Size alone is not enough: Ki-67 and invasion patterns identify high-risk pancreatic neuroendocrine tumors (pNETs)

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Original Article

SIZE ALONE IS NOT ENOUGH: KI-67 AND INVASION PATTERNS IDENTIFY HIGH-RISK PANCREATIC NEUROENDOCRINE TUMORS (pNETS).

O tamanho por si só não basta: Ki-67 e padrões de invasão identificam tumores neuroendócrinos pancreáticos de alto risco.

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Data Availability Statement

The information regarding the investigation, methodology and data analysis of the article is archived under the responsibility of the authors.

RESUMO

Racional: Os tumores neuroendócrinos pancreáticos (pNET) constituem uma doença heterogênea e rara em todo o mundo. O diagnóstico tem aumentado e a avaliação de fatores prognósticos tornou-se ainda mais importante no processo de decisão terapêutica.

Objetivos: Apresentar os resultados e fatores prognósticos em pacientes submetidos a tratamento cirúrgico para TNEP em um único centro brasileiro.

Resultados: O procedimento cirúrgico mais realizado foi a pancreatectomia corpo-caudal com esplenectomia (60,0%). A mediana de internação hospitalar foi de 8 (5-13) dias e a mortalidade pós-operatória ocorreu em 1,7%. A sobrevida global em 3 e 5

anos foi de 93,8% e 92,1%, respectivamente. A sobrevida livre de doença em 3 e 5 anos foi de 87,1% e 71,8%, respectivamente. Pacientes com tumores menores que 2, 0 cm não apresentaram comprometimento linfonodal ou recidiva, enquanto indivíduos com tumores entre 2,1 e 2,5 cm apresentaram comprometimento linfonodal em 11,1% dos casos e recidiva em 11,1%. Nas análises univariada e multivariada, a presença de invasão vascular linfática e perineural e o Ki67 (3-20) apresentaram forte correlação com doença linfonodal positiva e recidiva, respectivamente.

Conclusões: A presença de invasão vascular linfática e perineural, o Ki67 (3 a 20) e tumores maiores que 2,5 cm, correlacionaram-se com doença linfonodal positiva e reci diva.

Palavras-chaves: Tumores Neuroendócrinos. Oncologia Cirúrgica. Pâncreas. Pancreatectomia.

ABSTRACT

Background: Pancreatic neuroendocrine tumors (pNETS) constitute a heterogeneous and rare disease worldwide. Diagnosis has been increasing, and the evaluation of prognostic factors has become even more important in the treatment decision process. **Aims:** To present results and prognostic factors in patients undergoing surgical treatment for pNETS in a single Brazilian center.

Results: The most performed surgical procedure was corpus-caudal pancreatectomy with splenectomy 60.0%. The median hospital stay was 8 (5-13) days, and postoperative mortality occurred in 1.7%. Overall survival in 3 and 5 years was 93.8% and 92.1%. Disease-free survival at 3 and 5 years was 87.1% and 71.8%. Patients with tumors smaller than 2.0 cm did not present with lymph node disease or recurrence and 2.1-2.5cm individuals had lymph node disease in 11.1% and recurrence in 11.1%. In univariate and multivariate analysis, the presence of lymphatic and perineural vascular invasion and Ki67 (3-20) were strongly correlated with positive lymph node disease and recurrence, respectively.

Conclusions: The presence of lymphatic and perineural vascular invasion, Ki67 (3 to 20), and tumors above 2.5 cm correlated with positive lymph node disease and recurrence.

HEADINGS: Neuroendocrine Tumors. Surgical Oncology. Pancreas. Pancreatectomy.

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Conflicts of Interest: None

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Central message

Pancreatic neuroendocrine tumors (pNETs) are a heterogeneous disease, which can exhibit either an indolent or an overtly malignant behavior. The primary treatment for pNETs is surgical. Minimally invasive surgery (laparoscopic and robotic) has been increasingly performed, with superior outcomes in terms of morbidity and length of hospital stay. Currently, there is evidence to support active surveillance as a strategy for tumors smaller than 2 cm.

