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Distal Pancreatectomy, Pancreatoduodenectomy and Total Pancreatectomy for Pancreatic Neuroendocrine Tumors – Same Organ, Different Outcomes

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Keywords:

Pancreas; Neuroendocrine Tumor; Pancreatectomy

1. Abstract

1.1. Aims: The relationship between extent of pancreatectomy and survival for the management of pancreatic neuroendocrine tumors (PNET) is unclear. We hypothesize that tumor biology and completeness of resection dictate outcome more so than extent of pancreatectomy.

1.2. Methods: Patients who underwent Distal Pancreatectomy (DP), PancreatoDuodenectomy (PD), or Total Pancreatectomy (TP) for PNETs were identified in the National Cancer Database from 2004-2014. Data on demographics, tumor characteristics, surgical morbidity/mortality, and overall survival were collected. Univariate and multivariate analyses were performed using chi-squared, t-test, ANOVA, Kaplan Meier, and Log-rank test when appropriate.

1.3. Results: 7441 patients were identified, with 4084 (54.9%) DP, 2633 (35.4%) PD, and 724 (9.7%) TP. Thirty-day mortality was lower for DP compared to PD and TP (0.7% vs. 2.0% vs. 2.6%, p = <0.001). For all comers, 5-year OS for DP, PD, and TP was 84.8%, 79.7%, and 79.2%, p = < 0.001. As expected, survival was worse with more advanced stage disease, irrespective of the extent of pancreatectomy. The survival advantage of DP over TP was only significantly in stage IV disease 69.2% vs. 59.1% TP (p = 0.023).

1.4. Conclusions: More extensive resections for PNETs, including total pancreatectomy, have acceptable short- and long-term outcomes, especially in patients without metastatic disease. When dealing with metastatic disease, the morbidity of the extensive pancreatectomies outweighs the benefit of primary tumor removal. We support a conservative approach, reserving more extensive resections including total pancreatectomy when indicated for more extensive loco-regional disease.

2. Introduction

Pancreatic Neuroendocrine Tumors (PNETs) are rare tumors accounting for 7% of all pancreatic cancers with annual incidence of approximately 4000 cases in the United States [1]. Systemic therapies such as somatostatin receptor antagonists and peptide receptor radionuclide therapy can prolong progression free survival, but surgical resection remains the only chance for cure [2, 3]. Distal Pancreatectomy (DP) and PancreatoDuodenectomy (PD) are often performed to resect PNETs. Furthermore, operative de-bulking of PNETs, including partial hepatectomy or the removal of the primary tumor site, has been shown to prolong survival [4-9]. However, for multifocal disease or celiac axis involvement, Total Pancreatectomy (TP) may be required for a more complete resection [10, 11]. Previous studies have examined the safety of TP for pancreatic adenocarcinoma and Intra-Ductal Pancreatic Mucinous Neoplasm (IPMN) with acceptable morbidity rates and no long-term deaths from diabetes related complications [12, 13]. Given the safety of TP for adenocarcinoma and IPMN, we aimed to evaluate the role of TP in the management of PNETs with the hypothesis that tumor biology and completeness of resection dictate outcome more so than the extent of surgery. We queried the National Cancer Database (NCDB) to compare the short-term risks and long-term

outcomes of DP, PD, and TP for PNETs.

3. Materials and Methods

Patients who underwent DP, PD, or TP for histologically confirmed PNETs were identified in the National Cancer Database from 2004-2014. Patients were excluded if they had stage 0 disease, tumors confined to the duct or islet, or poorly differentiated histology (Figure 1). Patient demographics including age, sex, race, comorbidities, distance to hospital, facility type, household income and tumor characteristics including analytic stage, tumor size, grade, regional lymph nodes, surgical margins, and the use of adjuvant therapies such as chemotherapy and/or radiation therapy were collected and analyzed.

