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ABSTRACT

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Keywords: pancreaticoduodenectomy pancreatic fistula hemorrhage gastric emptying post operative complication.

Classification: NLMC CODE: WG 590

Language: English

London Journals Press

LJP Copyright ID: 392811

London Journal of Medical and Health Research

Volume 21 | Issue 4 | Compilation 1.0

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ABSTRACT

Pancreaticoduodenectomy remains a major ther-a- py in the management of adenocarcinoma of the head of the pancreas and the biliary-digestive tract tumors. Postoperative morbidity and mortality remain high. An operative mortality less than 5% in reference centers but can up to 25-50% in others hospitals. These complications are diverse, namely, early hemorrhage, which has the highest postoperative mortality rate, pancreatic fistula, which remains the feared complication, with its attendant complications, and Delayed Gastric Emptying, which remains the most frequent. The CT scan remains the gold standard for monitoring and detecting. No precise etiology could be found for these complications but some risk factors were found. The management of these complications depends on the degree of damage and the hemodynamic state of the patient. The International study group of pancreatic surgery (ISGPS) proposed a classification to harmonize the diagnosis, the degree of these complications, and the appropriate management.

Keywords: pancreaticoduodenectomy-pancreatic fistula-hemorrhage-gastric emptying- post operative complication.

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I. INTRODUCTION

Pancreaticoduodenectomy (PD) is an operative technique developed by Whipple in 1935 for the treatment of 3 patients with periampullary tumors [1]. The main indication is tumors of the pancreaticobiliary junction and, in order of frequency, adenocarcinoma of the head of the pancreas, ampulla of Vater, biliary and duodenal tumors. The others are chronic pancreatitis and neuroendocrine tumors. It has a high mortality and morbidity rate. It has been improved over time. It consists of resection of the duodeno - pancreatic block, ligation of the gastroduodenal artery, cholecystectomy. It will be completed by 3 types of anastomosis (figure 1) namely:

- Pancreaticojejunostomy or pancreatic - gastric
- anastomosis
- hepaticojejunostomy
- Gastrojejunostomy

This technique has developed considerably overtime and other variants of the classic technique have been developed in order to reduce complications [2,3]. This mortality and morbidity rate is linked to postoperative complications which are dominated by hemorrhage and pancreatic fistula, which remains the most dreaded. Other complications include vascular complications (thrombosis, arteriovenous fistulas), leaks from anastomoses, biliary fistula, abscesses, Delayed Gastric Emptying, and tumor recurrence. The CT scan plays an important role in the detection of complications. It is correlated with the patient's clinical and biological data. Depending on the case, the most serious complications require a surgical revision [3].

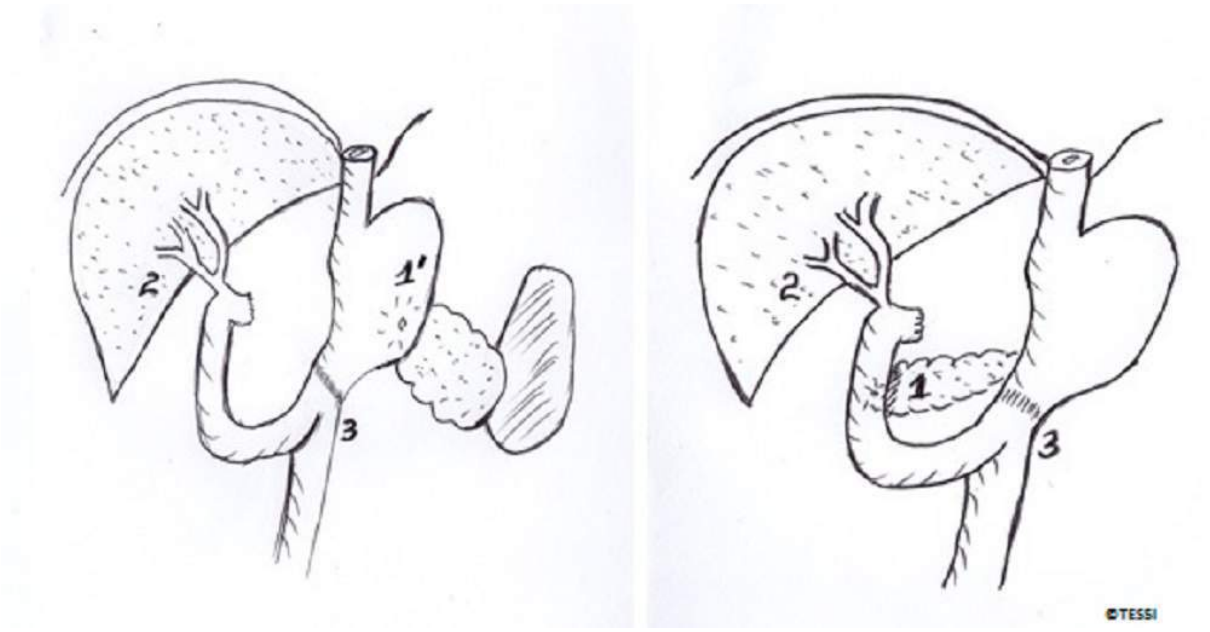

Figure 1: Figure of the anastomoses 1- Pancreatico-jejunal anastomosis 1'- Pancreatico-gastric anastomosis 2- Bilio-jejunal anastomosis 3- Gastro-jejunal anastomosis

