Original article

Outcome of surgery for pancreatic neuroendocrine neoplasms

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Background: **The incidence of pancreatic neuroendocrine neoplasms (pNEN) is increasing. This study aimed to evaluate predictors of overall survival and the indication for surgery.**

Methods: **Data collected between October 2001 and December 2012 were analysed. Histological grading and staging was based on the classifications of the World Health Organization, the International Union Against Cancer and the European Neuroendocrine Tumour Society.**

Results: **Some 310 patients (150 female, 48·4 per cent) underwent surgical resection. The final survival analysis included 291 patients. Five-year overall survival differed according to tumour grade (G): 91·0 per cent among 156 patients with pancreatic neuroendocrine tumours (pNET) G1, 70·8 per cent in 111 patients with pNET G2, and 20 per cent in 24 patients with pancreatic neuroendocrine carcinomas (pNEC) G3 ($P < 0·001$). Tumours graded G3 (hazard ratio (HR) 6·96, 95 per cent confidence interval 3·67 to 13·21), the presence of distant metastasis (HR 2·41, 1·32 to 4·42) and lymph node metastasis (HR 2·10, 1·07 to 4·16) were independent predictors of worse survival ($P < 0·001$, $P = 0·004$ and $P = 0·032$ respectively). Eight of 61 asymptomatic patients with pNEN smaller than 2 cm had tumours graded G2 or G3, and six of 51 patients had lymph node metastasis. Among patients with pNEC G3, the presence of distant metastasis had a significant impact on the 5-year overall survival rate: 0 per cent *versus* 43 per cent in those without distant metastasis ($P = 0·036$).**

Conclusion: **Neuroendocrine tumours graded G3, lymph node and distant metastasis are independent predictors of worse overall survival in patients with pNEN.**

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Introduction

The incidence of gastroenteropancreatic neuroendocrine neoplasms, including pancreatic neuroendocrine neoplasms (pNEN), has increased over the past few decades[1–4]. It has been suggested that the more frequent use of imaging and increased awareness among physicians may have contributed to this trend[5,6]. These latter findings may in part explain why the majority of patients with pNEN initially present with non-specific symptoms or are even asymptomatic[3,7–9].

The histopathological classifications of pNEN have undergone significant changes in recent years[10,11]. The World Health Organization (WHO)[12] classifies pNENs as pancreatic neuroendocrine tumours (pNET) grade G1 or G2, or as pancreatic neuroendocrine carcinomas (pNEC) G3. Two different staging systems have been introduced by the International Union Against Cancer (UICC)[11,13] and the European Neuroendocrine Tumour Society (ENETS)[10,14,15]. Even though modifications of both the WHO and UICC classifications have been implemented, the scientific debate concerning the clinical significance of the different classification systems is ongoing[10,11,13,16–20].

Although the role of surgery as the primary therapeutic option for patients with pNEN is not generally debated, there is ongoing discussion about the indication for surgery in patients with small and asymptomatic pNEN, as well as in patients with advanced tumours (pNEC G3)[21–24]. The non-operative management ('watch-and-wait' policy) of patients with incidentally detected pNEN smaller than 2 cm has been advocated[21]. On the other hand, the introduction of everolimus, an inhibitor of mammalian target of rapamycin, and sunitinib, a receptor tyrosine kinase inhibitor, as therapeutic options for patients with advanced pNEN has shown promising results.

The main aim of this study was to evaluate predictors of overall survival and the indication for surgery in patients with pNEN.

Methods

This study comprised an analysis of data registered prospectively from patients undergoing surgery for pNEN at the University Hospital of Heidelberg, Germany, between October 2001 and December 2012. Follow-up was conducted either during patient visits to the outpatient clinic or by means of a telephone questionnaire.

Histology

Histological grading and staging was based on the WHO classification for pancreatic neuroendocrine neoplasm (2010) and TNM classification of the UICC and ENETS. Histological examination included regular haematoxylin and eosin staining, and additional staining with neuroendocrine markers (synaptophysin, chromogranin A). Tumour grade (G) was determined by mitotic count in ten high-power fields and by immunohistochemically Ki-67-positive tumour cells. All specimens were re-evaluated and regraded accordingly.

