

Total Pancreatectomy with Islet Auto-transplantation in Chronic Pancreatitis is the Call of our Time

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Received: 3 June 2025 / Accepted: 24 June 2025 / Published online: 20 July 2025

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Abstract

Introduction: Total pancreatectomy with islet auto-transplantation is a realistic therapeutic choice and an advanced surgical operation for individuals with chronic pancreatitis.

The primary purpose of total pancreatectomy with islet auto-transplantation is to alleviate the debilitating pain caused by chronic pancreatitis and thereby significantly improve the quality of life of patients with chronic pancreatitis. Although the permanent loss of the function of the pancreatic endocrine occurs due to total pancreatectomy, it may be substituted by autologous transplantation of islets.

Patients receiving total pancreatectomy and Islet Transplantation may be less dependent on insulin than patients receiving total pancreatectomy. This process, although not without some difficulties, has consistently demonstrated promising results in reducing pain, improving glycemic control, mitigating diabetic complications, and enhancing the overall quality of life in patients with chronic pancreatitis. In this article, we review the global experience with Total pancreatectomy with islet auto-transplantation and examine the prospects for its implementation in the Albanian health system.

They can alleviate the burden of chronic pancreatitis, improve patients' prognosis, and enhance the country's healthcare system capacity. However, the introduction will also necessitate a strategic transformation of infrastructure, training, and health policy, which is discussed below.

Conclusions: Total pancreatectomy with islet auto-transplantation is a novel, effective treatment option for patients with recurrent acute pancreatitis and those with chronic pancreatitis. Its implementation in Albania, while promising, necessitates strategic reforms in infrastructure, training, and health policy. However, if constructed as a secondary project with the aim of institutional support, these reforms can significantly increase the quality of care for patients with chronic pancreatitis in our country.

Keywords: islet auto transplantation, pancreatectomy, chronic pancreatitis, diabetes, quality of life.

Original article, no submission or publication in advance or in parallel

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Introduction

Chronic pancreatitis (CP) is a fibro-inflammatory process that leads to irreversible alterations in the structure of the pancreas and impairment of exocrine and endocrine function in its wake. [1] Chronic pancreatitis can follow an episode of acute pancreatitis of any cause, particularly in those individuals who have multiple recurrent episodes of acute pancreatitis. [1, 2, 3]

CP syndrome results from the development of exposure to risk factors (both environmental and genetic). It is characterized by derangements in pancreatic structure (apparent in imaging or endoscopic studies) and function (digestive function and insulin release).

Chronic pancreatitis can produce numerous symptoms and signs, the most apparent of which is abdominal pain, a quality of life (QoL) concern, and the most significant surgical indication.

The etiology of pain arises due to increased pressure, pancreas ischemia and inflammation, trauma, changes in pain transmission of nociceptive neurons, and possible complications.

Pain, indigestion, pancreatogenesis diabetes, and complications need to be controlled in chronic pancreatitis. To reduce pain and improve QoL, surgical treatment is considered for CP or RAP patients with non-responsiveness to medical or endoscopic treatment. [4, 5]

Total pancreatectomy is a significant operation with potential mortality and significant morbidity. It is reserved for patients with intractable pain, failed medical treatment, and poor candidates for less surgery (Fig. 1).

History

In the 1970s, pancreatectomized dogs were used in experiments demonstrating that diabetes could be prevented by transplanting unpurified pancreatic islet tissue, dispersed by collagenase digestion, into the portal vein or spleen. [6, 7]

The initial trials of islet cell transplantation in humans were published in 1974, using isolated islets from cadaveric donors to treat diabetes. [8] Total pancreatectomy has been performed since the 1970s, and the operation has increased

over the last two decades.

In 1992, *Pyzdrowski et al.* [9] pointed out that an intrahepatic transplant of as little as 265,000 islets was enough to eliminate the need for insulin treatment. Since the technique was first described, numerous advances have been made, and the procedure is now performed in over 30 centers worldwide.

Over the past 20 years, numerous studies, systematic reviews, and meta-analyses have been conducted, with a particular emphasis on chronic pancreatitis and pain relief in these patients.

