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ORIGINAL RESEARCH

Evaluation of Risk Factors for Distant and Lymph Node Metastasis of Pancreatic Neuroendocrine Tumors

Bartosz Molasy[1,2], Patryk Zemła[1], Sławomir Mrowiec[3], Ewa Grudzińska[3], Katarzyna Kuśnierz[3]

[1]Students' Scientific Society of the Department of Gastrointestinal Surgery, Medical University of Silesia, Katowice, Poland; [2]Department of General Surgery, St Alexander Hospital, Kielce, Poland; [3]Department of Gastrointestinal Surgery, Medical University of Silesia, Katowice, Poland

Correspondence: Ewa Grudzińska, Department of Gastrointestinal Surgery, Medical University of Silesia, Medyków 14, Katowice, 40-752, Poland, Tel +48 32 7894252, Email ewa.grudzinska@sum.edu.pl

Purpose: Metastases of pancreatic neuroendocrine tumors (pNETs) can be found at the time of diagnosis in 20–50% of cases. Small asymptomatic tumors may be left for observation; however, they can metastasize. The aim of the study was to evaluate risk factors for distant and lymph node metastases of pNETs.

Patients and methods: One hundred and fourteen patients with postoperatively confirmed pNET were analyzed retrospectively in a single ENETS Center of Excellence. The relationship between location, size, differentiation of the tumor, and occurrence of lymph node and distant metastases was analyzed.

Results: pNETs' location was pancreatic head – 38 (33.3%), body or tail – 68 (59.7%), and 8 (7.0%) involved the entire organ. Fifty-six (49.1%) tumors were graded G1, 50 (43.9%) G2, and 8 (7.0%) G3. Seventy-two (63.2%) tumors were ≥2 cm in diameter, and 42 (36.8%) <2 cm. Twenty-two (19.3%) patients had distant metastases and 47 (41.2%) had lymph node metastases. In ≥2 cm tumors distant and lymph node metastases were more frequent ($p < 0.05$). Distant metastases incidence was significantly higher in distally located tumors ($p = 0.01$) and in G2 and G3 tumors ($p < 0.01$). In 9.5% of <2cm tumors, distant metastases were present at diagnosis.

Conclusion: Distant metastases are more often found in larger, distally located pNETs grade G2 and G3, while a higher occurrence of lymph node metastases seems to be associated only with larger tumor size. A considerable number of tumors <2 cm in size have distant metastases already at the diagnosis, which might indicate the need for careful qualification of smaller lesions for observation.

Keywords: pancreas, neuroendocrine tumor, lymphatic metastasis, lymph nodes, pancreatic surgery

Introduction

Pancreatic neuroendocrine tumors (pNETs) account for approximately 30% of gastrointestinal neuroendocrine tumors.[1] Most of them are non-functional, while some (mostly insulinomas and gastrinomas) are hormonally active.[2] They are slow-growing tumors with a poor prognosis, worse in the presence of distant metastases[3,4] and in tumor size >2 cm.[5,6] Also, nodal metastasis, poorly differentiated cells, and vascular invasion worsen the prognosis.[7] According to the literature, distant metastases are found at the time of tumor diagnosis in 20–50% of cases depending on the degree of tumor differentiation.[8,9] Lymph node metastases are observed in approximately 35% of resected pNETs.[5] The mean survival time for patients with pancreatic NET is approximately 3.5 years from diagnosis.[8]

Usually, surgery is the first line of treatment. Depending on the location of the tumor, a pancreatoduodenectomy (for pancreatic head location) or a distal pancreatectomy with or without splenectomy (for pancreatic body and tail location) is performed.[2,10] These procedures are extremely challenging and have high morbidity and mortality rates, reaching 2.7% and over 30%, respectively, for pancreatoduodenectomy.[11]

In recent years, a 7-fold increase in diagnosing of small (<2 cm) hormonally inactive tumors has been observed, and they account for 60–90% of pNETs.[1,12] These tumors can be asymptomatic for a long time, and prompt surgery is often not recommended.[13] Instead, enucleation or even observation may be applied.[2] If enucleation is performed, it is

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recommended since 2016 to obtain a lymph node for pathology exam, but full lymphadenectomy is not required.[13] Avoidance of risky surgery in is tempting, especially in small tumors located in the pancreatic head. However, the presence of lymph nodes or distal metastases also in tumors <2 cm in size can worsen the treatment results. Knowledge of features that elevate the risk of distant or nodal metastases is essential for deciding on patient observation or surgery. The aim of this study was to evaluate the risk factors for distant and lymph node metastasis of pNETs.

