The Liverpool duodenum and spleen preserving near-total pancreatectomy can provide long-term pain relief in patients with end-stage chronic pancreatitis
--Manuscript Draft--

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Abstract:	Purpose Total pancreatectomy may improve symptoms in patients with severe end-stage chronic pancreatitis. This might be achieved whilst preserving both the duodenum and spleen (DPSPTP). Mature clinical outcomes of this approach are presented. Methods Single centre prospective cohort study performed between September 1996 and May 2016. Demographic, clinical details, pain scores and employment status were prospectively recorded during clinic attendance. Results 51 patients (33 men, 18 women) with a median (interquartile range) age of 40.8 (35.3-49.4) years, a median weight of 69.8 (61.0-81.5) Kg, and a median body mass index of 23.8 (21.5-27.8), underwent intended duodenum-and spleen-preserving near-total pancreatectomy for end-stage chronic pancreatitis. Aetiology was excess alcohol in 25, idiopathic (no mutation) in 15, idiopathic (SPINK-1/CFTR mutations) in two, hereditary (PRSS1 mutation) in seven, and one each post-necrotising pancreatitis and obstructive pancreatic duct divisum in 1. The main indication for surgery was severe pain. Findings included parenchymal calcification in 79% and ductal calculi in 24%, a dilated main pancreatic duct in 57% and a dilated main bile duct in 17%, major vascular involvement in 27%, and pancreato-peritoneal fistula in 2%. Post-operative

complications occurred in 16 patients with one death. Median pain scores were 8 (7-8) preoperatively and 3 (0.25-5.75) at 5 years (p=0.013). Opiate analgesic use was significantly reduced post-operatively (p=0.048). Following surgery 22 (63%) of 38 patients of working age re-entered employment compared with 12 (33%) working pre-operatively (p=0.016). Conclusion Duodenum-and spleen-preserving near-total pancreatectomy provided long-term relief in adult patients with intractable chronic pancreatitis pain, with improved employment prospects.

Response to reviewers

Re: Duodenum and spleen preserving near-total pancreatectomy can provide long-term pain relief in patients with end-stage chronic pancreatitis

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Thank you for all the helpful comments from the reviewers.

We have amended the manuscript accordingly.

<u>Reviewer 1</u>

"The table III could be presented in a more clearly manner".

This has been made modified accordingly.

"also figure 5 could be improved in scaling."

This has been made modified accordingly.

"Figure 5 – meaning 4 - is showing that there is an increase of intake of strong opiates at the follow up time of five yaers, it could be interesting to find out the reason for this trend.

We have inserted in the Discussion:

"The longer-term oral morphine equivalent intake remained significantly lower after duodenum preserving total pancreatectomy (with or without spleen preservation), although from year to year there was a variance of opiate intake, reflecting the complex pathophysiological mechanisms of pain in CP [12]. "

There are already topic-related reviews published, e.g. Bellon et al. showed in 2019 that there is a high rate of patients who continued consuming alcohol (37.9%) after undergoing duodenum-preserving pancreatic head resection because of chronic pancreatitis.

We are aware of the excellent studies on from Hamburg, but the study by E Bellon et al in 2019 does not refer to end stage CP, and does not include total pancreatectomy.

<u>Reviewer 2</u>

1.	The authors already reported their experience with DPSPTP in the Br J Surg in 2003. These patients are included in the current series. The authors need to state more clearly what is the exact overlap of patients and what is the additional value of the current series other than its larger size.

This is now explained in the Methods:

"There were 19 patients between September 1996 and November 2002 (none in December) and a further 32 patients from January 2003 and May 2016. All patients with continued follow-up were included in this series."

2.	While the authors previously removed all pancreatic parenchyma (this is TP) along the duodenum they modified their technique to a subtotal head resection after 2003. Subtotal is not total and, therefore, the term DPSPTP is misleading.

In the Title, Abstract and the whole of the Manuscript we refer to the procedures as:

"Duodenum and spleen preserving near-total pancreatectomy"

3.	The authors report on 7 patients with hereditary pancreatitis. These patients are at increased risk for pancreatic cancer. In these patients TP is adequate, but I am not sure if leaving behind pancreatic tissue prone to cancer is adequate. How many of these patients received a subtotal head resection, why, and how long was the follow up in these patients.

We have provide further clarification in the Results:

"Five patients with Hereditary Pancreatitis (PRSS1 mutation) had a duodenum and spleen preserving total pancreatectomy before 2003 and two had a duodenum and spleen preserving near-total pancreatectomy from 2003, none of whom developed pancreatic cancer. Two additional patients with a PRSS1 mutation underwent DPSPTP without clinical evidence of CP as part of a pancreatic cancer screening program and are not included in this series, although both had good post-operative long-term outcomes."

4.	Of 51 patients with DPSPTP an unknown (but probably large) number of patients received a subtotal pancreatectomy along the duodenum, n=8 received splenectomy for technical and other reasons and n=2 received a radical TP with duodenectomy for neoplasia. How many patients indeed received a DPSPTP??

This is already clear from the aforementioned: 49 had a duodenum preserving near total or total pancreatectomy with or without spleen preservation – DP(SP)TP – and two had radical total pancreatectomy for neoplasia.

This is not a RCT comparing two interventions where an ITT analysis is crucial. If the authors intend to report outcomes for a specific procedure, they only should include patients who in fact did receive this specific procedure.

We agree that this is not an RCT. But the approach we have taken is to report all of the data as would take place in clinical practice (so called "real-world reporting) to avoid any bias in postoperative outcomes and long term outcomes.

Reviewer 3

1. Methods section: please explain better that bile duct is marsupialized (I understand but could be improved)

In the operative procedure we have now added:

"The bile duct is marsupialized within the bed of the pancreatic head by opening this longitudinally and then inserting six or more interrupted 4/0 sutures to approximate the edges of the cut bile duct to the adjacent tissues."

2. Operative outcomes: one patient had a pancreatic head resection. Coul you explain the reason to resect the rim of pancres left?

This is now better explained:

"resection of a large uncinate process remnant which had been incompletely removed at the first operation (1)"

3. Patient outcomes: How many moved to open access appointments and how many lost to follow up?

This has now been modified to:

"17 patients were lost to follow-up and 12 were discharged".

In the Discussion we have added:

"Compliance with long-term follow up is often a problem with this group of patients and must be regarded as a limitation in this as well as other studies. Nevertheless, there were 22 (57.9%) of 38 patients of working age who were able to return to gainful work, compared to 28.1% in the one only previously reported series of total radical pancreatectomy (with duodenectomy and splenectomy) for chronic pancreatitis [28]. "

4. Part of the procedure is like a Warshaw technique. Left portal hypertension had been frequently described in such cases. Did you daignose any case of left portal hypertension? If not wgy did you think that occur?

This might have occurred acutely during surgery and therefor a splenectomy was carried out.

Radiologically on CT we had a minor case of selenic infraction (Table III).

Otherwise we simply did not have this as a clinical problem. We have already stated in the Results that "No patients returned to theatre for splenic complications.".

Also we never had had nay cases of variceal bleeding.

5. Table 1 Bbody is Body

This has been corrected.

6. Table 6 Delayed gastric emptynig has been considered Clavien I and II Why? nasogastric tube vs waiting? Main problem with surgicl site infection (scar? or intraabdominal abscess?

Thank you – this has been adjusted.

Comment perhaps in title could be included Liverpool procedure if you like.

We have changed this to:

"The Liverpool duodenum and spleen preserving near-total pancreatectomy can provide long-term pain relief in patients with end-stage chronic pancreatitis".

Reviewer #4:

Major:
1.   The indication for this type of procedure has to be more specific. In the methods section is stated that it is indicated for a subset of patients with end-stage disease affecting the entire pancreas. What is exactly meant by affecting entire pancreas? Calcifications? Inflammation?

