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Original article

Multicentric Study on Total Pancreatectomies[☆]



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ABSTRACT

Introduction: Total pancreatectomy (TP) is an uncommon operation, with indications that have not been clearly defined and non-standardized postoperative results. We present a national multicentric study on TP and a comparison with the existing literature.

Methods: A prospective observational study using data from the national registry of patients after pancreaticoduodenectomy and TP performed for any indication during the study period: January 1–December 31, 2015.

Results: 1016 patients were included from 73 hospitals, 112 of whom had undergone TP. The percentage of TP from the total number of cases was 11%. The mean age was 63.5 years, and 57.2% were males. The most frequently suspected radiological diagnosis was pancreatic cancer (58/112 cases). The most common TP technique was “mesentery artery first” (43/112 cases). Venous resections were performed in 23 patients (20.5%). The percentage of postoperative complications within 90 days was 50%, but major complications (>IIIA) were only 20.7%. The overall 90-day mortality was 8% (9 patients). The average stay was 20.7 days. The 3 most frequent definitive histological diagnoses were: adenocarcinoma of the pancreas, intraductal papillary mucinous neoplasm and chronic pancreatitis. The R0 rate was 67.8%.

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Conclusions: This study shows that the morbidity and mortality results of TP in Spain are similar or superior to previous publications. More precise TP studies are necessary, focused on specific complications such as endocrine insufficiency.

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Estudio multicéntrico nacional sobre pancreatomectomías totales

R E S U M E N

Palabras clave:

Páncreas
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Revisión

Introducción: La pancreatomectomía total (PT) es una intervención infrecuente, con unas indicaciones no claramente definidas y unos resultados postoperatorios no estandarizados. Presentamos un estudio multicéntrico nacional sobre PT y una comparación con la literatura existente.

Métodos: Estudio prospectivo observacional realizado mediante el registro nacional de pacientes operados de duodenopancreatomectomía cefálica y PT realizadas por cualquier indicación durante el periodo comprendido entre el 1 enero y el 31 diciembre del 2015.

Resultados: Se incluyó a 1.016 pacientes, pertenecientes a 73 centros; de ellos, 112 correspondían a PT. El porcentaje de PT/número total de casos es del 11%. La edad media fue 63,5 años y eran varones un 57,2%. El diagnóstico radiológico de sospecha más frecuente fue cáncer de páncreas (58/112 casos). La técnica de la PT más habitual fue «arteria mesentérica primero» (43/112 casos). Se efectuaron resecciones venosas en 23 pacientes (20,5%). El porcentaje de complicaciones postoperatorias a 90 días fue 50%, pero las complicaciones mayores (>IIIA) solo el 20,7%. La mortalidad global a 90 días fue del 8% (9 pacientes). La estancia media fue 20,7 días. Los 3 diagnósticos histológicos definitivos más frecuentes fueron: adenocarcinoma de páncreas, neoplasia mucinosa papilar intraductal y pancreatitis crónica. La tasa de R0 fue del 67,8%.

Conclusiones: Este estudio demuestra que los resultados de morbilidad y mortalidad de la PT en España son similares o superiores a los publicados previamente. Es necesario un estudio más específico sobre PT centrado en complicaciones específicas, como la insuficiencia endocrina.

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Introduction

Total pancreatectomy (TP) was very popular in the 1960s and 70s because it was considered an excellent oncological procedure for pancreatic cancer as it treated all tumors in cases of multifocal involvement. It also avoided pancreaticojejunal anastomosis, which is the main cause of morbidity and mortality in pancreatic surgery.¹⁻⁵ However, the high incidence of short- and long-term complications mainly related to the absence of the pancreas (such as severe hypoglycemia and the long-term complications of diabetes mellitus) also entailed a lower quality of life. Furthermore, as there was no demonstrated oncological benefit compared to less radical options and the pancreatic fistula rate dropped as a result of technical refinement, the number of TP performed in the following decades decreased.¹⁻⁶

