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## Original Research Article

## Pancreatic neuroendocrine tumors: Surgical outcomes and survival analysis

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## ABSTRACT

**Background:** Pancreatic neuroendocrine tumors are rare, with rising incidence and limited clinicopathological studies.**Methods:** Adult patients with pNET at a single tertiary care center were retrospectively evaluated.**Results:** In total, 87 patients with histologically confirmed pNET who underwent resection were evaluated. 11% of patients had functioning pNETs: 9 insulinoma and 1 VIPoma. The majority (88.5%) were nonfunctioning. The most common surgical procedure performed was distal pancreatectomy with splenectomy (36.8%). 35.6% of cases were performed with minimally invasive surgery (MIS). MIS patients had fewer postoperative complications, shorter length of stay, and fewer ICU admissions. Disease-free survival (DFS) was unaffected by tumor size ( $p = 0.5$ ) or lymph node status ( $p = 0.62$ ). Patients with high-grade (G3) tumors experienced significantly shorter DFS ( $p = 0.02$ ).**Conclusions:** This series demonstrates that survival in patients with pNET is driven mostly by tumor grade, though overall most have long-term survival after surgical resection. Additionally, an MIS approach is efficacious in appropriately selected cases.

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## Introduction

Neuroendocrine tumors (NETs) are diverse neoplasms arising from neuroendocrine cells in various locations throughout the body. Pancreatic neuroendocrine tumors (pNETs) arise in the islets of Langerhans and are rare tumors with an incidence of 0.5 per 100,000 persons per year, although autopsy studies have demonstrated prevalence rates as high as 10%.<sup>1,2</sup> pNETs can broadly be divided into functioning and non-functioning tumors. While the majority of pNET cases are nonfunctioning (70–90%), functioning pNETs include tumors that produce hormones and can cause different clinical syndromes. The most common biologically active islet cell hormones include insulin, somatostatin, glucagon, pancreatic peptide, and ghrelin. The most common functioning pNETs include insulinomas, VIPomas and gastrinomas.<sup>3</sup> The median overall survival (OS) for pNETs is 3.6 years which is the worst survival for neuroendocrine tumors compared to other sites (ie lung, appendix, etc).<sup>1</sup>

Given the rarity of pNETs and the variation in pathology, grade, and location, the management of some of these tumors remains controversial. Surgical resection has been the traditional standard, particularly for localized tumors greater than 2 cm, or those that are functioning.<sup>3,4,5</sup> For those tumors that present with concomitant metastases or that are smaller than 2 cm and non-functioning, the optimal treatment is not well defined and is based on a variety of factors. For higher risk tumors that are large, have lymph node involvement, and/or have a high Ki-67 index, a formal oncologic resection, including appropriate lymph node dissection, is recommended.<sup>4</sup> Pancreatic enucleation can be considered for those tumors that have a low potential for malignancy, are small, and are not near the main pancreatic duct.<sup>4,5</sup>

This study represents a large, single-institution cohort of patients with both non-functioning and functioning pNETs. The aims of the study were to determine the proportion of functioning tumors, determine if a minimally invasive operative approach is safe and efficacious in appropriately selected cases, and evaluate post-operative, disease-free survival (DFS) and overall survival (OS) based on the grade and tumor size. We hypothesized that the percentage of functioning tumors would be similar to other

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published series with the majority being insulinomas. Additionally, we predicted that the minimally invasive approach was safe and effective in appropriately selected patients. We hypothesized that DFS and OS would be impacted by tumor size and tumor grade.

## Material and methods

### Study design and population

We conducted a retrospective cohort study of patients who underwent operative intervention for pNET from 2007 to 2019 at a single tertiary care center. A search was conducted in order to identify all patients who underwent resection during this time via surgical pathology specimen reports. Demographic and clinicopathologic data were collected, including age, gender, comorbidities, pathology, surgical approach, tumor location, length of stay, morbidity and mortality. Patients were then excluded if they were concurrently diagnosed with pancreatic adenocarcinoma, did not have a primary pNET, underwent emergent surgery, or had insufficient medical documentation. Patients converted from MIS to open were analyzed as open cases. This study was evaluated and approved by the institutional review board at Loyola University Chicago (LU 212307). This database is de-identified, therefore no consent was required or obtained.

