Total Pancreatectomy is as Feasible and Safe as Pancreatico-duodenectomy

Offir Ben-Ishay (o_ben-ishay@RMC.gov.il)
Rambam Health Care Campus https://orcid.org/0000-0003-3603-3843
Reem Abu Zhaya
Rambam Health Care Campus
Yoram Kluger
Rambam Health Care Campus

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Abstract

Background For many years total pancreatectomy (TP) had a notorious reputation due to the resulting brittle diabetes and pancreatic exocrine insufficiency, recent evidence suggests otherwise. The purpose of the current study is to evaluate the comparative perioperative results of TP and pancreatico-duodenectomy (PD).Methods The current study is a single center retrospective, case control study comparing the peri-operative outcomes of TP and PD over a period of 7 years for malignant and benign diseases of the pancreas. Primary and secondary measures of outcome were peri-operative mortality and morbidity respectively.Results 214 patients underwent pancreatic resection during the study period of which 35 patients underwent TP and 179 patients underwent PD. The two groups were homogenous in terms of demographics and clinical presentation. Mortality was not different between TP and PD and stands on 2.9% and 5% respectively (p-0.58). Overall complication rate was significantly lower in the TP group (17.1% vs. 55%, p<0.001) and the rate of major complications (Dindo-Clavien >3) was lower but did not reach statistical significance (2.9% vs. 11.2%, p-0.13).Conclusions Our study suggests that total pancreatectomy is not only feasible and safe, it might have better perioperative outcomes than PD with same mortality and reduced overall complication rate.

Background

Pancreatic cancer is an uncommon disease with increasing incidence over the years and minimal decrease in mortality (1-3). Pancreatic resections play an important role in the multimodal treatment of pancreatic diseases; (4) and in pancreatic cancer is the only hope for long term survival. The role of Pancreatico-duodenectomy (PD) and distal Pancreatectomy is well established, and all aspects are thoroughly discussed in the English literature. Total Pancreatectomy (TP) was not possible until the discovery of insulin, and the first successful TP was reported in 1943 (5). Although possible, some authors associated TP with high morbidity and mortality (6-10) and the pancreatic endocrine and exocrine insufficiency was considered brittle and unlikely to yield a reasonable quality of life. Improved surgical skills, perioperative care and outcome along side the invention of long acting insulin formulas and the use of pancreatic enzymes supplements allow more extensive pancreatic surgery. Hartwig et al. published the short and long term outcome of 434 total pancreatectomies for pancreatic and peri-ampullary tumors and concluded that TP is justified by improved survival rates, acceptable quality of life and stable vitamins and $HbA1_C$ levels (11). Currently, no randomized control trials comparing PD with TP have been reported in the English literature, but several retrospective comparative studies and meta-analyses addressed this issue in the past with controversial results (12-22). Patient selection for TP remain a difficult choice and the purpose of the current study is to evaluate weather TP is as feasible and safe as PD in terms of morbidity and mortality.

Methods

The study is a single center retrospective, case control study. All patients who underwent elective total Pancreatectomy or Pancreaticoduodenectomy at the department of surgery of the Rambam Health Care Campus in Haifa, Israel from January 2010 through December 2016 were included in the study. Indications included malignant and benign disease of the pancreas.

Electronic charts of all patients were reviewed for demographics, clinical, operative and postoperative data.

The study was approved by the institutional review board and local ethics committee (RMB-16-0581).

Preoperative decision making:

Preoperatively, all patients were evaluated by a multidisciplinary team of pancreatic surgeons, medical oncologists, gastroenterologists, and radiologists. Total pancreatectomy was offered in cases of multi-focal neoplastic lesions, total pancreatic Intraductal Papillary Mucinous Neoplasm (IPMN), in cases in which a vascular reconstruction was necessary TP was considered.

Clinical outcomes:

Primary measure of outcome was mortality and secondary measure of outcome was short-term morbidity. Length of hospital stay (LOS), Intensive care unit (ICU) stay and type of discharge were obtained to further evaluate postoperative outcomes.

Glycemic Control:

All patients undergoing total pancreatectomy had endocrinologist consult after surgery and prior to discharge. The same endocrinologist continued to follow the patient in the outpatient clinic. A specialized diabetes nurse practitioner is in charge of the glycemic control of the patient from the operation to discharge. The nurse complies with the department's glycemic control protocol for patients after TP and continues to follow the patient at home. Prior to discharge the patient must have a balanced glucose level, and must be self sufficient with the insulin treatment regimens.