Indication is a big problem with these types of surgery (TP / TP-IAT). In international literature, it is still unclear in which patients we have to perform these procedures. Maybe the authors can shed more light and make recommendations for indication in the discussion section.

We have added the word 'debilitating" to give the following definition:

"This operation is only offered to the subset of patients with debilitating end-stage disease affecting the entire pancreas with chronic severe abdominal pain unresponsive to optimal medical management. Patients having previously undergone partial pancreatectomy with on-going or recurrent symptoms due to progressive disease in the remnant pancreas are also considered. Patients without diabetes mellitus meeting the above criteria are considered after counselling regarding postoperative diabetes management and complications. All patients must demonstrate abstinence from alcohol for more than six months. The procedure is contraindicated if malignancy is suspected, but the presence of porto-mesenteric venous thrombosis with varices is only a relative contraindication."

This represents 51 0f 778 patients with confirmed CP 0r 6.6%.

Examples are given in Figure 2:

Figure 2a and b. Female with idiopathic (CFTR mutation) chronic pancreatitis. Extensive parenchymal and ductal calcification is seen throughout the pancreas with significant upstream main pancreatic duct dilatation and parenchymal atrophy. Figure 2c. Female with PRSS1 N29I mutation (hereditary pancreatitis). Calcification within the pancreatic head and upstream and main pancreatic duct dilatation. Significant disease progression over 12 months with large volume abdomino-pelvic pancreatic ascites from a pancreato-peritoneal fistula and new gastric and splenic venous collateralisation.

So in one case complete calcification, and in the other only calcification in the head of pancreas but with pancreatic ascites from a pancreato-peritoneal fistula and gastric and splenic venous collateralization from vascular involvement.

Both diabetics with exocrine failure.

The question of TPIAT is only relevant for mainly hereditary recurrent acute pancreatitis in children and young adults with preserved exocrine and endocrine function.

We have now inserted a paragraph in the Discussion (see below).

2.   There is little information about the insulin dependent diabetes after the surgery. It is known that patients can develop a so-called 'brittle' diabetes after TP, and this is very difficult to control. This is one of the reasons why the islet auto transplantation technique is developed. Please provide more information about the diabetes in these patients (units of insulin, number of hyper/hypoglycemia if possible).

Thirty-three patients (65%) were diabetic, 31 (61%) insulin dependent and two (4%) controlled with oral anti-hypoglycaemics before surgery.

All required insulin after surgery and were managed by the specialized diabetic service using the latest techniques as they evolved. We do not have any specific information other than there were few problems.

3.   The data of pain scores and opioid use during follow-up are based on low numbers of patients (pain score: between 8 and 21 patients; opioids between 7 and 25 patients). This is however a well-known and insurmountable problem in long-term outcome studies. But please report this as limitation in the discussion.

Yes – thank you, we have modified the Discussion:

"Compliance with long-term follow up is often a problem with this group of patients and must be regarded as a limitation in this as well as other studies. Nevertheless, there were 22 (57.9%) of 38 patients of working age who were able to return to gainful work, compared to 28.1% in the one only previously reported series of total radical pancreatectomy (with duodenectomy and splenectomy) for chronic pancreatitis [28]. "

Minor:
1.   Please use the STROBE reporting checklist. Some details are missing in the current manuscript

I appreciate the Reviewers intention, but this is a prospective study over 20 years. Application of STROBE is not strictly applicable – for example, it was impossible to ascertain 20 years ago what the sample size would be and what the primary hypothesis would be.

Many of the modern requirements are around statistics and statistical modelling. If we did all of these the paper would be unintelligible for what is - at the end of the day a specialist surgical topic in sample size of only 51 patients.

I have however been through the checklist – we have mentioned potential limitations however such as the difficulty in follow-up.

I think we have all of the ley points covered.

2.   Introduction, p2: The incidence rates are reported as numbers per 10^5. I would prefer to use 100.000 instead of 10^5.

I am used to using 10^5.

3.   Results: Previous medication use and previous surgery is reported in the results section. But I am missing the proportion of patients that had previous endoscopy.

We do not used endoscopy to treat patients with advanced CP.

4.   Results, p4: in one patient the predominant symptom was not pain. For which reason this patient underwent surgery?

In the Results we have added:

"This patient had CP associated with Hereditary Pancreatitis (with a PRSS1) along with parenchymal calcification and both endocrine and exocrine failure, who requested a DPSPTP in his sixth decade of life mainly as a prophylactic measure against pancreatic cancer."

5.   Page 5: Punctuation is missing last sentence of the first paragraph "patient outcomes"

6.   Discussion: TP-IAT is not mentioned in the manuscript. Please discuss TP-IAT in the discussion. It is nowadays a very important procedure in patients with end-stage CP.

As mentioned above, by definition patients with end stage CP have very few islets and so cannot have TP-IAT.

The indication for TP-IAT is mainly hereditary recurrent acute pancreatitis in children and young adults with preserved exocrine and endocrine function.

We have now inserted a paragraph in the Discussion (see below).

7.   Table 1: It will be more clear when the authors divide risk factors in "etiology" and "current preoperative risk factors (alcohol use and smoking preoperatively)".

I am not sure that I understand this point – we are referring to etiological risk factors.

8.   Table 1: Body mass index is written with two b's.

Thank you – corrected.

9.   Table 4: Title suggests that these are all existing studies about TP(IAT). I think that the authors mean that these are all studies about organ-preserving TP? There are many more articles about TP-IAT without saving the duodenum and spleen.

This is in reference to CP in adults.

Reviewer 5

Under the last section of introduction:
- TPIAT should be mentioned here (see Bellin MD, et al. No islets left behind: islet autotransplantation for surgery-induced diabetes., Bellin MD, et al. How Durable Is Total Pancreatectomy and Intraportal Islet Cell Transplantation for Treatment of

Chronic Pancreatitis? Chinnakotla S, et al. Factors Predicting Outcomes After a Total Pancreatectomy and Islet Autotransplantation Lessons Learned From Over 500 Cases, Walsh RM, et al. Improved quality of life following total pancreatectomy and auto-islet transplantation for chronic pancreatitis, and Wilson GC, et al. Long-term outcomes after total pancreatectomy and islet cell autotransplantation: is it a durable operation?)

- TPIAT also improves survival over TP alone (see Garcea G, et al. Patient satisfaction and cost-effectiveness following total pancreatectomy with islet cell transplantation for chronic pancreatitis.).
- TPIAT is a better option for children with hereditary forms of pancreatitis than TP-alone, given the excellent metabolic outcomes in younger patients (see Bellin MD, et al. Total Pancreatectomy With Islet Autotransplantation Resolves Pain in Young Children With Severe Chronic Pancreatitis, Bellin MD, et al. Quality of life improves for pediatric patients after total pancreatectomy and islet autotransplant for chronic pancreatitis, and Chinnakotla S, et al. Total pancreatectomy and islet autotransplantation in children for chronic pancreatitis: indication, surgical techniques, postoperative management, and long-term outcomes.).

Under study design: This study is more appropriately classified as a retrospective review of prospectively collected data (case series).

No – this was a prospective study.

Under indications for DPSPTP: TPIAT is a well-established, extensively studied treatment of chronic pancreatitis for relief of pain with mitigation of postoperative diabetes. Were these patients considered for TPIAT prior to DPSPTP (in which case this would be considered a salvage or palliative procedure compared with TPIAT)? If not, what were the reasons for proceeding straight to DPSPTP as opposed to considering TPIAT?

See below.

Under indications for DPSPTP: It is noted by the authors that, "Patients without diabetes mellitus meeting the above criteria are considered after counselling regarding postoperative diabetes management and complications." Table 1 indicates that 65% of the patients treated had pre-operative diabetes as a symptom, please explain more regarding the indication for surgery in the setting of pre-operative diabetes versus no pre-operative diabetes, and were patients counselled that their risk of post-operative diabetes might be less if they underwent concurrent islet autotransplantation.