### Statistical analysis

Patient characteristics are presented as means and standard deviations. Unadjusted comparisons of two or more proportions were performed using a Kruskal-Wallis H test. We compared outcomes of MIS and open surgery for those patients who underwent distal pancreatectomy with or without splenectomy, or enucleations only. Statistical significance was established at  $\alpha = 0.05$ . All analyses were performed using STATA 14 software (College Station, TX).

Morbidity includes urinary tract infection, ileus, surgical site infection, pneumonia, acute kidney injury, deep venous thrombosis, bleeding (requiring >4 units of red blood cells), sepsis, acute coronary syndrome, pancreatic leak and reintubation. Foley catheter duration represents time to discontinuation from periprocedural insertion, return of bowel function (ROBF) is defined as time to first flatus, and refeeding includes any method of enteral nutrition.

Median survival was calculated in months and survival analyses were performed using Kaplan-Meier Curves. To calculate survival, initial time was defined by the date of index operation and terminal event was defined as date of recurrence or death. Patients were censored from survival analysis at date of last contact only if this preceded death or recurrence. Log-Rank tests were used to determine significance between grade, size, and lymph node characteristics on the respective Kaplan-Meier Survival Curves at the 95% confidence interval.

## Results

### Demographics

A total of 87 patients underwent resection for pNET between 2007 and 2019. Table 1 depicts baseline demographic characteristics for this population. The mean age was 58.9 ( $\pm 14.7$ ) years and BMI was 27.6 ( $\pm 5.2$ ). Gender distribution was approximately equal (49.4% female). Race, ASA class and insurance information can be seen in Table 1.

### Pathology

Tumor pathology characteristics including grade, size, and lymph node status for patients who underwent pNET resection are depicted in Table 2. From the cohort, 10 patients had a functioning pNET (fpNET; 11.5%): 9 patients (9.6%) had an insulinoma, and 1 (1.1%) had a VIPoma. No patients with fpNET were found to have metastatic disease, and 11.1% of patients with insulinoma were found to have positive nodes on final surgical pathology.

The majority (88.5%) had nonfunctioning pNETs. Of these, 25 (28.7%) were found to have positive lymph nodes on final pathology, and 7 (8% overall) presented with metastatic disease. Of patients with metastatic disease, 5 (5.7% overall) presented with liver metastasis.

### Surgical approach & operative characteristics

The primary surgical procedures performed included 32 (36.8%) distal pancreatectomy/splenectomy, 29 (33.3%) pancreaticoduodenectomy, 6 (6.9%) total pancreatectomy and/or completion pancreatectomy, 9 (10.3%) enucleations, 10 (11.5%) distal pancreatectomy only, and 1 (1.2%) central pancreatectomy.

Of all cases, 31 (35.6%) were performed minimally invasively (18.4% laparoscopic, 17.2% robotic). Of the cases started minimally invasively, 9 (35.6%) were converted to open. Open surgery was the approach for 56 cases (64.4%). There was no statistically significant difference in EBL or length of surgery between MIS or open groups, though EBL did approach significance (1023 ml open, 327 ml MIS,  $p = 0.08$ ; 7.07 h open, 6.98 h MIS  $p = 0.79$ ) Table 3

### Postoperative outcomes and survival

When performing unadjusted comparisons of operative approaches between cases performed for pancreatic enucleations and distal pancreatectomy with or without splenectomy, there was no statistical difference in discharge disposition ( $p = 0.67$ ), with 94.12% of patients being discharged home overall (Table 3). Statistical differences were present between MIS and open approaches with regard to postoperative nursing unit disposition, with more patients being admitted to a general nursing floor (18.18% vs 68.97%;  $p = 0.01$ ), days to oral intake (6.45d [ $\pm 7.12$ ] vs 2.41d [ $\pm 1.40$ ];  $p < 0.01$ ), overall morbidity (50% vs 24.13%;  $p = 0.04$ ), minor or severe Clavien-Dindo Complication (0-II: 29 vs 19;  $p = 0.04$ , III-V: 0 vs 3;  $p = 0.04$ ), and length of stay (9.86d [ $\pm 8.47$ ] vs 4.86d [ $\pm 4.63$ ]). Caution must be used when interpreting these results given that these statistics were not adjusted for tumor characteristics and type of operation performed.