Definitions:

Mortality was defined as death within 90 days from the index operation or within the index admission. Postoperative morbidity included all complications occurring within 90 days of the index operation, the Dindo-Clavien classification was used for the severity of complications (23).

Statistical analysis:

Continuous parametric variables were analyzed using the Student's t-test. The Mann-Whitney U test was used to analyze non-parametric variables. Chi-square test was applied to analyze the association between frequencies in a Univariate fashion. Multivariate analysis was performed using a stepwise logistic regression model and a likelihood ratio test was applied to identify positive associations with the primary and secondary measure of outcome. JMP Pro for Mac (Version 14.0.0) was used to analyze the data. $P < 0.05$ (2-sided) was considered statistical significance.

Results

214 patients underwent pancreatic resection during the study period of which 35 patients underwent TP and 179 patients underwent PD. Patients who underwent distal pancreatectomy were excluded from the study. The most common indication for TP was IPMN in 57.1% of the cases followed by pancreatic adenocarcinoma in 34.3%. Table 1

depicts the indications for pancreatic resection in the two groups. It seems that PD is the operation of choice in patients with malignant diseases (38.2% vs. 76%, p<0.001), while TP is preferred in benign diseases such as IPMN (57.1% vs. 19.5%, p<0.001).

The two groups were homogenous in terms of demographics and clinical presentation with no age or gender preferences for each procedure. Clinically jaundice was more prevalent in the PD group (48.9% vs. 26.5%, p-0.02). Preexisting diabetes mellitus (DM) was more prevalent in the TP group (62.9% vs. 37.4%, p-0.005) and smoking was more prevalent in the PD group (9.7% vs. 39.4%, p-0.001) (Table 2). Operative time was significantly longer for the TP group (238.7±41.9 vs. 221.3±40.1, p-0.02). Sixteen patients (8.9%) of the PD group needed blood transfusion compared to none of the TP group. This did not reach statistical significance but showed a trend towards favoring the TP (p-0.08).

The primary measure of outcome was perioperative mortality, this was not different between TP and PD and stands on 2.9% and 5% respectively (p-0.58) (Table 3). Median overall procedure survival was not different between the two groups (67.7 vs. 67.5 months, Log rank 0.95) as depicted by the Kaplan Meier curve in Figure 1.

Secondary measure of outcome was short-term morbidity; we observed that overall complication rate was significantly lower in the TP group (17.1% vs. 55%, p<0.001) and the rate of major complications (Dindo-Clavien >3) in the TP group was lower but did not reach statistical significance (2.9% vs. 11.2%, p-0.13). Other outcomes such as length of stay in the hospital (LOS), need for admission in the intensive care unit and type of discharge did not differ between the two groups as depicted in table 3.

Table 4 depicts the rate of the specific complications in both study and control group; we can observe that complications such as surgical site infection (p<0.001), peritoneal abscess (p-0.03), bile leak (p-0.002) and cardiovascular complications (p-0.03) were all significantly more prevalent in the PD group. This might be attributed to the 29% pancreatic leaks present in this group and the impact it might have on patient's morbidity.

Oncologically, median number of lymph nodes harvested was significantly higher in the TP group 20 (14-25) vs. 15 (11-19) (p-0.003). In patients with malignant disease positive resection margins (R1) was observed in 3.4% (n-6) of the patients in the PD group and in 2.9% (n-1) of the TP group (p-0.88).

Median overall survival of the pancreatic adenocarcinoma patients was significantly higher for the TP group (21.6 vs. 10 months, log rank 0.006) as depicted by the Kaplan Meier Curve in Figure 2.

On Univariate analysis variables significantly associated with perioperative mortality included age (75.4±5.9 vs. 67.7±12.1, p-0.04), malignancy (40% vs. 70.6%, p-0.04) and major postoperative complications (Dindo-Clavien >3) (90% vs. 5.9%, p<0.001). Multivariate analysis showed that malignancy (p<0.001) and major complications (p<0.001) are independent predictors of perioperative mortality in this cohort of patients.

On Univariate and multivariate analysis age was the only independent predictor of major complications among all other variables.

Interestingly enough TP is negatively associated with perioperative mortality and postoperative major complications, with a protecting effect from major complications (OR 0.25 (CI95% 0.01-1.47)).

Table 5 summarizes the descriptive data and the perioperative outcome of the major studies comparing TP and PD.