The indications are clearly described.

This operation is only offered to the subset of patients with debilitating end-stage disease affecting the entire pancreas with chronic severe abdominal pain unresponsive to optimal medical management. Patients having previously undergone partial pancreatectomy with on-going or recurrent symptoms due to progressive disease in the remnant pancreas are also

considered. Patients without diabetes mellitus meeting the above criteria are considered after counselling regarding postoperative diabetes management and complications. All patients must demonstrate abstinence from alcohol for more than six months. The procedure is contraindicated if malignancy is suspected, but the presence of porto-mesenteric venous thrombosis with varices is only a relative contraindication.

Under data collection: A series like this should include diabetes outcomes, especially if the procedure is considered an alternative to TPIAT. Considering that TPIAT has such extensive documentation of diabetes outcomes (see above suggested references). In order to compare this procedure with other standard surgical treatments of pancreatitis, data on diabetes outcomes is essential. Again, if this procedure is being presented as a salvage or palliative therapy, this should be made explicit.

Under patient outcomes: Can the authors comment on the one-year post-operative daily doses of short- and long-acting insulin in the cohort, and the range of A1c.

Follow-up and management of diabetes mellitus was undertaken in the specialist diabetic clinic. We did not have all of this information for the duration of the 20-year study.

Under patient outcomes, second paragraph: What is the time to determining "complete recovery," as in, how long were patients followed before being "discharged from clinical follow-up"?

Complete recovery meaning they were completely stable requiring no variation in their management, other than monitoring of their diabetes mellitus.

Follow-up is clearly described in the Methods.

Under discussion, first paragraph: Table IV does not include TPIAT series, however if these patients were not first considered for TPIAT, the complication and mortality data for TPIAT should be presented for comparison. Clinicians trying to decide whether to refer a patient for TPIAT versus DPSPTP should be aware of these comparisons. Otherwise, if the patients in this series were considered not to be candidates for TPIAT, it should be made explicit throughout the article that this procedure is a salvage therapy when TPIAT is no longer an option.

Under discussion, second paragraph: Again, TPIAT is not referenced in comparison to this series, so the authors cannot claim that their operation "compares favorably… in terms of post-operative results and, unlike almost all these studies, we report sustained long-term benefits."

Under conclusion: This is only a meaningful conclusion if the patients were considered not to be candidates for TPIAT. 100% of this cohort had insulin-dependent diabetes after the procedure, whereas 30-40% of TPIAT patients end up insulin independent at one year, and those who remain on insulin are frequently maintained on one injection of long-acting insulin

daily. For the DPSPTP to be accepted as an *alternative to TPIAT*, the authors need to report more detailed metabolic outcomes and compare outcomes with TPIAT, which is already an established and increasingly used surgical treatment of chronic and recurrent acute pancreatitis. If it is to be accepted as a *salvage* or *palliative* procedure when TPIAT is not an option, then I again suggest that the authors make this distinction explicit throughout the manuscript, and in the conclusion.

Yes but only 7% are insulin-dependent diabetics in the first palce.

The role of TP-IAT is mainly hereditary recurrent acute pancreatitis in children and young adults with preserved exocrine and endocrine function.

For adults it is highly controversial, where its use has been in those with so called 'early CP", but the latest International Guidelines show that "early CP" cannot be diagnosed.

The studies by Bellin and Chinnakotla are the same series of patients.

In the latest study, Melena Bellin and her colleagues reported on 215 patients with following inmportant points: (a) they did not define CP or how it was diagnosed – an extrmely serious problem; (b) etiology was not defined idiopathic (not defined) 98 (45.6%), hereditary (not defined) in 31 (14.4%), alcohol (not defined) 17 (7.9%) and other (not defined) in 69 (32.1%); the mean age was 35.7 years with a standard deviation of 13.8 years meaning that the vast majority were children or young adults; 159 were female, this is 74% indicating an extremely serious problem in understanding exactly what the diagnosis was.

They also now recognise that in hereditary pancreatitis that TPIAT should be largely restricted to young adults and children under 21 years of age and only if there are symptoms of severe pain (see below).

As it seems of such interest that we should mention this topic we have added the following in the Discussion.

"The DPSPTP procedure was indicated in only 51 or 6.6%. of the 778 patients with confirmed CP in our clinic. We would mainly recommend this procedure in patients with advanced CP when all other medical measures to control symptoms have failed [3, 12]. As a special case it is also indicated in Hereditary Pancreatitis with PRSS1 mutations from the fifth decade onwards when the risk of pancreatic cancer rises dramatically [6]. Total pancreatectomy with auto-islet transplantation is not an option for these kinds of patient because there are little or no functioning islets in the vast majority [3]. The application of total pancreatectomy with auto-islet transplantation (TPIAT) should mainly be restricted to children and young adults with recurrent acute pancreatitis, especially when associated with PRSS1 mutations, although many can be supported well into adult life with medical management [3, 6]. Outside of this indication the role of total pancreatectomy with auto-islet transplantation is controversial, as it is now recognized that early CP cannot be reliably diagnosed and readily distinguished from chronic

abdominal pain syndrome with an otherwise normal pancreas [3, 33-35]. This challenging area is illustrated by the recent study from the University of Minnesota Medical School, Minneapolis, Minnesota with the largest series, in which 215 patients were followed up for at least 10 years [36]. In this study there was no definition of CP or how it was diagnosed; the causes although listed were not defined and given as idiopathic (not defined) in 98 (45.6%) patients, hereditary (not defined) in 31 (14.4%), alcohol (not defined) in 17 (7.9%) and other causes (not defined) in 69 (32.1%) patients [36]. The mean age was 35.7 years with a standard deviation of 13.8 years meaning that the majority were children or young adults [36]. Despite the relative young population, there were 50 deaths with a 1-year survival rate of 95% and a 10-year survival of 72%, mainly from unknown causes (58%) and sepsis and/or pneumonia (20)%, with death from enterocutaneous fistula, cerebrovascular accident, cancer, kidney failure, liver failure, and diabetic complications each contributing 2% whilst sudden death, suicide and other causes accounting for the remaining 6% [36]. Moreover 159 of the 215 patients were female, that is 74%, which casts serious questions as to patient selection and the actual underlying diagnosis as gender is not a determinant risk factor for CP [1-4]. In an analysis also from Minnesota Medical School restricted to patients with hereditary pancreatitis and PRRSS1 mutations, Bellin et al concluded that "age greater than 21 years or disease duration longer than 17 years at surgery resulted in insulin dependence after TPIAT, with or without partial islet function. When justified by severe pain symptoms, earlier age at surgery may improve diabetes outcomes after TPIAT" [37]."

For clarity in the Conclusion in the Abstract and Discussion we refer to using this this operation specifically in adults with ned-stage disease:

"Duodenum-and spleen-preserving near-total pancreatectomy provided long-term relief in adult patients with intractable chronic pancreatitis pain, with improved employment prospects."

"This study shows that duodenum-and spleen-preserving near-total pancreatectomy can provide positive surgical outcomes in adult patients with end stage severe chronic pancreatitis including a clinically meaningful reduction in pain and opiate use, and an improvement in employment status in nearly two-thirds of patients."

Title: The Liverpool duodenum and spleen preserving near-total pancreatectomy can provide long-term pain relief in patients with end-stage chronic pancreatitis

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ABSTRACT

Purpose Total pancreatectomy may improve symptoms in patients with severe end-stage chronic pancreatitis. This might be achieved whilst preserving both the duodenum and spleen (DPSPTP). Mature clinical outcomes of this approach are presented.

Methods: Single centre prospective cohort study performed between September 1996 and May 2016. Demographic, clinical details, pain scores and employment status were prospectively recorded during clinic attendance.