Median DFS and OS were calculated in months and analyzed by size, grade, and lymph node status (Table 2). Patients with tumors >4 cm experienced a median DFS and OS of 103 months and 118 months, respectively. Those with tumors 2–4 cm experienced both DFS and OS of 86 months, and those with tumors <2 cm experienced DFS of 95 months and OS of 121.8 months ( $p = 0.5$ ). Patients with high-grade (G3) tumors experienced a significantly shorter median DFS at 25 months, G2 tumors at 59 months, and G1 tumors at 103 months ( $p = 0.02$ ). OS for G3 tumors was 52.5 months, G2 was 79.8 months, and G1 was 121.8 months. There was not a difference in DFS or OS when patients were analyzed by lymph node positive vs lymph node negative status (DFS 95 vs 103 months, OS 121.8 vs 79.8 months;  $p = 0.62$ ). A Kaplan-Meier curve for DFS by grade can be seen in Fig. 1

## Discussion

The results from this large, single-institution, series of patients with pNETs demonstrated that most of the patients (89%)

**Table 1**  
Patient demographics.

Age ( $\pm$ SD)		58.9 ( $\pm$ 14.7)
Sex	Male	44 (50.6%)
	Female	43 (49.4%)
Race	Nonhispanic White	64 (73.6%)
	Hispanic	10 (11.5%)
	African American	11 (12.6%)
	Asian	2 (2.3%)
Insurance	Medicaid	6 (6.9%)
	Medicare	33 (37.9%)
	Private	40 (46.0%)
	Other	6 (6.9%)
	Uninsured	2 (2.3%)
ASA	Class 1	0 (0.00%)
	Class 2	18 (20.7%)
	Class 3	63 (72.4%)
	Class 4	6 (6.9%)
	Class 5	0 (0.0%)
Smoking History		26 (29.9%)
BMI ( $\pm$ SD)		27.6 ( $\pm$ 5.2)

ASA: American Society of Anesthesiologists Physical Status Classification System, BMI: Body Mass Index.

presented with non-functioning pNETs. The majority (71.4%) of the non-functioning pNETs were low-grade (G1). There were a significant number of pNET resections for small (<2 cm) tumors in our series. The most common indications for resection were symptomatic tumors, high-grade histology on preoperative fine-needle aspiration, or rapidly growing tumors. Of the 10 patients with fpNETs (11.5%), 90% were insulinomas and 10% VIPoma. All of the functioning tumors were low-grade. Similar to published data, the rate of non-functioning tumors in this cohort was 90% and the most common functioning tumors were insulinomas (9%). According to SEER database studies and institutional cohort studies, non-functioning pNETs range from 60 to 90%. Insulinomas tend to be more common compared to VIPomas (25% and 6%, respectively, of functioning tumors).<sup>6</sup>

In our series, a minimally invasive resection (either laparoscopic or robotic) was performed for 80% of the functioning tumors compared to 21% of the non-functioning tumors. Eight of the 10 cases for functioning pNETs were started minimally invasively (2 converted to open), with an equal mixture of laparoscopic and robotic. Patients who underwent minimally invasive operations had improved postoperative outcomes including fewer ICU admissions, shorter Foley catheter duration, shorter time to oral intake, decreased morbidity, and decreased length of stay compared to those undergoing open operations. In this series, for those patients with tumors >4 cm, only 20.8% underwent an MIS approach, and

there were no minimally invasive pancreaticoduodenectomies or total pancreatectomies performed, again emphasizing tumor size and location are critical for determining operative approach. This result mirrors other studies that suggest the minimally invasive approach is safe and feasible in pNETs, particularly for those with smaller tumors.<sup>4,5</sup>

There is increasing evidence supporting the use of minimally invasive platforms, particularly the robotic platform, for pancreatic surgery. Multiple studies have demonstrated equivalent oncologic outcomes when performed for malignancy with similar or improved postoperative outcomes.<sup>7,8</sup> The decision to proceed with a minimally invasive resection should be based upon the tumor characteristics, extent of disease, and the required oncologic resection including lymph node basins and/or debulking metastatic disease.