Resection margin status

Resection margin status was graded R0 (complete resection with no microscopic residual tumour), R1 (complete macroscopic resection but margins microscopically positive) or R2 (grossly residual tumour).

Chemotherapy

Patients with pNEC G3, those with liver metastasis and patients who had R2 resection were seen by oncologists to decide on the need for chemotherapy[12].

Statistical analysis

The distribution of age at operation, tumour size and follow-up are described as median (range). Overall survival from the date of surgery was calculated by the Kaplan–Meier method. Patients who were still alive at the time of the last follow-up were censored. The end of follow-up was December 2012. The log rank test was used to compare survival for different histological parameters, resection margin status, sex and age at the time of surgery. Univariable and multivariable Cox regression analysis was done to identify factors independently associated with prognosis. The multivariable analysis included

Table 1 Surgical procedure, resection margin, tumour location, tumour size, lymph node and distant metastases in patients with pancreatic neuroendocrine neoplasms

	G1 ($n = 168$)	G2 ($n = 118$)	G3 ($n = 24$)	All patients ($n = 310$)
Surgical procedure				
PD	3	5	1	9
PPPD	28	32	8	68
Total pancreatectomy	9	14	4	27
Distal pancreatectomy	61	48	7	116
Enucleation	47	3	0	50
Other resection	17	8	2	27
No resection	3	8	2	13
Resection margin status				
R0	152	79	8	239
R1	3	15	6	24
R2	10	15	8	33
Rx	0	1	0	1
Exploration/bypass	3	8	2	13
Tumour location				
Head	57	48	16	121
Body	32	16	0	48
Tail	49	37	7	93
Multiple	30	17	1	48
Tumour size (cm)*	1·5 (0·4–11)	3·5 (0·3–14)	5·0 (0·7–19)	2·5 (0·3–19)
Lymph node metastasis (N1)	28	70	16	114
Distant metastasis (M1)	15	34	14	63

*Values are median (range). G, tumour grade (World Health Organization classification, 2010); PD, partial pancreaticoduodenectomy; PPPD, pylorus-preserving partial pancreaticoduodenectomy.

clinically important parameters from the univariable survival analysis and those with $P \leq 0{\cdot}050$, and was adjusted for age. The hazard ratio (HR) with 95 per cent confidence interval (c.i.) is presented for all variables included in the final model. Variable selection was done using Akaike's information criterion and the general strategy for model selection described by Colett[25]. Two-sided P values were always computed and $P < 0{\cdot}050$ was considered statistically significant. SAS® software release 9.1 (SAS Institute, Cary, North Carolina, USA) was used for statistical analysis.

Results

From October 2001 to December 2012, 310 patients (150 female, 48·4 per cent) underwent surgical resection for pNEN. The median age was 57 (13–85) years. Clinical presentation was accompanied by specific symptoms of hormonal hypersecretion in 78 patients (25·2 per cent), of whom 41 (53 per cent) were diagnosed with an insulinoma. Sixteen patients (5·2 per cent) had multiple endocrine neoplasia and two (0·6 per cent) von Hippel–Lindau disease. All other patients had either non-specific symptoms or were asymptomatic.

Investigations before surgery in the 310 patients included CT in 276 (89·0 per cent), abdominal ultrasonography in 243 (78·4 per cent), MRI in 103 (33·2 per cent), octreotide scintigraphy in 28 (9·0 per cent), and PET or endoscopic ultrasonography in 4·5 per cent. All other preoperative imaging modalities were used rarely (in less than 2 per cent of the patients).