II. MORTALITY AND MORBIDITY OF COMPLICATIONS

PD is still indicated for peri-ampullary tumors, particularly adenocarcinoma of the head of the pancreas. Curative surgical resection is the only treatment likely to bring a cure at the cost of high operative morbidity which is less than 5% in reference centers [3]. Juli Busquets et al, in a study, carried out in a specialized center, found a similar 7% postoperative mortality rate in patients with adenocarcinoma of the pancreas who had undergone PD [4]. Peterman D. et al, in a specialized center, found a rate of 6% mortality at 30 days post-op [5]. Morbidity remains high and is between 20 - 50 % depending on the definitions used [6,7]. Mehta et al, found similar results with mortality of 2.3% and morbidity of 59% [8]. These postoperative complications are in order of frequency: Delayed Gastric Emptying, infections (intra-abdominal abscesses and wound infections), fistulas (mainly pancreatic, but also biliary and digestive), hemorrhage, pancreatitis, cholangitis and, postoperative ileus [5-7,9]. The most frequent postoperative complications of PD are delayed gastric emptying (DGE) in 20% and pancreatic fistula (PF) in 10-15% [5].

In order to standardize studies on complications, the International study group of pancreatic surgery (ISGPS) has proposed a standard classification (Table 1) [10-12]

Table 1: Major complications of duodenopancreatectomy grade (ISGPS)

NGT: Nasogastric tube		
Most common complications of duodenopancreatectomy International study group of pancreatic surgery definitions		Degrees of severity
Delayed Gastric Emptying	Inability to resume feeding (IRF) Standard at Day 7 and prolonged need for NGT	A: IRF D7 and NGT 4-7 days or reinsertion after D 3 B: IRF D14 and NGT 8-14 days or reinsertion after D7 C: IRF D21 and NGT >14 days or reinsertion after D14

Postoperative pancreatic fistula	Drainage containing > 3 x serum amylase value from D 3	A: no clinical consequences B: requires adjustment of postoperative management C: serious situation requiring heavy treatment
Hemorrhage	Can occur <24h00 or > 24h postop, intraluminal or extraluminal, moderate or severe	A:<24h00, intra- or extraluminal, medium severity B: <24h00, intra- or extraluminal, severe severity > 24h00, intra- or extraluminal, medium severity C: >24h00, intra- or extraluminal, severe severity

III. CT SCAN ROLE

Imaging plays an important role in the detection of these postoperative complications, particularly CT scans, which remain the gold standard in the postoperative follow-up of patients who have undergone PD. The analysis will find the different anastomoses (Figure 2, 3, 4). In the absence of clinical signs and postoperative complications, a CT scan is performed within 3 to 6 months. The technique will be a CT scan without injection and then a CT scan injected with radiologic contrast fluid at 3 to 5ml/s speed, with an acquisition at an arterial time at 30seconds and, then a portal time between 60-90 seconds. This will be followed by multi-planar 3D reconstructions [13]. These results must be correlated with the clinical examination and the biological work-up as appropriate. E. Cuellar et al, in a study on the contribution of CT scans in the postoperative period, noted that a systematic CT scan was performed with an average delay of 7.6 ± 0.8 days after surgery. Of the 138 CT scans analyzed, 94 (68%) were considered normal and 44 (32%) abnormal. The sensitivity of routine CT was 55% with a specificity of 75%. The positive predictive value was 39% and the negative predictive value was 85%. Routine CT scan may lead to early detection of complications in association with the presence of clinical and biological symptoms [14].

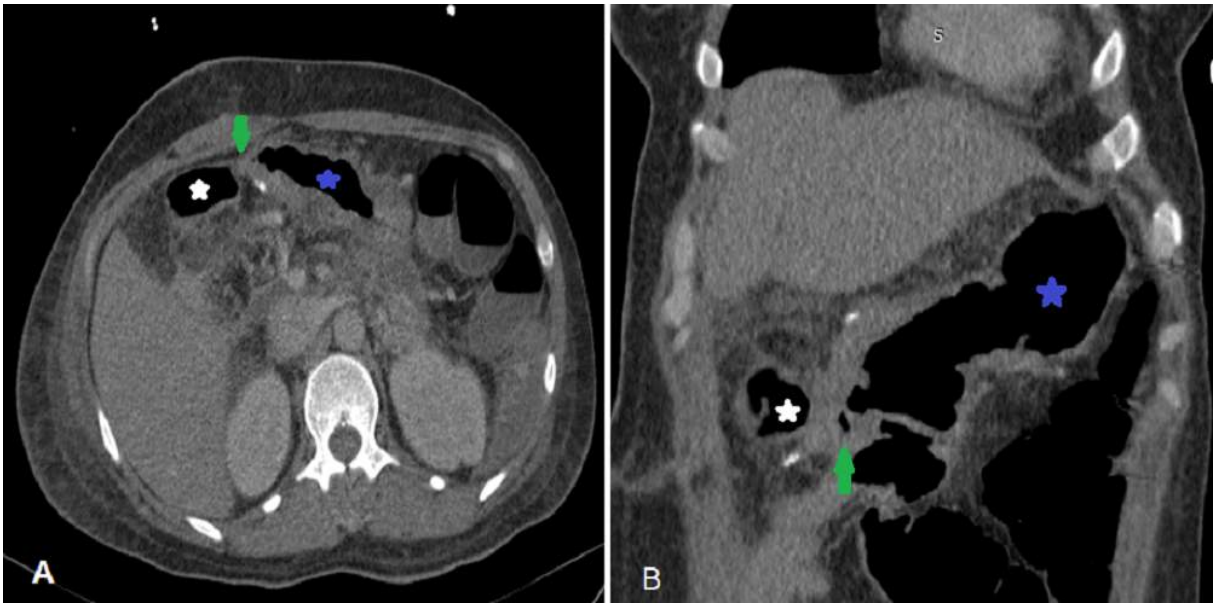

Figure 2: Non-injected abdominal and pelvic CT in axial (A) and coronal (B) sections showing the gastrojejunal anastomosis (green arrow) between the stomach (blue star) and the jejunum (white star). Note the presence of some spontaneously hyperdense clips

