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World J Gastroenterol. (2014.12) 20(47):17949-17954.

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World Journal of Gastroenterology

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DOI: 10.3748/wjg.v20.i47.17949

World J Gastroenterol 2014 December 21; 20(47): 17949-17954
ISSN 1007-9327 (print) ISSN 2219-2840 (online)
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RETROSPECTIVE STUDY

Clinicopathological features of small nonfunctioning pancreatic neuroendocrine tumors

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Received: January 25, 2014 Revised: May 9, 2014
Accepted: July 29, 2014
Published online: December 21, 2014

Abstract

AIM: To present our experiences in studying the clinicopathological features of small nonfunctioning pancreatic neuroendocrine tumors (NF-pNETs).

METHODS: The subjects included 9 patients with NF-pNETs who underwent pancreatectomy between April 1996 and September 2012. The surgical procedure, histopathological findings, and prognosis were assessed.

RESULTS: All tumors were incidentally detected by computed tomography. The median diameter was 10 mm (5-32 mm). One patient was diagnosed with von Hippel-Lindau disease, and the others were sporadic cases. For the histopathological findings, 7 patients were G1; 1 patient was G2; and 1 patient, whose tumor was 22 mm, had neuroendocrine carcinoma (NEC). One patient who had a tumor that was 32 mm had direct invasion to a regional lymph node and 1 patient with NEC, had regional lymph node metastases. Six of the 7 patients with sporadic NF-pNETs, excluding the patient with NEC, had tumors that were smaller than 10 mm. Tumors smaller than 10 mm showed no malignancy and lacked lymph node metastasis.

CONCLUSION: Sporadic NF-pNETs smaller than 10 mm tend to have less malignant potential. These findings suggest that lymphadenectomy may be omitted for small NF-pNETs after further investigation.

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Key words: Pancreatic neuroendocrine tumor; Pancreatic neuroendocrine carcinoma; Nonfunctioning; Lymphadenectomy; Treatment

Core tip: We present our experience in studying the clinicopathological features of small nonfunctioning pancreatic neuroendocrine tumors (NE-pNETs). In the present study, six of the 7 patients with sporadic NF-pNETs, excluding the patient with NEC, had small tumors that were less than 10 mm. These small tumors showed no sign of malignancy or lymph node metastasis. Additionally, these cases did not have recurrence, including lymph node and distant metastasis, for more than 10 years after surgery. These findings suggest that small NF-pNETs tend to have less malignant potential and no lymph nodes metastasis. Lymphadenectomy may be omitted in the future for small NF-pNETs after further investigation.

Furukori M, Imai K, Karasaki H, Watanabe K, Oikawa K, Miyokawa N, Taniguchi M, Furukawa H. Clinicopathological

features of small nonfunctioning pancreatic neuroendocrine tumors. *World J Gastroenterol* 2014; 20(47): 17949-17954 Available from: URL: http://www.wjgnet.com/1007-9327/full/v20/i47/17949.htm DOI: http://dx.doi.org/10.3748/wjg.v20.i47.17949

INTRODUCTION

Pancreatic neuroendocrine tumors (pNETs) are relatively rare, accounting for 1%-2% of all pancreatic neoplasms[1]. Although pNETs progress slowly and have better a prognosis than pancreatic cancer, pNETs have malignant potential, including features of local invasion, lymph node metastasis, and distant metastasis. The appropriate diagnosis and treatment of pNETs are crucial. These tumors are classified into functioning pNETs (F-pNETs), which present with specific symptoms due to excess hormones, and nonfunctioning pNETs (NF-pNETs), which do not present with these symptoms. Because NF-pNETs do not present with specific symptoms, they are often detected as large tumors in the advanced stage, with distant metastasis or invasion to adjacent organs. However, improvements in diagnostic imaging over the last few decades have led to the incidental detection of small NF-pNETs *via* diagnostic imaging for the work-up of other conditions. The incidence of malignancy reportedly increases with larger NF-pNETs[2,3]. However, even small NF-pNETs have malignant potential and may spread to lymph nodes or metastasize to distant sites. Therefore, once NF-pNETs are diagnosed, all cases are considered for surgical resection[4]. The significance of lymph node metastasis in the NF-pNETs has been reported[5-9]; the prognosis is poor with a 5-year survival of 49.4%, even after resection, in cases with lymph node metastasis[7]. Therefore, lymphadenectomy, in addition to tumor resection, is recommended when the tumor is malignant or when lymph node metastasis is suspected. However, there are no standard criteria for lymphadenectomy when small, asymptomatic, and incidentally detected NF-pNETs are identified. The inclusion of lymphadenectomy during surgery for NF-pNETs remains controversial.

