

Prognostic factors for survival and surgical complications in Whipple's pancreaticoduodenectomy during a 10-year experience

Factores de pronóstico de sobrevida y complicaciones quirúrgicas en la pancreaticoduodenectomía de Whipple durante 10 años de experiencia

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Abstract

Background: Periampullary neoplasms account for over 30,000 cancer-related deaths per year in the United States. Pancreaticoduodenectomy (PD) is considered the surgical standard and is the only curative treatment option for these pathologies.

Objective: The objective of this study was to report the prognostic factors in survival and surgical complications in PD.

Materials and Methods: A total of 178 cases are reported, several variables were reviewed and the same surgical technique was used by the same surgeon. **Results:** A total of 151 PD were reviewed. The most common initial symptoms were jaundice, 111 (73%), abdominal pain, 20 (13%), and oral intolerance, 10 (6%). Poor prognostic factors for survival were the presence of a previous pathology, days of hospitalization, positive margins, and weight loss. **Discussion:** With the experience gained, a decrease in surgical time, intraoperative bleeding, and transfusions performed was achieved. Our complication rate remained at 20%, lower than that reported in literature. **Conclusion:** PD is the only option of cure for patients with pancreatic and periampullary tumors. This procedure has been linked to high morbidity and mortality even in high-volume centers. A pancreatic fistula is the most feared complication; therefore, multiple pancreaticojejunostomy techniques have been described in literature. It is important to continue reporting these cases to reach a consensus on this technique.

KEY WORDS: Pancreaticoduodenectomy. Surgical technique. Perioperative management.

Resumen

Antecedentes: Las neoplasias periampulares suponen más de 30.000 muertes relacionadas con el cáncer por año en los EE. UU. La pancreaticoduodenectomía (PD) se considera el estándar quirúrgico y es la única opción de tratamiento curativo para esta enfermedad. **Objetivo:** Reportar los factores de pronóstico en la supervivencia y las complicaciones quirúrgicas de la PD.

Método: Se reportaron 178 casos; se revisaron varias variables y se utilizó la misma técnica quirúrgica por el mismo cirujano. **Resultados:** Se revisaron 151 DP. Los síntomas iniciales más comunes fueron ictericia (111; 73%), dolor abdominal (20; 13%) e intolerancia oral (10; 6%). Los factores de pronóstico para la supervivencia fueron la presencia de patología previa, los días de hospitalización, los márgenes positivos y la pérdida de peso. **Discusión:** Con la experiencia adquirida, se logró una disminución del tiempo quirúrgico, del sangrado intraoperatorio y de las transfusiones realizadas. Nuestra tasa de complicaciones se mantuvo en un 20%, inferior a la reportada en la literatura. **Conclusión:** La PD es la única opción de curación para los pacientes con tumores pancreáticos y periampulares. Este procedimiento se ha relacionado con una alta morbilidad y mortalidad incluso en centros de alto volumen. La fistula pancreática es la complicación más temida, por lo que se han descrito numerosas técnicas de pancreaticojejunostomía. Es importante seguir informando de estos casos para llegar a un consenso sobre esta técnica.

PALABRAS CLAVE: Pancreaticoduodenectomy. Técnica quirúrgica. Manejo perioperatorio.

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Background

Periampullary cancer accounts for over 30,000 cancer-related deaths per year in the United States¹. The incidence increases to 87.2 cases per 100,000 in patients over 80 years of age. Risk factors for pancreatic cancer are unknown; however, it is considered that some may be coffee, tobacco, and a history of chronic pancreatitis or diabetes².

Survival in periampullary bile duct cancer is 20-25%, for ampullary disease, it is 30-40% and for duodenal tumors, 50-60%; for this reason, some surgeons recommend only palliative care^{3,4}. At diagnosis > 80% are considered unresectable with a 5-year survival after pancreaticoduodenectomy (PD) of 15-20%⁵.

PD is considered the surgical standard for biliary, periampullary duodenal and pancreatic head neoplasms. It is the only curative treatment option in these pathologies. PD has an accepted low mortality rate of 3-5% with a high morbidity of 40-50% due to pancreatic fistulas and delayed gastric emptying⁶⁻⁸.