Results: 51 patients (33 men, 18 women) with a median (interquartile range) age of 40.8 (35.3-49.4) years, a median weight of 69.8 (61.0-81.5) Kg, and a median body mass index of 23.8 (21.5-27.8), underwent intended duodenum-and spleen-preserving near-total pancreatectomy for end-stage chronic pancreatitis. Aetiology was excess alcohol in 25, idiopathic (no mutation) in 15, idiopathic (SPINK-1/CFTR mutations) in two, hereditary (PRSS1 mutation) in seven, and one each post-necrotising pancreatitis and obstructive pancreatic duct divisum in 1. The main indication for surgery was severe pain. Findings included parenchymal calcification in 79% and ductal calculi in 24%, a dilated main pancreatic duct in 57% and a dilated main bile duct in 17%, major vascular involvement in 27%, and pancreato-peritoneal fistula in 2%. Post-operative complications occurred in 16 patients with one death. Median pain scores were 8 (7-8) preoperatively and 3 (0.25-5.75) at 5 years (p=0.013). Opiate analgesic use was significantly reduced post-operatively (p=0.048). Following surgery 22 (63%) of 38 patients of working age re-entered employment compared with 12 (33%) working pre-operatively (p=0.016).

Conclusion: Duodenum-and spleen-preserving near-total pancreatectomy provided long-term relief in adult patients with intractable chronic pancreatitis pain, with improved employment prospects.

Key words: Chronic pancreatitis; total pancreatectomy; duodenum preserving; spleen preserving; total pancreatectomy; surgery; hereditary pancreatitis.

Author contributions. A.R.G. Sheel: Study concept and design, Acquisition of data, Analysis and interpretation of data, Drafting of manuscript, Critical review of manuscript. R.D. Baron: Study concept and design, Acquisition of data, Analysis and interpretation of data, Drafting of manuscript, Critical review of manuscript. L.D. Dickerson: Acquisition of data, Critical review of manuscript. P. Ghaneh: Acquisition of data, Critical review of manuscript. F. Campbell: Acquisition of data, Analysis and interpretation of data, Critical review of manuscript. M.G.T. Raraty: Acquisition of data, Critical review of manuscript. C.M. Halloran: Acquisition of data, Critical review of manuscript. J.P. Neoptolemos: Study concept and design, Acquisition of data, Analysis and interpretation of data, Drafting of manuscript, Critical review of manuscript.

INTRODUCTION

Chronic pancreatitis (CP) is a chronic fibro-inflammatory disease of the pancreas, resulting in persistent pathological responses to parenchymal injury or stress and pancreatic failure[1]. This has a negative impact on quality of life in addition to life-threatening long-term sequelae reducing life expectancy[2, 3]. Incidence ranges between 5-14.4 cases per 10^5 with a prevalence of around 50 per 10^5, and possibly as high as 120-143 per 10^5 [3]. Aetiological factors include alcohol and tobacco, genetic predisposition, autoimmunity, pancreatic duct obstruction and post-necrotising pancreatitis [2-8]. Continuous pancreatic parenchymal inflammation causes progressive fibrosis of the pancreas leading to loss of exocrine and endocrine parenchyma, calcification and pancreatic duct obstruction, amongst others [3, 9]. Patients can experience steatorrhoea, weight loss, malnutrition, gastric acid related symptoms, bloating, vitamin deficiency and osteoporosis due to pancreatic exocrine failure, and type 3c diabetes mellitus from endocrine failure[3]. In the long-term there is a 5-25 fold risk of pancreatic cancer in sporadic CP rising to 70 fold in hereditary pancreatitis[6, 10].

Severe chronic abdominal pain is the most common and distressing symptom[2, 3]. The pathogenesis of pain is multifactorial, and the long-term management is extremely challenging[3, 11, 12]. Patients with end-stage CP who fail to respond to medical measures, may require surgical intervention[3]. The indications for surgery include chronic debilitating pain and complications including biliary and duodenal obstruction, pseudocyst, pancreatic ascites, pancreatic fistula, porto-mesenteric venous compression or occlusion, sinistral portal hypertension with venous collateralisation and pseudo-aneurysm [3, 11, 13-18]. The surgical options depend on disease extent, pancreatic exocrine function and the presence of diabetes. Both drainage and resectional procedures are described, however, symptomatic relief following drainage procedures is short lived and various resectional procedures are now the current standard of care[3]. Beger's duodenum preserving pancreatic head resection (DPPHR) is effective for head dominant disease, providing decompression of the duodenum, hepatic portal vein, main pancreatic duct and intra-pancreatic bile duct[13, 14]. Variants of the Beger operation include the Frey and Berne procedures[15, 16]. In situations where a classical Kausch-Whipple partial pancreato-duodenectomy and the duodenum-preserving variants are both possible, the outcomes are similar but the Beger-like procedures can be undertaken in more advanced cases[3, 17, 18]. A subset of patients with debilitating symptoms and disease affecting the entire pancreas will require a total pancreatectomy, this may be performed with duodenum, pylorus, or splenic preservation[3, 19-22]. The Liverpool procedure combines these concepts as a duodenum-preserving and spleen-preserving near-total pancreatectomy (DPSPTP) [23]. This paper covers our experience with this operation, modifications to the technique, and patient outcomes over the last 20 years.

MATERIAL AND METHODS

Study design
This was a single centre prospective cohort study of 51 symptomatic patients intended to undergo DPSPTP for end-stage CP between September 1996 and May 2016 at the Regional Pancreas Unit, Liverpool, UK. The follow-up censor date was the 31st March 2017. In the original series there were 19 patients between September 1996 and November 2002 (none in December) and a further 32 patients from January 2003 and May 2016 [23]. All patients with continued follow-up were included in this series.

Indications for DPSPTP
This operation is only offered to the subset of patients with debilitating end-stage disease affecting the entire pancreas with chronic severe abdominal pain unresponsive to optimal medical management. Patients having previously undergone partial pancreatectomy with on-going or recurrent symptoms due to progressive disease in the remnant pancreas are also considered. Patients without diabetes mellitus meeting the above criteria are considered after counselling regarding postoperative diabetes management and complications. All patients must demonstrate abstinence from alcohol for more than six months. The procedure is contraindicated if malignancy is suspected, but the presence of porto-mesenteric venous thrombosis with varices is only a relative contraindication.

Data collection
A prospective database recorded demographic, clinical, radiological, genetic and histopathological data along with performance status and employment status during initial patient clinical assessment. All patients were asked to complete patient reported pain scores on a visual analogue scale (0-10).
Following discharge, patients were routinely assessed at six weeks, three, six and twelve months, then annually with additional review as clinically required. Data collected at follow-up included weight, analgesia requirements, employment status and pain scores. To assist in data analysis, analgesia type was subclassified into: parenteral strong opiates (e.g. morphine, oxycodone, buprenorphine, fentanyl), enteral strong opiates (e.g. morphine, oxycodone), enteral weak opiates (e.g. codeine, tramadol), non-opiates (e.g. paracetamol, NSAIDs), and no regular analgesia. Data was censored at the point when patients were discharged, lost to follow-up, or died.

Diagnosis of Chronic Pancreatitis
The diagnosis of CP was based on clinical and radiological criteria and confirmed in all patients following histopathological assessment of operative specimens[3]. The diagnosis of hereditary CP required a germline PRSS1 mutation in phase with family history[6]. CP secondary to alcohol required alcohol consumption of ≥62

units per week for ≥1 year [4]. For the purposes of this study, idiopathic CP included patients with known CFTR or SPINK-1 mutations and those with no known cause for CP. Diabetes mellitus was diagnosed according to established WHO criteria. The presence of pancreatic exocrine insufficiency was based on clinical assessment and the response of steatorrhea to pancreatic enzyme replacement therapy.