In 2024, a systematic review and meta-analysis of randomized trials comparing early Endoscopy vs. surgery for the management of painful chronic pancreatitis showed that surgery is superior in terms of having a lower Izbicki pain score and more partial and complete pain relief on long-term follow-up compared to Endoscopy. [10]

The meta-analysis includes 199 patients from three randomized trials.

In the three trials, it was concluded that, at five years, there were more pain-free patients in those who underwent surgery compared with those who underwent Endoscopy (34 versus 15 %);

Patients undergoing surgery also experienced greater quality-of-life improvements, required fewer procedures, and had similar morbidity, length of stay, and pancreatic function compared with endoscopically managed patients. [11, 12]

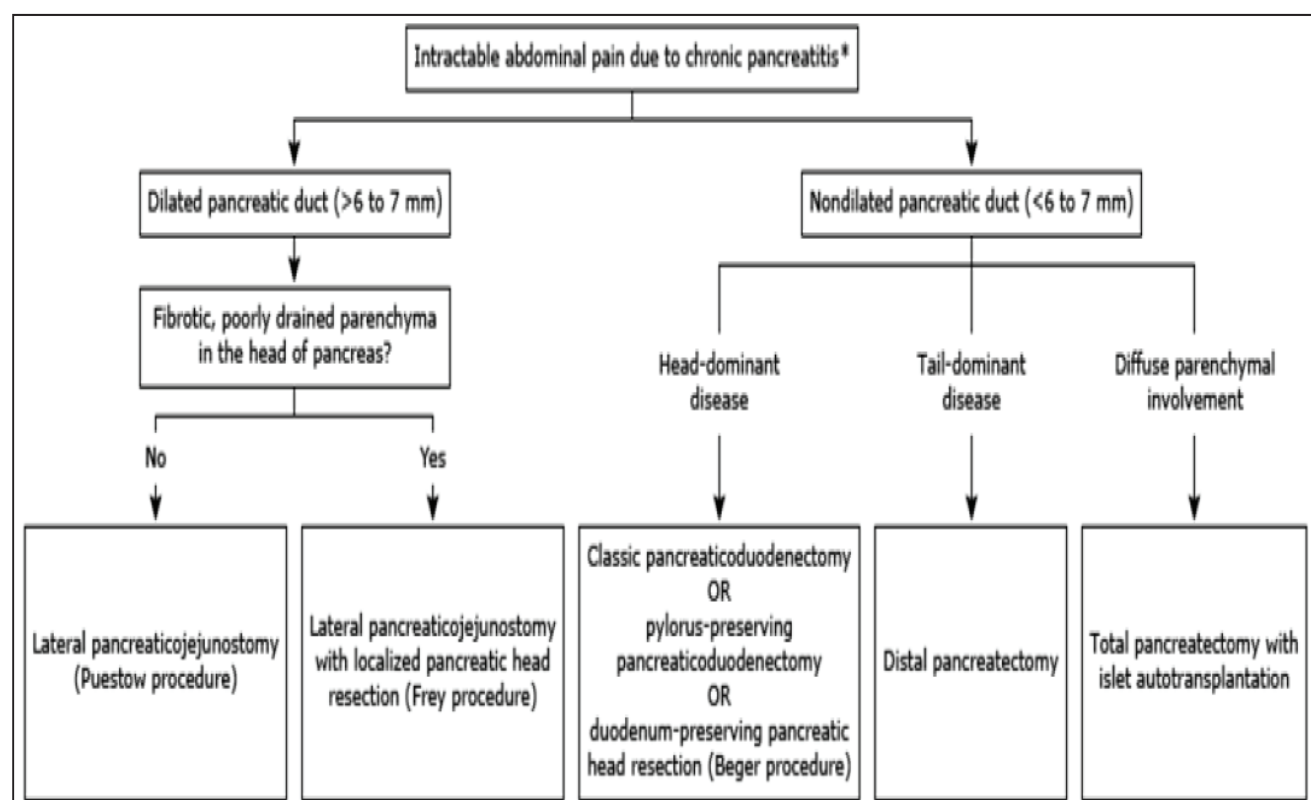


Figure 1: Surgical procedure algorithm in chronic pancreatitis.

