemorrhagic stroke, two patients died from myocardial infarction, one from hypoglycemic coma and one patient committed suicide.

Table 5: Causes of death.

Stroke (ischemic/hemorrhagic)	3
Myocardial infarction	2
Hypoglycemic coma	1
Suicide by gunshot wound	1
N of events	7

DISCUSSION

Chronic pancreatitis is a highly morbid and invalidating condition [20-22]. The mainstay of treatment is to preserve the residual exocrine and endocrine function, supplement insulin and pancreatic digestive enzyme and achieve pain control [23-25]. Surgery for chronic pancreatitis is reserved for the treatment of complications and as last resort to improve symptoms after failure of conservative management [1,8,26]. Pancreatic resection, duct derivation or splanchnic denervation are all viable options [27-29]. High intra-operative risks and post-operative morbidity linked to some of these procedures have discouraged surgeons from treating chronic pancreatitis surgically.

The robotic platform, however, has sparked new interest in these procedures which can be safely performed in a minimally invasive fashion [15].

The largest series of robotic-assisted treatment of chronic pancreatitis, has been recently reported by Zeh's group [3], where they report a series of 39 robotic procedures. The study reported short term outcomes and proved safety and feasibility of pancreatic surgery in the context of chronic pancreatitis.

Our study is the second largest series ever published on robotic surgery treatment for chronic pancreatitis, and reports the longest follow-up ever published.

When choosing the appropriate option for each patient (drainage vs resection) we referred to the best current medical evidence available [30,31]. The question of which procedure between resection and drainage is more appropriate in these patients has been previously debated [32,33]. It is beyond the scope of this paper to directly compared the two procedures. The consensus is that the two procedures are equally effective on the short term, with drainage having less post-operative complications [32]. We agree with this view and we reserved the option of resection mainly to patients who presented with suspicion of malignancy.

Our short-term outcomes, namely peri-operative morbidity and mortality are comparable to the one reported in other studies of both open and robotic surgery [3,34].

Very few authors have faced these technically challenging procedures with a pure laparoscopic approach. The largest series of pancreatic duct laparoscopic drainage feature between 6 and 12 patients and report minimal post-operative morbidity [35-37].

We found that the pain perception after any type of surgery was reduced by 35% to 80% across all treatment groups. The procedure that yielded the best pain control were the pancreato-gastrostomy, pancreatic resections and Puestow procedure. Previous reports from open surgical series suggest that resectional procedures yielded better results than drainage ones in terms of pain control [38].

Our experience is that both resections and drainage procedures provided a significant pain reduction.

It should be noted that in our study group, patients who underwent hepatico-jejunostomies had low pre-operative pain scores. There is an intuitive explanation for this in that CBD chronic obstruction does not clinically cause excessive symptomatology.

The splanchnicectomy procedure also yielded less effective pain control. Although supported by ample evidence, we found its ability to control pain not to be long lasting. This finding is in-keeping with previous reports [39].

With regards to the use of narcotics, we observed an overall reduction of their use.

Pancreato-gastrostomy, pancreatectomy and Puestow procedure patients had a statistically significant reduction of narcotic administration post-surgery.

Other authors have reported a decrease of narcotic use after pancreatic resections in chronic pancreatitis [20]. Unlike previous reports [38,40], where it is stated that pancreatic resections provide best pain control when offered within two

years of onset of pancreatitis, our study shows that also patients with longer histories of the disease benefitted from the robotic resection. Furthermore, also the Puestow procedure yield as much success as pancreatic resections in terms of decrease narcotic use.

In the context of chronic pancreatitis, where the quality of life also relates to the number of medical encounters and repeat intervention, EFS is a valid indicator of the success of the initial intervention on an 'intention to treat' basis.

It is important to note that the whole study group median EFS was 82 months. This is a remarkable outcome, as it indicates that some degree of long-lasting effective pain control was achieved.

The overall rate of re-intervention was 30%. More specifically, five out of 14 patients who underwent pancreato-gastrostomy required an ERCP. In these patients, in 3 cases a stricture was found at the pancreato-gastrostomy anastomosis site, whereas in one case, this was clearly at a more distal location.

Out of the 9 patients who underwent a hepatico-jejunostomy, one developed cholangitis 10 years after the procedure. The single isolated episode did not require further revision of the hepatico-jejunostomy.

One patient who underwent a Whipple procedure developed stump pancreatitis and underwent ERCP/EUS to evaluate the etiology of the pancreatitis. On EUS stump appeared edematous, no signs of necrosis were detected. The pancreatitis subsided spontaneously without any further intervention.

Amongst the splanchnicectomy groups, one patient required distal pancreatectomy for body and tail pancreatic duct dilatation and multiple calcifications 10 months after the initial splanchnicectomy, another patient required a PD stent due to a stricture, and a third one required a total pancreatectomy 18 months after the initial surgery.

One out of 4 patients in the Puestow procedure group underwent an ERCP and Common Bile Duct (CBD) stenting 20 months after the initial surgery.