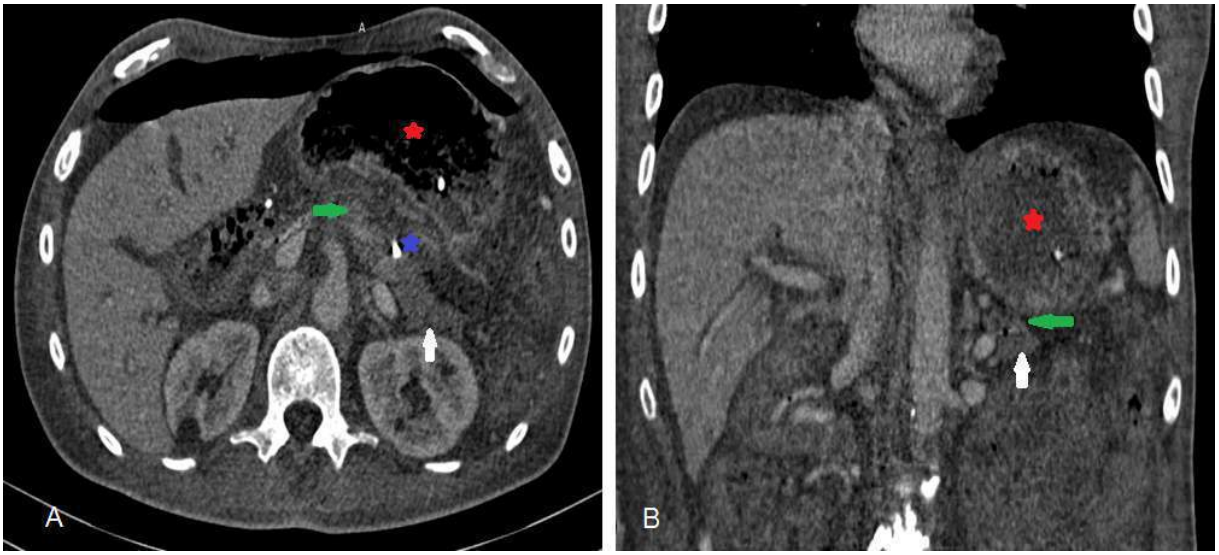

Figure 3: Non-injected abdominal and pelvic CT in axial (A) and coronal (B) sections showing the pancreatic-gastric anastomosis (green arrow) between the stomach (red star) and the residual pancreas (white arrow). Note the presence of external pancreatic stent (blue star)

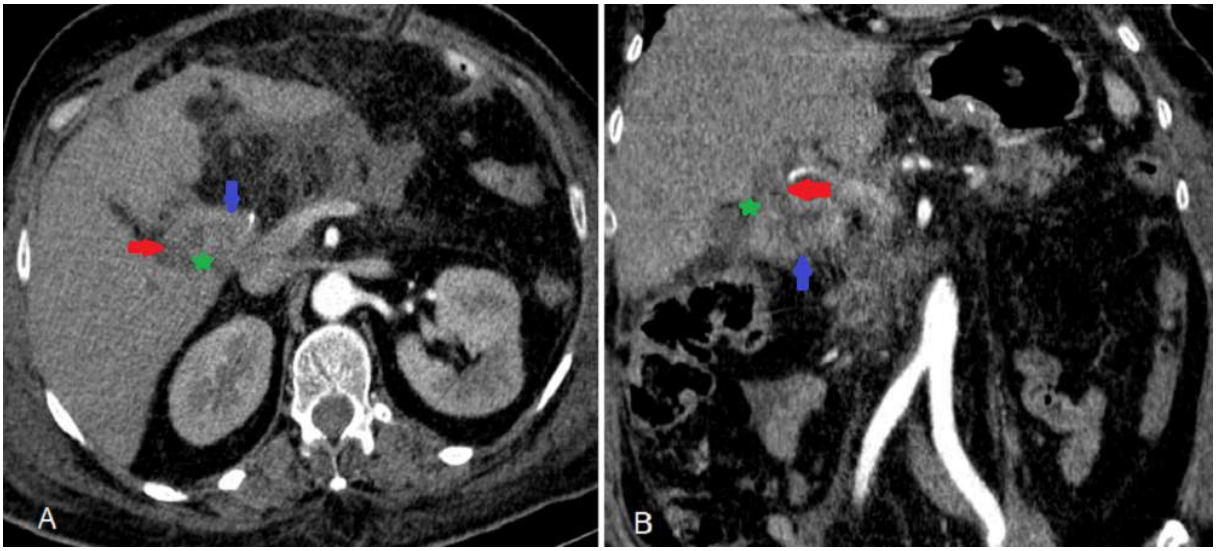

Figure 4: Abdominal and pelvic CT injected at an arterial phase in axial (A) and coronal (B) sections showing the biliary digestive anastomosis (green star) between the jejunum (blue arrow) and the residual bile duct (red arrow)