In the present study, we report 9 cases of NE-pNETs treated at our hospital over the last 16 years.

MATERIALS AND METHODS

Between 1996 and 2012, 26 patients with pNETs underwent pancreatectomy at Asahikawa Medical University Hospital, of whom 9 patients were diagnosed with NF-pNETs and were further investigated. The diagnosis of pNET was established by histopathological examination and immunohistochemical staining of surgical specimens with chromogranin A, synaptophysin, and neuron-specific enolase stain. Tumors were classified as nonfunctioning regardless of the plasma hormone levels or immune activity of the tissue if the patient lacked the clinical symptoms that are typically caused by excess hormones. The patients' medical records were retrospectively reviewed. All patients were pathologically classified according to the criteria established by the WHO 2010 classification of endocrine tumors[4]. An immunohistochemical staining assay for Ki67 was performed for all patients. The Ki67 proliferative index is expressed as a percentage based on the count of Ki67-positive cells in a set of 2000 tumor cells in areas with the highest immunostaining, which was evaluated with the MIBI antibody, and the cases were classified into the following 3 categories: G1 (mitoses/10 HPFs < 2 and/or Ki67 index < 3), G2 ($2 \leqslant$ mitoses/10 HPFs $\leqslant 20$ and/or $3 \leqslant$ Ki67 index $\leqslant 20$), and neuroendocrine carcinoma (NEC) (mitoses/10 HPFs > 20 and/or Ki67 index > 20). The tumor size was defined by the largest diameter of the tumor. A TNM stage group was assigned to each case based on the European Neuroendocrine Tumor Society (ENETS) staging classification for pNETs[10]. The postoperative follow-up included clinical examination, the blood neuron specific γ-enolase (NSE) level, and contrast-enhanced computed tomography (CT) scanning. CT scans were performed every 6 to 12 mo in the first year, then annually thereafter.

RESULTS

In this study, the tumors identified as NF-pNETs accounted for 2.8% of all pancreatic neoplasms (9/220) and for 35% of pNETs (9/26). Table 1 summarizes the clinical features, surgical procedure, histopathological findings, prognosis, WHO classification, and ENETS TNM classification of the 9 patients diagnosed with NF-pNETs. These patients included 3 men and 6 women with a mean age of 67 years (range, 47-75 years) at the time of surgery. One patient with von Hippel-Lindau disease had previously undergone enucleation of the pNETs; the others were sporadic cases. All patients with NF-pNETs were asymptomatic, and none had evidence of distant metastasis. In all cases, the pancreatic tumors were incidentally detected by radiological investigation during evaluations for unrelated conditions. None of the patients had a preoperatively elevated blood level of NSE. Three patients underwent endoscopic ultrasonography-fine needle aspiration (EUS-FNA) and were preoperatively diagnosed with pNETs (No. 2, 6, and 8). All patients underwent surgical resection of the pancreas: 3 patients underwent distal pancreatectomy (DP), 2 patients underwent pylorus-preserving pancreatoduodenectomy (PPPD), 2 patients underwent subtotal stomach-preserving pancreatoduodenectomy (SSPPD), and 2 patients underwent partial resection of the pancreas. R0 resection was performed in all patients, except in 1 patient who underwent partial resection with positive surgical margins (No. 5). Regional lymphadenectomy was performed in 5 of the 9 patients (No. 2, 3, 6, 7, and 8). The median tumor diameter was 10 mm (range, 5-32 mm). All patients, except for the patient with von Hippel-Lindau disease (4 tumors), had a single tumor. Six patients had tumors located in the head

