

Pancreatic Neuroendocrine Tumors – Analysis of Recurrence after Surgical Resection and its Effect on Overall Survival

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ABSTRACT

Introduction: Pancreatic neuroendocrine tumors (PNETs) are uncommon, representing fewer than 5% of all pancreatic malignancies. They are a diverse group of tumors with different biological behaviors, clinical features, and prognostic outcomes. Reported 5-year survival varies widely, from 25% up to 100% in some series. *Aim:* Evaluate recurrence patterns, risk factors, and their influence on disease free survival (DFS) and overall survival (OS).

Methods: Retrospective review of 87 patients undergoing curative surgical resection for PNETs in a tertiary referral center (2008–2022).

Results: The cohort included 47,1% males and 52,9% females, with mean age of 55,68 years (13-77 years). Recurrence occurred in 16 patients (18.4%), with a median time to relapse of 20.5 months (range 3–107) during a median follow-up of 57 months (range 7–175). The liver was the most frequent site of recurrence, and chemotherapy was the most common treatment. Median OS was 75 months. Survival among patients with recurrence (96.6%) was not significantly different from those without recurrence (100%), with only three deaths reported post-recurrence. Significant predictors of relapse in univariate analyses were tumor size, stage, Ki-67 index, necrosis, perineural growth, venous involvement, and lymphatic invasion.

Conclusions: Several pathological features, including tumor size, staging parameters, proliferative index, and patterns of invasion, are strongly associated with recurrence after surgical removal of PNETs. Nevertheless, OS in patients experiencing recurrence remains comparable to those without relapse.

Keywords: pancreatic neuroendocrine tumors, recurrence, pancreas, pancreatic surgery

INTRODUCTION

PNETs are rare, accounting for less than 5% of pancreatic tumors (1–3). Although infrequent, their incidence has risen in recent decades (4–6). These tumors vary considerably in terms of biological activity, clinical presentation, and long-term outcome (7,8).

They are categorized as functioning or non-functioning depending on hormone secretion. Most cases (50–90%) are non-functioning (7). Functioning tumors, such as insulinomas or gastrinomas, cause specific clinical syndromes

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and tend to be detected earlier. Non-functioning lesions often present late with vague symptoms such as pain, weight loss, or jaundice (5). With the growing use of advanced imaging, incidental diagnoses are increasingly common (5,6).

Despite progress in systemic therapy, surgery remains the only curative option (9). Still, recurrence after resection may reach up to 35% and has a negative effect on survival and quality of life (10-13). Five-year survival has been reported to range broadly between 25% and 100% (7). This study aims to determine recurrence frequency, patterns, and prognostic predictors in surgically treated PNETs, as well as their impact on survival.

METHODS

The study was performed at the Department of General Surgery, in a tertiary hospital center. In this study, we retrospectively examined our database of patients with PNETs who underwent surgical resection between 2008 and Dec. 2022 (n= 87).

Exclusion Criteria

Patients with incomplete clinical/follow-up data were excluded.

A detailed retrospective review of clinicopathologic data on patients with primary PNETs was carried out, based on electronic patient records, specialty consultation files, tumor registry and pathology archives. All available tumor slides were reviewed and subtyped by a pathologist. Clinicopathologic data, tumor recurrence and patient survival were analysed.

Our follow-up protocol was every 6 months for the first 3 years and annually thereafter and consisted in physical examination, imaging and chromogranin A testing.

Recurrence was considered when a lesion in the surgical bed, nodal or at distant was visible on imaging.

Statistical Analysis

Data was analysed by using SPSS (version 30.0).

Descriptive statistics were generated for all measures. Chi-Square Test was used to compare categorical variables and Wilcoxon Rank Sum Test was used for continuous variables.

Univariate and multivariate analysis were performed with Cox proportional hazard models, and survival analyses were performed using Kaplan-Meier Curves with Log Rank test for significance.

Differences were considered to be statistically significant at $p < 0.05$.

RESULTS

Eighty-seven patients with PNETs underwent surgical resection. The detailed patient characteristics are listed in *table 1*. 47,1% (n=41) were male and 52,9% (n=46) female, with mean age of 55,68 years (13-77 years). In the majority of the cases, it was an incidental finding. 25,3% (n=22) were submitted to distal pancreatectomy and 24,1% (n=21) to splenic preserving distal pancreatectomy, those were the most common procedures. 16,1% (n=14) had pancreatoduodenectomy, 14,9% (n=13) enucleation, 13,8% (n=12) pylorus-preserving pancreatoduodenectomy, and a minority of cases had central pancreatectomy (2,3%) or required a total pancreatectomy (3,4%).