IV. POSTOPERATIVE PANCREATIC FISTULA (POPF)

4.1 Diagnosis and CT scan findings

The amylase level in fluid and/or drain is recognized as the undisputed biochemical definition of POPF, but amylase activity can range from 100 to 1000 International Units depending on glandular activity. A clinically relevant POPF is defined as a drain output of any measurable volume of fluid with amylase level greater than 3 times the upper Institutional normal serum amylase level, associated with a clinically relevant development/condition related directly to the PF [11]. The CT scan shows, the presence of air bubbles and a collection opposite the pancreatico-jejunal or pancreatico-gastric anastomosis (figure 5) [13]. In a severe complications and in all patients with an aerated peripancreatic collection on the 5th aerated peripancreatic collection had a sensitivity and a sensitivity of 25% in the detection of study by E. Cuellar et al, the presence of an of 87% postoperative day on CT, the diagnosis of POPF was confirmed [14]. Clinically, POPF should be suspected early (on postoperative day 3) based on the quality of the drainage fluid. The drain plays an important role in the diagnosis [14]. However, it must be confirmed by observation over a period of time, as postoperatively there is inflammatory serositis not related to an anastomotic leak. Indeed, it is only after clinical recovery is complete that it is possible to distinguish and classify the POPF into grades A, B, and C according to the clinical impact. The volume of fluid output over a day is relative, as demonstrated by the wide range reported in the literature [15].

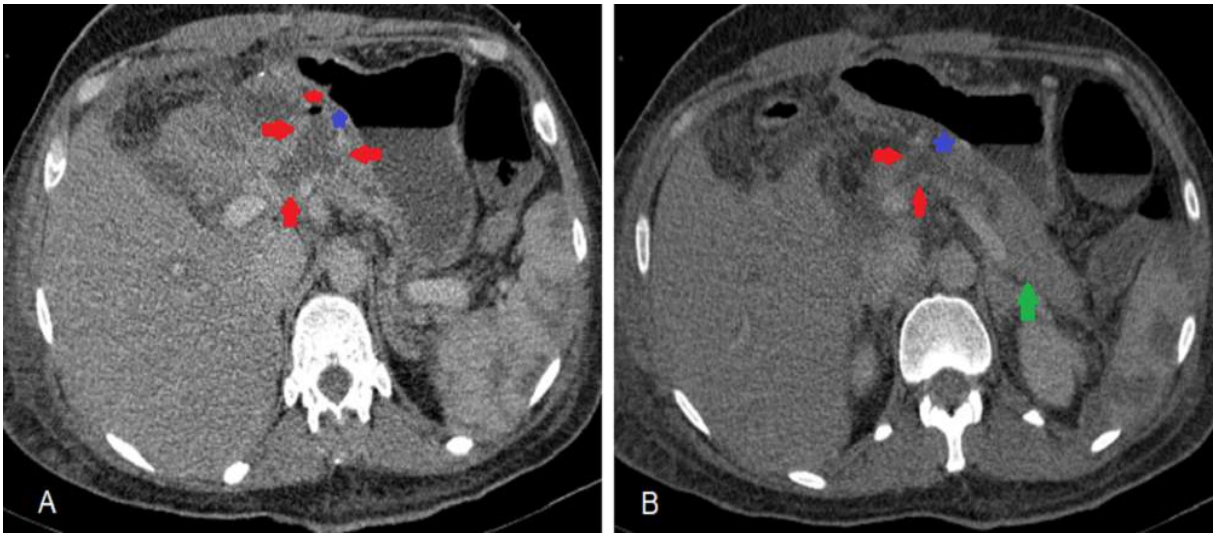

Figure 5: Abdominal and pelvic CT injected at portal phase in axial section (A and B) showing a collection (red arrow) with an air bubble (red star) opposite the pancreatic-gastric anastomosis (blue star) and the residual pancreas (green arrow) on the 5th postoperative day with a high amylase level in the draina

There are three grades of severity for pancreatic fistulas, according to The ISGPS 2016 update based on clinical, radiological, and therapeutic criteria and outcomes. (Figure 6) [11]:

- Grade A: BL (biochemical leak): Formerly grade of POPF ; a “biochemical fistula” in the literature, the BL has by definition no clinical impact. In particular, a BL implies no deviation in the normal postoperative pathway and therefore, does not affect the normal postoperative duration of stay

- Grade B: This grade refers to a properly defined fistula involving increased amylase activity in the fluid from any drain in association with a clinically relevant condition. A grade B POPF requires a change in the management of the expected postoperative pathway.

- Grade C: Whenever a grade B POPF leads to organ failure or to clinical instability such that reoperation is needed, the POPF becomes a grade C. Often, stay in an ICU is necessary, and the hospital stay becomes excessively prolonged secondary to the POPE-related problems. For the purpose of POPF classification, postoperative organ failure is defined as the need for reintubation.

Its incidence is approximately 8-25% in patients after PD following pancreatic anastomotic release or fistula. The correlation of the diagnosis of POPF with CT data is important and the diagnosis is based mainly on clinical and biological data [16]. The experiences of Lahey and Mayo Clinics found an incidence of 8% in 403 post-PD patients with direct mortality of approximately 26% [18,19].