Table 1 Clinical and pathological status of 9 patients with nonfunctioning pancreatic neuroendcrine tumors

No	Age (yr)	Sex	Size (mm)	Location	Number of tumor	EUS-FNA	Preoperative diagnosis	Surgical procedure	Lymphadenectomy	Metastases		Motoses	Ki67/ MiB-1 (%)	WHO classification 2010	TNM classification (ENET)	Prognosis (mo)
										Lymph node	Distant					
1	58	F	32	Ph	1	No	Pancreatic tumor	DP	No	Direct Invasion	No	0	0.2	NET G1	T2N1M0	59 alive
2	73	M	22	Ph	1	No	NET	PPPD	Regional	No	No	1	5.8	NET G2	T2NOMO	39 alive
3	67	F	22	Pb	1	Done	NET G1	DP	Regional	Positive	No	20	20	NEC	T2N1M0	14 alive
4	74	F	10	Pb	1	No	Islet cell tumor	DP	No	No	No	0	1.6	NET G1	T1N0M0	196 alive
5	61	M	10	Pb	1	No	Islet cell tumor	Partial resection	No	No	No	0	0.1	NET G1	T1N0M0	135 alive
6	51	F	9	Ph	1	Done	NET G1	PPPD	Regional	No	No	0	1	NET G1	T1N0M0	64 alive
7	47	F	6 2.1 1.2 1.2	Ph	4	No	NET	SSPPD	Regional	No	No	0	0.9	NET G1	T1N0M0 Stage I	22 alive
8	75	M	6	Ph	1	Done	NET G1	SSPPD	Regional	No	No	0	< 1	NET G1	T1N0M0	20 alive
9	56	F	5	Ph	1	No	Cartinoid	Partial resection	No	No	No	0	0.4	NET G1	T1N0M0	34 alive

EUS-FNA: Endoscopic ultrasonography-fine needle aspiration; Ph: Head of pancreas; Pb: Body of pancreas; DP: Distal pancreatectomy; PPPD: Pylorus-preserving pancreatoduodenectomy; SSPPD: Subtotal stomach preserving pancreatoduodenectomy.

of the pancreas, while 3 patients had tumors located in the body of the pancreas. Seven patients were classified as G1, and 1 patient with a tumor that was 22 mm in diameter was classified as G2. Although 1 patient, with a tumor that was 22 mm in diameter, was diagnosed as G1 by preoperative EUS-FNA, the final diagnosis was neuroendocrine carcinoma (NEC). None of the patients, except two cases, had no lymph nodes metastasis; one with lymph node metastasis had a tumor that was 32 mm in diameter with direct invasion to the regional lymph nodes, and the other had NEC with regional lymph nodes metastasis. Six of the 7 patients with sporadic NF-pNETs had small tumors that were less than 10 mm in size; one patient with NEC had a larger tumor. Tumors that were less than 10 mm in size showed no malignancy, were well differentiated, and lacked lymph node metastasis. Six patients were classified as Stage Ⅰ, 1 patient was classified as Stage Ⅱa, and 2 patients were classified as Stage Ⅲb. With respect to the postoperative complications, three patients had a pancreatic fistula, one patient was classified as Grade B (No. 3), and 2 patients were classified as Grade A (No. 1 and 2) according to the ISGPS criteria. None of the patients in this study had exocrine or endocrine insufficiency. The mean follow-up period was 63 mo (range, 14-196 mo). All of the patients are currently alive without disease recurrence according to radiological imaging.

DISCUSSION

In the present study, we examined the NF-pNETs in 9 patients who underwent pancreatectomy at our institution over the last 16 years. For all of the patients, the tumors were incidentally detected by diagnostic imaging during a work-up for other conditions. Most tumors were small, with a diameter of 5-32 mm (median: 10 mm), and none of the tumors showed evidence of distant metastasis. While the larger tumors tended to be associated with direct invasion of the lymph nodes and lymph node metastases, a high Ki-67 index, and an advanced TNM stage, tumors that were smaller than 10 mm in diameter lacked malignancy and lymph node metastasis.

