ORIGINAL PAPER

Submitted: 21.12.2023
Accepted: 22.12.2023
Early publication date: 21.02.2024

Endokrynologia Polska
DOI: 10.5603/ep.98635
ISSN 0423–104X, e-ISSN 2299–8306
Volume/Tom 75; Number/Numer 1/2024

Prediction of disease recurrence in patients after complete pancreatic NET (PanNET) G2 resection

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Abstract

Introduction: The number of detected pancreatic neuroendocrine tumours (PanNETs) has been increasing over the last decades. Surgical resection remains the only potentially curative treatment, but the management is still controversial. This study aimed to compare patients after radical PanNET G2 resection to determine the most important predictive factors for relapse.

Material and methods: All patients with histologically confirmed PanNET G2 who underwent successful surgery between 2006 and 2020 with the intention of radical treatment were enrolled.

Results: In total, 44 patients were eligible for the analysis. The average follow-up was 8.39 ± 4.5 years. Disease recurrence was observed in 16 (36.36%) patients. The dominant location of the primary tumour was the tail of the pancreas (43.18%), especially in the subgroup with disease recurrence (56.25%). The smallest tumour diameter associated with the PanNET G2 recurrence was 22 mm. The relationship between the largest dimension of the tumour with a division of < 4 cm *vs.* > 4 cm and the relapse was close to statistical significance. Recurrence was associated with a larger tumour size ($p = 0.018$). There was a statistically significant relationship and a weak correlation between proliferation index Ki-67 ($p = 0.036$, V Cramer = 0.371) and disease relapse.

Conclusion: For the group of PanNET G2 patients after radical surgery, the overall risk of recurrence was 36.36%, with the highest rate in the first 5 years after surgery, but in individual cases it occurred significantly later, even 10 years after surgery. The most important predictive factors of the PanNET G2 recurrence was Ki-67 over 5.75% and size of tumour > 4 cm. **(Endokrynol Pol 2024; 75 (1): 102–108)**

Key words: *PanNET G2; pancreatic NET; neuroendocrine tumours; pancreatic tumours; disease recurrence; NET*

Introduction

Neuroendocrine neoplasms (NENs) are relatively rare and heterogeneous lesions, originating from neuroendocrine cells of the diffuse endocrine system. NENs comprise approximately 2% of all malignancies, and pancreatic neuroendocrine neoplasms (PanNENs) account for 1–2% of all pancreatic tumours. The number of detected PanNENs has been steadily increasing over the last decade. According to a study by the Copenhagen European Neuroendocrine Tumour Society (ENETS) centre of excellence, the number of incidental findings of pancreatic neuroendocrine tumours (PanNETs) among other NETs increased from 19% (2010–2011) to 57% (2019–2020) [1]. The apparent increase in frequency is attributed to the increased awareness of NENs and the more sensitive detection methods.

According to the European Neuroendocrine Tumour Society (ENETS), the histological maturity of the tumour (G — grading) is of key clinical importance [1]. Since 2020, G2 PanNETs have been defined as tumours with a proliferation index (Ki-67) between 3% and 20% and a mitotic activity of 2–20 figures of division in 10 consecutive high-power fields (HPF). However, it has been suggested since the 1990s that Ki-67 > 5% may be an independent predictor of survival. Until now, the applicable ENETS, the World Health Organization (WHO), and national criteria do not recognize this value as a cut-off point [2–4]. It should be remembered that PanNETs G2 are a heterogeneous group of tumours in terms of Ki-67, lesion morphology, and other factors, all of which can determine the course of the disease and the probability of its recurrence.

Surgical resection is the only potentially curative treatment for PanNETs. However, numerous studies have shown that the prognosis of small localized PanNENs, especially G1, is good, and a watchful waiting strategy may be an alternative to surgery in patients with small, non-functioning tumours [2, 3].