Discussion

Total pancreatectomy was a notorious procedure, a procedure that pancreatic surgeons refrained from offering. The associated morbidity and mortality was high and reports on the brittle diabetes and pancreatic exocrine insufficiency led to believe that this procedure should be carefully suggested to patients. In recent years there is accumulated evidence that shows that results of TP is not as expected especially when compared to PD. Studies comparing these two procedures are not many, and results are quite controversial. Muller et al. reported a matched pair analysis of 87 TP and 87 PD, they concluded that there is no difference between the two procedures in terms of mortality, morbidity, hospital stay, and quality of life (12). Bhayani et al on the other hand used NSQUIP database to show better perioperative outcome in TP when compared with PD (17). Epelboym et al. addressed the issue of long term quality of life and suggested that this is comparable to the quality of life of patients after alternative pancreatic resections particularly PD (18). Finally Satoi et al. reported analysis of 45 TP for pancreatic cancer concluding that the two procedures have similar postoperative and oncological outcome (25).

In the current study our primary measure of outcome was perioperative mortality and we show an acceptable mortality (2.9%) in the TP group compared to the mortality of the PD cohort (5%). A procedure survival analysis showed that the median overall survival is similar to that of PD (Figure 1). In agreement with Bhayani et al. the results of our study show lower overall complication rates but more importantly when broken down to specific complications and to major or minor complications, it seems that TP reduces it even more. The reduction in major complications is evident although it did not reach statistical significance (2.9% vs. 11.2%, p-0.13).

Multivariate analysis showed that malignancy and major complications are the only independent predictors of postoperative mortality. For major complications the age of the patient is the only independent predictor of outcome. TP on the other hand has a strong negative association with mortality and major complications. We believe that this is explained by the troubled pancreatico-jejunostomy, which is an immense source of morbidity, and once this is eliminated morbidity is significantly reduced.

Our study is limited by the small number of pancreatic adenocarcinoma in the TP group therefore the oncological results should be interpreted cautiously. We found that the TP group has a higher number of lymph nodes harvested; the larger area of dissection easily explains this. The TP did not increase the rates of R0 resection compared to PD, these were quite low anyhow and are difficult to reduce even more. Interestingly the survival of patients with pancreatic adenocarcinoma in the TP group was significantly higher as shown by the Kaplan Meier Curve in Figure 2 (Log Rank 0.006), but as mentioned before the small number of patients limits our ability to draw firm conclusions regarding.

The current study study did not address the issue of long-term quality of life after TP, as we believe that this was fully addressed by Hartwig W et al. with the analysis of 434 patients after total pancreatectomy for pancreatic cancer.

Conclusions

In conclusion our study suggests that total pancreatectomy is not only feasible and safe, it might have better perioperative outcomes than PD with reduced overall complication rate. These results suggest that TP may be offered to patients with the proper indication and patients could be consulted with the relatively good outcome of the procedure.

Abbreviations

PD – Pancreaticoduodenectomy

TP – Total Pancreatectomy

IPMN – Intraductal papillary mucinous neoplasm

Declarations

Ethics approval and consent to participate:

The study was approved by the institutional review board of the Rambam Heath Care Campus in Haifa, Israel (RMB-0581-16). Informed consent was waived by the IRB committee due to the retrospective nature and the lack of clinical impact on the patients involved in the study.

Availability of data and materials:

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests:

All authors report no conflict interests and have nothing to disclose.

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Author contribution:

OBI*:* Study Conception and design, analysis of the data, drafting of the manuscript.

RAZ: Data Collection.

YK: Critical review of the manuscript

All authors read and approved the article in its current form

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Tables

Table 1 – Indication for Total Pancreatectomy and Pancreatico-duodenenctomy

	TP	*PD*	*Univariate*
	n-35	*n-179*	*p-value*
logy			***<0.001***
ctal Adenocarcinoma	34.3 (n-12)	63.7 (n-114)	
MN	57.1 (n-20)	19.5 (n-17)	
ncreatic cystic lesions	0	8.9 (n-16)	
ET	2.9 (n-1)	4.4 (n-8)	
pullary Adenocarcinoma	0	3.3 (n-6)	
pullary Benign polyps	0	2.8 (n-5)	
olangiocarcinoma	0	1.7 (n-3)	
odenal Adenocarcinoma	0	1.7 (n-3)	
odenal benign lesions	0	1.7 (n-3)	
rious	0		
gG4 Pancreatitis	0	0.55 (n-1)	
IST	0	1.1 (n-2)	
arcoma	0	0.5 (n-1)	
seudopapillary tumor	0	0.5 (n-1)	
ncreatitis	5.7 (n-2)	0	
nancy	38.2 (n-13)	76 (n-136)	***<0.001***

- Intraductal papillary mucinous neoplasm, PNET – Pancreatic neuroendocrine tumor, GIST – Gastrointestinal stromal tumor. TP – ancreatectomy, PD – Pancreatico-duodenectomy

2 – Demographic, clinical and laboratory characteristics of the study and control group.