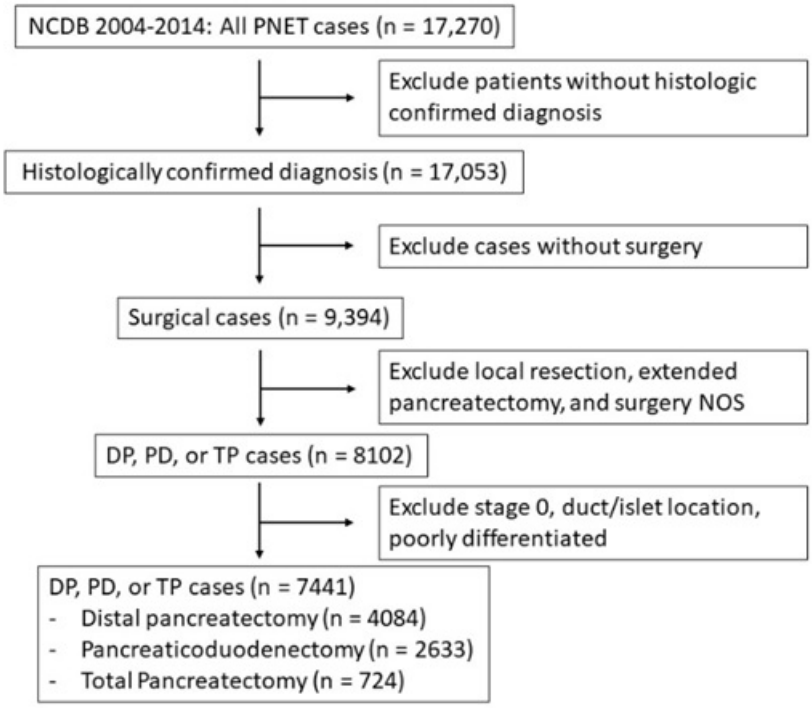

Figure 1: Flow Diagram of Patient Selection

Surgical morbidity and mortality were evaluated by obtaining data on length of stay, unplanned readmission, and patient mortality within 30 days. Evaluation of long-term survival was performed by analyzing overall survival (OS) at 1-, 3-, and 5-years. Overall survival was defined as time from PNET diagnosis to time of death or censored at last date of follow up. Survival data was available for patients from 2004 to 2014.

Univariate and multivariate analyses were performed to determine the degree to which patient, tumor, surgery, and treatment variables affected survival. Statistical analysis was performed using chi-squared, t-test, ANOVA, Kaplan Meier, and Log-rank test when appropriate using STATA version 14 (Stata Corp, College Station, TX).

4. Results

Of the 7441 patients undergoing pancreatectomies for PNETs, 4084 (54.9%) underwent DP, 2633 (35.4%) underwent PD, and 724 (9.7%) underwent TP. The majority of cases were performed at academic/research (57%) and comprehensive community cancer programs (21.8%). Most patients had private insurance (55.3%) or Medicare (33.8%). There was no significant difference in sex, race, comorbidities, distance to hospital, and median household income between DP, PD, and TP (Table 1).

A significantly higher proportion of patients undergoing DP had stage I disease (tumors <2 cm with no nodal or distant metastases), compared with PD and TP (53.4% vs. 38.3% vs. 37.3%, p = <0.001). Conversely, a lower proportion of patients undergoing DP had stage II disease (tumors 2-4 cm (T2) or tumors >4 cm and within the pancreas of any size either contained within the pancreas or invading into the distal common bile duct or duodenum (T3) without nodal or distant metastases) compared to PD, and TP (22.0% vs. 32.2% vs. 31.2%, p = <0.001). Stage III disease (tumors invading into adjacent organs, or any nodal involvement without distant metastases) accounted for only 67 (0.9%) of all patients, and PD accounted for 50.8% of this small group of patients. There were fewer patients with stage IV disease (distant metastases) in the DP group as compared to PD and TP (8.3% vs 10.7% vs. 11.1%, p = 0.001). Furthermore, DP was performed more frequently for early stage (stage I/II) disease compared to PD and TP (75.4% vs. 70.5% vs. 68.5% p = <0.001) (Table 2).