Methodology

We reviewed existing literature on surgery for chronic pancreatitis. We aimed to provide a summary of indications, contraindications, procedures, and outcomes of total pancreatectomy with islet auto-transplantation (TPIAT). We examined patient and disease predictors of TPIAT success or failure. We attempted to answer questions such as patient selection, indications for surgery with IAT, the timing and mode of the procedure itself, and the improvement or lack thereof in pain, diabetes, and quality of life in patients who underwent the procedure. In addition, emphasis was placed on debating future outlooks for applying this operational technique in our country.

Using TPIAT at a global level

Total Pancreatectomy with Islet Auto transplantation (TPIAT) is a highly sophisticated surgical intervention that has been successfully implemented in select centers worldwide. This extremely successful method of treating patients suffering from severe, chronic pancreatitis, which includes complete removal of the pancreas, digestion of the excised gland to obtain pancreatic islets, and reinfusion of the islets into the portal vein to prevent or minimize the development of diabetes, holds great promise for implementation in Albania.

Some of the most renowned centers that carry out this procedure are the University of Minnesota (one of the pioneers in the use of TPIAT, with extensive experience and well-documented results), the University of Chicago Medicine (there is a high-level TPIAT program that provides therapy to patients with chronic severe pancreatitis); Brigham and Women's Hospital in Boston (there is a group of experts that has carried out a series of TPIATs Since 2013); King's College Hospital in London (offer TPIAT as part of the therapy of chronic severe pancreatitis);

Statistics and clinical results:

- Improvement in the quality of life: A study showed that the overall health rate, according to QLQ-C30 was considerably improved after TPIAT, with additional points by 24. 26, 20.54 and 26.7 in 1, 2, and 3 years after the procedure, respectively.
- Reduction in pain: Over 90% of patients who have undergone TPIATS report a dramatic reduction or elimination of pain.
- Insulin Independence: Approximately 30–40% of patients require no daily insulin after the procedure. (Fig.2)

Technical and logistical aspects:

TPIAT is a surgery that requires the following:

- Multidisciplinary team: subspecialist surgeons, endocrinologists, gastroenterologists, transplanters, and other specialists.
- Specialized laboratory: in order to insulate and process Langerhans Islands cells.
- Hospital Infrastructure: to deal with postoperative care and monitoring function of transplanted cells.

It has been reported that more than 70% of patients experience a notable improvement in pain, and approximately 30–50% achieve an independent or minimal insulin level following island transplantation. TPIAT is the treatment of choice for selected cases of chronic severe pancreatitis

The current situation in Albania

In Albania, there is a lack of:

- Laboratory facilities for island cell insulation,
- Special surgical training in pancreatectomy with transplant coordination,
- Post-transplant metabolic support and integrated network of endocrinological monitoring.

No academic or clinical program in our country presently addresses TPIAT as a valid practice.