Perspectives

This study presents the largest series of neuroendocrine tumors operated on at a single Brazilian center, including epidemiological data, survival, and prognostic factors. Pancreatic surgery remains a procedure with high morbidity, and minimally invasive approaches are gaining more ground. Patients treated surgically showed a high 5-year overall survival rate of 92.1%. The identification of poor prognostic factors plays an important role in oncological follow-up and in better selecting patients for the "Active Surveillance" (AS) strategy and non-standardized surgeries. Important prognostic factors were correlated, such as tumor size greater than 2.0 cm, Ki-67 index, and lymphovascular invasion. In a subgroup analysis of patients with tumors measuring 2.1-2.5 cm, we found a recurrence and lymph node disease profile comparable to patients eligible for active surveillance.

HIGHLIGHTS

Pancreatic neuroendocrine tumors (pNETS) constitute a heterogeneous and rare disease worldwide.

This study presents the largest series of pNET operated on at a single Brazilian center.

Size is not enough to predict behavior in pNETS. Patients with 2.1-2.5cm tumor present with a pattern of recurrence similar do less than 2.0cm patients which are candidates for active surveillance strategy.

Authors' contributions

Conceptualization: Cortelli DASM, Coimbra FJF

Investigation: Cortelli DASM

Methodology: Cortelli DASM, Coimbra FJF, Farias IC

Data analysis: Cortelli DASM, Coimbra FJF

Writing original article: Cortelli DASM, Coimbra FJF, Farias IC, Diniz AL, Ribeiro HSC

Literature review: Cortelli DASM, Torres SM, Godoy AL, Gonçalves CA

The information regarding the investigation, methodology and data analysis of the article is archived under the responsibility of the authors.

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INTRODUCTION

Pancreatic neuroendocrine tumors (pNETs) are a heterogeneous disease, which can exhibit either an indolent or an overtly malignant behavior. The primary treatment for pNETs is surgical. Minimally invasive surgery (laparoscopic and robotic) has been

increasingly performed, with superior outcomes in terms of morbidity and length of hospital stay[1,12].

Currently, there is evidence to support active surveillance as a strategy for tumors smaller than 2 cm[2,11,15]. Some series have shown lymph node metastasis rates of 10.6-12.8% and recurrence rates of up to 17.9% in patients with tumors measuring between 1.5 and 2 cm[6,16]. Other case series have also identified associated risk factors, such as lymphovascular invasion, which increases the likelihood of lymph node metastasis by tenfold and is associated with an 18% rate of lymph node positivity in the surgical specimen[4].

The identification of poor prognostic factors plays an important role in oncological follow-up and in better selecting patients for the "Active Surveillance" (AS) strategy and non-standardized surgeries[5]. Due to the heterogeneity and rarity of these tumors, there is limited data in the literature regarding management, surgical treatment, perioperative morbidity and mortality, and the description of factors associated with poorer survival, especially in the Brazilian population.

The aim of the present study is to analyze a population of patients with pancreatic neuroendocrine tumors at a single Brazilian center, collecting data on morbidity, mortality, survival, and risk factors associated with recurrence and lymph node involvement.

METHODS

This is a retrospective observational cohort study based on the analysis of medical records of patients who underwent surgical treatment for pancreatic neuroendocrine tumors (pNETs). This research project was submitted to the Research Ethics Committee (CEP) of the A.C. Camargo Cancer Center / Fundação Antônio Prudente and was approved under CAAE: 50408721.4.0000.5432.

Patients who underwent surgical treatment for pancreatic pNETs between 1999 and 2020 were included. We included patients with pNETs who underwent pancreatic surgery, including those requiring vascular or multivisceral resection in association with pancreatectomy. We excluded patients with neuroendocrine tumors presenting with distant metastatic disease and those with missing data in the system.

We collected data on personal history, signs and symptoms, imaging exams, biopsy, surgical details, hospitalization records, histopathological findings, and postoperative follow-up.

RESULTS

Clinical and Demographic Characteristics

A total of 125 resected patients were included. The patients had a median age of 56 years (Interquartile range –- IQR 45-64 years), 53.6% were female, and 85.8% were classified as American Society of Anesthesiology - ASA I or II. Most patients (68.8%) were asymptomatic at diagnosis. Functioning tumors were identified in 7 cases (5.6%).