Table 1: Summary of Patient Characteristics

Patient Characteristics	DP	PD	TP	p-value
Age, mean (years)	58.7	57.5	57.6	0.005
Sex, % male	52.40%	49.80%	53.60%	NS
Race				NS
White	75.20%	73.60%	73.30%	
Black	11.10%	12.60%	12.20%	
Hispanic	5.50%	5.50%	6.10%	
Other	3.70%	3.90%	3.60%	
Unknown	4.50%	4.40%	4.80%	
Comorbidity Score				NS
0	70.30%	72.70%	71.30%	
1	23.30%	22.50%	22.80%	
2	6.40%	4.80%	5.70%	
Insurance				0.007
Private	54.20%	56.90%	55.70%	NS
Medicare	35.80%	31.10%	32.60%	<0.001
Medicaid	4.80%	5.90%	5.90%	NS
Uninsured	2.30%	3.00%	3.00%	NS
Other/unknown	2.90%	3.20%	2.80%	NS
Median household income				NS
<$38,000	14.40%	14.70%	14.50%	
$38,000-$47,999	21.20%	20.90%	20.40%	
$48,000-$62,999	26.50%	28.30%	26.50%	
>$63,000	37.20%	35.10%	37.30%	
Facility Type				0.006
Community Cancer Program	2.20%	1.70%	2.60%	NS
Comprehensive Community Cancer	22.80%	20.00%	22.50%	0.023
Academic/Research	56.30%	58.90%	53.90%	0.023
Integrated Network Cancer Program	10.10%	9.30%	12.20%	NS
Distance to Hospital, mean (miles)	56.3	65.4	58.2	NS
Chemotherapy, % yes	4.70%	6.80%	7.00%	0.002
Radiation Therapy, % yes	1.50%	3.40%	4.10%	<0.001

With regard to tumor grade, the majority of cases were performed for well differentiated tumors, but DP had a slightly higher proportion of well differentiated tumors compared to PD and TP (69.3 vs. 66.3% vs. 64.0%, p = 0.001) (Table 2).

A greater proportion of DP were performed for tumors ≤2 cm relative to PD and TP (34.9% vs. 26.6% vs. 23.9%, p = <0.001). In contrast, a greater proportion of TP were performed for tumors >5 cm relative to DP and PD (27.5% vs. 21.5% vs. 20.1%, p = <0.001) (Table 2).

A higher proportion of PD were performed for disease located in the head of the pancreas and a higher proportion of DP were performed for tumors located in the body and tail. For TP, there was no dominant tumor location, which may reflect the multifocality of the disease or vascular encasement necessitating a total pancreatectomy.

A higher proportion of patients undergoing DP achieved an R0 resection compared with PD and TP (90.4% vs. 85.8% vs. 87.4%, p = <0.001). The average lymph node yield was higher for PD and

TP compared to DP (13.2 vs. 13.3 vs. 8.9, p = <0.001). Patients undergoing PD and TP were more likely to have node positive disease compared with DP as reflected in the increased proportion of stage III/IV disease in these groups (p = <0.001).

Average length of stay was significantly shorter for DP compared to PD, and TP (7.2 vs. 11.0 vs. 10.3 days, p = <0.001). Unplanned 30-day readmission was similar between DP, PD, and TP (8.6% vs. 8.8% vs. 9.7%, p = 0.531). Thirty-day mortality was significantly lower for DP compared to PD, and TP (0.7% vs. 2.0% vs. 2.6%, p = <0.001) (Table 3).

Comparative survival between DP vs. PD vs. TP favored DP with 1-year OS of 97.8% vs 95.2% vs 93.8%, 3-year OS of 92.9% vs. 87.7% vs. 86.0%, and 5-year OS of 84.8% vs. 79.7% vs. 79.2% (p = < 0.001) (Figure 2).

As tumor size varied between groups, 5-year overall survival was further stratified by tumor size. In our analysis, there was no difference in 5-year OS between DP, PD, and TP for tumors 1-2 cm in size or 3-5 cm in size. However, for tumors 2-3 cm in size, PD had a slightly lower 5-year OS compared to DP and TP (82.0% vs. 87.5% vs 87.6%, p = 0.007). Additionally, for tumors >5 cm in size, DP had a higher 5-year OS when compared to PD and TP (80.3% vs. 74.7% vs 72.5%, p = 0.009).

Given the heterogeneity in the stage of disease, survival after total pancreatectomy was then stratified further by stage (Figure 3). We then compared survival between DP, PD, and TP by stage. For stage I disease, 5-year OS was similar between DP, PD, and TP (88.8% vs. 88.9% vs. 87.4%, p = 0.29) (Figure 4A). For stage II disease, PD had a significantly lower 5-year OS at 79.7% compared to 85.6% and 84.3% for DP and TP respectively (p = 0.016) (Figure 4B). For stage III disease, with the caveat of a low number of patients in this subset of patients, 5-year OS was not statistically different between DP, PD, and TP at 74.4%, 81.5%, and 65.2% respectively (p = 0.74) (Figure 4C). For stage IV disease, DP had a significantly higher 5-year OS of 69.2% compared to 57.8% for PD and 59.1% for TP (p = 0.023) (Figure 4D).