Table 1 - Patients clinical data

Variable	N = 87
Age (mean, range)	55,68 (13-77)
Sex	
Female	52,9% (46)
Male	47,1% (41)
Presentation	
Abdominal pain	16,1% (14)
Hypoglycemia	17,2% (15)
Incidental finding	31,0% (27)
Jaundice	4,6% (4)
Asthenia	1,1% (1)
Diarrhea	1,1% (1)
Not specified	28,7% (25)
ASA	
I	14,9% (13)
II	57,5% (50)
III	25,3% (22)
Not specified	2,3% (2)
Type of resection	
Pancreatoduodenectomy	16,1% (14)
Pylorus-preserving pancreatoduodenectomy	10,3% (9)
Proximal pancreatectomy	8,0% (7)
Distal pancreatectomy	25,3% (22)
Splenic preserving distal pancreatectomy	24,1% (21)
Total pancreatectomy	3,4% (3)
Enucleation	10,3% (9)
Central pancreatectomy	2,3% (2)
Surgical dressing	
Laparoscopic	46,0% (40)
Open	49,4% (43)
Converted	4,6% (4)
Complication (Clavien-Dindo)	61,5% (59)
I	16,1% (14)
II	16,1% (14)
III	19,5% (17)
IV	5,7% (5)
V	0% (0)
Pancreatic fistula	20,7% (18)

61,5% (n=59) had complications, but mostly Clavien-Dindo I-III. 20,7% (n=18) had pancreatic fistula.

Table 2 present the pathologic results. 72,4% (n=63) of the tumors were nonfunctional. The most common functional tumor type was insulinoma (n=11). In terms of tumor site, 36,8% (n=32) were located in the head, 31% (n=27) in the tail and 29,9% (n=26) in the body. Only 2 cases were multifocal.

The mean tumor size was 3,11 cm (range 0,5-12,5 cm). 42,5% (n=37) were at stage T1, 27,6% (n=24) at stage T2, 23,0% (n=20) at stage T3 and the minority at stage T4 (6,9%). 58,6% (n=51) were classified as G1, 33,3% (n=29) were G2 and 8,0% (n=7) G3.

Table 2 - Pathologic data

Variable	N = 87
Tumor site	
Head	36,8% (32)
Body	29,9% (26)
Tail	31,0% (27)
Multifocal	2,3% (2)
Tumor size (mean, range)	3,11 cm (0,5-12,5 cm)
T staging (TNM)	
T1	42,5% (37)
T2	27,6% (24)
T3	23,0% (20)
T4	6,9% (6)
Staging	
G1	58,6% (51)
G2	33,3% (29)
G3	8,0% (7)
Functional	27,6% (24)
Insulinoma	12,6 (11)
Gastrinoma	1,1% (1)
Glucagonoma	9,2% (8)
VIPoma	-
Somatostatinoma	4,6% (4)
Nonfunctional	72,4% (63)
Resection status	
Negative margins	60,9% (53)
Close (<1 mm)	11,5% (10)
Positive margins	20,7% (18)
Not specified	6,9% (6)
Ki67 (mean, range)	5,57 (0-40)
Positive nodes	
0	80,5% (70)
1-2	12,6% (11)
3-4	2,3% (2)
5+	4,5% (4)
Mitotic count	
<2 mitotic figures/10 HPF	59,8% (52)
2-20 mitotic figures/10 HPF	21,8% (19)
>20 mitotic figures/10 HPF	2,3% (2)
Not specified	16,1% (14)
Necrosis	12,6%
Perineural growth	23,0%
Venous invasion	36,8%
Lymphatic invasion	36,8%

The majority 60,9% (n=53) had R0 resection, but 20,7% (n=18) had positive margins.

The Ki-67 mean was 5,57 (range 0-40).

Table 3 specify the follow-up, recurrence rate, site and time to recurrence, DFS and OS. *Table 4* analyse the clinicopathologic characteristic of the patients that presented recurrence, specifying the site and time to recurrence, the treatment and OS of these patients.