NF-pNETs are relatively rare, and only 9 patients presented with NF-pNETs at our institution over the last 16 years. In Western nations, pNETs occur at an incidence of 1 per 100000 individuals and represent 1%-2% of all pancreatic neoplasms[1]. Over the last few years, however, this incidence has increased[11,12]. An epidemiological study by NETWork Japan in 2005 estimated that the incidence of pNETs per 100000 individuals is 2.23 patients in Japan. Compared with Western nations, Japan has a 2- to 3-fold higher incidence of pNETs[3]. In total, 30%-50% of all pNETs are nonfunctioning[3,13]; however, because NF-pNETs do not present with characteristic clinical symptoms due

to excess hormones, they often go unnoticed until they are in the advanced stages. Previously, NF-pNETs were often detected as larger tumors that were accompanied by nonspecific pressure symptoms, such as abdominal pain or discomfort; abdominal distension; or a palpable mass in advanced stages with distant metastasis or local invasion. The number of NF-pNETs that have been incidentally detected has increased due to the advances in diagnostic imaging over the last few decades. Compared with other pancreatic tumors, pNETs progress slowly and are associated with a better prognosis. However, they have malignant potential, including local invasion, lymph node metastasis, or distant metastasis. More than half of NF-pNETs are malignant[3,13]. Therefore, most recommendations favor surgical resection for all patients, even for small NF-pNETs[4].

Numerous retrospective studies have previously examined the poor prognosis for NF-pNETs[6,7,14-21]. According to these studies, the predictors of the prognosis for NF-pNETs include the presence of liver metastases and incomplete resection of the tumor.

Several studies have indicated that lymph node metastasis is a poor prognostic factor[5-9]. In addition, Boninsegna *et al*[8] reported that lymph node metastasis is a prognostic factor for the recurrence of malignant pNETs after curative surgery. If malignancy of the tumor or lymph node metastasis is suspected, pancreatic resection with the addition of lymphadenectomy is recommended. It is often difficult to judge preoperatively whether a tumor is benign or malignant, except in patients with distant metastases or local invasion.

The tumor size appears to correlate with the malignant potential of NF-pNETs. Bettini *et al*[2] reported that the chance of malignancy significantly increases when the size of NF-pNETs exceeds 20 mm. A Japanese epidemiological study also found a significant correlation between NF-pNETs that exceed 20 mm in diameter and the presence of distant metastases[3]. Pancreatic resection and prophylactic regional lymphadenectomy are recommended for treating possible malignancy when the tumors exceed 20 mm in diameter[4]. However, several studies have failed to identify a correlation between the tumor size and prognosis[5,13,22,23], and other studies have demonstrated that even tumors smaller than 10 mm can be malignant[24,25]. Therefore, surgical resection is recommended even in small tumors.

Currently, the association between the tumor size and the incidence of lymph node metastasis is controversial. Hashim *et al*[9] reported that there is an increased probability of nodal metastasis when the tumor size is larger than 15 mm. Tsutsumi *et al*[26] reported an increased prevalence of lymph node metastasis in patients with gastrinomas and non-gastrinoma who have tumor sizes of 15 mm or larger. In contrast, Parekh *et al*[27] reported that the tumor size is not associated with lymph node metastasis. A number of studies have reported that the incidences of lymph node metastases for patients with NF-pNETs smaller than 20 mm and 15 mm are 14.4% and 8%, respectively[2,9,26-29]. Over the last few decades, the number of NF-pNETs that are incidentally detected with diagnostic imaging has increased, and compared with symptomatic NF-pNETs, tumors that are incidentally detected have a good prognosis and low risk of malignancy[2,21].