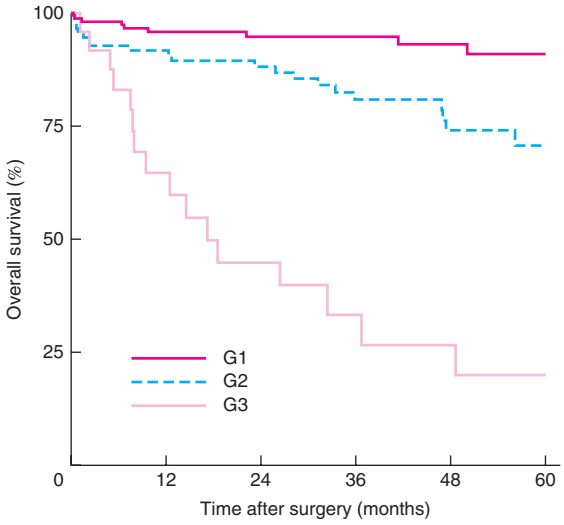
Details of the surgical procedure, including tumour location, resection margin status, tumour size, lymph node status and presence of metastases are shown in *Table 1*. Morbidity rates for all patients and for 61 asymptomatic patients with pNEN smaller than 2 cm are shown in *Table 2*. The median length of stay was 11 (i.q.r. 8–16) days. Eight patients (2·6 per cent) died in hospital. The 30- and 90-day mortality rates were 2·6 per cent (8 patients) and 4·2 per cent (13 patients) respectively

Median follow-up for the 238 patients who were still alive at the time of last follow-up was 31 (1–130) months. Nineteen patients were lost to follow-up and, of these, 13 came from abroad. Some 53 patients (18·2 per cent) died during follow-up. The final survival analysis included 291 patients. Overall survival among patients classified according to the 2010 WHO classification is shown in *Fig. 1*. The 5-year overall survival rate was 91·0 per cent for 156 patients with pNET G1, 70·8 per cent for 111 patients with pNET G2, and 20 per cent for 24 patients with pNEC G3. The results of univariable analysis are shown in *Table 3*.

Table 2 Morbidity rates for all 310 patients with pancreatic neuroendocrine neoplasm and for 61 asymptomatic patients with tumours smaller than 2 cm

	All patients ($n = 310$)	Asymptomatic patients with pNEN < 2 cm ($n = 61$)
Pancreatic fistula	59 (19·0)	15 (25)
Anastomotic leakage	9 (2·9)	4 (7)
Intra-abdominal abscess	33 (10·6)	4 (7)
Wound dehiscence	3 (1·0)	1 (2)
Wound infection	19 (6·1)	4 (7)
Bleeding	17 (5·5)	2 (3)
Thrombosis	7 (2·2)	0 (0)
Pneumonia	5 (1·6)	0 (0)
Urinary tract infection	2 (0·6)	1 (2)

Values in parentheses are percentages. pNEN, pancreatic neuroendocrine neoplasms.



No. at risk

G1	156	114	87	62	47	34
G2	111	81	67	50	30	19
G3	24	13	9	5	4	2

Fig. 1 Overall survival of patients with pancreatic neuroendocrine neoplasm according to the 2010 World Health Organization classification. G, grade. $P < 0{\cdot}001$ (log rank test)

Among others, male sex, lymph node metastasis, presence of distant metastasis, R1 and R2 resections, hormonally non-active pNEN, and a Ki-67 index of more than 5 per cent positive cells were predictors of worse survival. The results of the multivariable analysis are shown in *Table 4*.

Fig. 2 shows the impact of distant metastasis on overall survival for all patients. Patients without distant metastasis had better 5-year overall survival than those with distant metastasis (85·0 *versus* 43·7 per cent; $P < 0{\cdot}001$). Among the 24 patients with pNEC G3, ten without distant metastasis

Table 3 Results from univariable Cox regression analyses of variables potentially associated with overall survival after an operation for pancreatic neuroendocrine neoplasm