There were 16 (18,4%) recurrences, with median time to recurrence of 20,5 months (3-107 months), and a median follow-up of 57 months (range 7-175 months). The most common site of recurrence was the liver. The most common treatment of recurrences was chemotherapy.

Median DFS was 62 months (3-196 months) and median OS was 75 months (7-196 months). OS for those with and without recurrence was 96,6% and 100%, with only 3 deaths after recurrence (*table 4*). This was not considered a significantly different OS for those with or without recurrence (*fig. 1*). These patients were at stage T3-4 at the time of the diagnosis, all had R0 resection and presented recurrence to the liver in 7-11 months after surgery with an OS between 12 and 27 months.

Table 5 describes the univariate and multivariate analysis results highlining the variables associated with a higher risk of recurrence.

On univariate analysis, variables adversely impacting DFS were tumor size, staging, T-staging, Ki-67, necrosis, perineural growth, venous invasion, and lymphatic invasion, considered statistically significant predictors of recurrence. *Figures 2-9* respectively show DFS stratified by tumor size, staging, T-staging, Ki-67, necrosis, perineural growth, venous invasion and lymphatic invasion, graphically highlighting the effect of these variables in DFS.

Table 3 – Follow-up, recurrence and overall survival

Variable	N= 87
Follow-up (mean. median. range)	60.5/ 57 (7-175) months
Recurrence	16 (18.4%)
Recurrence site	
Liver	13
Pancreas	4
Ganglionar retroperitoneal	1
Mesentery	1
Bone	1
Time to recurrence (mean. median. range)	31/ 20.5 (3-107) months
OS (mean. median. range)	79.5/ 75 (7-196) months
OS	84 (96.6%)

Table 4 – Clinicopathologic analysis of the patients with recurrence

Patient	Age	Sex	TNM	Tumor site	Tumor size	Resection status	Recurrence site	Time to recurrence	Recurrence treatment	OS
1	32	M	T2	Head	2.7	Close margins	Pancreas. liver	52	Surgery	175
2	77	M	T3	Tail	3.3	Positive margins	Mesentery	38	TACE. Chemotherapy	75
3	77	F	T3	Head	3.5	Negative margins	Liver	24	Octreotide	74
4	70	F	T2	Head	6.5	Negative margins	Pancreas	53	Octreotide. Chemotherapy	67
5	64	M	T2	Body	2.5	Negative margins	Liver	73	Lanreotide	125
6	69	F	T3	Body	8.8	Negative margins	Liver	7	Octreotide. Lanreotide	12
7	54	M	T4	Tail	7.5	Positive margins	Liver	17	Chemotherapy	93
8	13	F	T1	Tail	0.8	Positive margins	Pancreas. liver	107	Octreotide	122
9	64	M	T3	Head	1.8	Negative margins	Liver	11	Sunitinib	27
10	57	M	T3	Head	10	Negative margins	Liver	37	Surgery	81
11	57	F	T3	Head	5.0	Negative margins	Liver	34	Surgery	55
12	67	F	T4	Tail	5.5	Negative margins	Liver. peritoneal carcinomatosis	8	Chemotherapy	13
13	43	M	T4	Body	12.5	Negative margins	Liver	17	Surgery	25
14	66	F	T4	Head	4.3	Close margins	Pancreas. Liver	5	Chemotherapy	20
15	50	M	T3	Head	3.6	Close margins	Liver. bone	3	Chemo + Radiotherapy	20
16	61	M	T3	Body	12.0	Close margins	Ganglionic retroperitoneal	10	Chemotherapy	25