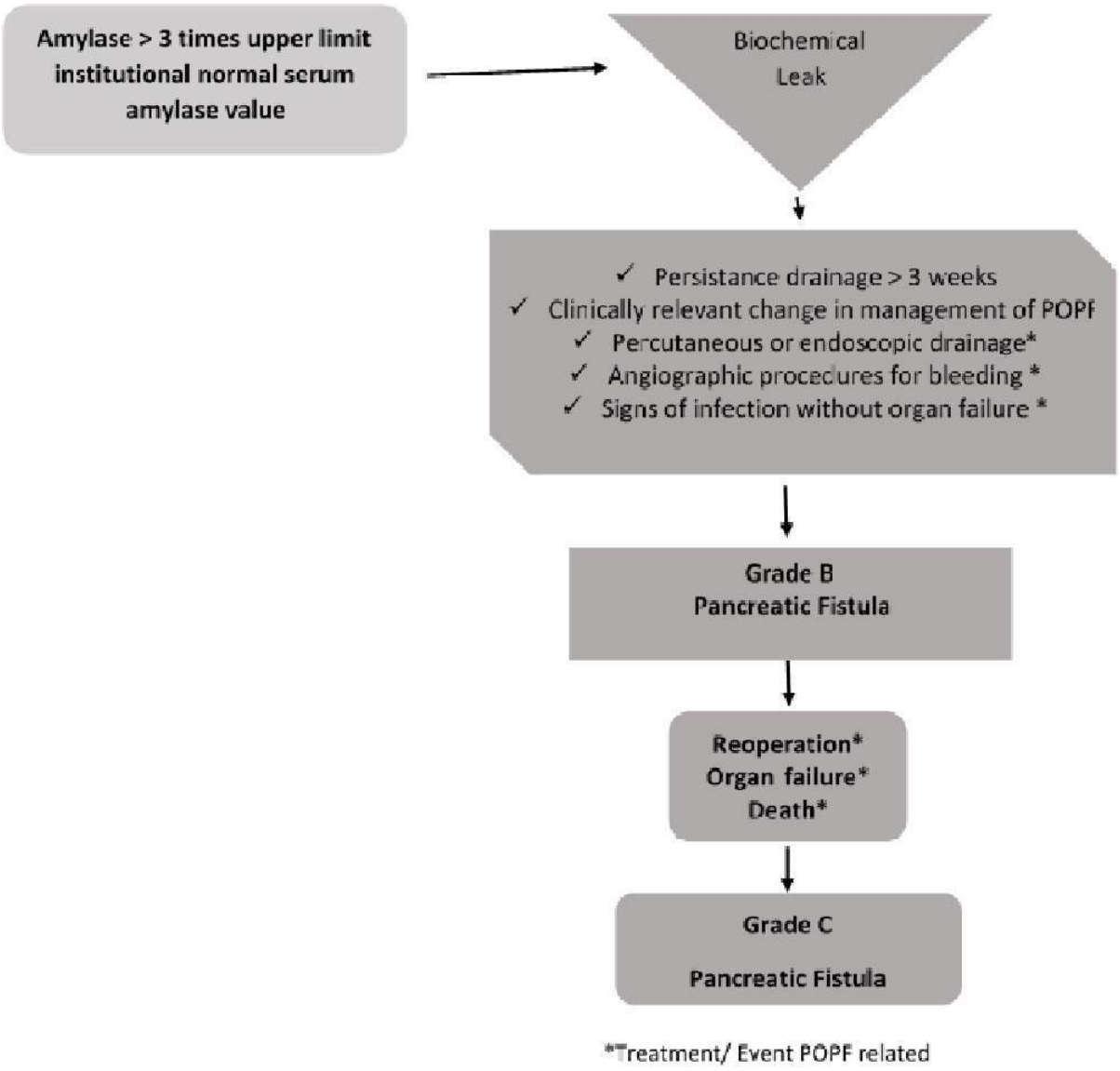

Figure 6: Algorithm for biochemical leak and Postopeartive pancreatic Fistula definition. The 2016 update of the International Study Group (ISGPS)

4.2 Risk Factors For Pancreatic Fistula

Many risk factors have been identified for the occurrence of POPF. For F-H Liu, the size of the main pancreatic duct is a predictive factor for the occurrence of pancreatic fistula [20]. Other authors recognize the important role of the preoperative CT scan in predicting the occurrence of POPF, notably by measuring the density of the pancreatic parenchyma, the smaller diameter < 3mm of the duct of Wirsung, which has a good prognosis

[21,22]. Fibrosis leads to hardening of the pancreas and rigidity of the pancreatic duct, which reduces the risk of postoperative POPF [23].

Some authors blame the decrease in serum albumin postoperatively as a factor in the occurrence of POPF. Fujiwara et al, suggests that the decrease in albumin in the postoperative period is at the origin of a decrease in the systemic anti-inflammatory response, which leads to an immuno nutritional disorder, thus increasing the risk of the occurrence of POPF [24]. For Utsumi et al, the improved nutritional state of the patient allows him/her to better cope with the risk of postoperative POPF [25].

Management of the fistula depends on the degree of severity. Nutritional measures, empirical antibiotic therapy, percutaneous drainage, and octreotide treatment are discussed. Surgical revision is only performed in cases of severe loosening or dehiscence of the anastomosis [13,26]. In a study by C.J. Yeo, approximately 15% of patients received percutaneous drainage, 80% conservative measures, and 5% revision surgery [17]. Bassi C et al found a similar rate of revision surgery in POPF of 3% [27]. For Busquets J et al, in one study POPF was not a risk factor for death post PD surgery [4]. A meta-analysis of English reviews by Pedrazzoli S. of 60,739 patients who underwent PD from 1990-2015 on the relationship between POPF mortality found only 1% mortality due to PD [28]. In a study by Shukla et al, In a two-year multicenter study of 718 cases of PD, POPF accounted for 17% of complications (77% grade A and B), there was clearly no significant association between postoperative mortality and POPF [29]. The use of three drains at the operative site in PD would also play an essential role in reducing complications, particularly POPF. This number varies according to the surgeon's habits and technique but on average between 2 and 3 drains are used in the study by Shukla et al. in the different centers [29]. Colon K et al, in a randomized study on the efficacy of aspiration drainage (external suction system via central suction or electric pump) in the occurrence of postoperative complications and mortality, didn't show the impact of aspiration drainage in reducing POPF or post-operative mortality. As a result, aspiration drainage is not recommended in PD and its place remains to be determined [30].