Previous studies have demonstrated the median OS for pNETs ranges from 7.1 to 10.5 years, though this must be interpreted with caution given the heterogeneity of pNETs.<sup>1</sup> Our data demonstrated a median OS for G1 pNETs of 7.9 years, G2 of 4.5 years, and G3 of 1.9 years. We demonstrated a significant improvement in survival based upon lower tumor grade, but not based upon tumor size or lymph node status. This supports other studies that have demonstrated significantly improved survival with lower tumor grade. However, our findings differ from some studies that have suggested a survival difference based upon tumor size.<sup>9</sup> Other studies have not shown a survival difference based upon tumor size alone. Our data suggests that tumor grade has greater prognostic significance than tumor size, which is supported by previous literature suggesting tumor grade has a greater prognostic impact on survival than stage.<sup>10</sup> The shorter OS in this study compared to some others could be due to limited follow-up information which is a limitation of the study when compared to larger single institution series.<sup>11,12</sup>

This study has several limitations. It is a single institution, retrospective study and is subject to bias in this regard. Comorbidities were accounted for broadly by ASA class only. While the number of functioning tumors included is expected based upon population studies, it remains a small, and as such, several of our conclusions, especially regarding MIS should be interpreted with caution. Follow-up information regarding neoadjuvant/adjuvant systemic therapy was unable to be examined in this study due to incomplete data, and thus its impact on survival was unable to be examined.

## Conclusion

pNETs are a rare, heterogeneous group of tumors defined mostly by their functionality, grade, and size. This study further supports

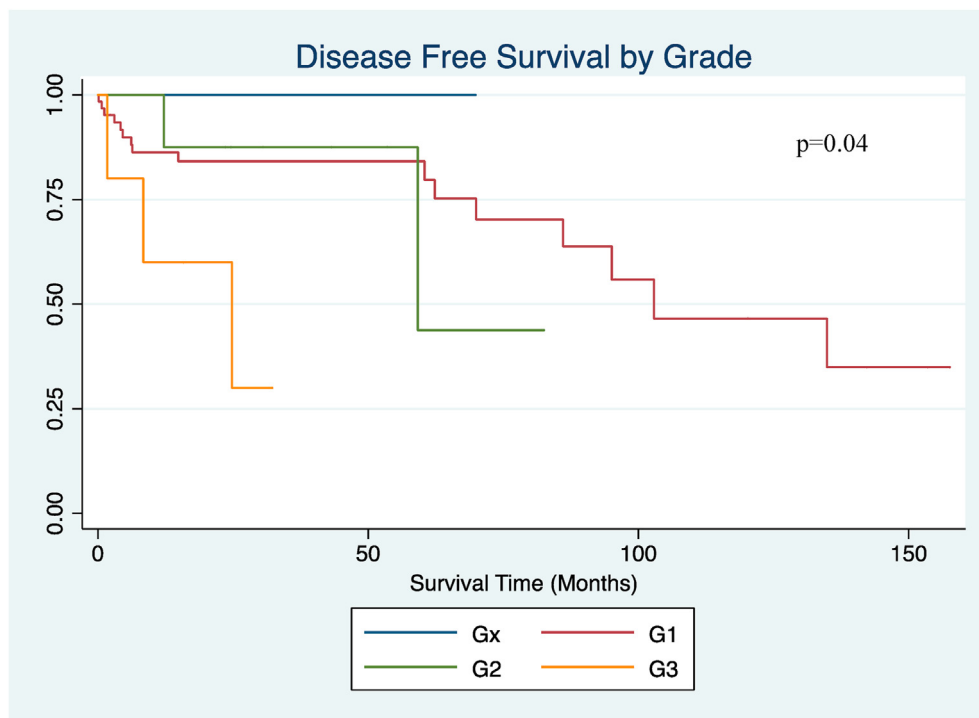
**Table 2**  
Pathologic features and median survival.