Materials and Methods

Material

A retrospective analysis of 114 patients operated on between 2015 and 2020 with a postoperative histopathological diagnosis of pNET was performed. This was a retrospective study of medical records, and all data were fully anonymized before our access. All procedures performed were in accordance with the 1964 Helsinki Declaration and its later amendments. Our study is exempted from institutional review board approval, according to national legislation.

The patients were individually qualified for surgery by the multidisciplinary Neuroendocrine Tumor Board of the European Neuroendocrine Tumor Society (ENETS) Center of Excellence, the Department of Endocrinology and Neuroendocrine Tumors. All surgeries were performed at the Department of Gastrointestinal Surgery, also part of the ENETS Center of Excellence. The diagnosis and surgery were executed according to the ENETS Consensus Guidelines on the treatment of pancreatic neuroendocrine tumors.[13,14] The main indications for surgical treatment in tumors <2 cm in size were as follows: symptomatic, hormonally active tumors, tumors with malignant features, eg enlarged lymph nodes in CT. For tumors 1–2 cm in size, the patient's age and preference were also considered.

Methods

Clinical data of patients (gender, age), type of surgery, size (<2 cm or ≥2 cm), location, histological differentiation of tumors, and occurrence of distant and nodal metastases were analyzed. The association of the analyzed parameters with the occurrence of distant metastases and lymph node metastases was investigated. Tumors were classified according to the 2019 WHO classification[15] (Table 1).

Statistical Analysis

Descriptive analysis was performed. A confidence interval of 95% was used. The distribution of quantitative variables was analyzed. In the case of variables with distribution close to normal, their mean was given; in the case of distribution different from normal, their median was given. Correlation analysis was performed between clinical as well as histopathological parameters and the presence of distant and nodal metastases, where $p < 0.05$ was considered statistically significant. The chi-square test or Fisher's exact test when needed were used during the analysis of nominal variables. Stratification analysis as well as multivariate and binary regression analysis for nodal and distant metastases were made. All calculations, as well as statistical analysis, were performed in IBM SPSS Statistics 26.

Table 1 2019 WHO Classification of Digestive System Neuroendocrine Tumors[15]

	Differentiation	Grade	Mitotic Index (Number of Mitoses/2 mm^2)	Ki-67 Index
NET, G1	Well differentiated	Low	<2	<3%
NET, G2	Well differentiated	Intermediate	2–20	3–20%
NET, G3	Well differentiated	High	>20	>20%
NEC	Poorly differentiated	High	>20	>20%

Abbreviations: NET, neuroendocrine tumor; NEC, neuroendocrine cancer; Ki-67, cell proliferation index.

Results

Demographic and Clinical Data

There were more females (55.3%) than males (44.7%) in the study group. The median age was 54.9 years (range 23–80).

In 68 (59.7%) cases, tumors were located in the distal part of the pancreas (body and tail) and 38 (33.3%) in the head. Eight (7.0%) patients had multifocal lesions, out of which 2 had MEN1 syndrome diagnosed preoperatively.

Thirty-two (28.1%) pancreatoduodenectomies were performed, 63 (55.3%) distal pancreatectomies, and 8 (7.0%) total pancreatectomies. Eleven (9.6%) enucleations were also performed, of which 5 (4.4%) with staging lymphadenectomy and 6 (5.3%) without lymphadenectomy (according to the ENETS guidelines present at the time of the surgery). In all enucleated tumors, an intraoperative pathology examination confirmed the removal of the whole tumor. Four enucleated tumors were insulinomas, all were G1. There were 42 (36.8%) tumors <2 cm in diameter and 72 (63.2%) ≥2 cm. Lymph node metastases were found in 47 (41.2%) of patients (N1) and distant metastases were in 22 (19.3%) of patients (M1) (Table 2). 63.2% of tumors of the head of the pancreas had G1 grade. In the peripheral part of the pancreas, 51.5% of the tumors were G2; when the entire pancreas was removed, 62.5% were G1 tumors. The full grading of the tumors is presented in Table 3. The distant metastases were located in the liver in 20 cases (91.0%) and in both liver and bones in 2 patients (9.0%).