The most common associated comorbidities were hypertension (41.6%) and obesity (24.0%). Table 1 presents the clinical and perioperative characteristics.

Table 1. Demographic and perioperative outcomes.

Variable	No	
Age (years), median (IQR)	124	56(45-64)
Female, n (%)	125	67(53.6%)
Diabetics, n (%)	125	28 (22.4%)
Hipertension, n (%)	125	52 (41.6%)

BMI, median (IQR)	120	27 (23-30)
ASA, n (%)	120	
1		19 (15.8%)
2		84 (70.0%)
3		17 (14.2%)
Diameter in CT scan(mm), median (IQR)	125	12 (4-19)
Reaction Type, n (%)	125	
DP		75 (60.0%)
SPDP		10 (8.0%)
Enucleation		2 (1.6%)
PPPD		22 (17.6%)
PD		8 (6.4%)
PC		6 (4.8%)
PT		2 (1.6%)

Vascular Resection, n (%)	122	4 (3.3%)
Surgery type, n (%)	125	
Open /conventional approach		51 (40.8%)
Laparoscopy		68 (54.4%)
Robotic		6 (4.8%)
Pancreatic Fistula, n (%)	125	
BL (biochemical leak)		33 (26.4%)
B		12 (9.6%)
C		0 (0%)
30 days mortality, n (%)	121	2 (1.7%)
No postoperative complications, n (%)	124	42 (33.9%)
Clavien-Dindo, n (%)	124	

I	27 (21.8%)
II	18 (14.5%)
III	27 (21.8%)
IV	8 (6.5%)
V	2 (1.5%)

BMI=body mass index; ASA=American Society of Anesthesiology; PPPD=Pylorus preserving pancreatoduodenectomy, DP=Distal pancreatectomy with esplenectomy, PD=Pancreatodudodenectomy, PC=Central pancreatectomy, SPDP=Spleen preserving distal pancreatectomy; CT=computed tomography; IQR=interquartile range

In the analyses, a predominance of hypervascular and isovascular lesions upon intravenous contrast infusion was demonstrated in 66.1% and 29.6%, respectively. On imaging, the median tumor size was 12 mm (IQR 4-19 mm).

The most commonly performed exams were abdominal computed tomography (CT) (72.6%) and magnetic resonance imaging (MRI) (67.2%). Endoscopic ultrasound and Gallium-68 PET (Positron Emission Tomography) were also used in 38.4% and 20.8% of the evaluated patients, respectively. Among patients who underwent Gallium-68 PET-CT and 18-FDG (fluorodeoxyglucose) PET-CT, uptake was observed in 92.3% and 100%, respectively.

Findings such as biliary duct dilation, dilation of the Wirsung duct, pancreatic atrophy, and regional lymphadenopathy were infrequent, observed in 4.8%, 7.2%, 8.0%, and 2.4%, respectively.

Body-caudal pancreatectomy with splenectomy (PCC+S) was the most frequently performed surgery (60.0%), followed by pancreatoduodenectomy (PD) (17.6%), body-caudal pancreatectomy without splenectomy (PCC) (8.0%),

gastroduodenopancreatectomy (GDP) (6.4%), central pancreatectomy (CP) (4.8%), and total pancreatectomy (TP), which was performed in only 2 patients (1.6%).

The predominant surgical approach was laparoscopic in 54.4% of patients, followed by open surgery in 40.8%, and robotic surgery in 4.8%. The median operative time was 335 minutes.

In the first decade of the study (1999-2010), fewer surgeries were performed (21), with open surgery being the most common approach (90.5%). In the second decade, more surgeries for pNETs were performed (101), and minimally invasive surgery (MIS) played a greater role (62.0%), $p < 0.001$.

The median hospital stay was 8 days. Only 9 cases (7.3%) experienced intraoperative bleeding, and 10 patients (8.0%) received blood transfusions during hospitalization. Four patients (3.2%) required surgical re-intervention during their hospital stay, and two patients (1.7%) died. The patients who died within 30 days after surgery had undergone total pancreatectomy. In the first case, a total pancreatectomy combined with total gastrectomy was necessary due to a large tumor mass infiltrating the celiac trunk, during which significant intraoperative bleeding occurred. In the second patient, total pancreatectomy was also performed, but in association with superior mesenteric artery resection, which progressed to acute thrombosis of the arterial graft.