Operative description

The pancreas and duodenum are exposed as described previously [23]. The common hepatic and splenic arteries are dissected at the coeliac axis trifurcation and the splenic artery ligated and divided close to this origin. The gastro-colic trunk of Henle is ligated and divided, followed by the inferior pancreatoduodenal vein. The pancreas is mobilized along its length dividing the superior and inferior peritoneal reflections. The inferior mesenteric vein and coronary veins are ligated and divided if arising from the splenic vein. The splenic hilum is dissected and transected with a linear stapler leaving the gastrolienal ligament intact, splenic vascular supply is maintained on the short gastric vessels. The pancreatic tail is mobilized from the retroperitoneal structures to the confluence of the splenic and hepatic portal veins and the splenic vein divided and over sewn 3-4 cm proximal to this confluence.

The pancreatic head is isolated by two rows of circumferential stay sutures, as described by Beger et al[13]. Near-total pancreatic head resection is performed, preserving a small rim of fibrosed pancreatic tissue on the left lateral aspect of the duodenum, between the intrapancreatic bile duct and the duodenum, inferior to the hepatic portal and superior mesenteric veins and adjacent to the superior mesenteric artery. It is important to preserve either the inferior pancreatoduodenal artery or the superior posterior pancreatoduodenal artery to maintain duodenal and distal bile duct vascularization (*Figure 1*). The bile duct is marsupialized within the bed of the pancreatic head by opening this longitudinally and then inserting six or more interrupted 4/0 sutures to approximate the edges of the cut bile duct to the adjacent tissues. The bare pancreatic rim is anastomosed to a Roux-en-Y loop. Before 2003, all pancreatic parenchyma was removed to avoid the necessity of constructing a Roux-en-Y loop. In our initial series, two cases of bile duct stricture and one case of duodenal stenosis were reported relating to local ischemia from this more radical technique[23]. Post-operative complications were categorized using the 2009 modification of the Dindo-Clavien classification[24].

Statistical analysis

Continuous variables are presented as median and interquartile range (IQR) and analysed using the Wilcoxon Rank test for paired data based on a 2-tailed alpha. Categorical variables are presented as frequency and percentage and were analyzed using Pearson's X^2 test or Fishers exact test. Significance was set at the 5 percent level (p<0.05). SPSS v22 was used for analyses.

RESULTS

Patients and Preoperative details

Since 1996, 1,247 patients have been screened with a possible diagnosis of CP. 778 had confirmed CP and gave consent to be recruited to the local database. Of these 412 (219 male, 193 female) patients have undergone pancreatic surgery.

Fifty-one patients underwent intended DPSPTP for end stage CP (Table I). Five patients with Hereditary Pancreatitis (PRSS1 mutation) had a duodenum and spleen preserving total pancreatectomy before 2003 and two had a duodenum and spleen preserving near-total pancreatectomy from 2003, none of whom developed pancreatic cancer. Two additional patients with a PRSS1 mutation underwent DPSPTP without clinical evidence of CP as part of a pancreatic cancer screening program and are not included in this series, although both had good post-operative long term outcomes. Eight patients required an intra-operative splenectomy for technical (n=6) or anatomical (n=2) reasons and two underwent radical total pancreatectomy following the discovery of an unexpected cancer and a main duct intraductal papillary mucinous neoplasm respectively.

The most common risk factors for CP were alcohol excess and smoking (Table I). Amongst those consuming excess alcohol the median intake was 140 (80-200) units/week for 6 (3-15) years. Amongst the ever smokers the

median cigarette consumption was 20 (13.3-28.8) pack-years. Other risk factors are listed in Table I. Fourteen patients had undergone previous pancreatic surgery. The predominant symptom was pain in all except one patient. This patient had symptomatic painful CP associated with Hereditary Pancreatitis (with a PRSS1 mutation) along with parenchymal calcification and both endocrine and exocrine failure, who requested a DPSPTP in his sixth decade of life mainly as a prophylactic measure against pancreatic cancer.

The median preoperative visual analogue pain score was 8 (7-8) out of a maximum score of 10. 90% of patients were taking daily opiate-based analgesia (Table I). The median daily oral morphine equivalent dose was 50 (24-90) mg/day. Thirty-three patients (65%) were diabetic, 31 (61%) insulin dependent and two (4%) controlled with oral anti-hypoglycaemics. Forty-four (86%) patients had documented pancreatic exocrine insufficiency with a median daily pancreatic lipase dose of 225,000 (150,000-320,000) units. Thirty-one patients were unemployed for medical reasons, 15 were employed, three were beyond retirement age and employment status was unknown in two patients. Performance status and the American Society of Anesthesiologists grade are listed in Table I.

Pre-operative Radiological Imaging

The most common radiological findings were parenchymal calcification, main pancreatic duct dilatation and pancreatic atrophy (there were missing scans in three patients). Almost a third of patients had vascular involvement including porto-mesenteric occlusion or thrombosis and varices (Table II). Examples of radiological features are demonstrated in Figure 2.

Operative Outcomes

All of the patients had CP confirmed histologically. Pancreatic intraepithelial neoplasia (PanIN) was found in five patients but no patient had invasive cancer. The median length of stay was 19.5 (11-39.5) days; pre-2003 (n=22) this was 25.5 (15.0-44.5) days and post-2003 (n=16) this was 13.5 (10.8-25.0) days (p=0.076); data was missing for 3 patients. There was a total of 20 early complications in 16 (39%) patients including one death (Table III). Before 2003, there were 15 complications in 11 (47.8%) out of 23 patients and since 2003, there have been 5 complications in 5 (27.8%) out of 18 patients, demonstrating a trend towards fewer complications post-2003 technique modification (p=0.192).

Nine (39%) patients were readmitted with late complications pre-2003 of whom eight required a total of twelve surgical procedures: adhesiolysis (4) and ileostomy (1) for small bowel obstruction, hepato-jejunostomies (2) and hepato-duodenostomy (1) for biliary obstruction, Roux-en-Y revision (1), resection of a large uncinate process remnant which had been incomplete removed at the first operation (1), feeding jejunostomy (1) and incisional hernia repair (1). From 2003, only six (33%) patients were readmitted with late complications, with two requiring further surgical procedures (p=0.142): an ileo-ilial bypass for small bowel obstruction (1) and a hepato-jejunostomy for a biliary obstruction (1). No patients returned to theatre for splenic complications.

Patient Outcomes

Patients were followed-up for a median of 3 years, 5 months (1 year - 6 years, 4 months). Post-operative pain scores were significantly reduced at 1, 3 and 6 months and 1, 2, 3 and 5 years (Figure 3). Post-operatively significantly more patients were opiate free by 3 months (p<0.001) and this remained significant to 5-years (p=0.001) (Figure 4). The daily oral morphine equivalent dose of analgesia required was significantly reduced at all post-operative time points (Figure 5). All patients had insulin dependent diabetes post-operatively

Following surgery 22 of 38 patients of working age returned to gainful employment compared to only 12 working preoperatively, 13 patients remained unemployed compared with 24 preoperatively (p=0.016); occupation data was unavailable pre-operatively for 2 patients and post-operatively for 3 patients. During the twenty-year study, 17 patients were lost to follow-up and 12 were discharged. For these 29 patients, the median pain score at last follow-up was 2 (0-4) (p<0.001) and the median oral morphine equivalent dose was 0 (0-30) mg/day (p=0.001). Only three of these 29 patients represented to clinic, after 3, 7 and 9 years respectively, and only two represented with recurrent pain.