Table 2 Occurrence of Lymph Node and Distant Metastases

Sex	
Male	51 (44.7%)
Female	63 (55.3%)
Median age at diagnosis	54.9 years (range 23–80)
Tumor size	
<2 cm	42 (36.8%)
≥2 cm	72 (63.2%)
Tumor location	
Pancreatic head	38 (33.3%)
Pancreatic body or tail	68 (59.7%)
Multifocal lesions in pancreas	8 (7.0%)
Type of surgery	
Panreatoduodenectomy	32 (28.1%)
Distal pancreatectomy	63 (55.3%)
Total pancreatectomy	8 (7.0%)
Enucleation	11 (9.6%)
With lymphadenectomy	5 (4.4%)
Without lymphadenectomy	6 (5.3%)
Grade	
G1	56 (49.1%)
G2	50 (43.9%)
G3	8 (7.0%)
Lymph nodes metastases	
Nx	8 (7.0%)
N0	59 (51.8%)
N1	47 (41.2%)
Distant metastases	
M0	92 (80.7%)
M1	22 (19.3%)

Notes: Nx- regional lymph node cannot be assessed, N0 – no regional lymph node metastases, N1- regional lymph node metastases.

Table 3 Tumor Grading in Different Locations

Grading	N (%)	Pancreatic Head (N=38)	Pancreatic Body and Tail (N=68)	Multifocal Lesions in Pancreas (N=8)
G1	56 (49.1%)	24 (63.2%)	27 (39.7%)	5 (62.5%)
G2	50 (43.9%)	12 (31.5%)	35 (51.5%)	3 (37.5%)
G3	8 (7.0%)	2 (5.3%)	6 (8.8%)	0

Distant Metastases

Among tumors ≥2 cm in diameter, significantly more had distant metastases compared to tumors <2 cm in diameter (18 (25.0%) vs 4 (9.5%); $p < 0.05$). Tumors located distally also had significantly more distant metastases compared to pancreatic head tumors and multifocal lesions (19 (27.9%) vs 3 (7.9%) and 0 (0%), respectively ($p = 0.01$)). G2 and G3 differentiation compared to G1 was associated with a higher rate of distant metastasis (13 (26.0%) and 5 (62.5%), respectively, vs 4 (7.1%); $p < 0.01$) (Table 4). Multivariate, binary regression analysis confirmed the relationship between grading, location of the tumors and distant metastases (G3 differentiation compared to G1, OR = 19.313, $p = 0.002$; pancreatic body and tail compared to pancreatic head tumors, OR = 4.747, $p = 0.036$). The multivariate analysis showed a non-significant difference in G2 vs G1 tumors concerning distal metastasis (Table 5, Figure 1).

Table 4 Relationship of Distant Metastasis to Tumor Size, Location, and Grading

		Distant Metastases	P value
Tumor size	<2 cm (n=42)	4 (9.5%)	p<0.05
	≥2 cm (n=72)	18 (25.0%)	
Tumor location	Pancreatic head (n=38)	3 (7.9%)	p=0.01
	Pancreatic body and tail (n=68)	19 (27.9%)	
	Multifocal lesions in pancreas (n=8)	0 (0.0%)	
Grading	G1 (n=56)	4 (7.1%)	p<0.01
	G2 (n=50)	13 (26.0%)	
	G3 (n=8)	5 (62.5%)	

Table 5 Multivariate, Binary Regression Analysis for Nodal and Distant Metastases

	Odds Ratio	95% CI for OR – Lower Bound	95% CI for OR – Upper Bound	Significance
Distant metastasis				
Tumor size	2.342	0.640	8.567	0.198
G2/G1	2.836	0.792	10.156	0.109
G3/G1	19.313	2.841	131.309	0.002
Pancreatic body and tail/pancreatic head	4.747	1.107	20.348	0.036
Nodal metastasis				
Tumor size	4.295	1.625	11.352	0.003

Abbreviations: OR, Odds Ratio, Exp(B); CI, Confidence Interval.