Table 5 – Univariate and multivariate analysis of predictors of recurrence

Predictors of recurrence	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR 95% CI (DFS)	p-value (DFS)	HR 95% CI (DFS)	p-value (DFS)	HR 95% CI (TR)	p-value (TR)	HR 95% CI (TR)	p-value (TR)
Age	1.02 (0.98; 1.06)	0.287			1.02 (0.99; 1.05)	0.164		
Gender	0.62 (0.23; 1.67)	0.342			0.86 (0.30; 2.45)	0.775		
ASA	1.08 (0.55; 2.14)	0.820			1.01 (0.28; 3.65)	0.986		
Complications	0.94 (0.74; 1.21)	0.636			0.93 (0.69; 1.26)	0.639		
Tumor size	1.37 (1.20; 1.57)	<0.001	1.29 (0.98; 1.70)	0.070	1.14 (0.98; 1.33)	0.09		
Staging	4.80 (2.40; 9.56)	<0.001	2.28 (0.66; 7.84)	0.192	1.59 (0.65; 3.89)	0.311		
T-staging	3.50 (2.02; 6.07)	<0.001	1.11 (0.37; 3.33)	0.849	5.34 (1.84; 15.49)	0.002	4.50 (1.28; 15.88)	0.019
Function	9.50 (0.76; 118.93)	0.081			0.90 (0.09; 9.03)	0.930		
Resection status	0.84 (0.51; 1.39)	0.498			0.78 (0.41; 1.45)	0.428		
Ki-67	1.12 (1.08; 1.16)	<0.001	1.04 (0.98; 1.10)	0.198	1.05 (1.01; 1.10)	0.029	1.01 (0.95; 1.07)	0.807
Positive nodes	1.10 (0.85; 1.41)	0.472			1.84 (1.06; 3.19)	0.030	1.45 (0.81; 2.58)	0.215
Mitotic count	1.04 (0.70; 1.55)	0.837			1.22 (0.53; 2.82)	0.645		
Necrosis	0.34 (0.14; 0.84)	0.019	0.65 (0.25; 1.66)	0.363	0.52 (0.21; 1.26)	0.146		
Perineural growth	0.22 (0.09; 0.54)	0.001	0.69 (0.25; 1.90)	0.469	0.66 (0.24; 1.86)	0.430		
Venous invasion	0.21 (0.08; 0.57)	0.002	0.89 (0.26; 3.08)	0.849	0.49 (0.18; 1.33)	0.161		
Lymphatic invasion	0.23 (0.08; 0.62)	0.004	0.55 (0.14; 2.14)	0.389	0.53 (0.17; 1.67)	0.275		

HR – Hazard ratio; CI – Confidence interval; DFS – Disease free survival; TR - Time to recurrence.

Concerning the time to recurrence, on univariate analysis, T-staging, Ki-67 and positive nodes were the variables considered statistically significant.

On multivariate analysis, in relation to DFS no variables were identified as statistically significant, but in relation to the time to recurrence, T-staging was considered a statistically significant predictor of an early recurrence.

DISCUSSION

Recent years have shown a growing number of incidental PNET diagnoses (4). In our series, 31% were found unintentionally. Data suggest that tumors <2 cm have increased in incidence by more than sevenfold over two decades (4).

Surgical resection is standard for localized disease, though pancreatic surgery carries notable morbidity and non-trivial mortality (7). In our study, complications