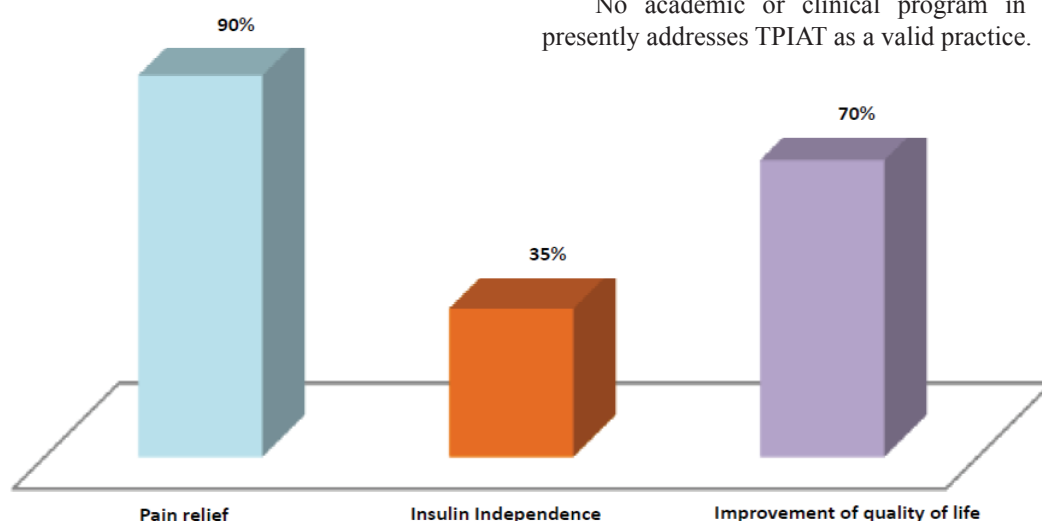


Figure 2 Clinical results of TPIAT from international references

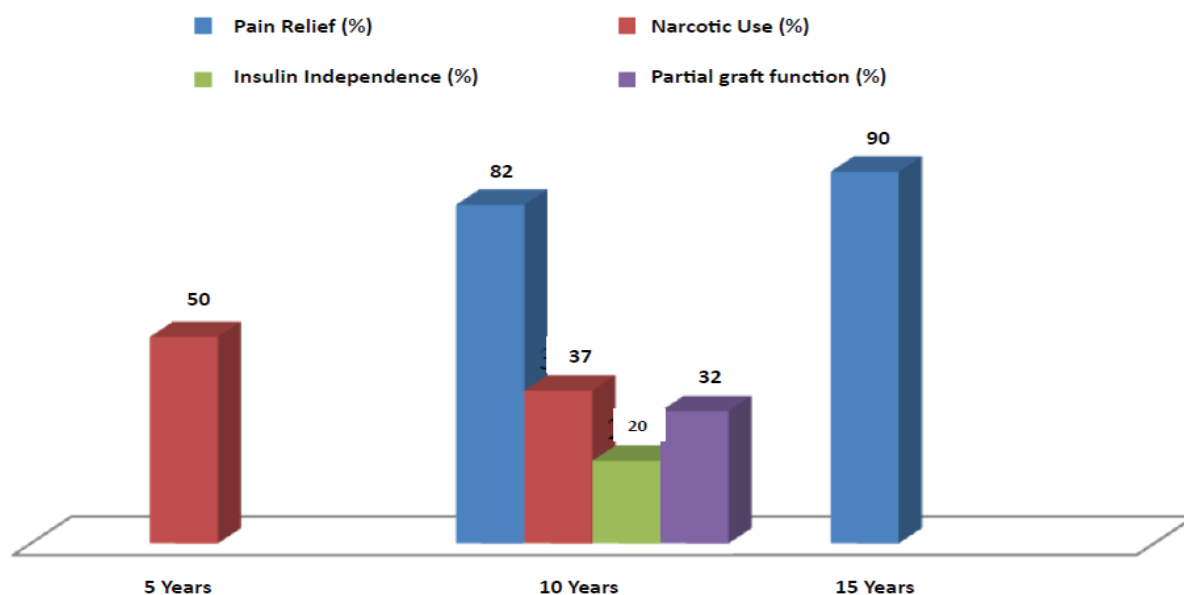


Figure 3: Outcomes over time after TPIAT

Medical and surgical treatment

There is no treatment for the cure of CP, and treatment is mainly symptomatic and management of the complications of the disease. Initial treatments may be analgesics, intravenous hydration, antioxidants, or pancreatic enzyme supplementation. [2, 13, 14]

ERCP must be performed in patients with strictures or ductal stones. [11]

Where the disease progresses to become disabling despite maximal medical and endoscopic therapy, surgical interventions may be considered.

Smokers and alcoholics can be urged to give up the habit. Loss of exocrine function is managed mainly with oral supplementation by pancreatic enzymes, and management of diabetes is often done with insulin. [14] Apart from relieving digestive issues, pancreatic enzyme therapy in the form of no-enteric tablets can also help limit the attacks and pain associated with pancreatitis. [15]

Non-narcotic analgesics are generally the first pain treatment but are often required by many patients in the form of narcotic analgesics. Along with narcotics, agents such as tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, selective serotonin reuptake inhibitors, and gabapentin have been utilized for controlling the pain of chronic pancreatitis but with lesser success. [16]

In those individuals in whom medical therapy for pain has failed, another possibility can be tried, such as nerve block, neurolysis, or endoscopic or surgical therapy. Surgical interventions to palliate pain try to preserve pancreatic function and are based on the nature and degree of pancreatic injury. In broad terms, the procedures are of two categories:

1. Drainage procedures (e.g., pseudocyst drainage, minimally invasive endoscopic duct drainage

by sphincterotomy or stenting, or both; pancreaticojejunostomy)

2. Resectional procedures (e.g., distal pancreatectomy, isolated head resection, pancreaticoduodenectomy, Whipple procedure, total pancreatectomy).