Some long-term consequences of PD are malnutrition associated to weight loss, malabsorption, and chronic need of supplementation due to a deficiency of micronutrients that are normally absorbed in the proximal intestine⁹. Pancreatic fistula is the most feared complication; therefore, multiple techniques of pancreateojejunostomy anastomosis have been described. No technique has proven to be a permanent solution to this problem.

Objective

The objective of this study was to report the prognostic factors in survival and surgical complications in PD.

Materials and methods

This was a retrospective cohort study of cases retrieved from the Department of Statistics of the "Dr. José Eleuterio González" University Hospital in Monterrey, Mexico. All PD cases from 2005 to 2014 were reviewed. This article does not contain any studies with human subjects performed by any of the authors, no informed consent was required, and no identifying information is included. Patients with resectable tumors defined by the absence of distant metastases and without local extension to the celiac

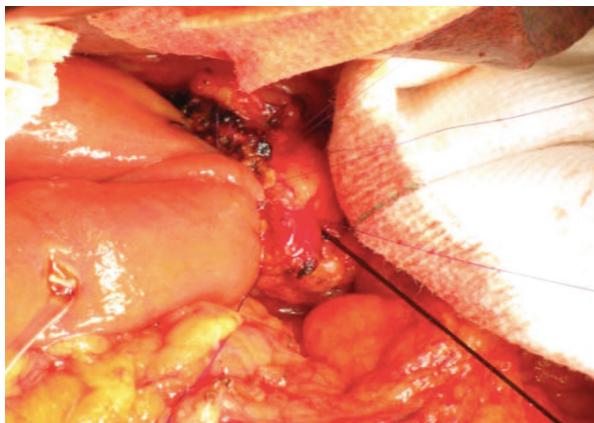


Figure 1. Terminoterminal telescoped pancreateojejunostomy.

axis, hepatic artery, and the superior mesenteric artery were included. Patients treated with derivative surgery or with the absence of a clinical record were excluded. We obtained 178 cases, of which 27 were excluded resulting in a total of 151 patients who underwent PD. This was a single surgeon and single-center study.

Other variables reviewed were age, gender, initial symptoms, medical history, comorbidities, hospital stay, pre-operative studies, number of transfusions, days in intensive care, classification of the American Society of Anesthesiologists (ASA), surgical time, clinical stage, post-operative complications, morbidities, and post-operative mortality.

With regard to the surgical technique, all patients were approached with a bilateral subcostal laparotomy. Resectability without vascular invasion or extrahepatic disease was confirmed during surgery. The Kocher maneuver was performed and the common bile duct was divided. Subsequently, an anterior plane is created, the portal vein and superior mesenteric artery are dissected, and the distal stomach is divided preserving the pylorus. Afterward, the distal jejunum was divided near the ligament of Treitz and the previous pancreas was divided in front of the portal vein; subsequently, the branches of the superior mesenteric vein are ligated and the hepatic artery is dissected. Three anastomoses are performed:

(1) antecolic terminoterminal hepaticojejunostomy; (2) terminoterminal telescope pancreateojejunostomy, which was performed in all cases with duct mucosa and pancreatic duct cannulation (Fig. 1), with additional intermittent circumferential points to the jejunum, which were reinforced with a second circumferential layer and placement of a pancreatic duct catheter; and (3) laterolateral gastrojejunostomy. Selection bias was

avoided by the patient list provided by the statistics department, performance bias with all the procedures done by a single surgeon, and reporting bias was avoided by the revision of surgery professors.

For statistical analysis, SPSS version 22 (IBM, Armonk, NY, USA) was used. The variables were compared using the Mann-Whitney U-test and the Chi-square test with a statistical significance of $p < 0.05$.

Results

A total of 151 cases with a mean age of 55 years and a total of 91 men (60%) and 60 women (40%) were reviewed. The mean body mass index was 25 kg/m², with 76 (50%) patients above 25. Regarding the clinical history, a diagnosis of Type 2 diabetes mellitus was found in 50 (33%) patients and hypertension in 40 (26%), and 15 patients had a previously diagnosed carcinoma.

The most common symptoms were jaundice in 110 (73%), abdominal pain in 20 (13%), and oral intolerance in 10 (6%). Of all patients with jaundice and abdominal pain, 63% also presented oral intolerance. Regarding pre-operative weight loss, 35 (23%) patients had a loss of > 5 kg, and 40 (27%) patients had a high nutritional risk score greater than 3 points.