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Therefore, the management of non-functioning PanNENs, particularly G2, is still controversial [5, 6]. Despite evidence of a different malignancy potential of PanNETs G1 and G2, postoperative management is the same in all patients [3]. If radical removal of the G1 or G2 tumour is successful, there are no indications for adjuvant chemotherapy. So far, no consistent protocols have been developed based on the likelihood of relapse, although it affects nearly 20% of patients with well-differentiated PanNETs and significantly shortens their survival [4]. Ki-67 value, lymph node involvement, and tumour size are essential for prognostic significance. However, these parameters do not affect medical management after curative resection of PanNET G1 or G2. Various authors have already described the estimation of PanNET recurrence risk as challenging [7, 8]; better knowledge of prognostic factors will enable correct and personalized decisions regarding follow-up and treatment.

The aim of the study was to determine the most important clinical factors predisposing to relapse of PanNET G2 after radical resection.

Material and methods

The database of the Endocrinology Department at the University Hospital in Krakow was searched for patients with both functional and non-functional tumours, histologically confirmed as PanNET G2, who successfully underwent surgery with the intention of radical treatment from 2006 to 2020.

The exclusion criteria included PanNENs at a grade other than G2 at the time of diagnosis, PanNENs as a component of hereditary syndromes, NENs in more than one location, and a positive history of other malignancies.

A CONSORT diagram for the final study population is shown in Figure 1. Histological differentiation was assessed according to the current WHO classification for PanNEN, valid at the time of diagnosis, based on the morphological mitotic index [G1 < 2/10 high-power field (HPF), G2 2–20/10 HPF, and G3 > 20/10 HPF] or immunohistochemically evaluated tumour proliferative activity according to the Ki-67 index (G1, G2, and G3 < 3%, 3–20%, > 20%, respectively). In cases where the mitotic index differed from the Ki-67 index, a higher index was used.

Recurrence of the disease was defined as local relapse or the appearance of local or distant metastases. The follow-up time was defined as the time from surgery to the patient's last visit or the time to death.

In all patients, sex, age at diagnosis, presence of clinical symptoms, and diagnostic path were evaluated (Tab. 1). The differences between genders, tumour location, Ki-67 index, largest dimension, hormonal activity, and relapse were analysed.

Statistical analysis

The statistical analysis was performed using IBM SPSS Statistics 26.0. The descriptive statistics were provided as mean, median, range, and percentage values. The normality of the data was tested using the Shapiro-Wilk test. Correlations were calculated using the Spearman's rho correlation coefficient. The U Man-Whitney test, Kruskal-Wallis test, and χ^2 test were used to assess the statistical significance of differences between groups. For statistically significant values in the χ^2 test, Cramer's V correlation coefficient was calculated. Receiver operating characteristic (ROC) curves were used to calculate the Youden index to define the optimum cut-off values for Ki-67 for the binary classification of patients. The results were considered to be statistically significant with $p < 0.05$.

Ethics statement

The study protocol was approved by the Local Ethics Committee of the Jagiellonian University in Krakow, decision number KB 1072.6120.106.2022 (25.05.2022). Written informed consent for participation was not required for this study, in accordance with the national legislation and the institutional requirements.

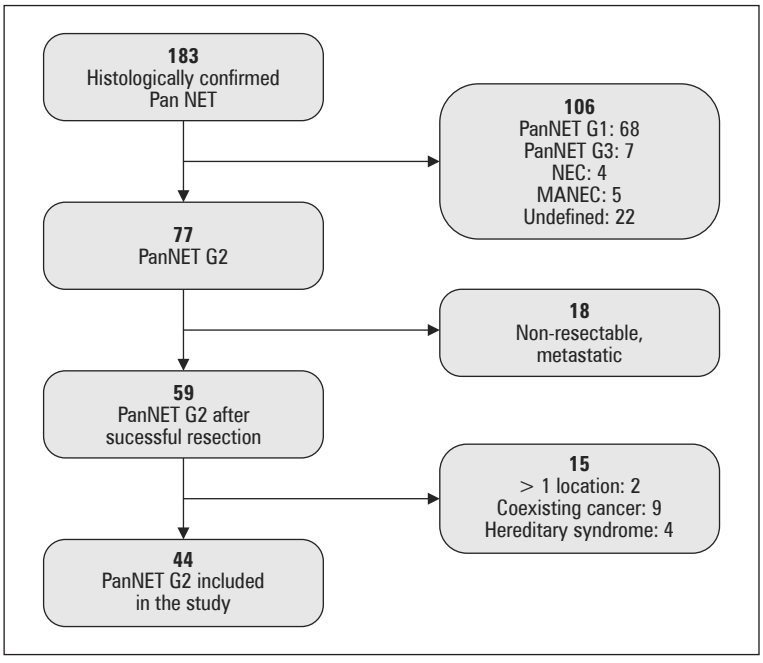

Figure 1. *Patient inclusion and exclusion algorithm. PanNET — pancreatic neuroendocrine tumour; NEC — neuroendocrine carcinoma; MANEC — mixed adenoneuroendocrine carcinoma*