DISCUSSION

CP remains a challenging disease to manage and chronic abdominal pain is difficult to treat[3, 11, 12]. The primary aim of surgery in CP is to provide long-term pain relief and control associated complications, enabling social rehabilitation and the opportunity to increase the prospect of gainful employment. The longer-term oral morphine equivalent intake remained significantly lower after duodenum preserving total pancreatectomy (with or without spleen preservation), although from year to year there was a variance of opiate intake, reflecting the complex pathophysiological mechanisms of pain in CP [12]. Longitudinal studies have shown that around 40-75% of patients with CP will require surgical intervention at some point during the disease process [25-28]. In our series 412 (54%) out of 778 patients required surgery. Despite evidence that earlier intervention improves pain outcomes and preserves pancreatic function [28] there remains a cohort of patients who present with end-stage disease, develop associated complications and fail to respond to other treatment modalities. In this case total pancreatectomy remains the only option. Once a patient has developed both endocrine and exocrine failure the longer-term improvement in symptoms may outweigh the immediacy of post-operative complications, especially in high volume pancreatic centers. Several series have reported immediate postoperative outcomes of total pancreatectomy for CP with mortality ranging from 2.9% to 20.6% and complication rates of 15.3% to 51.9% (Table IV) [19, 20, 22, 29-31]. In our series there were post-operative complications in 16 (31.4%) patients with one (1.96%) death. Compliance with long-term follow up is often a problem with this group of patients and must be regarded as a limitation in this as well as other studies. Nevertheless, there were 22 (57.9%) of 38 patients of working age who were able to return to gainful work, compared to 28.1% in the one only previously reported series of total radical pancreatectomy (with duodenectomy and splenectomy) for chronic pancreatitis [28].

Although duodenum preserving total pancreatectomy has been previously reported [19, 20, 29, 30], and also spleen preserving total pancreatomy for chronic pancreatitis [21,29,30], ours is the only series in which these procedures are combined. The duodenum-and spleen-preserving near-total pancreatectomy conforms to the principle of restricting excisional surgery to the target organ with the intention of optimizing preservation of physiological function whilst facilitating the procedure itself. Preserving the duodenum helps reduce nutritional compromise and preserving the spleen lessens the risks of sepsis from encapsulated bacterial organisms[14, 32].The duodenum-and spleen-preserving near-total pancreatectomy compares favorably with these larger procedures in terms of post-operative results and, unlike almost all these studies, we report sustained long-term benefits.

The key step to this procedure is identification of a readily accessible plane by finger dissection posterior to the splenic hilar vessels between the pancreatic tail and the spleen allowing transection with a linear stapler. This plane is usually easy to dissect in the absence of severe chronic pancreatitis but more challenging to define with end-stage disease affecting the entire distal pancreas. This plane is not previously well described in anatomical or surgical textbooks. In the series by Garcea et al. duodenum preservation was attempted in their first six patients. They abandoned this technique, after two patients required reoperation for duodenal ischemia [31]. Our operative technique was modified post-2003 to preserve a rim of pancreatic tissue on the inner aspect of the duodenum, to avoid disruption of the blood supply to the duodenum and distal bile duct. This was based on the principles of duodenum preserving pancreatic head resection introduced by Beger in 1980 [13, 14]. There have been fewer post-operative complications in the post-modification cohort and no deaths. None of the patients developed malignancy in the rim of pancreatic tissue preserved along the duodenum. Limitations to the current study include a relatively small patient cohort that required this special operation.

The DPSPTP procedure was indicated in only 51 or 6.6%. of the 778 patients with confirmed CP in our clinic. We would mainly recommend this procedure in patients with advanced CP when all other medical measures to control symptoms have failed [3, 12]. As a special case it is also indicated in Hereditary Pancreatitis with PRSS1 mutations from the fifth decade onwards when the risk of pancreatic cancer rises dramatically [6]. Total pancreatectomy with auto-islet transplantation is not an option for these kinds of patient because there are little or no functioning islets in the vast majority [3]. The application of total pancreatectomy with auto-islet transplantation (TPIAT) should mainly be restricted to children and young adults with recurrent acute pancreatitis, especially when associated with PRSS1 mutations, although many can be supported well into adult life with

medical management [3, 6]. Outside of this indication the role of total pancreatectomy with auto-islet transplantation is controversial, as it is now recognized that early CP cannot be reliably diagnosed and readily distinguished from chronic abdominal pain syndrome with an otherwise normal pancreas [3, 33-35]. This challenging area is illustrated by the recent study from the University of Minnesota Medical School, Minneapolis, Minnesota with the largest series, in which 215 patients were followed up for at least 10 years [36]. In this study there was no definition of CP or how it was diagnosed; the causes although listed were not defined and given as idiopathic (not defined) in 98 (45.6%) patients, hereditary (not defined) in 31 (14.4%), alcohol (not defined) in 17 (7.9%) and other causes (not defined) in 69 (32.1%) patients [36]. The mean age was 35.7 years with a standard deviation of 13.8 years meaning that the majority were children or young adults [36]. Despite the relative young population, there were 50 deaths with a 1-year survival rate of 95% and a 10-year survival of 72%, mainly from unknown causes (58%) and sepsis and/or pneumonia (20)%, with death from enterocutaneous fistula, cerebrovascular accident, cancer, kidney failure, liver failure, and diabetic complications each contributing 2% whilst sudden death, suicide and other causes accounting for the remaining 6% [36]. Moreover 159 of the 215 patients were female, that is 74%, which casts serious questions as to patient selection and the actual underlying diagnosis as gender is not a determinant risk factor for CP [1-4]. In an analysis also from Minnesota Medical School restricted to patients with hereditary pancreatitis and PRRSS1 mutations, Bellin et al concluded that "age greater than 21 years or disease duration longer than 17 years at surgery resulted in insulin dependence after TPIAT, with or without partial islet function. When justified by severe pain symptoms, earlier age at surgery may improve diabetes outcomes after TPIAT" [37].

CONCLUSION

This study shows that duodenum-and spleen-preserving near-total pancreatectomy can provide positive surgical outcomes in adult patients with end stage severe chronic pancreatitis including a clinically meaningful reduction in pain and opiate use, and an improvement in employment status in nearly two-thirds of patients.

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COMPLIANCE WITH ETHICAL STANDARDS

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TABLES

Table I - Demographics of patients listed for DPSPTP

Intended DPSPTP	Frequency (Percentage)/Median (IQR)
Total patients	51
Male	33 (65%)
Age, years	40.8 (35.3-49.4)
Weight, Kg	69.8 (61.0-81.5)
Body mass index	23.8 (21.3-27.8)
Symptoms	
Primary symptom severe pain	50 (98%)
Diabetes	33 (65%)
Pancreatic Exocrine Insufficiency	44 (86%)
Risk factors	
Alcohol (>62 units per week for > 1year)	25 (49%)
Current Smokers	33 (65%)
Ever Smokers	39 (76%)
Idiopathic (no mutation)	15 (29%)
Idiopathic (CFTR/PRSS1)	2 (4%)
Hereditary CP (PRSS1)	7 (14%)
Previous Severe Acute Pancreatitis	1 (2%)
Pancreas divisum	1 (2%)
Previous Surgery	
Beger's Procedure	8 (16%)
Spleen preserving left pancreatectomy	2 (4%)
Pseudocyst jejunostomy	3 (6%)
Pancreatectomy necrosectomy	1 (2%)
Analgesia*	
Parenteral strong opiates	3 (6%)
Enteral strong opiates	21 (43%)
Enteral weak opiates	20 (41%)
Non-opiates	2 (4%)
No analgesia	3 (6%)
Performance status	
0	5 (10%)
1	11 (22%)
2	9 (18%)
3	22 (43%)
4	1 (2%)
Unknown	3 (6%)
ASA Grade	
I	4 (8%)

II	37 (73%)
III	8 (16%)
IV	2 (4%)
Employment status	
Unemployed (medical reasons)	31 (61%)
Employed	15 (29%)
Retired	3 (6%)
Unknown	2 (4%)

*Preoperative analgesic usage was unknown in 2 patients.