	TP	*PD*	*Univariate*
	n-35	*n-179*	*p-value*
)	67.7±8.5	68.1±12.6	0.88
er (male) (%)	18 (51.4)	88 (49.2)	0.8
actors			
oking (%)	3 (9.7)	63 (39.4)	***0.001***
betes Mellitus (%)	22 (62.9)	67 (37.4)	***0.005***
onic pancreatitis (%)	4 (11.4)	17 (9.5)	0.75
ohol Abuse (%)	2 (5.7)	10 (6.4)	0.87
on of symptoms (days) (median)	30 (18-105)	45 (15-120)	0.65
t loss (%)	15 (42.9)	91 (51.1)	0.37
ea (%)	11 (31.4)	41 (23.3)	0.29
s (%)	4 (11.8)	25 (14)	0.72
ea (%)	5 (14.7)	16 (9)	0.30
lice (%)	9 (26.5)	87 (48.9)	***0.02***
in Total (median) (mg/dl)	0.6 (0.3-2.3)	0.8 (0.4-5)	0.18
globin (gr/dl)	12.3±1.9	12.2±1.7	0.64
ets	243.6±102.3	267.5±102.8	0.2

3 – Comparison of postoperative outcomes of both study and control group

	TP	*PD*	*Univariate*
	n-35	*n-179*	*p-value*
tive Time (min)	239±42	221±40	***0.02***
for blood transfusion	0	8.9 (n-16)	0.08
erative mortality (%)	2.9 (n-1)	5 (n-9)	0.58
ll Complications	17.1 (n-6)	55 (n-99)	***<0.001***
o-Clavien Grade			***<0.001***
de 0 (%)	80 (n-28)	39.7 (n-71)	
de 1 (%)	5.7 (n-2)	18.4 (n-33)	
de 2 (%)	11.4 (n-4)	30.7 (n-55)	
de 3 (%)	0	6.2 (n-11)	
de 4 (%)	0	0	
de 5 (%)	2.9 (n-1)	5 (n-9)	
days)	11 (7-30)	12 (5-239)	0.53
ay (y)	2.9 (n-1)	2.2 (n-4)	1.0
of discharge			0.88
me (%)	88.6 (n-31)	89.9 (n-152)	
nabilitation (%)	11.4 (n-4)	10.1 (n-17)	

eak down of specific complications. Note the differences between in major complications presents namely in the PD

	TP	*PD*	*Univariate*
	n-35	*n-179*	*p-Value*
ficial	0	22.3 (n-40)	***<0.001***
	0	2.8 (n-5)	0.32
Abscess	0	12.3 (n-22)	***0.03***
c Leak	0	29.1 (n-51)	***<0.001***
leak	0	1.1 (n-2)	0.53
	0	11.1 (n-21)	***0.002***
	8.8 (n-3)	14 (n-25)	0.41
ia	5.9 (n-2)	14.5 (n-26)	0.17
y embolism	0	1.1 (n-2)	0.54
	0	0.5 (n-1)	0.66
	0	3.9 (n-7)	0.24
	0	11.7 (n-21)	***0.03***
	14.7 (n-5)	12.8 (n-23)	0.76

al Site infection, DVT – Deep Vein Thrombosis, PVT – Portal Vein Thrombosis, CV – Cardiovascular, UTI – Urinary Tract

Table 5 – Over time not many studies compared the results of TP and PD, this table summarizes the data of the most recent ones.