In the last 2 decades, however, the concept of preventive surgery in patients at high risk of developing cancer, the emergence of autologous transplantation, better glycemic control after TP or the performance of extended surgeries in advanced neoplasms seem to have led to a resurgence of TP.^{1,3,7} Currently, there are no clear indications for TP and they

are based more on personal experiences than on solid scientific evidence.^{1,4}

In 2015, the Hepato-Biliary-Pancreatic Surgery (HBP) Division of the Spanish Association of Surgeons (AEC) conducted a prospective study on pancreatic surgeries (TP and pancreaticoduodenectomies [PD]) performed in Spain. We present the morbidity and mortality results obtained with in TP.

Methods

Sponsored by the HBP Division of the AEC, a nationwide prospective registry was designed for all patients undergoing PD and TP performed for any indication during the period from January 1 to December 31, 2015. Participation in the study was voluntary and open, and the only condition was that the hospital was either a public or private Spanish institution that had performed PD or TP in 2015, regardless of the annual volume ([Appendix C, Addendum I](#)). TP performed after PD for oncological reasons or anastomotic problems were not included.

A database was designed and sent to the hospitals when they agreed to participate in the study. Each medical center

was responsible for the inclusion of their data in a form created on the www.typeform.com platform, linked to a single Excel database (Microsoft[®], Microsoft Corp., Redmond, WA, United States) but unable to access the entire database. To comply with Data Protection requirements, each participating hospital was assigned a specific identification code, and each patient included was assigned an identification code known only to the coordinators of each unit. Only the 3 coordinators of the study had access to the definitive database, but they were unaware of the identity of the patients included. All patients included in the study signed a specific consent form. Fifty-four variables were studied, subdivided into 4 blocks: demographic data; diagnosis/preoperative treatment; operative variables and postoperative variables. The evaluation of specific postoperative complications of pancreatic surgery were categorized by severity according to the classification recommended by the International Study Group of Pancreatic Surgery (postoperative hemorrhage and delayed gastric emptying) and the International Study Group Liver Surgery (biliary fistula).⁸⁻¹⁰ Postoperative morbidity and mortality were measured after 90 days according to the Clavien-Dindo classification.¹¹ From the database, patients who had undergone TP were selected, without exclusions.

The statistical analysis was merely descriptive, using mean, median, ranges for quantitative variables and percentage (%) for the study of non-numerical variables.

Results

A total of 1016 patients from 73 hospitals were included in the database (see [Appendix B, Addendum 1 for participants](#)). In 904 patients, PD was performed, while 112 underwent TP, and these subjects made up our study group. [Table 1](#) includes the distribution of the TP studied by autonomous communities. The percentage of TP out of the total number of cases included (TP+PD) was 11%, but this varied among the

'autonomous communities' of Spain, ranging from 4.9% to 54.5%. Median age was 61 years (range: 35-83), and the distribution by sex was: 64 males (57.2%), 45 females (40.2%), and this datum was not available 3 cases (2.6%). The distribution by ASA category was: 5 ASA I(4.5%); 59 ASA II(52.7%); 40 ASA III(35.7%); 6 ASA IV (4.7%); and this datum was not available for 2 patients (3.1%).

The diagnostic methods performed were: CT in all patients except one; 55% underwent MRI or magnetic resonance cholangiopancreatography; PET/CT was only used in 18.7%. The most frequent suspected preoperative radiological diagnosis was: pancreatic cancer (62 cases), followed by intra-ductal papillary mucinous neoplasm (IPMN) (22 cases) ([Table 2](#)). The radiological location of the tumor was: head of the pancreas in 74 patients (66.1%); body of the pancreas in 5 (13.4%); periampullary in 3 (2.7%); distal common bile duct in 3 (2.7%); ampullary in 2 (1.8%); duodenal in 1 (0.9%); and other locations in 14 (12.5%). Based on the radiological studies, 20.6% of the patients presented some type of venous invasion and 7.1% arterial invasion ([Table 3](#)). Six patients received neoadjuvant treatment (5.2%), 3 with chemotherapy and 3 chemoradiotherapy.