We observed that patients who underwent body-caudal pancreatectomy with splenectomy (PCC+S) had type B fistula rates of 10.6% and a median hospital stay of 6 days (IQR 5-10), whereas patients who underwent pancreatoduodenectomy (PD) had significant type B fistulas (4.5%), no type C fistulas, and a median hospital stay of 14 days (IQR 10-23).

Histopathological Characteristics and Survival

Most of the resected patients had well-differentiated tumors (95.8%), with 48% classified as G1 pNET and 47.2% as G2 pNET. The tumors were predominantly located in the pancreatic body and tail (70.4%). The median tumor size in the surgical specimen was 25 mm, and 15 patients (12%) had positive lymph nodes in the specimen (Table 2).

Table 2. Pathology and Survival.

Category	No	Pnet (n=125)
Well differentiated tumors, n (%)	119	114 (95.8%)
Poor differentiated tumors, n (%)	119	5 (4.2%)
Size (mm), Median (IQR)	124	25 (14- 35)
Positive Lymph nodes, n (%)	125	15 (12%)
Positive Lymph nodes, median (IQR)	125	3 (1-10)
IVS, n (%)	124	17 (13.7%)
IVL, n (%)	125	28 (22.4%)
IPN, n (%)	125	26 (20.8%)

R0, n (%)	125	118 (94.4%)
WHO 2022, n (%)	125	
G1pNET		60 (48%)
G2pNET		59 (47.2%)
G3pNET		4 (3.2%)
G3pNEC		2 (1.6%)
Recurrence, n (%)	121	20 (16.5%)
Follow-up(months), median (IQR)	123	46 (20-76)
Loss of follow-up, n (%)	125	4 (3.2%)
3-year Overall survival, % (Standard Error)	121	93.8% (2.2%)
5-year Overall survival, % (Standard Error)	121	92.1% (2.9%)
3-year Disease free survival, % (Standard Error)	121	87.1 % (3.4%)

5-Year Disease free survival, % (Standard Error)	121	71.8% (5.2%)

IVS=Vascular invasion; IVL=Lymphatic invasion; IPN=perineural invasion; WHO=World Health Organization; R0=Free pathology surgical margins; pNET=pancreatic neuroendocrine tumors; IQR=interquartile range.

During oncological follow-up, the median duration was 46 months. At 3 and 5 years, overall survival rates were 93.8% and 92.1%, and disease-free survival rates were 87.1% and 71.8%, respectively (Figure 1). The presence of pancreatic endocrine or exocrine insufficiency was minimal, occurring in 2 patients (1.6%) for each condition, respectively.

When disease-free survival was analyzed in both univariate and multivariate analyses, all variables showed statistical significance ($p < 0.05$) (Table 3).

Table 3. Subgroup Analysis versus positive lymph nodes and recurrence.

Size	No	LF+	N	Recurrence
<=2.0 cm	41	0 (0%)	0	0 (0%)
2.1-2.5 cm	18	2 (11.1%)	18	2 (11.1%)
2.6-3.0 cm	16	3 (18.8%)	16	5 (31.3%)

3.1-4.0 cm	1 3	4 (30.8%)	1 2	3 (25.0%)

LF+=positive lymphnode.

When we performed a comparative analysis of the groups, we observed that patients with tumors larger than 2.5 cm had a higher risk of recurrence ($p < 0.001$).

Tumors Smaller Than 2.0 cm

When we analyzed the cohort of resected pNETs smaller than 2.0 cm, we had 41 patients. Most were ASA I and II, with 39 patients (97.5%). Minimally invasive surgery was used in 33 patients (80.5%). Lower complication rates were observed, with 2 cases (4.8%) of grade B pancreatic fistula, and the median hospital stay was 8 days. Postoperative complications classified as Clavien-Dindo III occurred in 8 cases (36.4%).

The median tumor size was 13 mm, with 29 patients (70.7%) classified as G1 pNET and 12 (29.3%) as G2 pNET. Among these, 22 patients (55%) had tumors smaller than 15 mm. No resected patient had positive lymph nodes in the surgical specimen or recurrence during a median follow-up of 47 months.