	Muller[12]		Nikafarjam[19]		Satoi[25]		Casadei[20]		Xiong[21]		Ben-Ishay	
Year	2007		2014		2015		2016		2017		2019	
Country	Germany		Australia		Japan		Italy		China		Israel	
Design	Prospective		Retrospective		Prospective		Retrospective		Retrospective		Retrospective	
Disease	Multiple		Multiple		PACA		Multiple		PACA		Multiple	
Procedure	TP	PD	TP	PD	TP	PD	TP	PD	TP	PD	TP	PD
No. Patients	87	87	15	150	45	45	73	184	50	50	35	179
Mortality (%)	6.9	3.5	6.7	2	0	0	4.1	4.9	6	4	2.9	5
Complications (%)	35.6	25.4	86.7	57.3	31.1	40	32.9	23.9	52	48	17.1	55
Op time (min)	385±72	359±88	630±98	420±768	526±104	530±106	380±50	335±90	415±22	395±25	239±42	221±40
Hospital Stay (days)	11±6	12±3	17±22	19±6	N/A	N/A	16±14	16±29	19±7	18±6	11 (7-30)	12 (5-239)

Op time – Operation time, Multiple – Refers to benign and malignant disease, PACA – Pancreatic Adenocarcinoma, TP – Total Pancreatectomy, PD – Pancreatico-duodenectomy

Figures

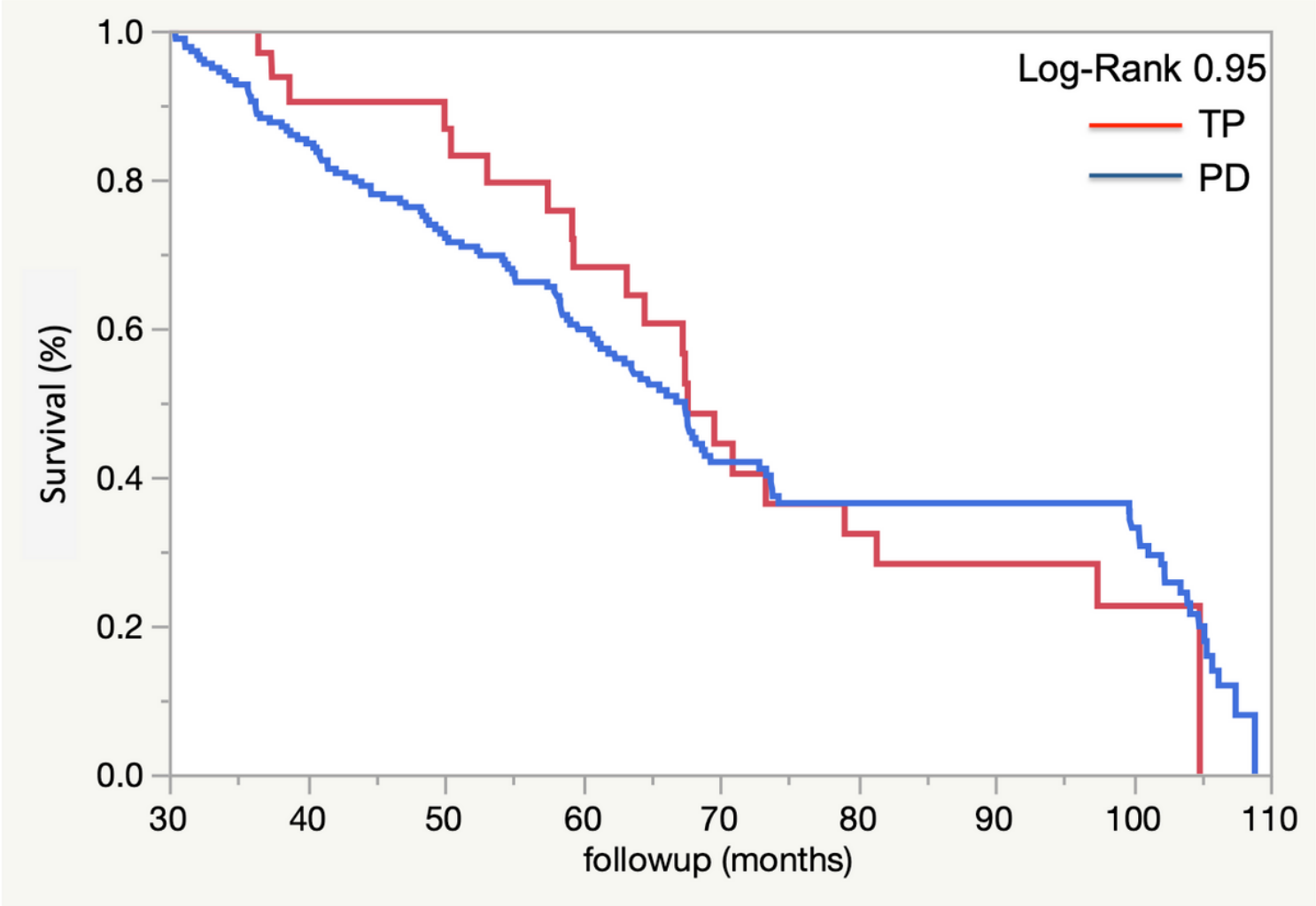

Figure 1

Procedure survival analysis showing the same median overall survival for the two procedures.