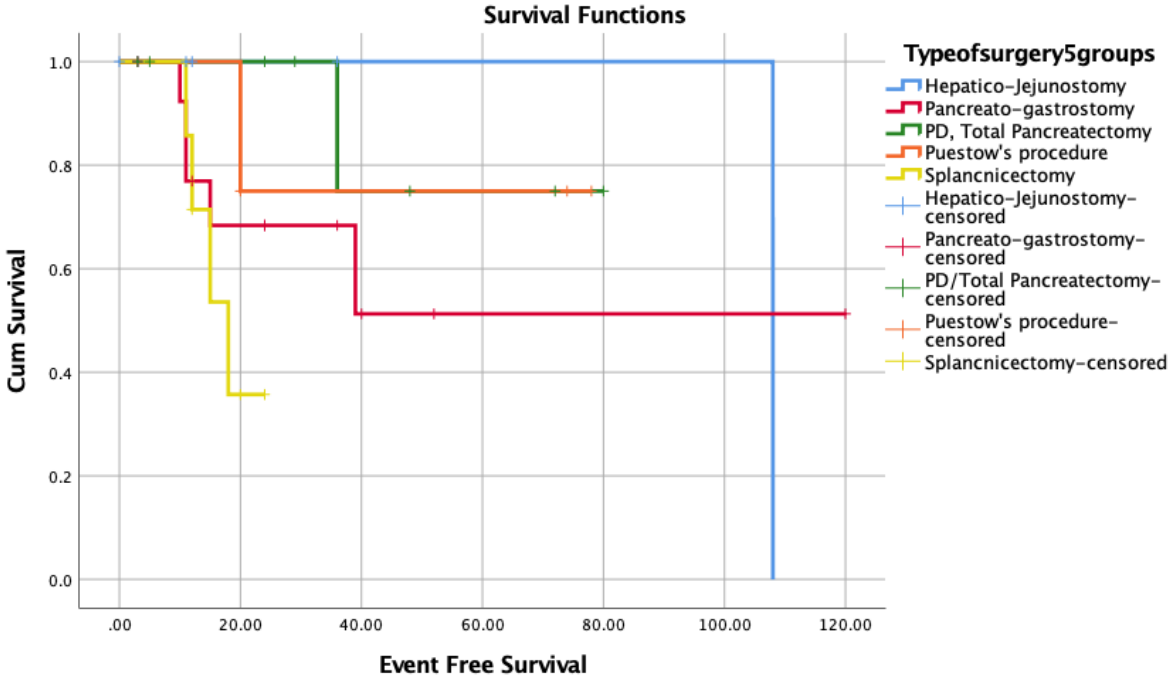

Figure 1: Event free survival by surgery group splanchnicectomy group experienced shortest EFS compared to all other groups, (log-rank test $p<0.05$).

We found that the most durable procedures were hepatico-jejunostomies, pancreatic resections, and Puestow procedures.

Pancreato-gastrostomies were affected by a high re-intervention rate within the first 20 months (42%). Passed the 20-month time point, this group enjoyed a relatively long 'EFS' (Figure 1).

The shortest EFS was recorded in the splanchnicectomy group.

This may be due to several factors, including the fact that it is offered as a 'palliative' procedure in selected patients with high co-morbidities and low compliance toward other surgical options.

There is little literature available on the EFS in the context of chronic pancreatitis and therefore data on this particular outcome are difficult to evaluate.

The overall 5-year survival was 77%. The estimated median survival of the study group was 94 months.

These findings show that despite the presence of chronic pancreatitis this patient population has a relatively long-life expectancy and therefore require a solution which is as long lasting as possible (Figure 2).

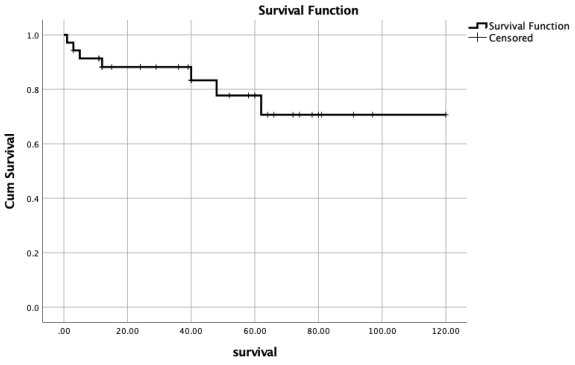

Figure 2: Overall survival of the study group.

CONCLUSION

In conclusion, robotic assisted resection procedures have the best results in terms of pain control and EFS. Drainage procedures, (pancreato-gastrostomies and Puestow procedure) had an intermediate efficacy in controlling pain on a long-term basis. Splanchnicectomies were the procedures that required the highest rate of re-intervention and the least effective pain control.

The results reported so far in the literature have shown the feasibility and safety of the robotic approach in the management of chronic pancreatitis and its sequelae. However, despite the growing scientific corpus reporting promising results, most of the evidences are short retrospective case series with short follow-up or case reports. De facto, we need more studies and with higher level of evidence to validate these interesting initial/pioneering experiences.

Notably, besides still having some limitations inherent to its retrospective nature, our sample has the longest follow-up ever reported on the topic. Moreover, our data represent the second largest series ever published worldwide (after the data shown by Zeh's team) regarding robotic surgery and chronic pancreatitis. The conclusions that can be drawn from our experience (as well as from the literature) have to be further validated by additional well powered prospective, randomized controlled trials.

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