Table II – Frequency and percentage of observed radiological features

Radiological Feature	Number Assessed	Frequency (percentage)
Parenchymal calcification	48	38 (79%)
Dilated main pancreatic duct	46	26 (57%)
Pancreatic atrophy	48	21 (47%)
Pseudocyst	47	19 (40%)
Vascular involvement	44	12 (27%)
Ductal calculi	45	11 (24%)
Dilated main bile duct	48	8 (17%)
Pancreato-peritoneal fistula	47	1 (2%)

Table III. Post-operative complications

Dindo-Clavien Classification Grade	Complications 1996-2003	Complications 2003-2016	Total Number of patients
I	Surgical site infection (n=1) Delayed gastric emptying (n=2) Splenic infarction (n=1)	Surgical site infection (n=1)	5
II	Abdominal collection (n=1) Chest infection (n=1) Subclavian vein thrombosis (n=1)	Abdominal collection (n=2)	5
IIIa	Biliary stricture - stented (n=1) Collection/abscess - interventional drainage (n=3)	Biliary stricture- stented (n=1) Collection/abscess – interventional drainage (n=1)	6
IIIb	Duodenal stenosis – duodeno-duodenostomy (n=1)	None	1
Iva	Re-laparotomy for bleeding, single organ failure (n=1)	None	1
IVb	Multi-organ Failure (n=1)	None	1
V	Multi-organ failure, Death (n=1)	None	1
Total	**15**	**5**	**20**

Table IV. Studies since 1980 with 20 or more patients that had a total pancreatectomy for chronic pancreatitis.

First author and reference number	Year of Publication	Number of patients	Operation*	Post-operative complications	Post-operative mortality	Significantly improved pain relief	Weight gain	Post-operative employment (% of patients)
Gall et al [28]	1981	68	TP	**NR	14 (20.6%)	NR	57.7%	28.1%
Cooper [19]	1987	83	TP, DpTP	NR	4 (4.8%)	83%	NR	NR
Flemming [29]	1995	40	TP, DpTP, SpTP	15 (37.5%)	2 (5%)	79%	NR	NR
Russell [20]	1995	52	Tp, DpTP	27 (51.9%)	2 (3.8%)	39%	NR	NR
White [21]	2000	35	SpTP, TP	10 (28.6%)	1 (2.9%)	82%	NR	NR
Garcea [30]	2009	85	DpTP, SpTP, TP (+/- AIT)	13 (15.3%)	3 (3.5%)	73%	NR	NR

*Type of operation: TP = Total pancreatectomy, DpTP = duodenum-preserving TP, SpTP = Spleen-preserving TP, AIT = Auto islet transplantation. **NR=not reported.

LEGENDS TO FIGURES

Figure 1. Operative field following duodenum preserving and spleen preserving near-total pancreatectomy.

Figure 2. Clinical examples of radiological features.

Figure 2a and b. Female with idiopathic (CFTR mutation) chronic pancreatitis. Extensive parenchymal and ductal calcification is seen throughout the pancreas with significant upstream main pancreatic duct dilatation and parenchymal atrophy. Figure 2c. Female with PRSS1 N29I mutation (hereditary pancreatitis). Calcification within the pancreatic head and upstream and main pancreatic duct dilatation. Significant disease progression over 12 months with large volume abdomino-pelvic pancreatic ascites from a pancreato-peritoneal fistula and new gastric and splenic venous collateralisation.

Figure 3. Post-operative pain scores at each follow-up time period.

Figure 4. Proportion of patients classified by strongest analgesic group used at each follow-up time period.