TP was performed by subcostal laparotomy in 111 patients and laparoscopically in one case. The 'mesenteric artery first' TP technique was the most frequently used (43 cases), the 'no-touch technique' in 36 cases and the classical approach in 33 cases. Venous resections were performed in 23 patients (20.5%), with 15 complete and 8 partial portal resections, 15 end-to-end anastomoses, venorrhaphy in 7 patients and in one case venous patch. In the reconstruction technique, a single loop was used in 63 patients (58.9%), 2 loops (one biliopancreatic and one intestinal) in 45 (40.2%), and 'not available' in 4 cases. Bile loop access to the supramesocolic region was transmesocolic (107 patients), antecolic³ and retromesenteric.² Access to the digestive loop was antecolic in 75 patients and transmesocolic in 37. The number of drains used were 2 in 91 patients, one in 18 patients and none in 3. Blood transfusion was not performed in 76 patients (67.8%).

Table 1 – Distribution of TP Cases by Autonomous Communities (Regions).

Autonomous Community	Total Cases (PD+TP)	Cases of TP	Percentage TP/Total Cases
1	144	7	4.9%
2	52	8	15.4%
3	31	3	9.7%
4	21	1	4.8%
5	37	5	13.5%
6	15	2	13.3%
7	44	6	13.6%
8	46	6	13%
9	221	14	6.3%
10	129	11	8.5%
11	31	3	9.7%
12	40	7	17.5%
13	123	17	13.8%
14	33	18	54.5%
15	5	1	20%
16	44	3	6.8%
Total	1.016	112	11%

Table 2 – Preoperative Radiological Diagnosis.

Radiological Diagnosis	n	Definitive Histology	n
Pancreatic adenocarcinoma	62	Pancreatic adenocarcinoma	51
IPMN	22	IPMN	13
Neuroendocrine tumors	7	Chronic pancreatitis	12
Other tumors	7	Neuroendocrine tumors	5
Mucinous cystic neoplasms: cystadenoma/mucinous cystadenocarcinoma	5	Other tumors	5
Cholangiocarcinoma	4	Mucinous cystic neoplasms: cystadenoma/mucinous cystadenocarcinoma	5
Metastasis	2	Cholangiocarcinoma	3
Solid pseudopapillary tumors	2	Solid pseudopapillary tumors	1
Ampulloma	1	Ampulloma	4
		Non-differentiated pancreas carcinomas	5
		Signet ring cell carcinoma of the pancreas	2
		Serous cystadenoma	4
		Pancreatic squamous cell carcinomas	1
		Autoimmune pancreatitis	1

IPMN: intraductal papillary mucinous neoplasm.

The mean number of transfused packed red blood cell units was 1.6 (range: 0–18).

The percentage of postoperative complications within 90 days was 50%, and their distribution according to the Clavien-Dindo classification is shown in Table 4. When we consider the major complications alone (>Clavien-Dindo IIIA), the percentage decreases to 20.7%. Ten patients were re-admitted after being discharged from hospital (8.9%). The overall 30-day mortality was 5.35% (6 patients) and increased to 8% (9 patients) within 90 days. Complications are listed in Table 5. Mean hospital stay was 20.7 days (range: 7–88).

The histological study (Table 2) showed that the 3 most frequent diagnoses were pancreatic ductal adenocarcinoma, including adenocarcinomas over IPMN (50 patients), IPMN without malignant degeneration¹² and chronic pancreatitis,¹³ but 30% of patients presented other histological diagnoses. The mean tumor size was 43 mm (range: 10–250 mm). The definitive tumor location was: head of the pancreas (n=51), the entire pancreas (n=44), body of the pancreas (n=8), ampulla (n=4), distal common bile duct (n=3) and 'not available' (n=2). The number of resected lymph nodes was 21.7 (0–73), in 26 patients (23.2%) the number of nodes obtained was less than 15, and 39 patients (47.5% of

tumor patients) had lymph node involvement. The R0 rate of all the margins studied (retroperitoneal and vascular) was 67.8%.