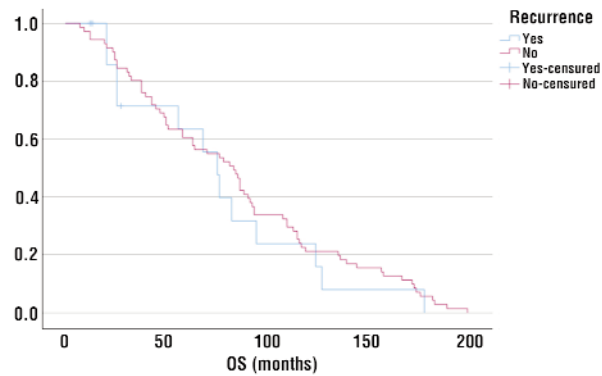


Figure 1 – Overall survival stratified by disease recurrence

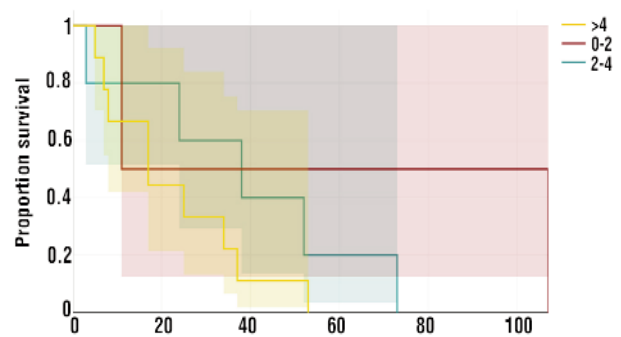


Figure 2 – Disease free survival stratified by tumor size

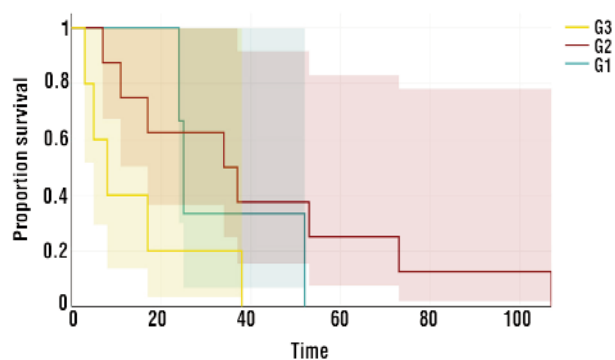


Figure 3 – Disease free survival stratified by staging

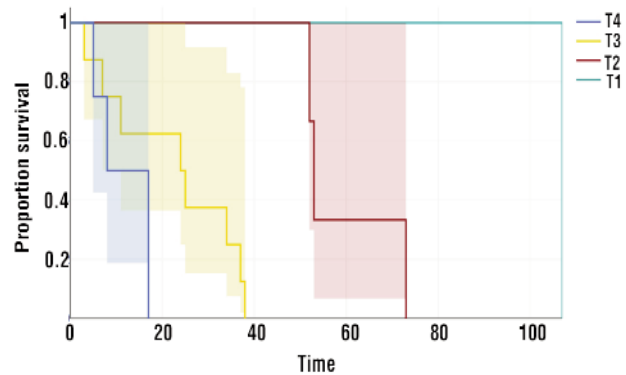


Figure 4 – Disease free survival stratified by T-staging

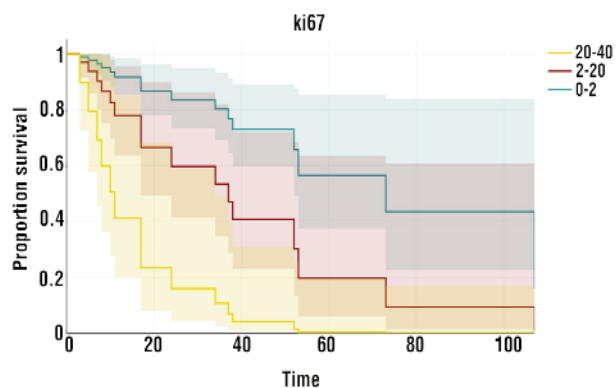


Figure 5 – Disease free survival stratified by Ki-67

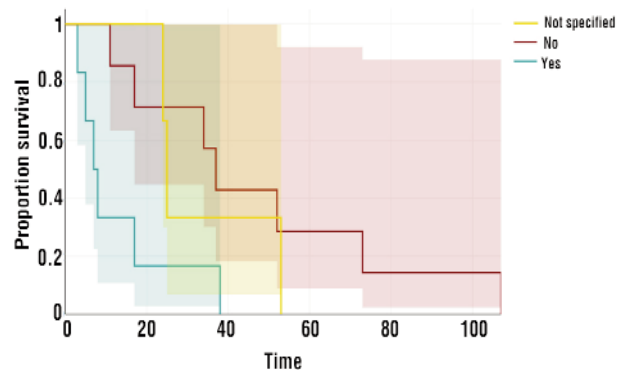


Figure 6 – Disease free survival stratified by necrosis

occurred in 61.5%, mostly Clavien-Dindo I–III, with 20.7% developing pancreatic fistulas.

Management of small, non-functioning PNETs remains controversial. European Neuroendocrine Tumor Society (ENETS) and North American

Neuroendocrine Tumor Society (NANETS) recommend surveillance for tumors <2 cm, whereas National Comprehensive Cancer Network (NCCN) guidelines suggest observation mainly for low-grade lesions <1 cm (7). The optimal threshold distinguishing indolent from