	n	Non-Functioning	Insulinoma	VIPoma	Median Disease-Free Survival (Months)	Median Overall Survival (Months)
<b>Size (cm)</b>						
Avg Size ( $\pm$ SD)	—	3.5 ( $\pm$ 3.0)	2.4 ( $\pm$ 1.3)	—	—	—
<2 cm (%)	28	23 (29.9%)	5 (55.6%)	0 (0.0%)	95.0	121.8
2–4 cm (%)	35	33 (42.9%)	2 (22.2%)	0 (0.0%)	86.0	86.0
>4 cm (%)	24	21 (27.3%)	2 (22.2%)	1 (100%)	102.9	117.5
<b>Grade</b>						
Gx	5	4 (5.2%)	1 (11.1%)	0 (0.0%)	—	—
G1	64	55 (71.4%)	8 (88.9%)	1 (100%)	102.9	121.8
G2	13	13 (16.9%)	0 (0.0%)	0 (0.0%)	59.1	79.8
G3	5	5 (6.5%)	0 (0.0%)	0 (0.0%)	24.8	52.5
Node Positive (%)	62	24 (31.2%)	1 (11.1%)	0 (0.0%)	95.0	121.8
Node Negative	25	—	—	—	102.9	79.8
Metastatic Rate (%)	7	7 (9.1%)	0 (0.0%)	0 (0.0%)	—	—
Liver Metastasis (%)	5	5 (6.5%)	0 (0.0%)	0 (0.0%)	—	—

**Table 3**  
MIS vs Open Outcomes for Distal Pancreatectomy (+/– Splenectomy) and Pancreatic Enucleations.

		Overall	Open	MIS	p
Preoperative	ASA Class 1–2	13 (25.49%)	6 (27.27%)	7 (24.14%)	0.80
	ASA Class 3–4	38 (74.51%)	16 (72.73%)	22 (75.86%)	
Operative	Length of Case (avg ± SD, hours)	7.02 (±3.04)	7.07 (±4.20)	6.98 (±1.81)	0.79
	EBL (avg ± SD, cc)	619.9 (±959.42)	1023.8 (±1290.2)	327.4 (±459.2)	
Postoperative	Floor (%)	24 (47.06%)	4 (18.18%)	20 (68.97%)	<0.01
	Stepdown (%)	6 (11.76%)	3 (13.64%)	3 (10.34%)	
	ICU (%)	21 (41.18%)	15 (68.18%)	6 (20.69%)	
	Foley Duration (avg ± SD, days)	3.22 (±3.48)	4.38 (±4.76)	2.38 (±1.82)	
	ROBF (avg ± SD, days)	4.27 (±2.74)	5.05 (±2.77)	3.69 (±2.62)	
	Days to Oral Intake (avg ± SD, days)	4.16 (±5.15)	6.45 (±7.12)	2.41 (±1.40)	
	Morbidity (%)	18 (35.29%)	7 (50%)	11 (24.13%)	
	Clavien-Dindo Complication Grade 0-II (%)	48 (94.12%)	19 (86.36%)	29 (100%)	
	Clavien-Dindo Complication Grade III-V (%)	3 (5.88%)	3 (13.64%)	0 (0.0%)	
	Length of Stay (avg ± SD, days)	7.02 (±6.96)	9.86 (±8.47)	4.86 (±4.63)	
Discharge Disposition	Home (%)	48 (94.12%)	21 (95.45%)	27 (93.10%)	0.67
	SNF (%)	3 (5.88%)	1 (4.55%)	2 (6.90%)	
	Death (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	

ASA Class: American Society of Anesthesiologists Physical Status Classification, EBL: Estimated blood loss, ICU: Intensive Care Unit, ROBF: Return of bowel function, SNF: Skilled nursing facility.



**Fig. 1.** Disease-free survival by tumor grade.

the clinical impact of grade on prognostication and overall survival, and adds to a limited body of literature on pNET characteristics and management. Additionally, minimally invasive approaches are a safe and effective means of surgical management in appropriately selected patients.

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### Conflict of interest

The authors have no conflicts of interest, financial or otherwise, to disclose.

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