Figure 5. Analgesic use in oral morphine equivalents at each follow-up time period
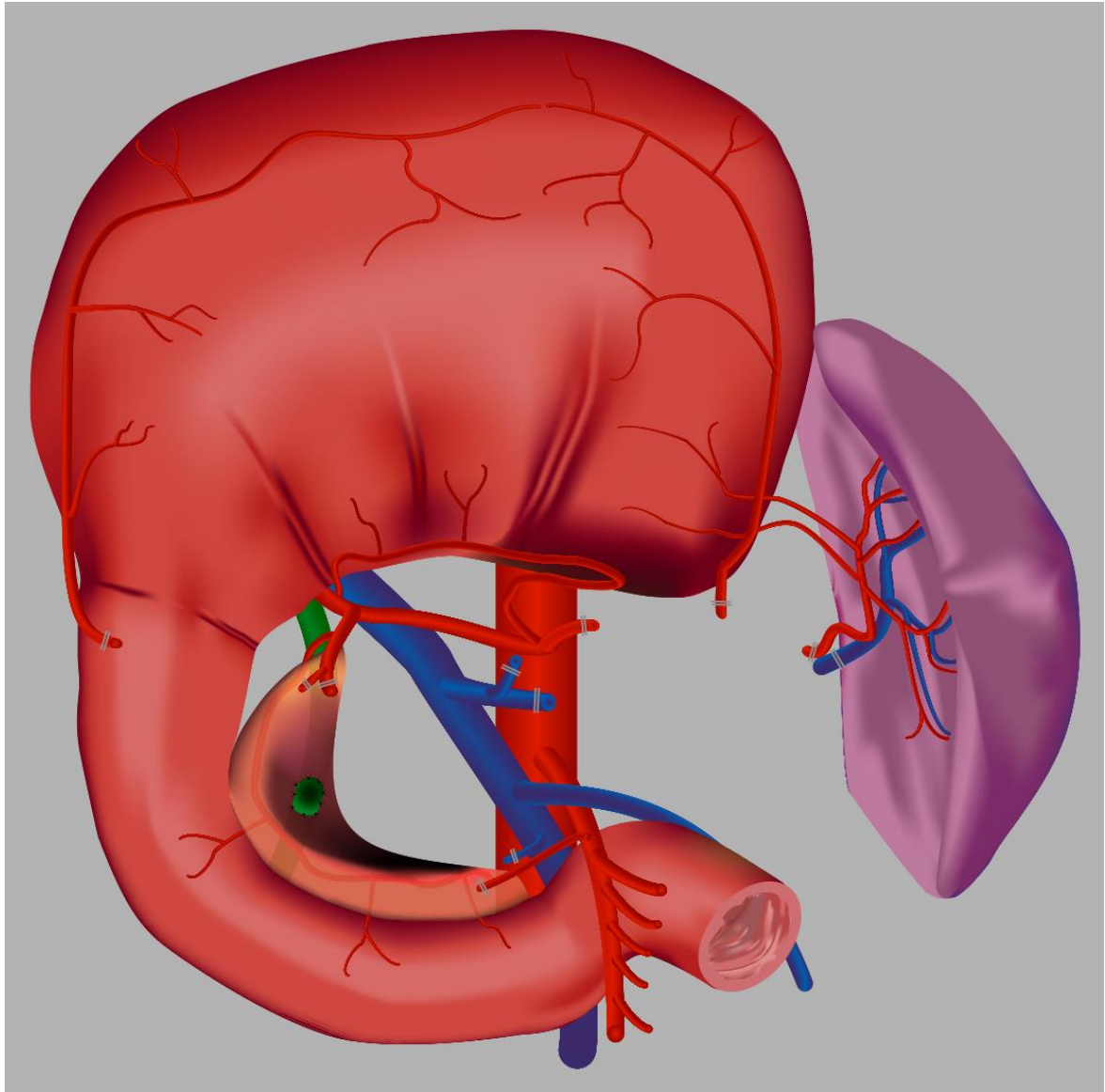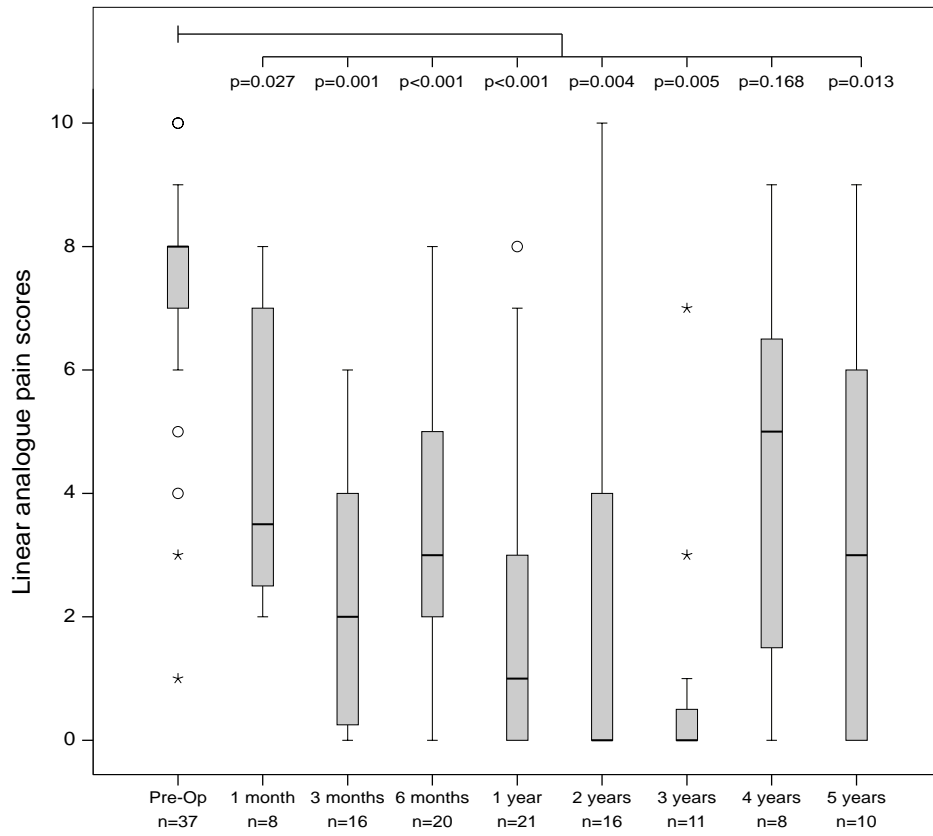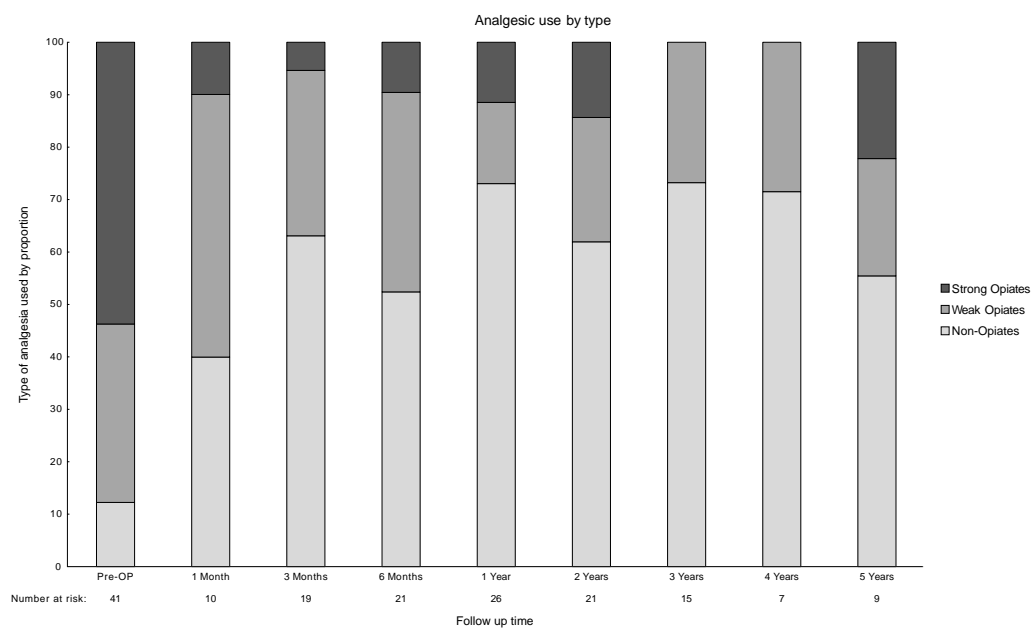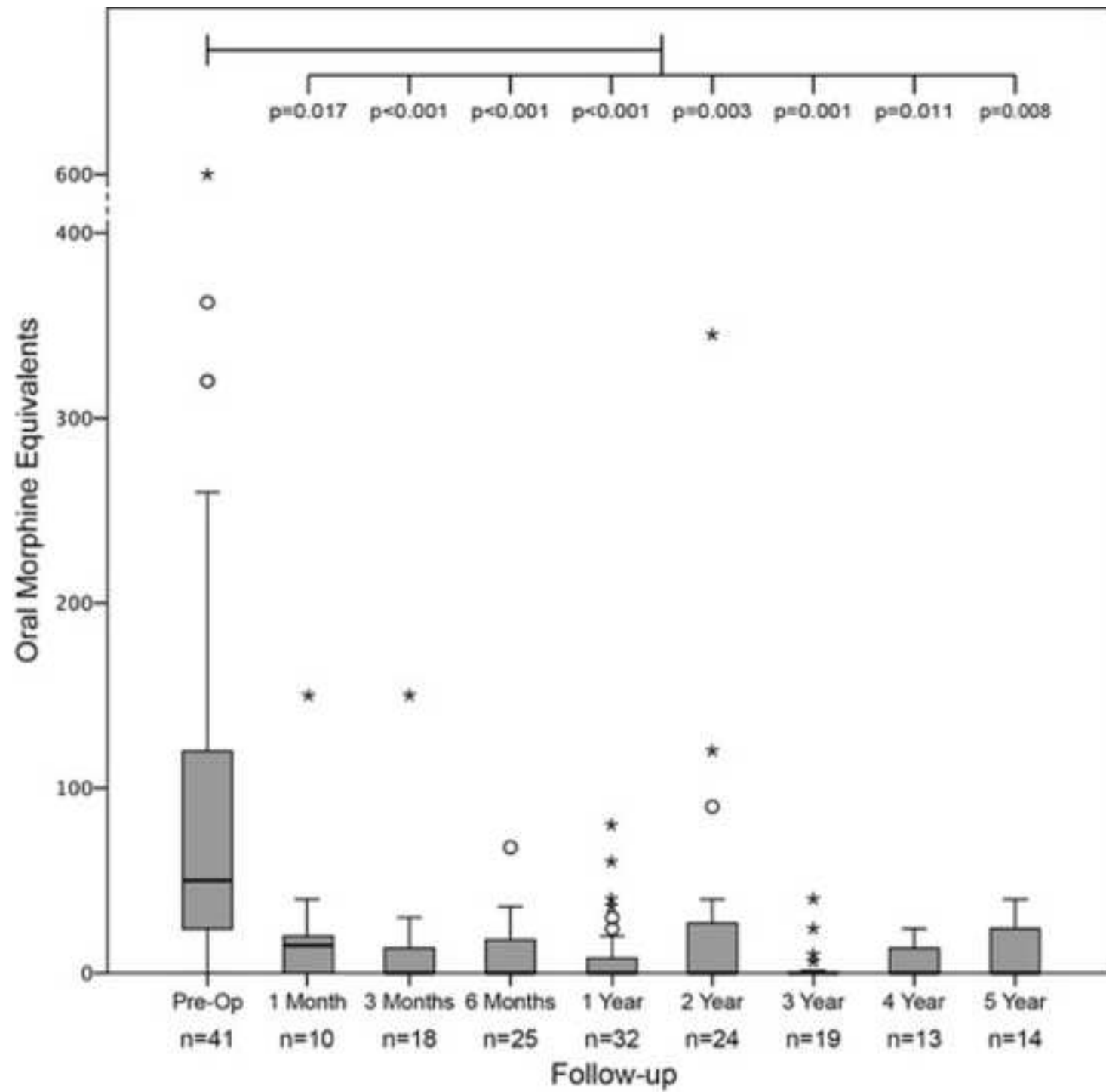
Figure 1

Figure 2

Figure 3

Figure 4

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