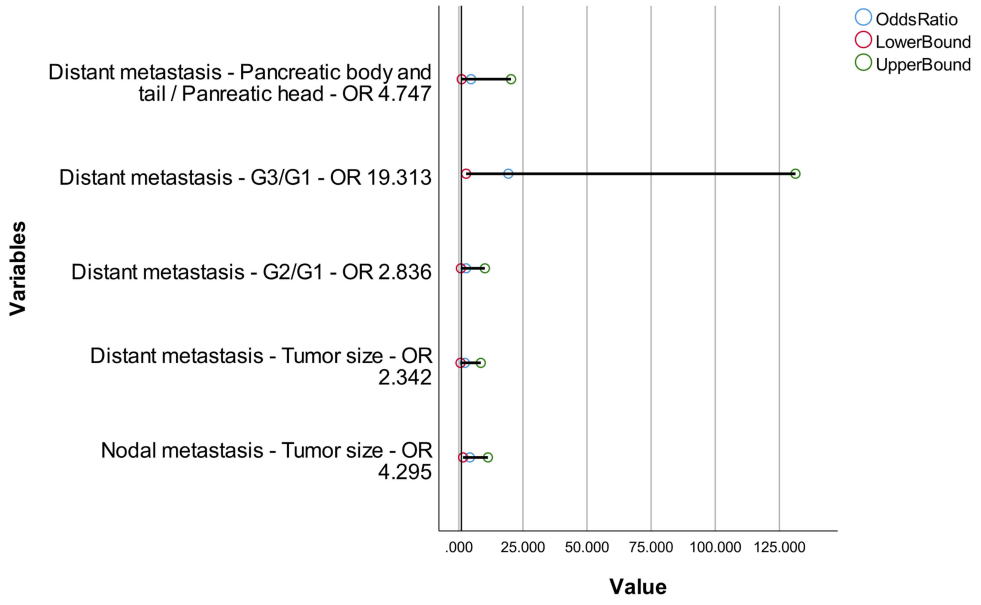

Figure 1 Forrest Plot with Odds Ratios and their Confidence Intervals for Multivariate, Regression Analysis

Lymph Node Metastases

Lymph node metastases were significantly more common in tumors ≥2 cm compared to smaller tumors (39 (54.2%) vs 8 (19.0%); p = 0.02). No relationship was found between tumor location or grading and lymph node metastasis (Table 6). These findings were confirmed in multivariate, binary regression analysis for nodal and distant metastases while controlling for the size of the tumors (Table 5, Figure 1).

Discussion

The size of asymptomatic pNETs, in which surgical treatment should be applied, remains controversial, especially for tumors 1–2 cm large.[6,16–18] It must be noted that even in tumors <2 cm, distant and nodal metastases are found in a considerable number of cases (0–27.3% and 0–9.1%, respectively)[11,19,20] and a high degree of histological malignancy can be encountered.[5,18] Some authors accept watchful waiting for lesions <1 cm in size and advise resection for larger tumors.[21] Observation is considered in small tumors in patients with comorbidities, elevating the surgical risk if no features of malignancy are found in the imaging results.[20,21] Also, the patient's age and preference are considered.[19,20,22] Even though routine preoperative biopsy is still under debate, it is recommended by some authors to grade the tumor to

Table 6 Relationship of Nodal Metastasis to Tumor Size, Location, and Grading

		Lymph Node Metastases (N1)	P value
Tumor size	<2 cm (n=42)	8 (19.0%)	p=0.02
	≥2 cm (n=72)	39 (54.2%)	
Tumor location	Pancreatic head (n=38)	17 (44.7%)	p>0.05
	Pancreatic body and tail (n=68)	27 (39.7%)	
	Multifocal lesions in pancreas (n=8)	3 (37.5%)	
Grading	G1 (n=56)	19 (33.9%)	p>0.05
	G2 (n=50)	23 (46.0%)	
	G3 (n=8)	5 (62.5%)	

avoid the risk of observing a malignant lesion.[19] In our study, 42 tumors <2 cm in diameter were removed and in 9.5% of them, distant metastases were present already at the diagnosis.

The required surgical procedures have a high incidence of complications: pancreatoduodenectomy for tumors of the pancreatic head and a slightly safer distal pancreatectomy for tumors in the pancreatic body and tail.[23] To lower the operative risk and the postoperative endocrine insufficiency, enucleation is accepted but remains controversial. It may be applied to symptomatic tumors <2 cm in size, preferably insulinomas[24,25] and/or with confirmed Ki67%<3%, located >-3 mm from the main pancreatic duct, and when no signs of malignancy are visible in the preoperative imaging results.[21,26,27] Recurrence rates are similar to the patients undergoing more extensive surgeries.[24,25,28,29] In our study, in only 11 cases of small tumors (all were G1, 4 insulinomas), enucleation was performed, in 5 cases with staging lymphadenectomy (as the ENETS guidelines changed in 2016[13]).