Total pancreatectomy may be offered in selected persons to remove the cause of pain. [17] The procedure is most commonly performed in individuals with small-duct disease, a hereditary condition, or those whose previous operation has failed. [18].

Proposed criteria for total pancreatectomy and islet auto-transplant

Bellin et al. presented five patient selection criteria for the procedure based on imaging studies, pancreatic function tests, and histopathology to confirm pancreatic fibrosis. [18]

Patients must satisfy all of the following five criteria:

1. Chronic pancreatitis diagnosis, based on more than 6 Months' chronic abdominal pain with either at least one of the following: pancreatic calcifications on computed tomography; at least two of the following: four or more of nine criteria on endoscopic ultrasonography described by *Catalano et al.* [19] a compatible ductal or parenchymal abnormality on secretin magnetic resonance cholangiopancreatography; abnormal endoscopic pancreatic function test (peak $\text{HCO}_2 \leq 80 \text{ mmol/L}$); histopathologically confirmed diagnosis of chronic pancreatitis; compatible clinical history and documented hereditary pancreatitis (PRSS1 gene mutation) OR; history of recurrent acute pancreatitis (more than one attack of typical pain associated with imaging diagnostic of acute pancreatitis or raised serum amylase or lipase > 3 times the upper limit of normal).

2. At least one of the following: daily narcotic use dependence; pain resulting in compromised quality of life, which might include inability to attend school, repeated hospitalizations, or inability to participate in typical age-appropriate activities.
3. Total evaluation with no reversible cause of pancreatitis found or remaining.
4. Non-response to maximal medical and endoscopic therapy.
5. Adequate islet cell function (nondiabetic or C-peptide-positive). Patients considered for total pancreatectomy alone for C-peptide-negative diabetes who fulfill criteria 1 through 4.

Minnesota criteria about TPIAT for pancreatitis

1. Chronic or severe abdominal pain that directly results in at least one of the following:
 - a. Chronic narcotic dependence (narcotics on a daily or near-daily basis for >3 months)
 - b. Impaired quality of life (QOL), as assessed by the RAND Medical Outcomes Study 36-Item Short-Form Health Survey
1. Assessment without reversible cause of CP or RAP (present or untreated)
2. Unresponsiveness to maximal medical therapy and endoscopic therapy
3. Chronic abdominal pain from CP or RAP requiring ongoing narcotic treatment
4. Normal islet function (i.e., either diabetes-free or non-insulin-dependent
5. diabetes with favorable C-peptide levels) [20]

When to consider the procedure

Arguably, one can perform this operation earlier in the course of the disease than later, after all other alternatives have been attempted. The reason for doing so is that chronic pain has been found to induce central sensitization, a condition in which the pain threshold is lowered due to damage to nociceptive neurons resulting from repeated stimulation and inflammation. [21]

Also, long-term opioid therapy can cause opioid-induced hyperalgesia, which has the effect of making patients even more pain-sensitive and increasing their underlying pain. [21, 22]

Furthermore, even though operative drainage procedures and partial resections are typically regarded as the gold standard for managing chronic pancreatitis, patients who undergo partial pancreatectomy or lateral pancreaticojejunostomy (Puestow procedure) will retain fewer islet cells available for harvesting (about 50% less) should they later become candidates for total pancreatectomy and islet cell auto-transplantation. [22, 23]

Therefore, getting TPIAT done earlier can keep the patient from chronic pain syndromes and chronic opioid

complications, including hyperalgesia, and give the patient the best shot at harvesting enough islet cells to either prevent or reduce diabetes in the future.

