Neuroendocrinal tumor of pancreas: incidence, prognosis, and surgical outcomes: a single-center experience

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Background
Pancreatic neuroendocrine tumors (PNETs) are rare pancreas tumors, which represent less than 2% of all pancreatic tumors. The purpose of this study was to determine the incidence, clinicopathological characteristics, and prognostic factors for PNET survival predictions.
Patients and methods
This study included patients with PNETs treated at our center during the period from January 2007 until December 2017. For patients with PNETs, preoperative data, operative, postoperative data, and records of survival were analyzed.
Results
In our center, 720 patients underwent pancreatic surgery, including 71 patients (9.86%) with pathologically confirmed PNETs. There were 43 women (60.6%) and 28 men (39.4%), with a median age of 35 years, range 12–74 years. The PNETs were solitary in 65 (91.5%) patients, and the median diameter was 7 cm (range 1–18 cm). The tumors were located in the pancreatic head in 35 (49.3%) patients, body in six (8.5%) patients, and tail in 30 (42.2%) patients. Abdominal pain was the commonest presentation in 57 (80.3%) patients. Nonfunctioning PANETs presented in 65 (91.5%) patients. The overall recurrence rate was seven (9.9%) patients. The overall survival at 1, 3, and 5 years for all cases was 96, 85, and 72%, respectively, with a median survival of 85 months. Grade of tumor was the only independent factor for survival.
Conclusion
PNETs are rare pancreatic neoplasm more common in female sex. Nonfunctioning PNETS presented in most cases. Surgical resection was based on the site, size, and extension of the tumor. Grade of tumor was the only independent factor for survival.

Keywords:
midpancreatectomy, pancreatic cyst, pancreatic leakage, pancreaticoduodectomy

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Introduction

Pancreatic neuroendocrine tumors (PNETs) are rare neoplasm of the pancreas with a prevalence less than 1 per 100 000 persons per year, representing less than 2% of all pancreatic tumors [1–4]. Depending on the capability of hormonal production, PNETs are classified clinically into functioning and nonfunctioning ones. Nonfunctioning tumors may be asymptomatic or presented by abdominal pain, obstructive jaundice, local invasion, or distant metastasis. Functioning PNETs are subdivided according to their presentation. In this regard, insulinomas are the most frequent functioning PNETs. Other tumors include gastrinomas, glucagonomas, somatostatinomas, and VIPomas [2–7].

According to tumor morphology and proliferation, the WHO classified PNETs as NET G1, NET G2, and neuroendocrine carcinoma (NEC). Another classification for PNETS was suggested by the European Neuroendocrine Tumor Society based on the size of the primary tumor [3]. In the same year, the American Joint Committee on Cancer classification projected a new classification for typical ductal pancreatic adenocarcinomas based on the previously developed classification [8–10].

The first line of treatment for localized and locally advanced PNETs is surgery as long as it is feasible. The approach of the surgical technique is built on the site and diameter of the tumor. The surgery varies from enucleating and atypical resection of small localized PNETs lesions up to extensive resection and may be

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complex arterial reconstruction for locally advanced tumors [11–18].

Few previously published data evaluated the prognostic factors for disease progression and survival of PNETs [2–5,15–20]. The aim of this study was to show the prevalence, clinicopathological characteristics, and prognostic aspects for predicting survival in PNETs.

Patients and methods

Patients

Patients diagnosed with PNET at Gastrointestinal Surgery Center, Mansoura University, Egypt from January 2007 and December 2017, were enrolled in this study. The Institutional Review Board approved this study.

Demographic data, as well as preoperative, operative, and postoperative records were reviewed for these patients. The hospital medical records were searched to determine clinical presentation, tumor characteristics, staging, and operative and postoperative data to be analyzed and evaluated.

Preoperative assessment

Clinical presentation included vomiting, abdominal pain, and/or mass, jaundice, and loss of weight; however, few cases were asymptomatic. Laboratory investigations were done, including liver and renal function tests and tumor markers. Abdominal computed tomography was done for all patients to determine site, size, extent, and vascular invasion of the tumor. Magnetic resonance cholangiopancreatography was done for jaundiced patients.