	No. of patients	No. of events	Hazard ratio	*P*
Age (years)				
< 50	100	13	1·00 (reference)	
≥ 50	191	40	1·59 (0·85, 2·98)	0·144
Continuous variable	291	53	1·02 (0·99, 1·04)	0·130
Sex				
M	150	37	1·00 (reference)	
F	141	16	0·40 (0·22, 0·71)	0·002
WHO grade*				
G1	156	13	1·00 (reference)	
G2	111	23	2·58 (1·29, 5·03)	0·006
G3	24	17	13·56 (6·47, 28·39)	< 0·001
ENETS tumour category				
T1	90	6	1·00 (reference)	
T2	40	1	0·41 (0·05, 3·43)	0·412
T3	121	36	4·38 (1·85, 10·41)	0·001
T4	20	5	3·91 (1·19, 12·82)	0·025
UICC tumour category				
T1	90	6	1·00 (reference)	
T2	41	1	0·38 (0·05, 3·18)	0·375
T3 and T4†	140	41	4·41 (1·87, 10·38)	0·001
Lymph node metastasis				
N0 (negative)	135	14	1·00 (reference)	
N1 (positive)	110	34	2·57 (1·37, 4·79)	0·003
Distant metastasis				
M0 (negative)	220	27	1·00 (reference)	
M1 (positive)	62	26	4·07 (2·37, 7·00)	< 0·001
Tumour location				
Body	44	4	1·00 (reference)	
Head	111	27	3·65 (1·27, 10·49)	0·016
Tail	90	17	2·44 (0·81, 7·37)	0·115
Multiple	46	5	1·19 (0·30, 4·76)	0·807
Resection margin status				
R0	225	25	1·00 (reference)	
R1	22	8	3·94 (1·76, 8·79)	0·001
R2	32	16	5·29 (2·81, 9·98)	< 0·001
Exploration/bypass	11	3	3·55 (1·06, 11·89)	0·040
Angioinvasion				
No	209	25	1·00 (reference)	
Yes	78	27	2·80 (1·62, 4·82)	0·001
Hormone status‡				
Non-active	129	39	1·00 (reference)	
Active	115	10	0·34 (0·17, 0·69)	0·003
Insulinoma excluded	41	3		
Ki-67-positive cells (%)				
≤ 2	173	14	1·00 (reference)	
> 2–5	64	11	2·15 (0·98, 4·74)	0·057
> 5–20	29	10	4·52 (2·01, 10·18)	< 0·001
> 20	24	17	13·39 (6·52, 27·51)	< 0·001

Values in parentheses are 95 per cent confidence intervals. *World Health Organization (WHO) classification, 2010. †Four patients with T4 tumours. ‡Independent of clinical symptoms, tumours were classified as hormone-secreting when histological examination showed that the tumour was positive for one or more of the following markers: gastrin, insulin, glucagon or somatostatin. ENETS, European Neuroendocrine Tumour Society; UICC, International Union Against Cancer.

had improved 2-year (57 *versus* 35 per cent) and 5-year (43 *versus* 0 per cent; $P = 0{\cdot}036$) overall survival compared with 14 patients with distant metastasis. Patients with pNEC G3 without distant metastasis had a median overall survival of 37 months compared with 14 months for those with distant metastasis. The 5-year overall survival rate was 27 per cent for 16 patients with NEC G3 and lymph node metastasis. It was 29 per cent among 14 patients with pNEC G3 who underwent macroscopically complete resection (R0 and R1) and zero for ten who had R2 resection or exploration.

Table 4 Multivariable Cox regression analysis of variables associated with overall survival in patients operated on for pancreatic neuroendocrine neoplasm

	Hazard ratio	*P*
Tumour grade (G3 *versus* G1/2)	6·96 (3·67, 13·21)	< 0·001
Distant metastasis (M1 *versus* M0)	2·41 (1·32, 4·42)	0·004
Lymph node metastasis (N1 *versus* N0)	2·10 (1·07, 4·16)	0·032
Age (years)*	1·03 (1·00, 1·06)	0·086

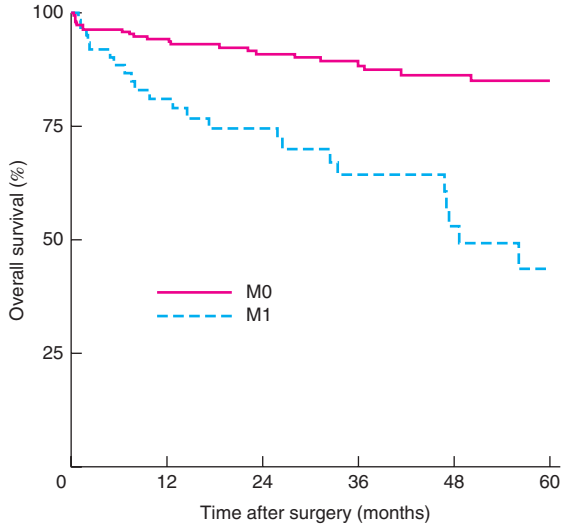
Values in parentheses are 95 per cent confidence intervals. *Continuous variable. Variables not included in the final model[25]: percentage of Ki-67-positive cells (more than 5–20 per cent, $P = 0·167$), resection margin status (R1, $P = 0·888$; R2, $P = 0·265$), tumour location (head, $P = 0·428$; tail, $P = 0·597$), hormone status (active, $P = 0·308$; insulinoma, $P = 0·998$), tumour grade according to World Health Organization classification, 2010 (G2, $P = 0·265$), angioinvasion ($P = 0·322$), tissue infiltration ($P = 0·646$), tumour category (T3/4, $P = 0·896$) and sex ($P = 0·118$).