Table 1. *Patients' complaints leading to diagnosis*

Symptom	Number of patients
Symptomatic patients	15 (34.09%)
Abdominal pain and weight loss	8
Hypoglycaemia	4
Ankle swelling	1
Erythematous changes	2
Asymptomatic patients	29 (65.91%)

Results

We identified 183 patients diagnosed with confirmed PanNETs, who were treated and followed up in our centre from January 2006 to February 2020 (Fig. 1). The mean age of the patients was 58.4 ± 11.8 years (range 26–91), and 32% (n = 14) of patients were male. The dominant location of PanNETs was the tail of the pancreas (43.2%, n = 19). The average follow-up was 8.39± 4.5 years. Disease relapse was observed in 16 (36.36%) patients, and the mean time to recurrence was 3 years and 5 months (range: 3–132 months, median 26 months). The localization of metastatic lesions at recurrence is shown in Table 2. In 4 patients (4/42; 9.52%) relapse occurred within one year of follow-up. In 5-year follow up, 3 patients were lost and a further 7 experienced disease recurrence (7/39; 17.94%). Within 10 years, 2 more patients with progression were lost to follow-up, and the next 4 patients experienced relapse (4/37; 10.81%). On further observation, 2 patients with progression failed to follow-up, and one patient experienced relapse (1/35; 2.86%). Two others dropped out of the follow-up group. During the entire follow-up period, 4 patients died, 2 from NET progression (10 and 11 years after surgery, respectively) and 2 from causes other than NET.

At 5-year and 10-year follow-up, the OS (overall survival) was 100% and 88.57%, respectively, and recurrence-free survival (RFS) was 71.79% and 48.57%, respectively. Time to recurrence, OS, and RFS for the whole cohort are presented in Table 3.

Table 2. *Localization of metastatic lesions at recurrence*

Recurrence localization	Number of patients
Distant metastases	9 (56.25%)
Liver	5
Abdominal lymph nodes	2
Liver + abdominal lymph nodes	1
Bones	1
Local recurrence	5 (31.35%)
Local recurrence + liver metastases	2 (12.5%)
TOTAL	16 (100%)

Clinical features influencing the risk of recurrence

All patients included in the study underwent surgery with the intention of radical treatment. The average time from diagnosis to surgical treatment was 3–5 months, and 2 patients who initially refused surgery were operated on 4 and 7 years after diagnosis, respectively. Distal pancreatectomy with splenectomy (n = 17, 38.6%) was the most common surgical procedure performed. The most frequent postoperative complication was the formation of an abscess in the surgical bed found in 15 (34.09%) patients. The Ki-67 ranged from 2.5% to 15% (median of 5%). The radical nature of surgery was confirmed by follow-up imaging studies, including computed tomography, and somatostatin receptor imaging (SRI). At the time of the first follow-up visit after the surgery, chromogranin A (CgA) was elevated in 50% of obtained samples, with the average level being 6.74 ± 5.05 nmol/L (ref. range 0–6 nmol/L). The patients' and lesions' characteristics are presented in Table 4.