Surgical procedures

Surgical resection was based on the site and extension of the tumor. Distal pancreatectomy was done for tumors in the tail. Midpancreatectomy was performed for lesions of the body of the pancreas. Pancreatoduodenectomy (PD) was done for tumors of the pancreatic head. Enucleation was done for functioning tumors. Intraoperative ultrasound was performed for localization of small PNETS. The frozen section had a role in some cases to achieve a free safety margin.

Postoperative management

Patients were admitted to the ICU on the day of their surgery for close monitoring. A prophylactic antibiotic was intraoperatively administered and continued postoperatively for 4 days. Somatostatin was subcutaneously administered postoperatively to all patients.

Follow up was done at 1 week, 3 months, 6 months after discharge, and then annually. During each follow-up visit, the clinical, laboratory, and radiological examinations were done for early detection of recurrence.

Postoperative pancreatic fistula (POPF) was diagnosed according to the definition of the International Study Group of Pancreatic Fistula (ISGPF) [21]. Dindo classification was used for grading of postoperative complications [22].

Postoperative pathological data, including grade, safety margin, lymph node, and lymphovascular and perineural infiltration, were reviewed.

Statistical analysis

Categorical variables are expressed as group percentages. Continuous data are presented as medians with range. Survival was assessed using a life table, Kaplan–Meier method, and log-rank test. Multivariate analysis was done using a Cox-regression analysis to determine the independent prognostic variable for overall survival. Multivariate analysis was performed for variables, with a P value less than 0.1 in univariate analysis. Statistical analyses were performed using SPSS version 17 (SPSS Inc., Chicago, Illinois, USA) was used for analysis.

Result

Demographic data

In our center, 720 patients underwent pancreatic surgery between January 2007 and December 2017, including 71 (9.86%) cases that underwent resection for pathologically confirmed PANTs. There were 43 women (60.6%) and 28 men (39.4%), with a median age of 35 years, range: 12–74 years (Table 1**)**.

Abdominal pain was the main presentation in 57 (80.3%) patients, jaundice in 20 (28.2%) patients, palpable abdominal mass in 13 (18.3%) patients, weight loss in seven (9.9%) patients, and diarrhea in five (7%) patients. Two (2.8%) patients whose PANETs were found on computed tomography were asymptomatic (Table 1).

The level of carcinoemboryoic antigen (CEA(was increased greater than 5 ng/dl in 33 (46.7%) patients and the level CA19-9 was increased greater than 37 IU/dl in 21 (29.6%) patients.

Operative data

The tumor was solitary in 65 (91.5%) patients, and the median diameter of PNETs was 7 cm (range:

Table 1 Demographic data

	Total [*n* (%)]
Age	35 (12–74)
<60	54 (76.1)
>60	17 (23.9)
Sex	
Male	28 (39.4)
Female	43 (60.6)
BMI	
<25	46 (64.8)
>25	25 (35.2)
Clinical symptoms	
Asymptomatic	2 (2.8)
Abdominal pain	57 (80.3)
Jaundice	20 (28.2)
Palpable mass	13 (18.3)
Loss of weight	7 (9.9)
Diarrhea	5 (7)
DM	10 (14.1)
Serum bilirubin (mg/dl)	0.78 (0.4–20)
Serum albumin (gm/dl)	4.3 (3.2–4.8)
WBC	6.3 (3.5–12.5)
Hemoglobin	11 (9–14)
Blood sugar	120 (51–410)
Type of tumor	
Nonfunctioning	65 (91.5)
Functioning	6 (8.4)
CEA	3.3 (0.8–142)
<5	38 (53.3)
>5	33 (46.7)
CA 19-9	23 (0.5–984)
<37	50 (70.4)
>37	21 (29.6)

CEA, carcinoemboryoic antigen; DM, diabetes mellitus; WBC, white blood cell.

Table 2 Intraoperative data

	Total [*n* (%)]
Liver cirrhosis	7 (9.9)
Tumor size	7 (1–18)
Tumor location	
Head	35 (49.3)
Body	6 (8.5)
Tail	30 (42.3)
Type of operation	
Pancreaticodudenectomy	30 (42.3)
Midpancreatectomy	5 (7)
Distal pancreatectomy	30 (42.3)
Enucleation	6 (8.5)
Approach	
Open surgery	65 (91.5)
Laparoscopic PD	2 (2.8)
Laparoscopic distal pancreatectomy	4 (5.6)
Pancreatic texture	
Soft	45 (63.4)
Firm	26 (36.6)
Blood loss	300 (200–2500)
Blood transfusion	0 (0–4)
Portal vein resection	2 (2.8)
Time of operation	4 (2.5–7)

1–18 cm). The tumor was located in the pancreatic head in 35 (49.3%) patients, pancreatic body in six (8.5%) patients, and tail of pancreas in 30 (42.2%) patients.