Factors Associated with Recurrence and Positive Lymph Node Disease

We stratified patients into two tumor size groups: the first from 2.1 to 2.5 cm and the second from 2.6 to 4.0 cm. Comparing recurrence rates, we observed that 2 out of 18 patients (11.1%) in the first group experienced recurrence, while 8 out of 29 patients (27.6%) in the second group recurred. This demonstrates that patients with tumors larger than 2.6 cm have a higher risk of recurrence ($p < 0.001$).

Tables 4 present univariate and multivariate analyses for positive lymph nodes in the surgical specimen and recurrence.

Table 4. Univariate and Multivariate Analysis for Positive Lymph Nodes and for recurrence.

Analysis for Positive Lymph Nodes				
Category	Univariate analysis	p	Multivariate analysis	p
IVL+	10.22 (3.12-33.48)	<0.001	10.11 (3.09-33.12)	<0.001
PNI+ and IVL+	5.10 (1.66-15.71)	0.005		
Size (cm)	1.13 (0.97-1.32)	0.125		
Analysis for recurrence				
Category	Univariate analysis	p	Multivariate analysis	p
Ki67(3-20)	11.17 (3.06-40.77)	<0.001	8.76 (2.30-33.34)	0.001
Size (cm)	1.32 (1.13-1.55)	0.001	1.25(1.06-1.48)	0.010
PNI +	3.29 (1.17-9.28)	0.002		

PNI=perineural invasion; CI=confidence interval; IVL=Lymphatic invasion;

OR=odds ratio.

The presence of lymphovascular invasion increased the risk of positive lymph nodes by 10.22 times in univariate analysis (odds ratio - OR 10.22, 95% confidence interval - CI 3.12-33.48, $p < 0.001$) and in multivariate analysis [OR 10.11, 95% CI 3.09-33.12, $p < 0.001$].

In the recurrence analysis, a positive association was observed for Ki-67 between 3% and 20%, with an increased risk [OR 11.51, 95% CI 3.15-42.06, p < 0.001].

Regarding tumor size, each 0.5 cm increase was associated with a higher risk of recurrence [OR 3.29, 95% CI 1.17-9.28, p = 0.001].

DISCUSSION

We present the largest Brazilian case series from a reference center on pancreatic neuroendocrine neoplasms treated surgically. This is a rare disease with scarce data in the literature.

A considerable increase in surgical treatment for pNETs has been observed, due to the widespread use of imaging exams[7,13]. In our cohort, there was a significant increase in the number of surgeries when comparing the first and second decades (21 versus 101, respectively) of the 2000s (p<0.001). The minimally invasive approach showed an increase in indications, being used in 9.5% in the first decade of the study and 62.4% in the following decade (p<0.001). Surgical treatment remains the only modality capable of achieving cure[12]. This is mainly due to the indolent behavior of well-differentiated tumors. Surgery is the main pillar in the treatment of pancreatic neuroendocrine tumors.

The demographic and clinical characteristics of the resected patients were comparable to the literature, with the majority of patients being asymptomatic (68.8%), having non-functioning tumors (94.4%), and sporadic cases[8,10]. We observed a median age of 56 years, with a slight predominance of females (53.6%). Systemic arterial hypertension was the most common comorbidity (41.6%), followed by obesity (24.0%) and diabetes (22.4%).

The most performed surgery for pNETs was distal pancreatectomy with splenectomy in 60.0% of cases, followed by pancreaticoduodenectomy (17.6%) and distal pancreatectomy without splenectomy (8.0%). Few patients underwent multivisceral resections (2.4%) or required associated vascular resection (3.3%), data consistent with the literature[17].

Atema et al.[3] had a median hospital stay of 11 days in the operated patients compared to 8 days in our cohort. In our analyses, Clavien-Dindo grade III and IV complications occurred in 28.3% of patients, and the postoperative mortality rate was 1.7%, occurring in patients who underwent total pancreatectomies.

Pancreatic surgeries are procedures with a high potential for morbidity, often requiring advanced diagnostic and interventional methods. In this study, we observed a median surgical time of 335 minutes (IQR 240-493), intraoperative bleeding in 7.3%, transfusion in 8.0%, and reoperation in 3.2%. Tamburrino et al.[19], in a systematic review with meta-analysis, found that laparoscopic surgery was associated with fewer days of hospital stay ($p<0.001$), less blood loss ($p<0.001$), and showed no difference regarding the presence of pancreatic fistula, recurrence, and postoperative mortality when compared to the open approach.