Other authors have attempted to demonstrate the occurrence of POPF according to the type of pancreatico-jejunal or pancreatico-gastric anastomosis. Shukla et al, in their study of 718 patients who underwent PD, a majority of pancreatico-jejunal anastomosis in 491 patients (68.3%) versus 227 (31%) pancreatico-gastric anastomosis showed no statistically significant benefit in preventing PF [29]. Randomized studies have also failed to show any statistical difference in the prevention of POPF by the different anastomoses [12,27].

4.3 The place of somatostatins and derivatives

The use of octreotide remains controversial. Its inhibitory property on pancreatic hormone secretion has been proposed in order to limit the occurrence of fistula. In the various comparative studies, its effectiveness has not been proven. Its routine use should be limited to centers where the fistula rate is >10%, a residual pancreas remains friable or a Wirsung duct >3mm [3, 31, 32]. C.J. Yeo's experience with the use of octreotide has been inconclusive [17]. Randomized controlled trials in Europe and the United States have shown no benefit from the use of octreotide in the prevention of POPF [33,34]. The same is true in Predrazzoli's meta-analysis of 60,739 patients, which also failed to find a proven beneficial effect of somatostatin and its various analogs (Octre otide, Vapreotide.....), with no statistical difference in the impact on the incidence and mortality of POPF [28].

4.4 Intubation of the pancreatic duct (Figure 7)

Other authors have studied the impact of stenting during PD. Roder J et al, in a study of 41 patients, reported that the rate of occurrence of POPF in the group of patients without pancreatic duct stenting was 6.8% compared to 29.3% in patients with pancreatic duct intubation, suggesting an increased risk of fistula in patients with pancreatic duct intubation, which calls into question this method [35].

In the meta-analysis by Pedrazzoli S, there was no significant difference between non-stented (pancreatic duct), external stent, and internal pancreatic duct stent patients with respect to POPF mortality and overall PD mortality. No conclusion could be drawn from this analysis regarding the impact of stenting on PD [28]. A meta-analysis by Dong Z et al, on 1018 patients, notes that external stenting may have a beneficial effect in preventing POPF and reducing the length of hospital stay for patients, but due to low statistical evidence, the benefit between no stenting, and external or internal stenting remains uncertain. Therefore, a rigorous randomized trial is needed to reach a reliable conclusion [36].

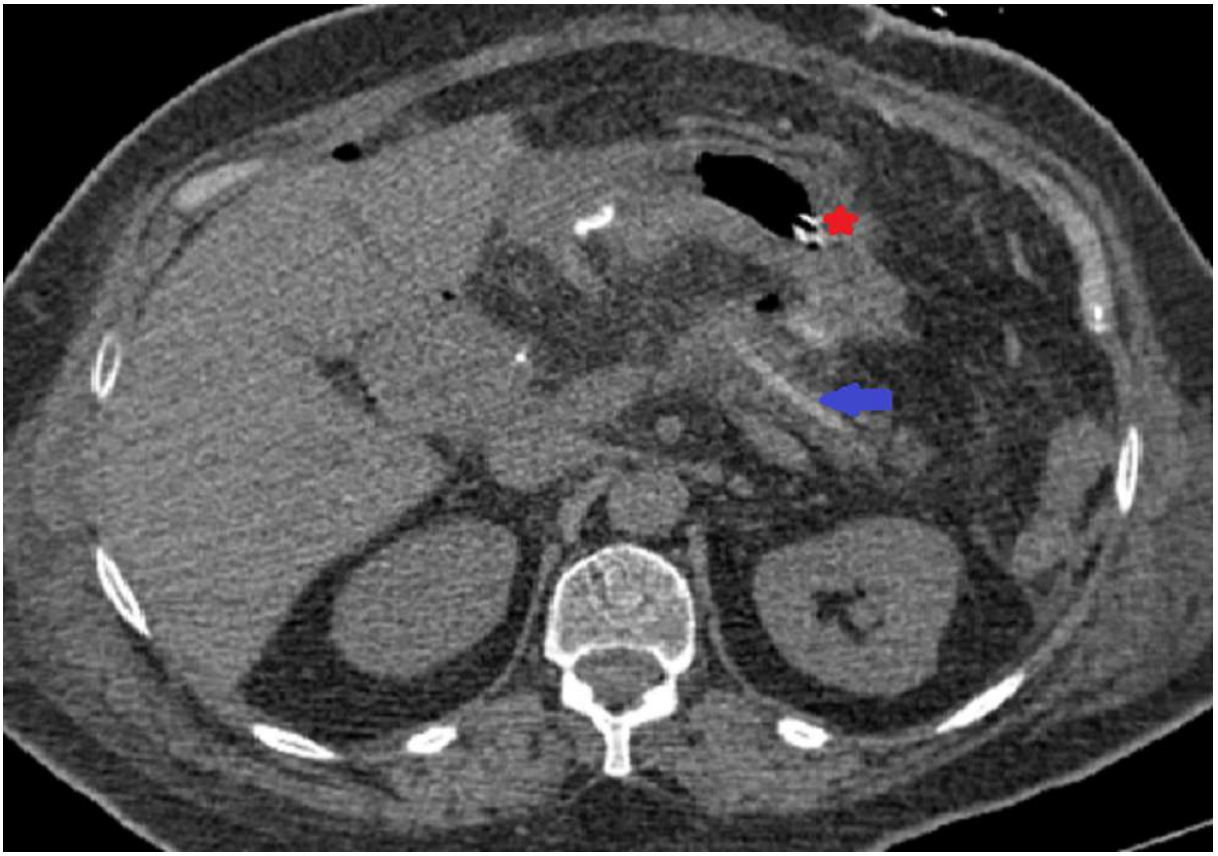

Figure 7: Non-injected abdominal and pelvic CT showing an internal stent (blue arrow) of the residual pancreas postoperatively. Note the presence of a nasogastric tube (red star)