A total of 30 (42.3%) patients with tumor located in the head underwent PD, five (7%) patients underwent midpancreatectomy for tumor in the body, six (8.5%) patients underwent enucleation, and the remaining 30 (42.3%) patients underwent distal pancreatectomy. The median operative time was 4 h (range: 2.5–7 h) (Table 2).

Postoperative data

The median hospital stay was 7 days (4–30 days). The median time to start oral intake was 4 days postoperatively (3–24 days).

Postoperative complications developed in 16 (22.5%) patients: eleven patients (15.5%) had POPF (nine patients developed POPF grade B and the other two patients had POPF grade C), biliary leakage was found in two (2.8%) patients, two (2.8%) patients had wound infection, and six (8.5%) patients showed delayed gastric emptying (Table 3).

Nonfunctioning PANETs presented in 65 (91.5%) patients. Insulinoma presented in five (7.1%) patients. One (1.4%) case presented with gastrinoma. A total of 33 patients had grade 1 PANETs, 22 patients had grade 2 PANETs, and 16 patients had grade 3 PANETs.

Prognosis and survival

The overall recurrence rate was seven (9.9%) patients at 5 years postoperatively. Complete resection of the recurrent tumor was performed for three cases.

The overall survival rates at 1, 3, and 5 years for all cases were 96, 85, and 72%, respectively, with a median survival of 85 months. Univariate analysis revealed that tumor size less than 2 cm, preoperative jaundice, CA 19-9 less than 37 U/ml, the grade of tumor, perineural infiltration, and perivascular infiltration were prognostic factors for survival. Multivariate analysis demonstrated that grade of the tumor was the only independent factor of survival (Table 4 and Figs. 1–5).

Discussion

PNETs are rare, with an occurrence of ~1/100 000 per year and constitute 2–4% of all pancreatic tumors.

Table 3 Postoperative data

	Total [*n* (%)]
Time to resume oral	4 (3–24)
Drain amount	600 (80–5400)
Postoperative complication	16 (22.5)
Grade I/II	11 (15.5)
Grade III/IV	4 (5.6)
Grade V	1 (1.4)
POPF	11 (15.5)
Grade B	9 (12.7)
Grade C	2 (2.8)
Biliary leakage	2 (2.8)
Postoperative bleeding	3 (4.2)
Collection	4 (5.6)
DGE	6 (8.5)
Wound infection	2 (2.8)
Hospital stay	7 (4–30)
Re-exploration	3 (4.2)
Hospital mortality	1 (1.4)
Postoperative pathology	
Nonfunctioning	65 (91.5)
Insulinoma	5 (7.1)
Gastrinoma	1 (1.4)
Grade	
G1	33 (46.5)
G2	22 (31)
G3	16 (22.5)
Lymph node involvement	
Yes	18 (25.4)
No	53 (74.6)
Lymphovascular invasion	15 (21.1)
Perineural invasion	12 (16.9)
Resection margin	
R0	67 (94.4)
R1	4 (5.6)
Recurrence	7 (9.9)
Median survival (months)	85

POPF, postoperative pancreatic fistula.

Most PNETs are sporadic, but ~10% are part of inherited syndromes. PNETs comprise a variety of lesions with different morphology and clinical behaviors. Recent studies showed a trend toward increasing incidental diagnosis of PNETs, whereas functioning lesions are less common among PNETs. Moreover, in the current study, most PNETs were nonfunctioning (91.5%) [23,24].

According to the WHO classification for PNETS and the high power fields mitotic count (HPF) and a Ki-67 index as a cell proliferation marker, PNETs are graded into 3 grades [7,8,11]. G1 and G2 are generally well-differentiated PNETs and called neuroendocrine tumors (PNETs), whereas G3 is poorly differentiated PNETs, which are called neuroendocrine carcinomas (PNECs). WHO classification 2017 was published. In that, G3 is further divided into PNET G3 (well-differentiated NEN) and PNEC (poorly differentiated NEN, small cell type, and large cell type) [7,8,11].