Table 2: Tumor Characteristics

Tumor Characteristics	DP	PD	TP	p-value
AJCC Analytic stage				<0.001
Stage I	53.40%	38.30%	37.30%	
Stage II	22.00%	32.20%	31.20%	
Stage III	0.50%	1.30%	1.70%	
Stage IV	8.30%	10.70%	11.10%	
Unknown	15.80%	17.60%	18.80%	
Tumor grade				0.001
Well	69.30%	66.30%	64.00%	0.003
Moderate	12.50%	13.10%	11.50%	<0.001
Undetermined	18.20%	20.60%	24.60%	NS
Tumor size				<0.001
<1.0 cm	8.90%	6.40%	6.10%	
1 - <2.0 cm	26.00%	20.20%	17.80%	
2 - <3.0 cm	20.80%	21.40%	19.90%	
3 - <5.0 cm	23.20%	28.40%	26.70%	
>5.0 cm	20.10%	21.50%	27.50%	
Undetermined	1.10%	1.90%	2.10%	
Surgical Margins				<0.001
R0	90.40%	85.80%	87.40%	
R1/R2	7.00%	10.40%	9.30%	
Undetermined	2.10%	3.20%	2.90%	
Regional lymph nodes				
number examined, mean	8.9	13.2	13.3	<0.001
positive, % yes	22.10%	38.30%	36.70%	<0.001

Table 3: Post-operative outcomes and survival

Post-operative Outcomes	DP	PD	TP	p-value
Length of Stay, mean (days)	7.2	11	10.3	<0.001
Unplanned 30-d readmission, % yes	8.60%	8.80%	9.70%	NS
30-day mortality				<0.001
yes	0.70%	2.00%	2.60%	
unknown	19.40%	16.90%	13.80%	
Overall survival				<0.001
1 year	97.80%	95.20%	93.80%	
3 year	92.90%	87.70%	86.00%	
5 year	84.80%	79.70%	79.20%	
5-yr OS				
Stage I	88.80%	88.90%	87.40%	NS
Stage II	85.60%	79.70%	84.30%	0.016
Stage III	74.40%	81.50%	65.20%	NS
Stage IV	69.20%	57.80%	59.10%	0.023