Discussion

The first TP was published in 1943 by Rockey in Portland (Oregon).^{2,3,6} After some initial enthusiasm, the existence of serious complications and few oncological benefits led to a drastic decrease in the number of TP performed.^{2,6,13} Currently, there has been a slight increase in TP use for certain indications.^{2,4,6,7,12,13}

The most common indications for TP are: malignant tumors in the head of the pancreas where a free-margin resection (R0) cannot be ensured; chronic pancreatitis with complete gland involvement; multifocal IPMN with malignant potential; multiple primary, metastatic or neuroendocrine malignant tumors; patients with hereditary pancreatic cancer or other premalignant diseases. To these indications, we must also add the so-called 'two-stage TP', referring to when the pancreatectomy is later completed due to recurrence in the pancreatic remnant or rescue pancreatectomy after pancreaticojejunal anastomotic leak, although this indication has

Table 3 – Vascular Invasion on Imaging Tests.

	Yes	No
Venous invasion	23 (20.6%)	89
Portal vein	18 (16.1%)	94
Other veins	5 (4.5%)	107
Degree of contact vein/tumor		
<180°	16	
>180°	7	
Arterial invasion	8 (7.1%)	104
Mesenteric artery 1 (<180°) and 1 (>180°)	2	
Celiac trunk and hepatic artery	3	
Hepatic artery	2	
Celiac trunk	1	

Table 4 – Distribution of Complications According to the Clavien-Dindo Classification After 90 Days.

	n	Percentage
0	56	50
1	9	8.2
2	24	21.4
3A	7	6.2
3B	5	4.5
4A	2	1.8
5	9	8.2

Table 5 – Type of Complications.

	n	A	B	C
Delayed gastric emptying	16 (14.3%)	7	7	2
Intra-abdominal bleeding	15 (13.4%)	5	5	5
Biliary fistula	1 (0.9%)			
Intestinal anastomotic fistula	1 (0.9%)			
Re-operations	10 (8.9%)			
Hemoperitoneum	5			
Intra-abdominal abscess	2			
Other	3			
Infectious complications	37 (33%)			
Pneumonia	12			
Intra-abdominal abscess	9			
Urine infection	6			
Catheter sepsis	6			
Wound infection	3			
Thrombophlebitis	1			
Medical complications	28			
Renal insufficiency	4			
Lung edema	4			
Atrial fibrillation	1			
Diarrhea	5			
Pulmonary thromboembolism	2			
Cerebrovascular accident	1			
Other	11			

decreased in the last decade.^{1,5-7,12} More controversial indications are TP in elderly, fragile patients with a high risk of pancreatic fistula and diabetes before surgery, or in patients with complex vascular reconstruction.^{1,7}

Below, we will comment in greater depth on the characteristics of the three most frequent indications, which account for 70% of the total indications in our series: pancreatic cancer, chronic pancreatitis and IPMN.

Pancreatic cancer is usually the most frequent indication in TP series, ranging from 38% to 66%, while in our series it represented 45% of patients.^{1,4,5} In the published series, the median survival is 15 months, with a 5-year survival rate from 11.3% to 15.9%. There is a growing acceptance that TP in pancreatic cancer enables R0 margins to be obtained, as it increases survival.¹³

TP can reduce pain, increase quality of life and lower the risk of cancer in patients with chronic pancreatitis. The indications for TP in chronic pancreatitis are not clearly defined, although the most accepted use is in patients with small duct and diffuse glandular involvement, and resistance to medical treatment.¹ The possibility of combined auto-transplantation could increase TP indications in these patients in the future.^{12,14}

IPMN is being diagnosed more and more frequently.¹⁵ Multifocal or diffuse pancreatic involvement makes these lesions difficult to manage. The options are to perform partial resections (which can leave unresected malignant foci) or TP.^{1,15} The most accepted indications for TP in IPMN are: extensive multifocal disease, diffuse involvement of the main duct and inability to obtain margins without high-grade dysplasia.^{1,15,16} In 17%–23%, TP is the intervention chosen for patients with IPMN, which in one hospital reached 56% of the total planned TP and 36% of the unplanned procedures.^{4,5,15,16} It accounted for 11% of our cases.