Table 5 World Health Organization classification (2010), lymph node and distant metastasis, and resection margin status in patients with non-functional and asymptomatic pancreatic neuroendocrine neoplasm smaller than 2 cm

	No. of patients ($n = 61$)
Tumour grade*	
G1	53 (86)
G2	7 (11)
G3	1 (2)
Lymph node metastasis†	
N0	45 (88)
N1	6 (12)
Distant metastasis	
M0	61 (100)
M1	0 (0)
Resection margin status	
R0	61 (100)
R1	0 (0)
R2	0 (0)

Values in parentheses are percentages. *World Health Organization classification, 2010. †Because the pathological specimens contained no lymph nodes, for example after enucleation or distal pancreatectomy with preservation of the spleen, the node status was unknown (Nx) in ten patients.

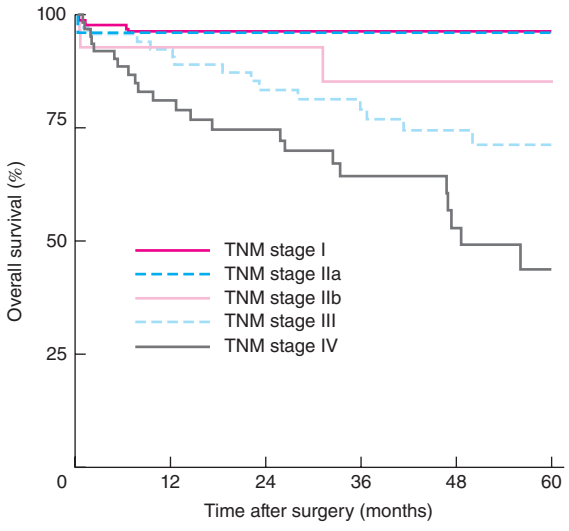
Of the 310 patients, 61 asymptomatic patients (19·7 per cent) were operated on for pNEN smaller than 2 cm. The median tumour size in these patients was 1·2 (0·4–1·9) cm. Of these 61 patients, 21 underwent distal pancreatectomy, 14 partial pancreaticoduodenectomy, 13 tumour enucleation, five total pancreatectomy, and eight had other types of resection. All 61 patients underwent complete resection of the tumour (R0) (*Table 5*). Morbidity rates are shown in *Table 2*. Notably, eight of the 61 patients were diagnosed with pNET G2 or pNEC G3, and six of 51 patients with excised lymph nodes had lymph node metastasis; the nodal status was unknown in ten patients who underwent



No. at risk

M0	220	161	124	92	69	48
M1	62	40	32	23	14	7

Fig. 2 Overall survival of patients with pancreatic neuroendocrine neoplasm with respect to distant metastasis. M0, no distant metastasis; M1, distant metastasis. $P < 0·001$ (log rank test)



No. at risk

I	87	63	48	34	26	22
IIa	25	17	12	8	6	3
IIb	28	19	15	10	8	6
III	69	54	43	36	26	14
IV	62	40	32	23	14	7

Fig. 3 Overall survival of patients with pancreatic neuroendocrine neoplasm according to the European Neuroendocrine Tumour Society classification. $P < 0·001$ (log rank test)

enucleation or distal pancreatectomy with preservation of the spleen. The 5-year disease-free survival rate in this subgroup was 95 per cent. One patient developed liver metastasis 36 months after surgery.