V. POSTOPERATIVE HEMORRHAGE

Postoperative hemorrhage is defined as intra- or extraluminal bleeding, early if it occurs within 24 hours of surgery or late otherwise [10]. The severity of bleeding is classified into three groups according to the ISGPS: moderate severity bleeding (group A) if medical treatment alone is sufficient, severity bleeding if intervention is required (group B) or if the patient is in shock (group C)(Table 1). Sentinel hemorrhage is defined as the presence of a small amount of blood in the drains or in the nasogastric tube (NGT) [15, 37, 38]. It remains a rare complication of PD, but with a high mortality rate. Shukla P et al. found an incidence of 6% in the postoperative complicati- on cations of PD [29]. Jacquemin found in his study of 194 postoperative PD patients over a period of three years, an incidence of 17.5% (34/194) with a high 90-day mortality rate of 17.6% (6/34) [37]. Raman et al. in their study reported an incidence of 4% with a high mortality rate of 38% [39,40].

These hemorrhages can be subdivided into two groups: early hemorrhages in the first 24 hours most often related to bleeding from the stump of the gastroduodenal artery (Figure 8) due to a ligation defect. Late hemorrhage generally occurs

on the 5th postoperative day in relation to a vascular anomaly involving the mesenteric vessels, or an erosion of the hepatic artery, the celiac trunk, the splenic artery, but also a pseudoaneurysm of the stump of the gastroduodenal artery [13, 39, 40]. This hemorrhage can be externalized by the intraluminal digestive route in the form of hematemesis or melena or extraluminal via the drains. Jacquemin M. found that in 65% (n=22 /34) of cases, the bleeding was externalized by the drains, 38% (n=13/34) by the digestive tract, 18% by hematemesis or by the presence of blood in the NGT (n=6/34) and 21% by melena. Bleeding was externalized through the drains in 63.2% (n=12/19) of cases and through the gastrointestinal tract in 42.1% (n=8/19). In total, 55% (n=19) of the patients presented a sentinel hemorrhage. It preceded 37.5% (n=6/16) of arterial bleeds, 100% (n=4/4) of venous bleeds and 43% (n=6/14) of anastomotic bleeds [37].

Figure 8: Abdominal and pelvic CT scan injected at the arterial phase showing the stump of the gastro duodenal artery without any anomaly (red arrow) postoperatively. Note the presence of a clip (blue star)

5.1 Imagery

The CT scan remains a means of diagnosis, especially at the arterial stage, except in cases of hemodynamic instability of patients. It highlights spontaneous hyperdensity in relation to the vessels or the surgical site or extravasation of contrast product; a pseudoaneurysm or a vascular anomaly may be detected at a later stage and will guide the angiography for good identification of the surgical site [40].

In a study by Wolk on the management of post-PD bleeding, a CT scan was performed in 83% of cases before endovascular treatment, the bleeding

sites involved in most cases were the hepatic artery 19,2% (10 cases), the stump of the gastro-duodenal artery 36.5% (19 cases), followed by the splenic artery 15.4% (7 cases), the celiac trunk 11.5% (6 cases), the dorsal pancreatic artery 1.9% (1 case), and the inferior pancreaticodu- odenal artery 1.9% (1 case) [41].

5.2 Risk factors

Certain factors would be linked to the occurrence of early or late postoperative hemorrhage, namely, POPF, followed by abdominal infections [37, 42]. The explanation would be the erosion of the vascular walls, weakening of the anastomoses by abdominal infection, by lytic pancreatic juice; it should be noted that aneurysm formation would also play a large role in the occurrence of these hemorrhages [37,42].

5.3 Treatment

Management depends on the hemodynamic status and the cause of the hemorrhage. In the case of hemodynamic stability and arterial hemorrhage, the first-line treatment is angiography. The artery involved may be embolised or a stent placed [43]. Yekebas EF et al, in a series of 1669 pancreatic resections, recommended angiography for sentinel hemorrhage because of its association with the arterial origin [44]. If these procedures fail, a second attempt to avoid repeat surgery may be considered with a high excess mortality rate due to surgical site inflammation, adhesions, and tissue friability [45]. For intraluminal hemorrhage, digestive endoscopy is of great interest. In the case of pseudoaneurysms, angiography shows better efficacy and good prevention of aneurysmal rupture [46]. The current treatment of pseudoaneurysms is based on radiological embolization using coils. Surgical revision is technically difficult, exposes a high risk of bleeding, and may result in the completion of pancreatectomy with the consequence of diabetes that is difficult to control. Radiological embolization is less burden some for the patient and its effectiveness is between 63% and 100% [46-49].

VI. DELAYED GASTRIC EMPTYING

Delayed Gastric Emptying (DGE) is defined as failure to resume normal feeding by the end of the first postoperative week, with prolonged maintenance of a nasogastric tube aspiration or its reintroduction. It accounted for approximately 19-57% of the patients operated on [5]. It remains the most frequent complication of PD with an incidence varying between 14-36% for Sastre B. et al [3]. Sakamoto et al, in a study of 387 postoperative patients with PD, found a similar rate of 38% [50]. Its mechanism is multifactorial and remains poorly understood. It is thought to be secondary to a disturbance of gastric innerva- tion secondary to surgery. For Kunstman JW et al, the occurrence of other complications at the surgi- cal site could also explain this DGE, notably POPF, abscesses, and severe blood loss during the operation [51]. Another factor is gastric atony on the one hand in response to the reduction of motilin levels in circulation and on the other hand the resection of the duodenal stimulator and the disturbance of gastroduodenal innervation [52, 53].