Hormonally active pancreatic NETs are usually eligible for surgical treatment. Also, NETs ≥2 cm in size, regardless of location in the pancreas and their hormonal function, are recommended to be removed[13,16] because the larger size of NETs is known to have a positive correlation with the clinical stage of the disease and the presence of distant and lymph node metastases.[12,17,30–32] Our results confirm these data in both univariate and multivariate analysis (19.0% of tumors <2 cm and 54.2% of tumors ≥2 cm with lymph node metastases). Nevertheless, Mintziras et al in a study of a large group of patients did not find any correlation between the tumor size and the occurrence of metastases in the lymph nodes.[33]

Distant metastases occur in about 20% of cases, most often in the liver and less often in the bones.[3,4] They are 4 times more frequent in tumors ≥2 cm in size.[3,5,34] Our study confirmed this data in univariate analysis, as distant metastases were found in 22 (19.3%) patients, in 9.5% of tumors <2 cm, and in 25.0% of tumors ≥2 cm. Twenty (91.0%) cases involved liver, and 2 (9.0%) both liver and bones. Usually, distant metastases are found during the diagnosis of the primary tumor lesion,[34,35] however, because our analysis had no follow-up data and only involved distant metastases found at the time of primary lesion diagnosis, the total number of distant metastases is possibly underestimated. This may have an impact on the lack of correlation between the presence of distant metastases and the tumor size in the multivariate analysis.

According to the available literature, as the histologic differentiation of the tumor cells decreases, the incidence of distant metastases increases.[4,33] In G3 tumors, this concerns more than 60% of cases.[9] These data were confirmed in our study, where for tumors with G1 grade only 7.9% had distant metastasis, and in G2 and G3 tumors, they were found in 26% and 62.5% of cases, respectively. The difference between G3 tumors versus G1 and G2 tumors was statistically significant in univariate and in multivariate analyses. Many studies have reported that poor histologic differentiation correlates with a higher incidence of lymph node metastases.[5,30,36] In our study, lymph node metastasis occurred in 33.9%, 46.0%, and 62.5% of G1, G2, and G3 tumors, respectively, with no statistically significant difference. This may be due to the different sizes of study groups in other publications.[5,30,36]

Pancreatic neuroendocrine tumors are more often found in the distal location (pancreatic body and tail).[5,37] According to most publications, the location of NETs in the pancreas has no influence on the presence of distant metastases.[38] However, there are recent reports by which distal location is a risk factor for distant metastases.[36] In our study, 19 (27.9%) tumors in the distal location compared to 3 (7.9%) tumors located in the pancreatic head had distant metastases and this was found to be a statistically significant difference in univariate and multivariate analyses. In our study group, G2 and G3 tumors were found more often in the distal region. This may be due to the fact that the distally located non-functional tumors longer remain asymptomatic.

Regarding the correlation of NET location in the pancreas with the presence of nodal metastases, the available data are conflicting. Some authors believe that tumor location in the body or tail of the pancreas is a risk factor for metastasis of local lymph nodes.[4,36] There are also studies showing a higher incidence of nodal metastasis among pancreatic head NETs.[30–32] In our study, we found no significant relationship between tumor location and the presence of lymph node metastases.

Undoubtedly, a limitation of our analysis is the retrospective nature of the study and the moderate size of the study group. The lack of follow-up makes it impossible to supplement the study with survival time and the occurrence of distant metastases is most probably underestimated. However, the collected data indicate important features of pancreatic NETs that should be considered in therapeutic decisions.

Conclusions

Larger tumor size of pNETs is associated with a higher incidence of lymph node metastasis and distant metastasis. G2 and G3 grading of the tumor, as well as its distal location, are also associated with the occurrence of distant metastases; however, these tumor features do not affect the occurrence of lymph node metastases. It is important to note that a considerable number of tumors <2 cm in diameter showed distant metastasis at the diagnosis, which might indicate the need for careful qualification of smaller lesions for observation. Decisions during the therapeutic process should be made on an individual basis, keeping in mind the aforementioned risk factors for distant and lymph node metastasis.

Disclosure

The authors report no conflicts of interest in this work.

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