In the present study, one of the 9 patients was diagnosed with von Hippel-Lindau disease, and this patient should be considered separately because the biological properties of sporadic pNETs and hereditary pNETs, such as MEN-1 and von Hippel-Lindau disease, are different with respect to the incidence, number of tumors, and prognosis. One of the 8 patients with sporadic NF-pNETs had NEC with a tumor size of 22 mm. Except for the case with NEC, the direct invasion and metastasis to the lymph nodes was only observed in a relatively large tumor with a diameter size of 32 mm. Tumors smaller than 10 mm in diameter showed no signs of malignancy, were well differentiated, and lacked lymph node metastasis. Additionally, none of the cases had recurrence, including in the lymph nodes or direct metastasis, for more than 10 years after surgery. Lymphadenectomy may be omitted in the future after further investigation of a large number of small NF-pNETs. However, Hashim *et al*[9] reported that even tumors smaller than 10 mm metastasize at a rate of 12%. Additionally, lymphadenectomy is often omitted for small pNETs that are larger than 10 mm in size; the possibility of lymph node metastasis may be underestimated in those cases. Omission of lymphadenectomy needs to be carefully considered with further study. Even when lymphadenectomy is omitted, long-term follow-up is essential because there is a risk of late recurrence. If malignancy is confirmed postoperatively, oncologically appropriate lymphadenectomy must be considered based on the factors that determine the malignant potential, such as the Ki67 index, tumor differentiation status, surgical margin, and vascular invasion such as lymphoductal, neural, and venous[19,20].

In the present study, CgA, PP, and other hormones were not measured; it is important to measure these hormones to identify recurrences during follow-up.

The present study is limited by its small sample size, single institution bias, and retrospective nature. In the future, a larger number of patients at multiple centers should be studied.

In summary, we found that small NF-pNETs tend to have less malignant potential. In the present study, six of 7 cases of sporadic NF-pNETs, except for a case with NEC, were small tumors (smaller than 10 mm diameter). These small tumors showed no evidence of malignancy, were well differentiated, and lacked lymph node metastasis. This finding indicates that lymphadenectomy may be omitted in the future for small NF-pNETs, particularly for those tumors that are incidentally detected after further investigation. When lymphadenectomy is omitted, long-term follow-up is essential, and additional resection should be considered if malignancy is confirmed postoperatively. The tumor size can easily be measured pre-

operatively, and further study is expected to find other factors for predicting the malignant potential of small NF-pNETs.

COMMENTS

Background

Even small NF-Pancreatic neuroendocrine tumors (pNETs) have malignant potential and may spread to lymph nodes or metastasize to distant sites. Therefore, oncologic resection with regional lymphadenectomy is currently recommended. Increasingly smaller NF-pNETs are being identified with improved and more frequent radiological imaging. However, because the clinicopathological features of extremely small NF-pNETs are not yet known, there are no standard criteria for performing a lymphadenectomy when small, asymptomatic NF-pNETs are identified.

Research frontiers

NF-pNETs have malignant potential and may spread to lymph nodes or metastasize to distant sites. However, the clinicopathological features of extremely small NF-pNETs are not yet known. In this study, the authors present their experience with the clinicopathological features of small NF-pNETs (diameters less than 10 mm).

Innovation and breakthroughs

Small NF-pNETs are being identified with improved and more frequent radiological imaging. However, few studies have examined small NF-pNETs with diameters less than 10 mm. In this study, tumors with diameters less than 10 mm showed no evidence of malignancy, were well differentiated, and lacked lymph node metastasis. Additionally, there were no recurrences after the operations, including in the lymph nodes or direct metastasis, for more than 10 years after surgery.

Applications

A previous study reported that the incidence of lymph metastasis is higher for larger tumors. Our findings indicate that lymphadenectomy of small NF-pNETs may be omitted in the future after further investigation of a large number of patients with small NF-pNETs.

Terminology

pNETs are relatively rare disease and progress slowly and are associated with a better prognosis. However, they have malignant potential, including local invasion, lymph node metastasis, or distant metastasis. pNETs are classified into functioning pNETs, which present with specific symptoms due to excess hormones, and nonfunctioning pNETs (NF-pNETs), which do not present with these symptoms.

Peer review

The present manuscript by Furukori *et al* focuses on the need of lymphadenectomy in NF-pNETs < 10 mm and suggests that in these tumors the lymphadenectomy can be omitted. The concept is very challenging.

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P- Reviewer: Kleeff J, Tsolakis AV
S- Editor: Qi Y **L- Editor**: A **E- Editor**: Liu XM

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ISSN 1007-9327

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