The CT scan remains an excellent diagnostic tool for the visualization of gastric distension with stasis [14] (Figure 9).

The ISGPS proposes a classification based on the inability to resume feeding a standard diet (IRF) on the 7th postoperative day and the prolonged heed for a nasogastric tube. It recognizes three evels of severity A, B, and C (Table 1).

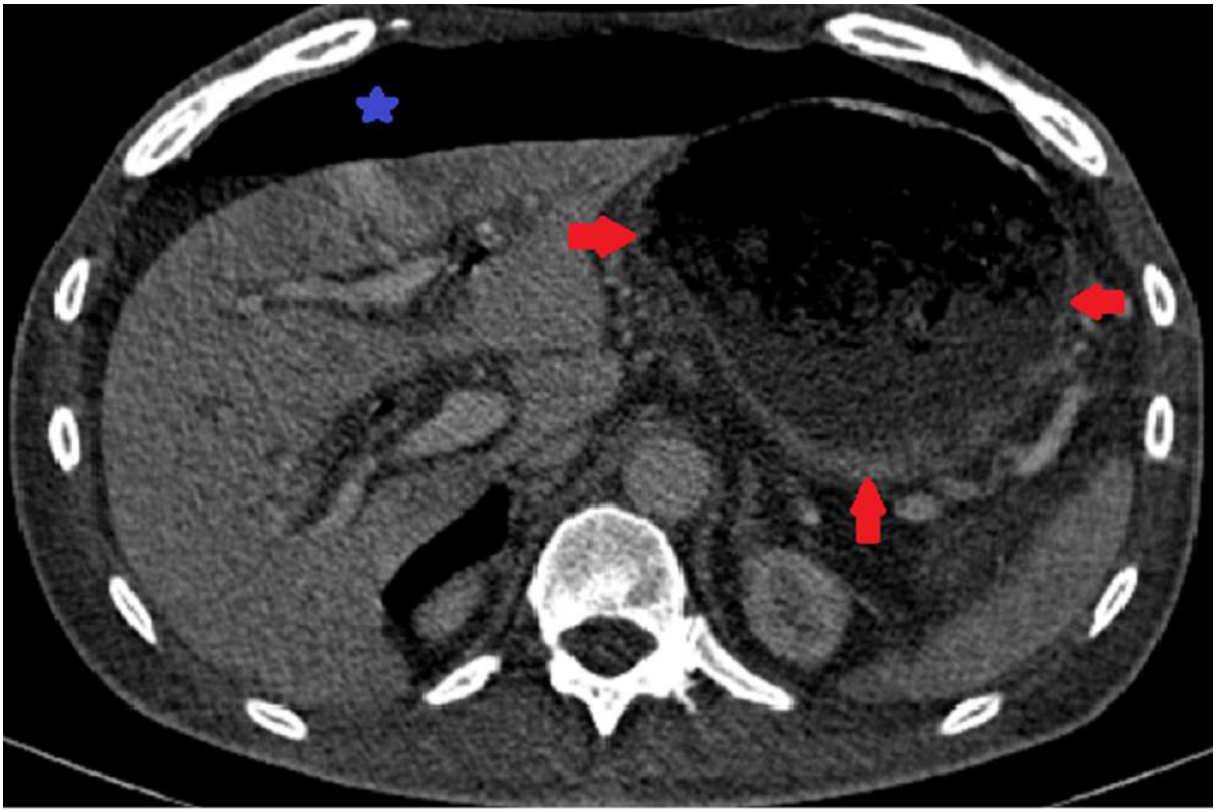

Figure 9: Abdominal and pelvic CT injected at the portal phase in axial section showing a stasis stomach (red arrow) in a patient on the 7th postoperative day who presented with intermittent vomiting. Note a postoperative pneumoperitoneum (blue star)

VII. THE PLACE OF ERYTHROMYCIN

Erythromycin is thought to play a role in the early resumption of feeding postoperatively, thus reducing the rate of DGE. Yeo et al, in a study of 118 patients divided into two groups: group 1 receiving erythromycin and the other saline: the results show an early resumption of feeding in group 1 and a reduction in the occurrence of DGE to 19% in group 1 and 30% in group 2. Therefore, He concluded that erythromycin accelerated gastric emptying and reduced the rate of postoperative gastroparesis [54]. Ohwadda et al. found similar results for the use of erythromycin postoperatively in the early resumption of gastric emptying and reduction of DGE rates [55].

VIII. CONCLUSION

Pancreaticoduodenectomy remains an operative technique in the management of tumors of the bilio-pancreatic crossroads. It remains fraught with complications, the most prominent of which are hemorrhage with a high mortality rate, very frequent delayed gastric emptying, and pancreatic fistula which remains a dreaded complication. Other complications are also observed, notably infections/abscesses, vascular complications, anastomosis loosening and later recurrence, and others.

The CT scan remains an excellent imaging tool for post-operative follow-up and for detecting various complications. These data must be associated with the patient's clinical condition and the biological assessment.

Several factors have been identified in the occurrence of these major complications including pancreatic fistula. These factors require further study to provide statistically proven results for a reduction in postoperative mortality and morbidity.

IX. DISCLOSURES

Data Availability: The data used to support the findings of this study are included within the article.

Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info**: All authors have declared that no financial support was received from any organization for the submitted work.

Funding statement: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work.

Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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