A pre-operative tumor size > 2 cm was reported in 50 (32%) patients. Total and direct bilirubin was reported elevated in 106 (70%) patients. Aspartate aminotransaminase increased more than twice its normal value in 55 (36.6%) patients, and alanine aminotransferase increased more than twice in 40 (26%) patients; finally, CA 19 was reported in 55 (36.6%) patients. No patient underwent preoperative chemotherapy (CT) or radiotherapy (RT) and a risk of the ASA was reported in two or higher in 116 patients (76%).

Diagnosis of ampulloma (duodenal or pancreatic head tumor) was done in a total of 131 (86.5%) patients, five cholangiocarcinoma, 10 insulinomas, and five neuroendocrine tumors. The mean operating time was 248 min with a mean bleeding volume of 1000 ml reported. For transfusions, only 25 (16.6%) patients required three or more transfusions. 35 (23%) patients required intensive care, lasting a mean of 9 days. Mean hospitalization was 11 days with 110 (73%) patients staying < 10 days.

As for morbidity, 30 (20%) cases reported: 12 collections (7.9%), 10 pancreatic fistulas (6.6%), and 8 episodes of post-operative bleeding (5.2%). Patients with post-operative bleeding were reoperated and

patients with intra-abdominal collection were managed with percutaneous catheter placement. Five post-operative mortalities (3.3%) were reported due to pancreatic fistula and abdominal sepsis.

The pathological diagnosis of 131 patients admitted to surgery was ampulloma, from which a total of 81 patients presented duodenal adenocarcinoma and 50 tumors included pancreatic head adenocarcinomas, cholangiocarcinomas, neuroendocrine tumors, and insulinomas. Mean tumor size was 1.5 cm for adenocarcinomas, 60 (46%) patients had positive nodes, and positive margins were found in 15 (11.5%).

In post-operative management, 60 (40%) patients were followed, of which 25 received CT only, another 10 RT only, and 25 received a combination of CT and RT. Distant metastases were found in 40 (26%) patients during follow-up at 2 years. 2-year survival was 38%.

Statistical analysis was done comparing the group of patients who survived and the group of patients who died (Table 1) to obtain predictors of mortality. These were the presence of a previous medical disease, days of hospital stay, post-operative margins, and weight loss.

In addition, the node-positive group and the node-negative group were compared and no statistical significance was found. Finally, the groups of patients who suffered complications versus those without complications and only days of hospital stay and weight loss were significant ($p \leq 0.05$).

Discussion

Halsted, in 1898, was the first to successfully attempt local resection of a periampullary carcinoma. Alessandro Codivilla was the first surgeon to perform a PD. Allen Whipple subsequently modified this technique in 1935. This technique for handling pancreatic tumors and periampullary was complex and was associated with a very high morbidity and mortality¹⁰.

During our 10-year experience, different aspects of this technique progressed achieving reduction in surgical times, intraoperative bleeding, and number of transfusions¹¹. Our morbidity rate remained 20%. A serious complication is post-operative bleeding, which can be managed using interventional angiography with embolization; however, in our case, due to our available resources, reoperation was our preference.

A comparison of surgical procedures performed from 2006 to 2010 and from 2011 to 2015 was made

Table 1. Comparison between survival and 2-year mortality during the 2-year follow-up

Variables	2-year survival (%)	2-year mortality (%)	Survival versus mortality
Patients	106 (70)	45 (30)	
Mean age	54	57	ns
Mean BMI, kg/m ²	24	26	ns
Comorbidities	50 (47)	20 (44)	<0.05
Initial symptoms			ns
Jaundice	70 (66)	40 (88)	
Pain	20 (19)	5 (12)	
Weight loss (kg)	10 (9)	0	
Others	5 (4)	0	
Mean nutritional risk	2.29	2	ns
Biliary dilatation	40 (38)	20 (44)	ns
Total bilirubin	7.9	7.76	ns
Direct bilirubin	5.11	4.76	ns
AST	113	110	ns
ALT	106	105	ns
AP	392	294	ns
Lewis antigen (CA19-9)	57.72	71.02	ns
Mean ASA	2	2.2	ns
Mean surgical time, minutes	253	236	ns
Mean bleeding, milliliters	995	1194	ns
Transfusions, units	0.9	1.6	ns
ICU admission	0.5	1.7	ns
Complications	20 (19)	25 (55)	ns
Inpatient days	9.5	16.5	<0.05
Tumor size >2 cm	50 (47)	25 (55)	ns
Positive nodes (post-operative)	45 (42)	15 (33)	ns
Positive margins	10 (9)	5 (12)	<0.05
Post-operative clinical phase			ns
T1	40 (38)	25 (55)	
T2	20 (19)	0	
T3	40 (38)	15 (33)	
T4	5 (4)	5 (12)	
Post-operative follow-up			
CT (±) RT	45	15 (33)	ns
Weight loss, kg	0	8.5	<0.05
Metastases	20 (19)	15 (33)	ns
Mean 2-year survival		11 m	ns