PNETs and pancreatic ductal adenocarcinoma are different in tumor biology and line of treatment. Ultimate treatment option for patients with PNET is surgical resection, as it has a much better prognosis than patients with pancreatic ductal adenocarcinoma [7,8]. If well-differentiated PNENs are single and accessible, enucleation is performed. Recent reports concluded that extensive surgery improves survival rate and controls malignant tumors better than enucleation [7].

Although conservative surgery has increased postoperative complications (76%) and POPF (69%) compared with extensive surgery (58 and 42%), the patients preserve exocrine and endocrine functions [7,8,23–25]. In this study, postoperative complications developed in 16 (22.5%) patients, where 11 (15.5%) patients developed POPF (nine patients had POPF grade B, and the other two developed POPF grade C).

Laparoscopy appears to be a good option for PNETs that are benign, located in the pancreatic body or tail and small in size; complications have been found to be low in this approach [25–29]. The conversion rate is frequent because of the difficult preoperative and operative localization of the tumor.

There is continuous argument related to the effect of lymph node removal in surgery for PNETs. When performing enucleation for low-risk PNETs, recent studies found lymph node metastases present in up to 23% of low-risk PNETs with significantly shorter disease-free survival. The positive lymph node status was found to be more for PNETs greater than 1.5 cm, tumors in the pancreatic head, tumors with G3, and with lymphovascular invasion (L1) [30,31].

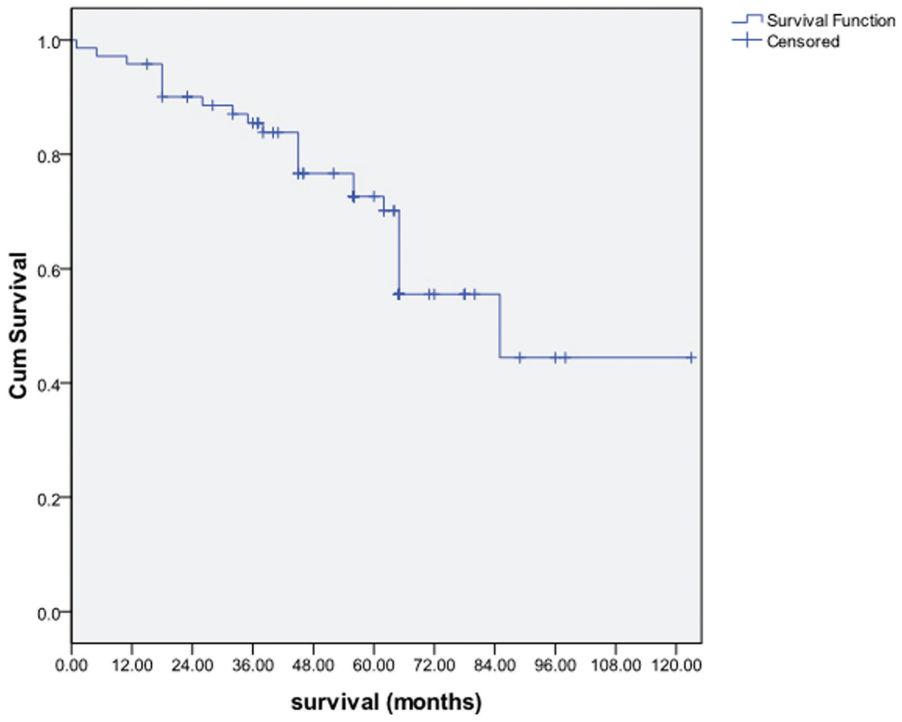
Re-operation for recurrent PNETs could be needed to improve 10 years of survival up to 70% [32]. In this study, the overall recurrence rate was seven (9.9%) patients at 5 years postoperatively. Complete resection of the recurrent PNETs was performed for only three cases. PNETs with a high KI-67 index explain an increased possibility for recurrence and metastasis with a poor survival rate. Therefore, surgical resection of PNECs should be aggressive to achieve R0 resections. Cytoreductive surgery has no role in these highly malignant cases [33].