No significant relationship was found between symptomatic presentation and the disease recurrence; however, the percentage of patients with relapse was higher for asymptomatic patients (42.9% *vs.* 25%). There was no significant relationship between location of the tumour and recurrence (p = 0.298); however, tumours in the pancreatic tail relapsed more frequently than in the body or head (47.4% *vs.* 42.9%

Table 3. *Frequency of relapse, overall survival (OS), and recurrence-free survival (RFS) for < 1 year, 1-5 years, 5-10 years, > 10 years follow-up*

Time range	Relapse (%, mean age at relapse)	OS	RFS
< 1 year	4/42 (9.52%, 59.75 ± 5.74)	42/42 (100%)	38/42 (79.17%)
1–5 years	7/39 (17.94%, 58.28 ± 14.24)	39/39 (100%)	28/39 (71.79%)
5–10 years	4/37 (10.81%, 68.75 ± 7.14)	37/37 (100%)	22/37 (59.46%)
> 10 years	1/35 (2.86%, 78)	31/35 (88.57%)	17/35 (48.57%)

Table 4. *Characteristics of patients and pancreatic neuroendocrine tumours (PanNET) G2 lesions. For variables with a distribution other than normal, the range is given in parentheses*

Variable	All patients (n = 44)	Recurrence (n = 16)	No recurrence (n = 28)	Hormonally active (n = 15)	Hormonally inactive (n = 29)
Sex (female)	65.9%	31%	69%	75%	25%
		p = 0.307		p = 0.336	
Age at diagnosis	58.36 ± 11.84	59.31 ± 10.41	57.46 ± 12.58	57.07 ± 13.91	59.03 ± 10.82
		p = 0.855		p = 0.508	
Location: tail of pancreas (%)	43.18	56.25	35.71	40	48.27
		p = 0.186		p = 0.954	
Ki-67 (%) Median (range)	Me = 5 (3–15)	Me = 5.5 (3–15)	Me = 4.0 (3–12)	Me = 5 (3–6)	Me = 5 (3–15)
		Z = –1.640; p = 0.101		Z = –0.195, p = 0.846	
Lesion (largest dimension) [mm] Median (range)	Me = 26 (9-122)	Me = 25.0 (22–79)	Me = 25.0 (9–122)	Me = 25 (16–65)	Me = 27.17 (9–122)
		Z = –2.372; **p = 0.018**		Z = –0.063, p = 0.949	
CgA after surgery [nmol/L] Mean ± SD	6.74 ± 5.25	6.87 ± 6.98	6.67 ± 4.02	7.49 ± 6.54	6.56 ± 5.12
		p = 0.306		0.723	
Relapse (%)	36.36	–	–	31.25	37.93
		–		p = 0.906	
Hormonal activity of lesion (%)	34.09	31.25	35.71	–	–
		p = 0.906		–	

Me — median value; CgA — chromogranin A; SD — standard deviation

vs. 21.4%, respectively). There was a trend showing a difference between the ages of symptomatic and asymptomatic patients at diagnosis (53.31 ± 13.12 years *vs*. 60.89 ± 10.12 years, respectively, p = 0.057), i.e. asymptomatic patients were older. Spearman's rho correlation coefficient showed that higher age was negatively correlated with lower Ki-67 (p = 0.043) and postsurgical CgA (p = 0.002). No relationship was found between the relapse and the time to surgery or longer duration of symptoms.

Larger tumour size significantly increased the risk of recurrence; the mean diameter of tumours with recurrence was 46.3 mm *vs*. 28.9 mm in tumours that did not recur (p = 0.018). The smallest tumour that recurred had a diameter of 22 mm. Overall, there was a trend indicating that recurrences were more common in patients with tumours > 4 cm (62.5%) than in patients with tumours up to 4 cm (28.0%), p = 0.077.

In the histological examination, CgA and synaptophysin were positive in all patients. The other markers cannot be reliably compared due to the discrepancy of the tests performed by different laboratories and at different times. As PanNET G2 tumours are extremely rarely encapsulated, the lesion invades the pancreatic parenchyma in each case. Vascular infiltration (n = 5), adipose tissue infiltration (n = 2), or nerve infiltration (n = 1) were described as histopathological findings in 20% of patients.