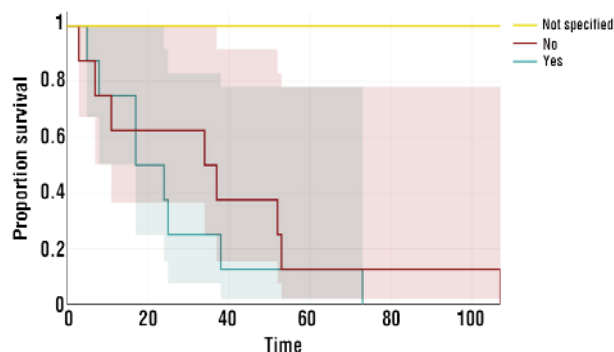


Figure 7 – Disease free survival stratified by perineural growth

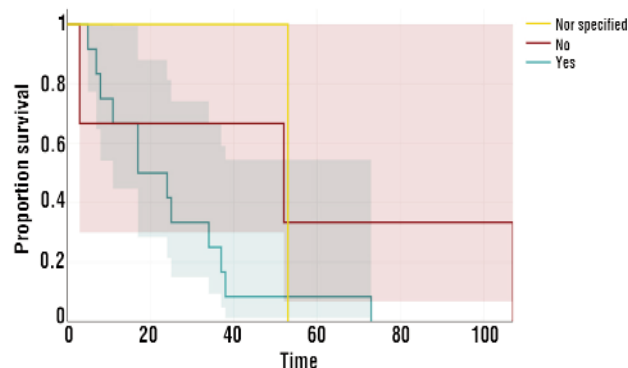


Figure 8 – Disease free survival stratified by venous invasion

aggressive tumors may lie between 1.5–2 cm (15). Since PNETs are rare, their natural history remains insufficiently understood, complicating predictions of malignant potential (14).

Although some series report recurrence in <10% of resected tumors <2 cm (7), others describe recurrence rates up to 35% overall (10–13). Our cohort showed an 18.4% recurrence rate. While generally considered indolent, PNETs are prone to relapse, which significantly influences prognosis. Understanding timing, distribution, and predictors of recurrence is essential for tailoring follow-up and guiding adjuvant treatment strategies (7,8,14).

Risk factors for aggressive disease include larger tumor size, vascular and lymphatic invasion, nodal or distant metastases at presentation, and higher grade (1,2,13,16–18). Patients with nodal involvement show reduced 5-year disease-free survival compared to node-negative patients (1,2,4,16,18,19). Other prognostic determinants include WHO grade, Ki-67 index, mitotic rate, degree of differentiation, and functionality (7,16).

Predictors consistently reported in literature are size, lymph node metastases (×5 increased recurrence risk), Ki-67 index, vascular/perineural invasion, necrosis, grade G3 tumors, and positive surgical margins (13–22). Surveillance strategies should therefore be tailored to high-risk individuals, as recurrence may appear late (14).

In our study, variables with significant adverse impact on DFS were tumor size, staging, T-staging, Ki-67, necrosis, perineural growth, venous invasion, and lymphatic invasion. On multivariate analysis, T-staging was also considered a statistically significant predictor of an early recurrence.

The most common site of relapse is the liver, accounting for over half of cases, followed by pancreatic

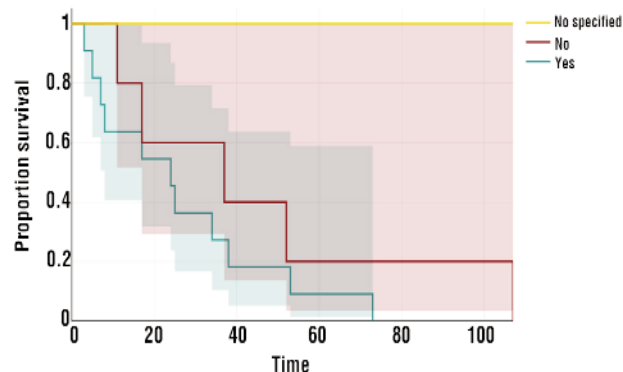


Figure 9 – Disease free survival stratified by lymphatic invasion

remnant and lymph nodes (2,4,8,16). In our series, liver recurrence predominated, with chemotherapy being the most frequent salvage treatment.

Median OS was 75 months. Survival rates were high in both groups - 96.6% in patients with recurrence and 100% in those without, with only three deaths occurring after relapse.

CONCLUSION

PNET recurrence after curative resection is relatively common, predominantly affecting the liver. Identification of risk factors - such as tumor size, pathological staging, proliferation index, and invasive features - is critical to stratify patients for intensive monitoring or adjuvant treatment. Despite recurrence, OS outcomes remain favorable. Given the rarity and heterogeneity of PNETs, additional multicenter studies are required to refine prognostic markers and optimize follow-up strategies.

Author's Contributions

Conceptualization: EC, RRD. Data curation: EC, RRD, SR, MA, JL. Methodology: EC, RRD, MA. Visualization: EC, RRD, MA. Writing - original draft: EC, RRD. Writing - review & editing: SR, MA, JL, HC, LG, SC.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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