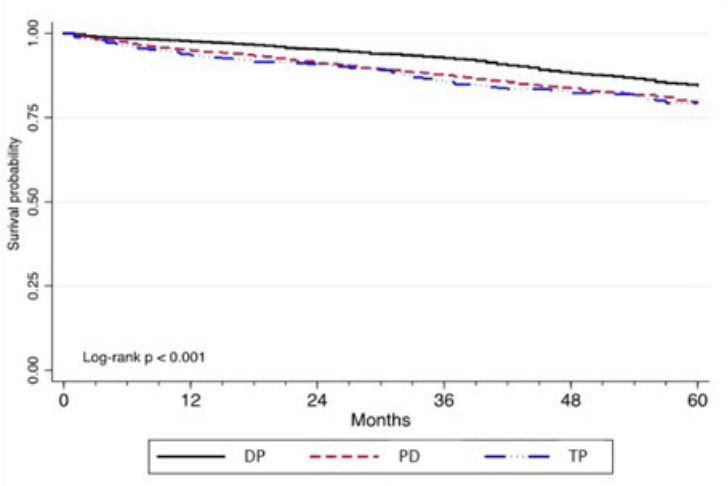

Figure 2: Overall Survival by Procedure

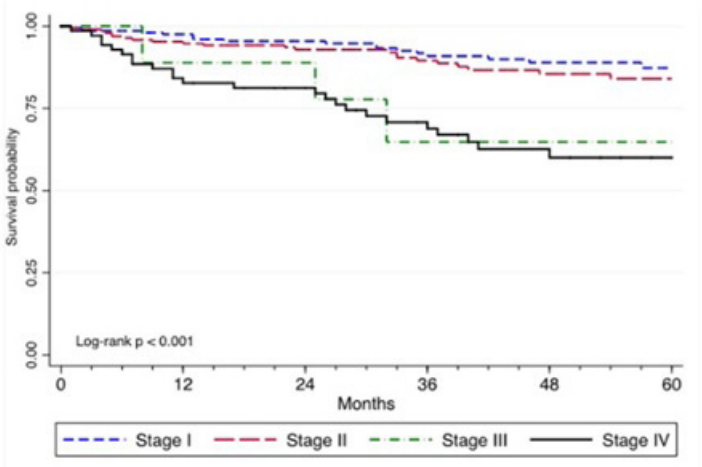

Figure 3: Overall Survival after Total Pancreatectomy Stratified by Stage

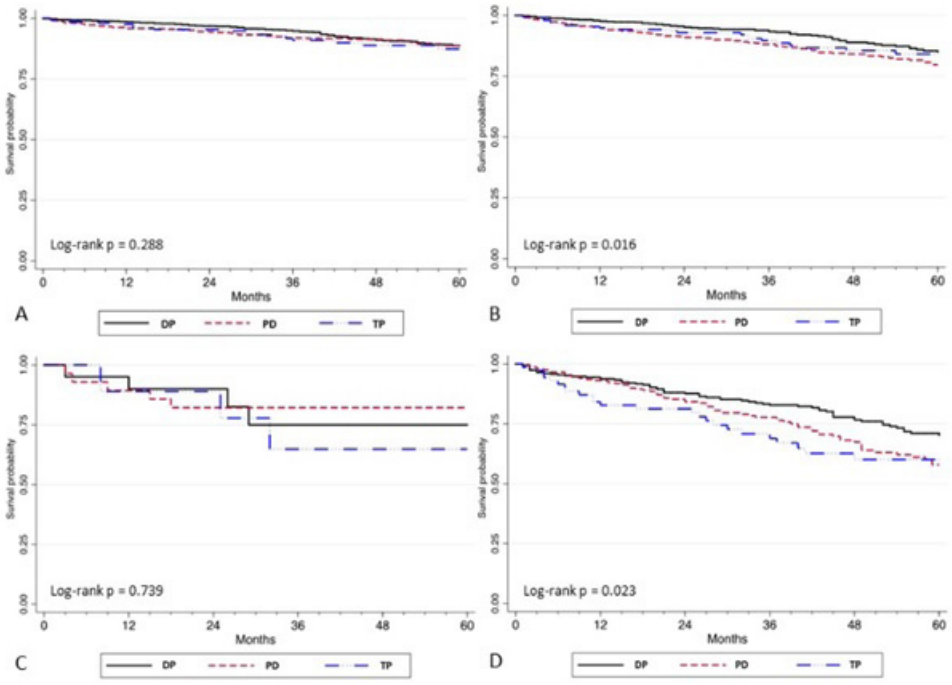

Figure 4: Overall Survival of Distal Pancreatectomy, Pancreatoduodenectomy, and Total Pancreatectomy – Stratified by Stage. Stage I disease (4A). Stage II disease (4B). Stage III disease (4C). Stage IV disease (4D). DP = distal pancreatectomy, PD = pancreaticoduodenectomy, TP = Total Pancreatectomy

5. Discussion

Surgical resection of PNETs remains the best chance for cure and it is important to be appropriately aggressive with resect able disease. Given that PNETs represent a relatively indolent entity on the spectrum of pancreatic malignancies, how far to push the limits of surgical resection are widely debated. In addition to surgical resection, there are many additional therapies such as somatostatin receptor antagonists (octreotide and lanreotide), chemotherapy, targeted therapies (everolimus and sunitinib), and more recently peptide receptor radionuclide therapy. Several studies have shown that even in the setting of metastatic disease, removal of the primary lesion and tumor de-bulking has shown survival benefit [8, 9, 14-16]. It is for this reason, that we elected to include stage IV patients in our analysis. Enucleation, DP, and PD are commonly performed for PNET, however given the concerns for the associated morbidity and mortality, TP is generally avoided unless absolutely necessary. Current consensus guidelines for the management of functional and non-functional PNETs reflect the sentiment of proceeding with the least extensive surgical option, reserving more morbid resections for cases in which they are truly needed [17].

Total pancreatectomy is a historically morbid surgery with post-operative mortality rates as high as 10-15%, with associated short- and long-term complications of brittle diabetes, exocrine pancreatic insufficiency, and non-alcoholic fatty liver disease [18-20]. Improvements in surgical technique, peri-operative care, and the ability to rescue have decreased 30-day mortality rates to 2-5% in recent series [21, 22]. The improvement in management of brittle diabetes and exocrine pancreatic insufficiency with improved insulin formulations and dosing strategies as well as pancreatic enzymatic replacement have allowed for reduced morbidity and improved quality of life [23, 24].