Table 4 Multivariate analysis of factors influencing survival of pancreatic neuroendocrinal tumor

		Multivariate analysis			
				95.0% CI for Exp(*B*)	
	Univariate analysis *P* value	*P* value	Exp(*B*)	Lower	Upper
Site	0.32				
Age group	0.48				
Sex	0.79				
Jaundice	0.07	0.186	2.120	0.696	6.455
Palpable mass	0.52				
Loss of weight	0.45				
BMI	0.73				
CA19 group	0.09	0.694	1.225	0.447	3.356
CEA group	0.44				
Approach	0.62				
Size of tumor	0.08	0.175	0.922	0.820	1.037
Pathology	0.66				
Grade of tumor	0.002	0.005	2.171	1.257	3.749
LN ratio	0.58				
Safety margin affected	0.05	0.189	2.733	0.609	12.258
Perineural infiltration	0.08	0.166	2.773	0.655	11.741
Perivascular infiltration	0.01	0.132	2.453	0.764	7.878
Complication	0.69				
Re-exploration	0.46				
Recurrence	0.87				

CEA, carcinoemboryoic antigen; CI, confidence interval; LN, lymph node.

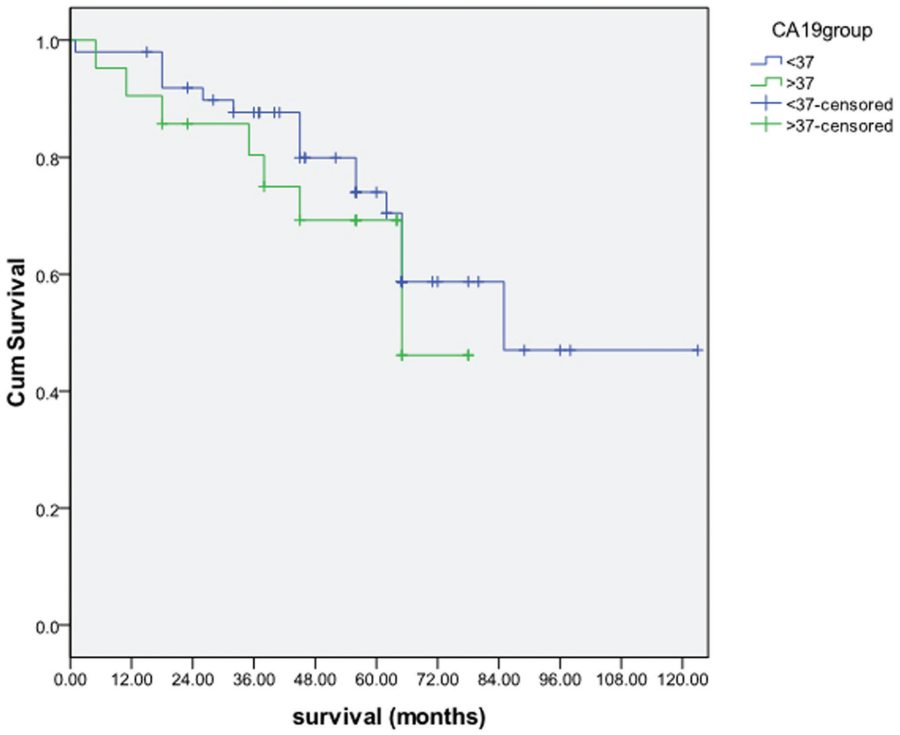
Figure 1



Actuarial survival (Kaplan–Meier analysis) after resection of neuroendocrinal tumor. Median survival was 85 months.