In histopathological analyses, we observed a high prevalence of well-differentiated tumors (95.8%), most commonly G1 (48%) and G2 (47.2%), with only 3.2% of tumors being G3 and 1.6% of patients having neuroendocrine carcinoma. An analysis of the SEER database from 2000 to 2020, including 8,944 patients, showed 68.9% G1 tumors, 17.3% G2, and 13.8% G3[18].

With a median follow-up of 46 months (IQR 20-76), overall survival was 93.8% at 3 years (standard error 2.2) and 92.1% (standard error 2.9%) at 5 years. Disease-free survival was 87.1% (standard error 3.4%) at 3 years and 71.8% (standard error 5.2%) at 5 years. During survival analyses, there was a loss to follow-up of 3.2%.

In univariate and multivariate analyses for disease-free survival (DFS), we observed that positive lymph nodes [OR 4.30 (2.01-9.18), $p<0.001$], tumor size >2.0 cm [OR 3.74 (1.30-10.78), $p=0.014$], and Ki67 =3 [OR 3.52 (1.58-7.84), $p=0.002$] were associated with worse outcomes. The presence of G1 pNET tumors was identified as a protective factor for DFS [OR 0.19 (0.07-0.50), $p=0.001$]. Gao et al.[9], in a meta-analysis study, a correlation with overall survival was demonstrated, associating factors such as tumor grade, positive lymph node disease, distant metastases, and lymphovascular invasion.

Regarding morbidity, surgery for tumors smaller than 2.0 cm showed a trend toward equivalence with the overall cohort, with a median hospital stay of 8 days, Clavien-Dindo grade III complications in 36.4%, and grade B fistula in 4.8%. The most used surgical

approach was minimally invasive (80.5%). In this subset, no patient presented recurrence or positive lymph node disease.

These presented data may be associated with the smaller median size of these lesions, 13 mm (11-17 mm), and the prevalence of well-differentiated G1 tumors at 70.7%. Dong et al.[6], in 392 tumors smaller than 2.0 cm, demonstrated rates of positive lymph nodes resected in tumors smaller than 2.0 cm (12.8%), as well as differences in disease-free survival rates of 81.7% versus 94.1%, p=0.022 for tumors with negative and positive lymph nodes, respectively. Additionally, recurrence rates were 8.0% for tumors between 1.5-2.0 cm versus 4.5% for tumors smaller than 1.5 cm.

Partelli et al.[15], in a systematic review with meta-analysis including a total of 540 patients, compared surgery versus active surveillance, demonstrating an absence of recurrence in the analyses. However, 14.1% were converted to the surgical arm due to an increase in nodule size. It is interesting to note that in the studies compiled in this review, patients had tumors smaller than 3.0 cm and 4.0 cm. The data suggest that tumors smaller than 2.0 cm have a more indolent behavior, consistent with the results presented in this case series.

Heidsma et al.[10], in a cohort of 76 patients with pNETs smaller than 2.0 cm, reported a follow-up period of 17 months and tumor progression rates of 11%. Six patients were switched to the surgical arm due to tumor growth. Among the converted patients, none presented distant metastases.

Tanaka et al.[20], in a systematic review and meta-analysis including 5,883 articles with a total of 13,374 patients with non-functioning tumors smaller than 2.0 cm, reported 11.2% lymph node metastases. For G1 tumors, lymph node involvement was 10.3%. These results are in agreement with our analyses, which showed a low rate of positive lymph nodes for well-selected tumors smaller than 2.0 cm.

In our analyses, we found 2 cases of recurrence and positive lymph nodes among 18 patients with pNETs between 2.1-2.5 cm (11.1% and 11.1%). When expanding the selection range to 2.6-3.0 cm and greater than 3.1-4.0 cm, we observed increases in the rates of positive lymph nodes and recurrence to 18.8% and 31.3%, and 30.8% and 25.0%, respectively. Bolm et al.[5], in their publication on 810 tumors smaller than 3.0 cm, demonstrated similar oncologic outcomes for both standard and non-standard resections.