The study of the series published on TP is not simple. Some series focus on a certain disease, usually pancreatic cancer. In others, the data are given by diseases. Sometimes, there is a control group made up of patients who have undergone PD. Others also include rescue TP during the postoperative period, and the studies are usually retrospective.

The percentage of TP out of the total number of pancreatectomies at each of the participating hospitals was very variable and ranged from 4.8% to 54.5% among the various Spanish autonomous communities; the average was 11%. This difference may be due to different indication criteria among the participating medical centers (for example, performing TP instead of a risky anastomosis, in patients with large vascular resections, or in patients with different diseases being treated). In the published series where this datum is provided, reports range between 8.3% and 28%.^{2,6,7,12}

The percentage of laparoscopic surgery in our study was minimal (0.9%). In other countries, the rate reaches 30% at very specific centers.¹² One advantage of TP compared to laparoscopic PD is the absence of pancreatojejunal anastomosis, which is one of the most complex technical points. This percentage will likely increase progressively in coming years.

The morbidity rate in the published TP series ranges between 31.1% and 87%, and is usually determined after 30 days.^{1,12} Our complication rate after 90 days was 50%, which dropped to 20.7% when only major complications >Clavien IIIA were analyzed, which is lower than the 32% published by Zakaria et al.¹² The 30-day mortality rate for TP is 0%–12.5%, while our 30-day mortality rate was 5.35% and reached 8% after 90 days.^{1,2,4,12,13} A German study on pancreatic surgery, using hospital data from almost 5000 TP over a 5-year period, reported a TP mortality rate of 23%, which rose to 50% when TP was associated with colon resection.¹⁷ Hartwig et al. carried out a multivariate analysis on mortality, finding that operative times over 420 min, intraoperative bleeding greater than 2000 mL and arterial resections are associated with higher mortality.⁴ The vascular resection rate of the published series ranges from 11.8% to 50%^{3,12} and was 20% in our patients. The hospital stay in the literature is 10–14 days,^{4,5,12} while the stay in our study was longer (20.7 days).

We have only found 10 retrospective series since 2007 comparing TP and PD, with disparate results.^{1,18-23} The morbidity of TP is higher than PD in 3 series, lower in 2 series and similar in the rest.^{20,22,23} In the series by Casadei et al., the average stay is longer for PD, although the TP has a higher operative time and more vascular resections.⁷ The quality of life of both techniques is similar in the three related series.^{1,7,21} Survival in TP is lower in 3 series and similar in the rest.^{1,18,19} In short, it can be concluded that there are no clear differences in morbidity, mortality, quality of life or survival comparing TP and PD. The great bias of these studies is that the patients analyzed do not present comparable lesions, as the TP group frequently presents more advanced lesions, more vascular resections and a greater potential for malignancy. Likewise, there are no pancreatic fistulae in TP, which is the cause of the more severe morbidity of PD. But, above all, they are not randomized studies, so their results should be taken with caution.^{1,7}

One of the strengths of our study is that it is a prospective study that has had the participation of a large number of pancreatic surgery units in our country. The weaknesses are that it is a multicenter study on non-specific pancreatic surgery for TP, where very important aspects have not been assessed (such as endocrine and exocrine insufficiency); also, there were different indications for TP and varying perioperative management among the hospitals. The E-AHBPA has initiated an exclusive prospective study about TP that may provide us with more specific information.

In conclusion, in this national study on pancreatectomies, we have found that most epidemiological data are similar to other large series. Pancreatic cancer, chronic pancreatitis and IPMN are the 3 most frequent indications. The 90-day morbidity and mortality rates are comparable to published international series.

Conflict of Interests

The authors have no conflict of interests to declare.

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Addendum 2. Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.cireng.2019.07.009](https://doi.org/10.1016/j.cireng.2019.07.009).

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