According to our study, the cut-off point based on the Youden index in the ROC analysis for Ki-67 in relation to the recurrence was 5.75% (recurrence risk 55.6% *vs*. 21.7%, p = 0.064). There was a statistically significant relationship and weak correlation between sex and Ki-67 value; Ki-67 > 5.75% was more frequent in women (42.1% *vs*. 7.7%, p = 0.033, V Cramer = 0.376). There was no difference between the risk of relapse in men and in women (46.7% *vs*. 31%; p = 0.307). No relationship was found between values of Ki-67 (over *vs*. under 5.75%) and the hormonal activity of the tumour, the occurrence of symptoms before diagnosis, the presence of postoperative complications, or the location of the tumour within the pancreas. Patients with Ki-67 > 5.75% had larger tumours on histopathological examination (45.0 *vs* 25.0 mm, p = 0.028). Tumours > 4 cm were more frequently connected with Ki-67 > 5.75% (p = 0.053). Patients with tumours of Ki-67 > 5.75% showed a trend toward shorter time to recurrence (p = 0.076). The comparison of patients with Ki-67 < 5.75% and > 5.75% in terms of quantitative variables is shown in Table 5.

Table 5. *Comparison of patients with proliferation index Ki-67 < 5.75% and > 5.75% in terms of quantitative variables*

Variables	Ki-67 (%)		Mann-Whitney U Test	
	< 5.75	> 5.75		
	M ± SD/Me	M ± SD/Me	Z	p
Age at diagnosis [years]	58.65 ± 12.63	51.00 ± 10.86	–1.637	0.102
Time to surgery [months]	4.0	3.0	–0.696	0.486
Lesion (largest dimension) [mm]	25.00	45.00	–2.202	0.028
CgA after surgery [nmol/l]	5.55	4.32	–0.435	0.664
Recurrence-free survival [months]	29.40	16.10	–1.776	0.076

M — mean value; Me — median; SD — standard deviation; CgA — chromogranin A; for ages with normal distribution, mean value ± SD are given

Discussion

The grading and staging of PanNETs are prognostically useful in the assessment of the course of the disease [9–12]. To date, several attempts have been made to identify prognostic factors affecting the risk of PanNET recurrence. Ausania et al. indicated that tumour size > 2 cm, Ki-67 > 5%, or MC > 2 HPF, as well as lymph node metastases, allow the identification of patients with G1–G2 PanNENs with a high risk of recurrence after tumour resection and therefore a much shorter survival [13]. Takikawa et al. developed a new preoperative scoring system for predicting the aggressiveness of non-functioning PanNETs (NF-PanNETs). They identified tumour size > 2 cm on contrast-enhanced computed tomography (CT), tumour non-vascularity, and Ki-67 ≥ 5% on endoscopic ultrasound-guided fine-needle aspiration specimens as independent factors associated with relapse [4]. Genç et al. proposed a new categorization G1/G2 PanNET to predict recurrence after curative resection based on the Ki-67 index. Lesions with Ki-67 6–20% were more likely to relapse within 5 years and cause significantly shorter survival, thereby Genç et al. stratified patients with such lesions into a high-risk group [6].

Literature reports about PanNET size determining unfavourable prognosis are inconsistent [14]. In the current study, tumour size > 4 cm seems a reasonable cut-off point because it was close to statistical significance. Genç et al. reached similar conclusions in 2018, stating that size > 4 cm is independently associated with recurrence [6].

Also, the value of Ki-67 being a cut-off point is under debate. A Dutch study involving 280 patients confirmed that shifting the cut-off point for PanNET G2 tumours to Ki-67 > 5% will allow for better identification of tumours at high risk of disease recurrence [2]. In this way, patients with Ki-67 in the 3–5% range will avoid unnecessary tests that burden both them and the health care system. In our study 80% of patients with disease recurrence had Ki-67 > 5%, and the cut-off point based on the Youden index in the ROC analysis for Ki-67 in relation to the recurrence was 5.75%, i.e. even higher. Genç et al. indicated that tumour size greater than 4 cm, tumour grade according to WHO, Ki-67 > 5%, lymph node metastases, perineural invasion, and vascular infiltration were unfavourable prognostic factors for recurrence within 5 years of surgery. It is worth noting that cases of late relapse even 10 years after curative surgery have been described in the literature [4], which was also seen in our observation.

Sixty to ninety per cent of PanNETs are hormonally inactive, and they used to be detected in advanced stages due to their asymptomatic course. This trend changed in recent years with improvements in diagnostic methods [6]. Partelli et al. found no correlation between age and NF-PanNET size or proliferative index in patients after curative resection; therefore, an a priori aggressive approach is not justified in young patients with small NF-PanNET, because the long-life expectancy probably does not increase the risk of malignant transformation [15]. Li et al. stated that asymptomatic course, primary location other than head of the pancreas, and being female and married were protective factors, especially in the elderly, among the whole population with PanNET [16].