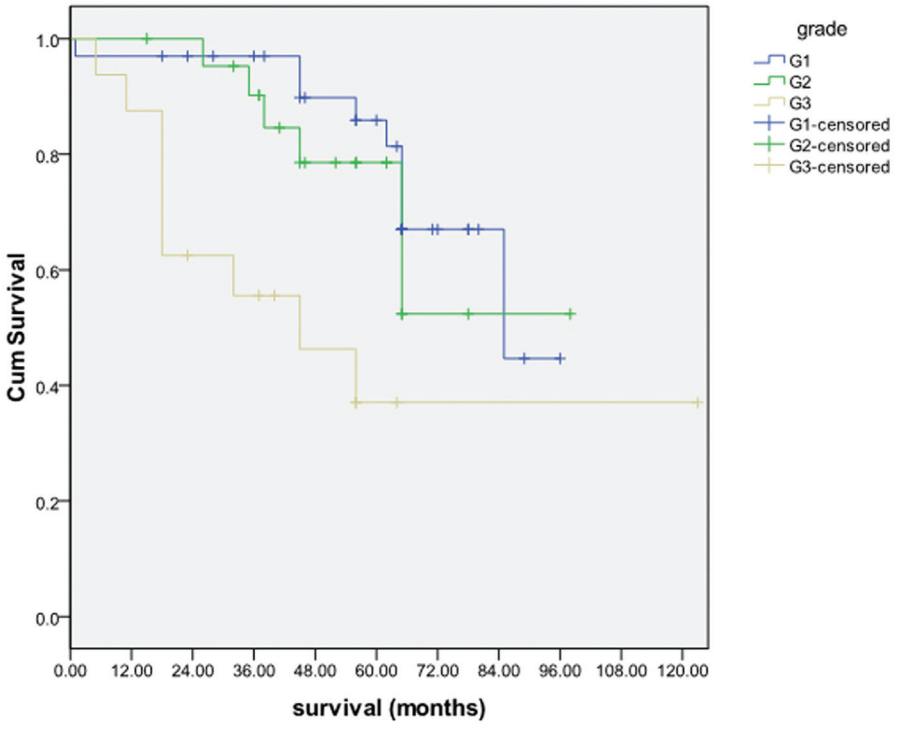
The survival rates for all PNETs at 5 and 10 years are ~65 and 45%, respectively [34]. Favorable prognostic factors included tumor grade 1, age less than 55 years, and no distant metastases [35]. Bilimoria and colleagues *et al.* made a prognostic score for expect survival after surgical resection based on age, grading, and metastases, and each variable is scored from 0 to 3 [35]. They reported that patients with a prognostic score of 1 had a 5-year survival of 76.7%, 50.9% for prognostic score 2, and 35.7% for prognostic score 3.

Figure 2



Actuarial survival (Kaplan–Meier analysis) after resection of neuroendocrinal tumor according to CA 19-9. Median survival of CA 19-9 less than 37 U/ml was 85 months, and for CA 19-9 greater than 37 U/ml was 65 months.

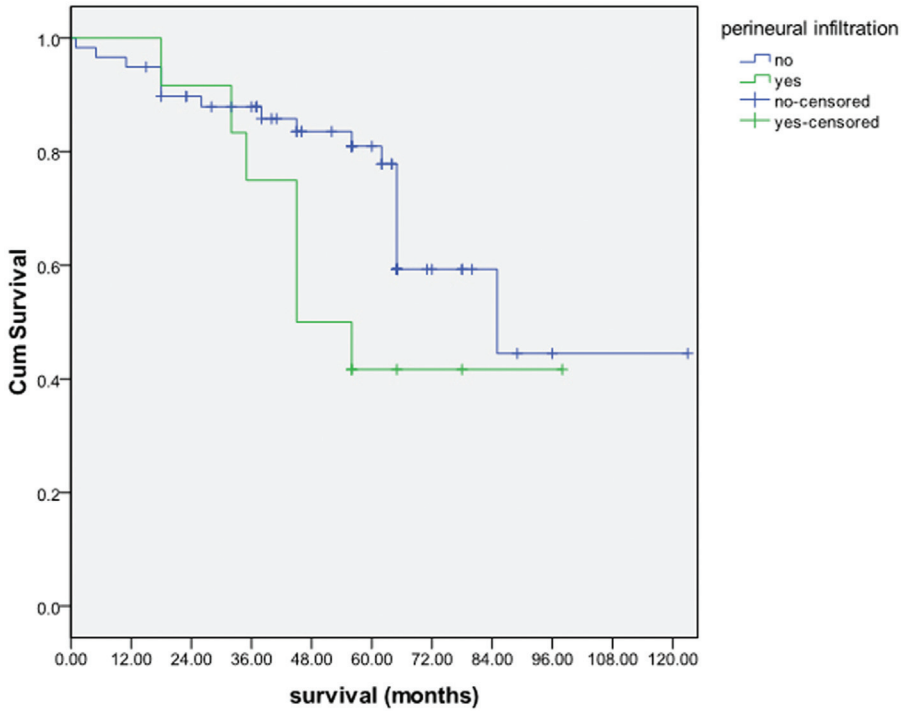
Figure 3



Actuarial survival (Kaplan–Meier analysis) after resection of neuroendocrinal tumor according to grade of the tumor. Median survival of G1 tumor was 85 months, grade 2 was 70 months, and for grade 3 was 45 months.