Despite positive lymph node rates of 15% for non-standard resections versus 19.2% for standard resections (p=0.988), it was demonstrated that surgical radicality can be reduced for tumors <3.0 cm. These data suggest a patient profile in which tumors smaller than 3.0 cm may be selected for treatments with omitted radicality. In our data analysis, we hypothesize that well-selected patients with tumors between 2.1-2.5 cm, based on pancreatic biopsy and risk factor analysis, could undergo conservative treatments such as active surveillance and parenchyma-sparing surgery.

Blakely et al.[4], in a regression analysis of 2,499 pNETs smaller than 2.0 cm, observed lymphovascular invasion in 11% of cases and a difference in mean survival between patients with positive and negative lymph nodes of 115 months versus 95 months (log-rank p<0.0001). The presence of lymphovascular invasion was identified as a strong predictor of lymph node involvement (OR 10.4, p<0.0001). In univariate and multivariate analyses, a significant difference was found regarding lymphovascular invasion depending on the selected risk category. For example, in tumors smaller than 1.0 cm, only 4% presented lymphovascular invasion (p<0.0001). Comparatively, in our analyses, the presence of lymphovascular invasion increased the risk of positive lymph nodes by 10.22 times (p<0.001).

Dong et al.[6] found a 2.20-2.70-fold increase in univariate and multivariate analyses for the presence of lymph node metastases (p=0.009 and p=0.045) when comparing Ki67 <3% versus =3%. Li et al.[14], in a systematic review with meta-analysis, included 2,863 resected pNETs. The overall recurrence rate was 13%, with worse survival for G2 tumors, positive lymph nodes, and vascular or perineural invasion.

We present risk factors well described in the literature, which correlated with recurrence-free survival for patients with tumors larger than 2.0 cm, Ki67 =3, G1 pNET, and positive lymph node disease. There was also an increased risk of lymph node involvement for patients with vascular, lymphatic, perineural invasion, and increased tumor size. Additionally, we observed an increased risk of recurrence for patients with Ki67 (3-20), tumor size, and positive perineural invasion.

As limitations, we can mention the retrospective nature of data collection and a relatively small number of patients included; however, the rarity of the disease should be taken into account when considering the number of patients studied. We also emphasize that in rare diseases, conducting prospective and randomized studies is more challenging.

The surgical strategy remains the main approach for cure, highlighting the increased use of minimally invasive techniques in recent years. We observed a higher tendency for significant fistulas in left pancreatic resections and non-standard surgeries, as well as a high morbidity for pancreatic surgeries overall, with 21.8% of patients experiencing Clavien III and 6.5% Clavien IV complications. Patients showed high overall survival at 3 and 5 years, at 93.8% and 92.1%, respectively. Patients with tumors smaller than 2.0 cm appear to have similar rates of grade B pancreatic fistulas (4.8%) and morbidity and mortality, but no recurrence was observed during a 47 months follow-up.

In subgroup analysis, we observed populations with a biologically less aggressive profile when selecting tumor sizes <2.0 cm and 2.1-2.5 cm. In the analysis of factors related to recurrence, we highlight the presence of lymphovascular and perineural invasion and Ki67 as important biological markers of aggressiveness. Patients with tumors <2.0 cm in our analyses showed lower rates of recurrence and lymph node disease compared to the literature; however, we emphasize a median tumor size of 13 mm in our population.

CONCLUSIONS

This study presents the largest series of neuroendocrine tumors operated on at a single Brazilian center, including epidemiological data, survival, and prognostic factors. Pancreatic surgery remains a procedure with high morbidity, and minimally invasive approaches are gaining more ground. Patients treated surgically showed a high 5-year overall survival rate of 92.1%.

Important prognostic factors were correlated, such as tumor size greater than 2.0 cm, Ki-67 index, and lymphovascular invasion. In a subgroup analysis of patients with tumors measuring 2.1-2.5 cm, we found a recurrence and lymph node disease profile comparable to patients eligible for active surveillance.