In our examination of the available NCDB dataset, post-operative outcomes such as length of stay and 30-day mortality favored DP over PD and TP, however, there was no difference in 30-day readmission rates between DP, PD, and TP. The lack of an increased readmission rate could suggest adequate management of the post-operative metabolic sequelae of TP, thus preventing readmissions [25]. Alternatively, the potential complications of a pancreatic leak that could occur with DP and PD may be just a morbid as brittle diabetes in the post-operative period.

When stratified by stage, there was no difference in 5-year OS for DP, PD, and TP for stage I disease. While PD had a significantly worse survival for stage II disease, the absolute difference was only 5%. Furthermore, there was no difference in 5-year OS between DP and TP for stage II disease. The etiology of the worse survival for stage II patients undergoing PD remains unclear and a more dedicated evaluation of this subset of populations in a more granular dataset would be needed.

Our findings on the lack of statistical difference in 5-year OS for stage III disease despite a clinically significant 16% worse overall survival of TP compared to DP is due to our low number of stage III patients in this dataset resulting in an underpowered analysis

in this subset of patients. Perhaps the low number of patients with stage III disease specifically within the DP cohort is a function of the lower number of lymph nodes collected/evaluated during a DP when compared to PD and TP. Further evaluation of patients with stage III disease would be warranted in a larger dataset to better evaluate if there is indeed a significant difference in survival.

As expected, stage IV disease portends a poorer prognosis across all procedure types. The improved overall survival for DP relative to PD and TP for stage IV disease may represent the additional morbidity of the larger resections. Another explanation could be that DP patients had a collection of favorable characteristics including, lower grade disease, smaller tumors, and higher R0 resection rates, which may have translated into improved survival. However, survival in all groups was still much better than the reported 3-year overall survival of 47% in patients with PNETs in which the primary tumor was not resected [16].

The decreased impact of total pancreatectomy on long term survival is likely due to improvements in the management of brittle diabetes that have reduced sequelae such as severe hypoglycemia and diabetic ketoacidosis. Advances in Continuous Glucose Monitoring (CGM) allow for closer monitoring of blood glucose levels to prevent episodes of severe hypoglycemia. The combination of CGM to insulin pumps have resulted in closed loop systems and "hybrid artificial pancreas" systems, which have been shown to increase the proportion of time spent near normoglycemia [25]. Furthermore, the recent development of bihormonal completely automated systems have been shown to reduce the mean glucose level and percentage of time with hypoglycemia [26, 27].

Limitations of this study are similar to those of all large database studies. Mainly that there is inherent lack of granularity. A major limitation is the inability to determine the rationale behind performing total pancreatectomies, which are most commonly due to multifocal disease or celiac axis involvement. Additionally, documentation of additional therapies such as somatostatin receptor antagonists and targeted therapies may not be well captured in this dataset as they may not fall into the traditional chemotherapy category.

This study showed a reduced peri-operative morbidity and mortality of DP for PNET. This is in support of current guidelines that recommend undergoing the least extensive operation to achieve a complete resection to minimize morbidity and mortality. However, there are situations such as multifocal disease and celiac axis involvement in which total pancreatectomy is necessary to achieve a complete resection. In this study, TP had a comparable post-operative morbidity and mortality profile to PD, especially in the non-metastatic setting. Furthermore, the safety of TP has been demonstrated in series examining TP for pancreatic adenocarcinoma as well as IPMN [12, 13]. While the decision to pursue a total pancreatectomy is not to be taken lightly, the peri-operative morbidity in the modern era is significantly reduced and long-term outcomes are close to other forms of pancreatectomy when adjusted for stage of disease. As such, TP should remain a reasonable option for surgical resection in appropriately selected patients with PNETs.

6. Conclusions

More extensive resections for PNETs, including total pancreatectomy, have acceptable short- and long-term outcomes, especially in patients without metastatic disease. In particular, total pancreatectomy has no difference in morbidity or long-term survival when compared PD as the sequelae of diabetes have been mitigated by advances in glycemic control. When dealing with metastatic disease, the morbidity of extensive pancreatectomies outweighs the benefit of primary tumor removal. As such, we support a conservative approach with less extensive pancreatectomy for PNETs when possible, reserving more extensive resections including total pancreatectomy when indicated for more extensive loco-regional disease.

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