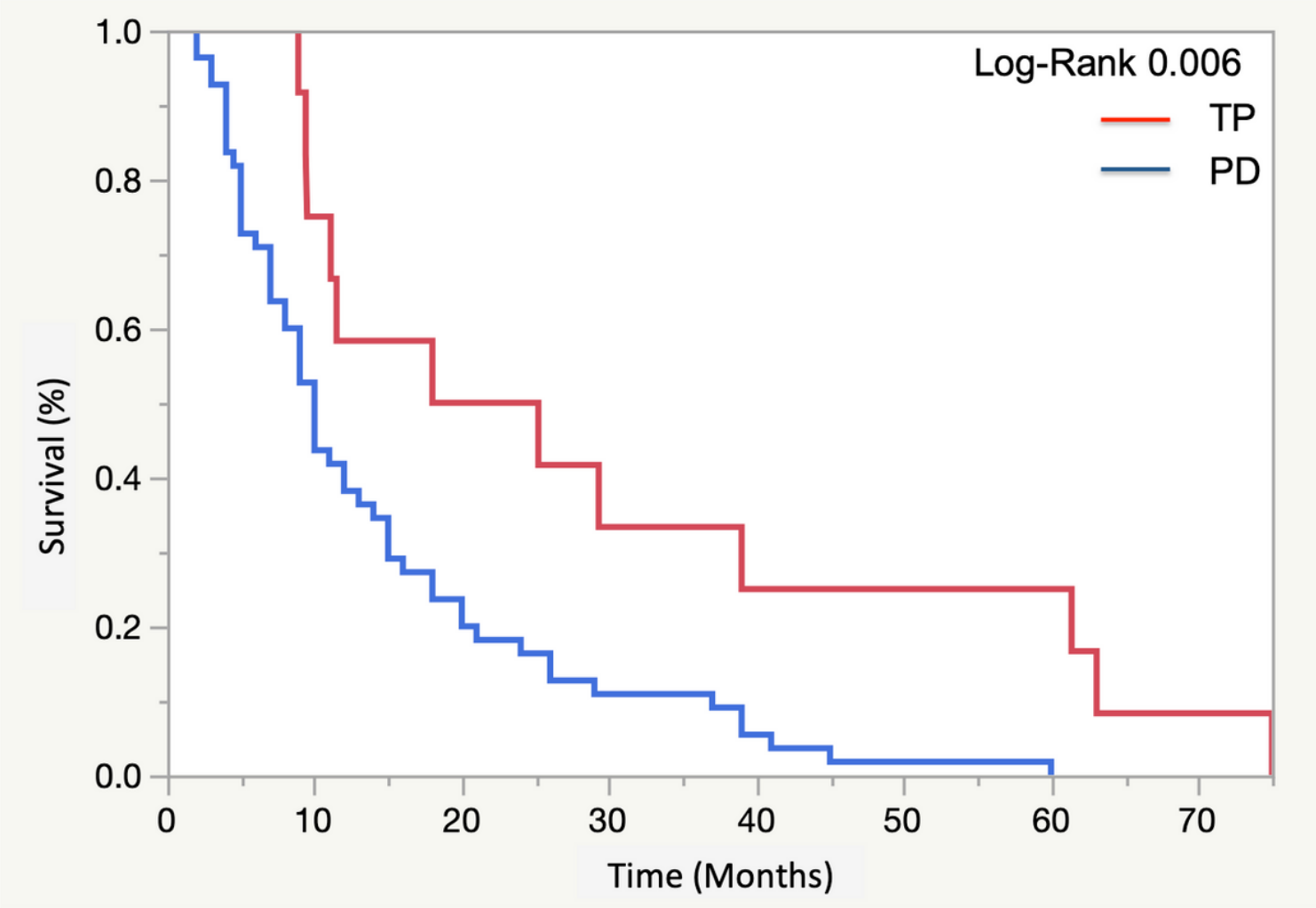

Figure 2

Survival Analysis of the patients with pancreatic adenocarcinoma of the two groups. The Kaplan-Meier curve shows an improved overall survival of the TP group (Log Rank 0.006)