Bettini et al. showed a close correlation between the tumour size and its malignancy in non-functioning PanNETs, and in randomly detected, asymptomatic PanNETs ≤ 2 cm in size a non-operative approach is recommended [17]. Other authors suggest preoperative biopsy and determination of Ki-67 in patients with tumours 1–2 cm in size to evaluate the indications for surgery [18]. Such a management appears rational; in our cohort the smallest lesion associated with recurrence was 22 mm in diameter. In the retrospective work of Primavesi et al., patient histories were analysed in terms of preoperative diagnosis, postoperative complications, and subsequent control, treatment, and the disease recurrence. Tumour size of 2 cm, 60 years of age, poor grading, and metastatic disease at the time of surgery

were independently associated with worse overall survival (OS) [19]. A comparison of Primavesi's results with the conclusions of this article is not possible due to the different groups of patients; in Primavesi, patients with G2 or G3 tumours were analysed as one group, and Ki-67 values for individual patients were not provided. Prospective studies such as ASPEN are necessary to determine the predictors with greater accuracy [20]. Lingaku Lee et al. found CgA and NETest to be most useful during the follow-up period in the diagnosis of residual disease, as well as in the early detection of relapse [21]. However, the determination of CgA concentration appears to be imperfect because it is influenced by factors not related to neuroendocrine tumours (in particular medications used and /or kidney insufficiency), and the NETest is not performed routinely.

PanNETs are rarely encapsulated, which makes tissue infiltration of the surrounding structures an important problem. According to the ENETS 2017 guidelines, a necessary element in the histopathological report is the evaluation of the surgical margins; however, long-term survival was confirmed also among patients with G2 PanNETs that infiltrates surgical margins [22]. Zhang et al. showed in a multivariate analysis that perivascular invasion, vascular invasion, and positive margins had no significant effect on postoperative PanNET recurrence [23]. Similarly, in our study, the tissue infiltration seems to have little to no impact on disease recurrence.

Ziogas et al. tried to analyse whether surgery for non-functional PanNETs of 1–2 cm would be beneficial or if surgery should be individualized [24]. At the same time, other authors stated that surgery is currently the only curative option [24, 25]; therefore, surgery should be offered to each patient with lesions > 2 cm and is absolutely necessary in those with lesions > 4 cm. However, some authors suggest that survival in patients with PanNET is driven mostly by tumour grade and not by other factors [26].

The main limitation of our study is the retrospective nature of collecting data from only one centre. This led to the analysis of a relatively small group of patients with different follow-up times. In addition, the patients were selected from the group who underwent surgery, so we did not compare them with patients selected for PanNET follow-up.

Conclusion

For the entire group of PanNET G2 patients after radical surgery, the overall risk of recurrence was 36.4%, with the highest rate in the first 5 years after surgery, but in individual cases it occurred significantly later, even 10 years after surgery. Due to the relevant heterogeneity of G2 tumours, it is advisable to individualize its management, taking into account the tumour parameters. The most important predictive factors of the PanNET G2 recurrence after radical surgery were Ki-67 > 5.75% and the largest dimension of the tumour > 4 cm. The smallest tumour diameter associated with PanNET G2 recurrence was 22 mm. Age at diagnosis was negatively correlated with Ki-67. To determine the significance of these parameters, it is necessary to analyse a larger number of patients with disease relapse combined with a longer follow-up.

Acknowledgments
None declared.

Data availability statement
The data presented in this study are available on request from the corresponding author.

Author contributions
H.O., M.O., and A.S.S. contributed to the conception of the work; H.O., K.M.S., A.K., M.K., and E.T. extracted data; M.O., H.O., and M.S. drafted the manuscript and contributed to the acquisition, analyses, and interpretation; M.O., A.S.S., and A.H.D. critically revised the manuscript and contributed to interpretation. All authors gave final approval and agreed to be accountable for all aspects of the work, ensuring integrity and accuracy. All authors have read and agreed to the published version of the manuscript.

Conflict of interest
None declared.

Funding
None declared.

Acknowledgements
None declared.

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