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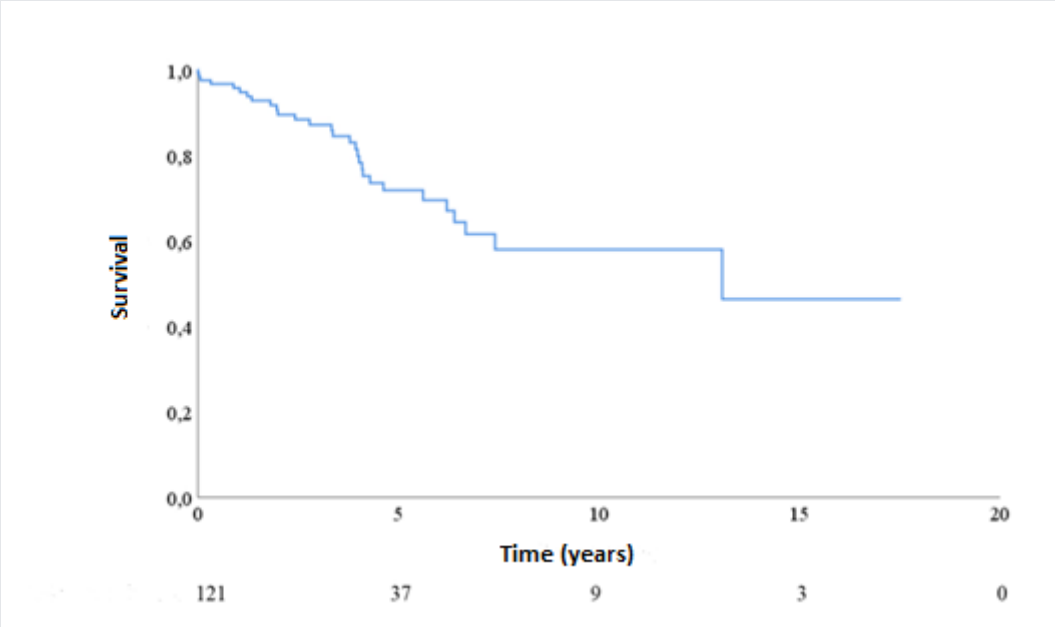
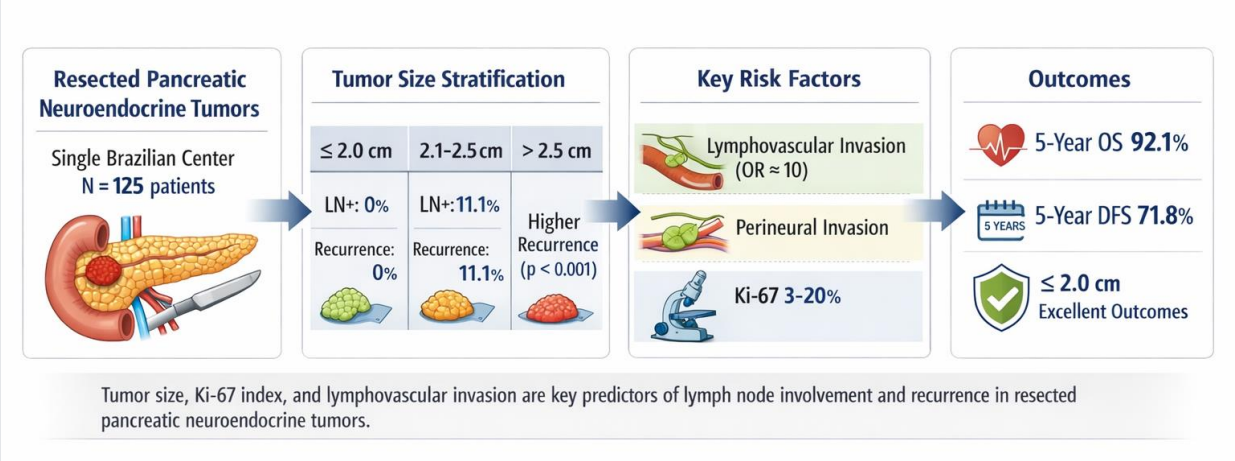


Figure 1. Disease free Survival

VISUAL ABSTRACT



Tumor size, Ki-67 index, and lynphovascular invasion are the key predictors of lymph node involvement and recurrence in resected pancreatic neuroendocrine tumors.

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