Statistical tests were done with the Mann-Whitney U-test and Chi-square test with a significance of $p < 0.05$, ASA: American Society of Anesthesiologists, AST: aspartate aminotransferase, ALT: alanine aminotransferase, AP: alkaline phosphatase, ICU: intensive care unit, CT: chemotherapy, RT: radiotherapy, ns: not significant, BMI: body mass index.

Table 2. Surgical evolution of patients in a 10-year period

Year of surgery	Total patient	Surgical time, min	Transoperative bleeding, mL	Transfusions, units
2006	13	323	768	2.5
2007	16	315	618	2.8
2008	14	357	620	2.3
2009	16	269	664	1.6
2010	17	289	632	1.1
Total 2006-2010	76	310.6	660.4	2.06
2011	15	317	779	2.3
2012	18	315	675	1.7
2013	16	282	560	2
2014	12	190	267	0.5
2015	14	250	700	1.3
Total 2011-2015	75	270.8	596.2	1.56
Improvement	151	-39.8	-64.2	-0.5
Statistical significance		ns	ns	ns

Statistical tests were done with Chi-square test with a significance of $p < 0.05$, ns: not significant.

(Table 2) and found an improvement in surgical time (-39.8 min), a reduction in intraoperative bleeding (-64.2 ml) and in the number of blood units transfused intraoperatively (-0.5). Characteristically, most of our patients arrive at late stages of disease with obstructive jaundice and advanced tumor sizes¹². This is why distant disease and advanced cancer stage in our post-operative patients were reported. Early diagnosis is important and a high clinical suspicion is essential in this pathology.

Our technique with duct-mucosal anastomosis and pancreateojejunal telescope anastomosis with cannulation of the pancreatic duct (Fig. 1) managed to maintain a rate of pancreatic fistula of 6.6%. This technique helps decrease the rate of pancreatic fistula and leakage preventing accumulation of pancreatic secretions and anastomosis to exclude direct contact with the pancreatic juices, the most important handicap includes patients with hard pancreas which is associated to a higher fistula rate¹³.

Mortality in our review is 3.3%. One of the most feared complications is a pancreatic fistula, which can quickly endanger the patient's life because it leads to peritonitis and severe sepsis. All patients who died before 2 years had similar symptoms and laboratory findings compared to patients with a better outcome. Factors such as personal background, post-operative complications, and surgical time were significantly

different between these groups. Patients with a poor prognosis characteristically presented a significant weight loss during their post-operative evaluations.

Despite maintaining a low mortality rate, some surgeons, due to a lack of technical resources, identify an advanced stage of disease, and therefore, only a derivative procedure can be offered. Laparoscopic PD is considered only in a subset of patients because this procedure is associated with an increased incidence of pancreatic fistulas¹⁴. Therefore, open surgery remains our institutional choice. The number of procedures performed in recent years has been increasing. It has already been reported that the effect of high-volume centers in the evolution of patients involves a reduction in perioperative morbidity and mortality.

Several limitations of this study include that this was a single institution and single surgeon experience, an important number of patients did not attend their follow-up in our institution.

Conclusion

Negative prognosis predictors in our study include the presence of previous comorbidities, positive resection margins, and post-operative weight loss. Pancreatic fistula is the most feared complication; no technique has proven to be a permanent solution to

this problem. The end-to-end telescope anastomosis with duct-to-mucosa anastomosis and cannulation of the pancreatic duct appears to have a lower fistula rate than reported before.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

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Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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