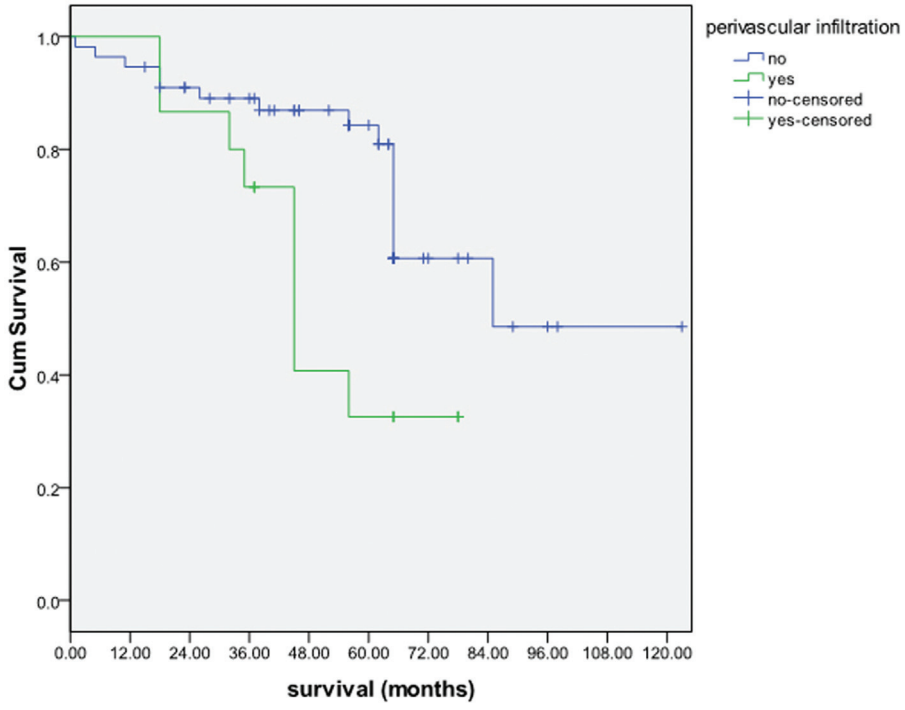
[35]. In this study, the overall survival rates at 1, 3, and 5 years for all cases were 96, 85, and 72%, respectively, with a median survival of 85 months. Univariate analysis revealed that tumor size less than 2 cm, preoperative jaundice, CA 19-9 less than 37 U/ml, the grade of tumor, perineural infiltration, and

Figure 4



Actuarial survival (Kaplan–Meier analysis) after resection of neuroendocrinal tumor according to perineural infiltration. The median survival of negative perineural infiltration was 85 months and positive perineural infiltration was 45 months.

Figure 5



Actuarial survival (Kaplan–Meier analysis) after resection of neuroendocrinal tumor according to perivascular infiltration. The median survival of negative perivascular infiltration was 85 months and positive perivascular infiltration was 45 months.

perivascular infiltration were prognostic factors for survival. Multivariate analysis demonstrated that grade of the tumor was the only independent factor of survival.

This study had many limitations, including first, it is retrospective study, but the data are prospectively recorded in our center, and second, the heterogeneity of tumors and their management.

Conclusion

PNETs are rare pancreatic neoplasm. The surgery varies from enucleation and atypical resection of small localized PNETs lesions up to extensive resection. Surgical resection was based on the site, size, and extension of the tumor. Laparoscopy seems to be a good option for PNENs that are benign, sited in the body or tail of the pancreas, and small in size. Univariate analysis revealed that tumor size less than 2 cm, preoperative jaundice, CA 19-9 less than 37 U/ml, the grade of tumor, perineural infiltration, and perivascular infiltration were prognostic factors for survival. Multivariate analysis demonstrated that grade of the tumor was the only independent factor of survival.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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