The procedure of TPIAT

During the process, perfusion to the pancreas should be kept up until the point of its resection to minimize warm ischemia of islet cells. [19, 23] There are several surgical alternatives, but most commonly, the operation is a pylorus-preserving total pancreatectomy with duodenectomy, often with a splenectomy, to preserve perfusion to the body and tail. [24]

The resected pancreas is transported to the islet isolation facility. There, the pancreatic duct is cannulated to inject the organ with a cold collagenase solution and mild mechanical dispersion with the semiautomated Ricordi method, freeing the islet cells from the exocrine tissue. [25]

In islet cell auto-transplantation of chronic pancreatitis, purification can be avoided since the amount of tissue obtained from the normally atrophic and fibrotic pancreas is minimal. [26]

The decision to purify rests with the tissue volume; generally, a volume greater than 0.25 mL/kg body weight is a cue to purify at least partially. The final product is returned to the operating room. After administration of heparin, the islets are infused into portal circulation through a stump of the splenic vein by direct puncture of the portal vein or by umbilical vein cannulation. [26, 27]

If the portal pressure is 25 cm H₂O, the infusion is stopped, and the remaining islets can be placed in the peritoneum or elsewhere. [28]

Depositing the islets into the liver or peritoneum will make the islets secrete insulin into the hepatic portal circulation, the same pathway used by the native pancreas.

Contraindications

Total pancreatectomy and islet auto-transplantation are not to be performed in patients with active alcoholism, illicit drug use, or untreated or poorly controlled psychiatric illness that would interfere with the patient's ability to adhere to a complicated postoperative medical regimen.

The inadequate support system may be a relative contraindication due to the cost and complexity of diabetic and pancreatic enzyme replacement therapy. [22, 26]

Postoperative management

Similar to islet allotransplantation, autologous islets are not maximally functional at the time of transplant, and intraoperative blood glucose management with continuous intravenous insulin infusion is necessary to prevent hyperglycemic toxicity. [27, 28] Because the patient's cells are being transplanted, unlike the protocol used in allo-islet transplantation, immunosuppressive medications are

not administered. Subcutaneous insulin injections are then maintained to reach euglycemia within 3 months of TPAIT.

Moreover, exogenous insulin can also reduce functional stress on beta cells continually during the engraftment (angiogenesis) period. [29] Exogenous insulin dosage is then weaned with the ideal HbA1C target of $\leq 6.5\%$ and insulin therapy is continued if not achieved.

Complications of TPIAT

Complications of TPAIT are primarily associated with surgery. Complications of islet auto-transplantation are rare. [30] The most common complications of TPAIT are infections like surgical site infection, pneumonia, UTI, and sepsis. [31, 32] Infectious complications are more common with longer CP duration. [33].

Delayed gastric emptying (DGE) is the most common post-transplant complication following hyperacute rejection. Conservative therapy is the most used method of treating DGE, wherein patients are put on fasting and administered metoclopramide and low-dose erythromycin.

Whereas less common than TP complications, portal vein thrombosis (PVT) is one recognized complication of islet cell transplantation and is a potentially severe complication. [34, 35]

Recommendations for implementation

Creation of an interdisciplinary pilot staff from University Hospital “Mother Teresa” that includes surgeons, gastroenterologists, endocrinologists, pathologists, and laboratory staff; creation of international cooperation in training and technical exchange (e.g., Erasmus+, Horizon Projects); creation of a testing lab for island cell isolation with the collaboration of the Faculty of Medicine and Bio-Medical Research Centers; design of a national protocol for the selection of cases adequate for TPIAT; financing initial pilot procedures using overseas funding or donations.

Conclusions

TPIAT is a novel therapy that is life-changing for those with chronic pancreatitis and recurrent acute pancreatitis. Its introduction in Albania will require a strategic transformation in infrastructure, training, and health policy but is feasible if developed as a secondary project with institutional commitment. The institution of TPIAT would be a step towards qualitative advancement in the treatment of severe pancreatic disease and the development of modern Albanian surgery and transplant units.

COI Statement: This paper has yet to be submitted in parallel, presented fully or partially at a meeting, podium, or congress, published, or submitted for consideration beforehand.

This research received no specific funding from the public, commercial, or non-profit sectors. The authors declare that they, their relatives, or next of kin have no financial relationships with external companies that could be considered relevant or minor.

Disclosure: The authors declared no conflict of interest. No funding was received for this study.

Abbreviations

TPIAT - Total Pancreatectomy with Islet Auto-transplantation; CP - Chronic Pancreatitis; IAT - Islet Transplantation; QoL - Quality of Life; RAP - Recurrent Acute Pancreatitis; ERCP - Endoscopic Retrograde Cholangiopancreatography; DGE - Delayed Gastric Emptying; PVT - Portal Vein Thrombosis; TP - Total Pancreatectomy;

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