When the TNM classifications for pNEN of ENETS[10] and UICC[11,13] were applied, the tumour category was not consistent between the ENETS and UICC classifications in 21 patients (data not shown). However, a prognostic stratification could be achieved using both the ENETS and UICC criteria (*Table S1*, supporting information). The overall survival rates for patients with ENETS I–IIb/UICC IA–IIA tumours were better than those of patients with ENETS IIIb/UICC IIB or ENETS IV/UICC IV ($P < 0{\cdot}001$) (*Fig. 3*).

Discussion

Even though there has been an emerging debate about the optimal treatment for patients with pNEN, particularly patients with advanced disease[26–28], the benefits of surgery as the primary therapeutic option in patients with pNEN is generally not doubted[9,22,23,29–31].

The results of the present study allow two main conclusions. First, the multivariable analysis showed that tumours graded G3 and the presence of lymph node and distant metastasis are independent predictors of worse prognosis in patients with pNEN. Second, surgery may be considered as a treatment option even in patients with asymptomatic pNEN smaller than 2 cm or for patients with pNEC G3.

It has been suggested that small non-functioning pNEN usually exhibit minimal growth over time, and that there is a strict correlation between tumour size and malignancy[21,24]. However, the results from one study[23] indicated that small, non-functioning pNEN sometimes display aggressive behaviour. One investigation[2] showed that age over 55 years and G3 tumour grade predicted a greater risk of death in patients with non-functioning pNEN. These findings suggest that resection may be considered for such patients regardless of tumour size[22]. In the present investigation, there was only a limited number of patients with small asymptomatic pNEN and a relatively short median follow-up of 31 months. However, a considerable number of these patients initially presented with tumours graded G2 or even G3, and lymph node metastases, which indicates that 'watch-and-wait' strategies cannot be recommended unequivocally. The indication for resection is also supported by results of the multivariable analysis, which showed that the presence of lymph node metastasis and G3 grade were independent predictors of worse overall survival. It is also important to note that all asymptomatic patients with pNEN smaller than 2 cm had complete tumour resection (R0), which was a predictor of improved overall survival in the univariable analysis. However, even though most of these small tumours were resected by pancreas-preserving operations such as enucleation or distal pancreatectomy, possible morbidity should be taken into consideration.

The finding of G3 tumour grade as an independent predictor of worse overall survival raises the question of whether surgical or general medical therapy should be considered for these patients. The results achieved by treating pNEN with everolimus and sunitinib are promising. Although everolimus has shown improved progression-free survival compared with placebo, the RADIANT-3[26] study showed no difference in overall survival. One explanation for the discrepancy between progression-free and overall survival could be that an objective tumour response was achieved in less than 10 per cent of all patients (5 per cent in the everolimus group and 2 per cent in the placebo group). Furthermore, the trial allowed crossover to the treatment group after disease had progressed[32,33]. Based on the data presented here, the 5-year overall survival rate for patients with pNEC G3 was 20 per cent. In the absence of distant metastasis, 5-year overall survival increased to 43 per cent. Even though there were few patients with NEC G3 and the median follow-up was less than 3 years, these data support the argument for a surgical approach in patients with pNEC G3, particularly those without distant metastasis.

Based on the 2010 WHO classification, univariable analysis showed that male sex was a predictor of worse overall survival. This finding is in accordance with results from a large European cohort study[17], where male patients were found to have larger tumours, a more advanced tumour stage and a higher Ki-67 index.

Although 21 patients had a different tumour category according to the ENETS *versus* UICC classification systems, these differences did not affect the final TNM stages. Even though larger studies have shown that the ENETS classification may be the best system available[17], it is difficult to validate its applicability for staging pNEN in individual patients[18].

In patients with pNEN, tumour grade G3, and lymph node and distant metastasis were independent predictors of worse overall survival. A 5-year overall survival rate of approximately 40 per cent could be achieved after tumour resection in patients with pNEC G3 without distant metastases. For small asymptomatic pNEN a 'watch-and-wait' strategy cannot be recommended unequivocally.

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Supporting information

Additional supporting information may be found in the online version of this article:

Table S1 TNM staging of patients with pancreatic neuroendocrine neoplasm according to the International Union Against Cancer and European Neuroendocrine Tumour Society classifications (Word document)