Management of Small Nonfunctioning Pancreatic Neuroendocrine Tumors: An analysis of the US SEER Database and a Chinese Single-center Cohort

Shunrong Ji
Fudan University Shanghai Cancer Center
Mengqi Liu
Fudan University Shanghai Cancer Center
Zeng Ye
Fudan University Shanghai Cancer Center
Xiaowu Xu
Fudan University Shanghai Cancer Center
Xianjun Yu
Fudan University Shanghai Cancer Center
Qifeng Zhuo (zhuoqifeng@fudanpci.org)
Fudan University Shanghai Cancer Center

Research

Keywords:

Posted Date: March 19th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-17909/v1

Abstract

Background. Nonfunctional pancreatic neuroendocrine tumors (NF-pNETs) are often small, slow growing, clinically silent neoplasms. Currently, 'wait-and-see' policy is recommended by the European Neuroendocrine Tumor Society (ENETS) for NF-pNETs (<2 cm). But the scientific basis for such recommendation is scarce.

Methods. Data of NF-pNETs cases were reviewed retrospectively from the Surveillance, Epidemiology, and End Result (SEER) database during 2004-2015. Statistic description and survival analysis were done. Patients who underwent surgery for NF-pNET in our center during 2010-2018 were identified and analyzed retrospectively.

Results. 1828 NF-pNET with tumor size between 1-4cm were identified in SEER database. Observation was recommended for 172 patients (9.4%). 1656 patients received surgery. The observation group was significantly older and mainly with tumor located in pancreatic head. There was no survival difference between the two groups with NF-pNET ≤2 cm. Median survival time was significantly longer in surgery group with NF-pNET >2 cm. 143 NF-pNETs with tumor size between 1-4cm were identified in our center.

Conclusion. In selected older patients, nonoperative management of asymptomatic small NF-pNETs is safe. Preoperative grading with EUS-FNA may be a good option for making practice decision. Larger and prospective multicentric studies with long-term follow-up are now needed to validate this wait-and-see policy.

Introduction

Pancreatic cancer is one of the most lethal malignant neoplasms across the world. More than 85% of cases are adenocarcinoma[1]. The rest main solid tumor types of pancreas are pancreatic endocrine tumor (pNET) and solid pseudopapillary neoplasm (SPN), which accounts for 2% of all pancreatic neoplasms respectively[2]. Compare with pancreatic adenocarcinoma, pNETs are more indolent. pNETs differ from adenocarcinoma significantly in terms of biological features, treatment and prognosis. Based on characteristic clinical symptoms and measurable hormone level, pNETs are generally classified as functional or non-functional. Up to 90% of pancreatic neuroendocrine tumors are non-functional. Insulinomas have approximately a 10% malignancy rate whereas non-functional tumors have a 92% malignancy rate [1]. However, the overall prognosis is good. 5-year survival rate may achieve 73.4% [3].

Recently, incidental identification of non-functional pNETs at a small size is increasing with the widespread use of cross-sectional abdominal imaging. Although some studies have reported that small pNETs >0.5 cm have a malignant potential[4,5], small NF-pNETs are more commonly associated with lower tumor stages and better prognosis. Therefore, the indolent nature of pNETs makes therapeutic decisions difficult especially for these small tumors. Curative resection is always recommended whenever possible. However, pancreatic resections are associated with a risk of postoperative morbidity, mortality, and of long-term complications, such as diabetes and dyspepsia, even

in high-volume centers. Because of this, focal non-anatomic resections have been performed to preserve as much pancreas as possible and control damage, such as enucleation. Nevertheless, non-anatomic resections are associated with higher incidence of pancreatic fistula. In this regard, some authors recommend clinical observation rather than surgery for selected patients with small incidentally discovered NF-pNETs. Therefore, 'wait-and-see' policy is recommended by the European Neuroendocrine Tumor Society (ENETS) for NF-pNETs (<2 cm).

Despite many related studies, management of small NF-pNETs remains controversial. The aim of this study was to compare the results of observation patients and operative patients with sporadic NF-pNETs 1–4cm from the SEER database and analyze the possible postoperative clinicopathological features of NF-pNETs 1–4cm in our center.

Methods

Patients and Data Collection

pNET cases registered in the SEER database from 2004 to 2015 were retrieved. Patients were collected on the basis of International Classification of Diseases for Oncology, 2nd and 3rd editions (ICD-O–2/3) for pancreatic tumors: C25.0 to C25.9. The ICD–0–3 diagnosis codes used for retrieving are as follows: Pancreatic endocrine tumor (8150), Carcinoid tumor(8240), Enterochromaffin cell carcinoid(8241), Enterochromaffin-like cell tumor (8242), Goblet cell carcinoid(8243), Neuroendocrine carcinoma(8246), Atypical carcinoid tumor(8249). Functional tumors, such as Insulinoma (8151), Glucagonoma (8152), Gastrinoma (8153), Vipoma (8155), Somatostatinoma (8156), were excluded. We collected TNM data according to the following codes: derived the American Joint Committee on Cancer (AJCC) stage group 6th ed (2004+)，collaborative stage (cs) tumor size 2004, cs extension 2004, cs lymph nodes 2004, cs metastasis at dx 2004, Regional nodes positive (1988+), and Regional nodes examined (1988+). Baseline clinicopathological features were collected including age, gender, race, tumor size, tumor location and differentiation.

And then pathologically diagnosed NF-pNETS from Shanghai Pancreatic Cancer Institution (SHPCI) was analyzed. The data of demographics, including age, sex, grade, location of the primary site and pathological information were analyzed. TNM stage was classified on the basis of the AJCC staging system (8th). The follow-up data were acquired from medical records to confirm disease progression and vital status or date of death.

The study was approved by the ethics committee of Fudan University Shanghai Cancer Center. In both cohorts, patients with overall survival time less than 3 months were excluded to rule out perioperative mortality.

Statistical Analysis

Clinicopathological characteristics were analyzed using chi-squared tests. Survival time was calculated from the date of initial diagnosis until the date of last follow-up or time of death. Kaplan-Meier method and log-rank tests were used to analyze the overall survival. All the statistical analyses were performed using IBM SPSS Statistics version 21.0 software (IBM Corp, Armonk, NY, USA) and GraphPad Prism 7.0. All tests were two-sided and tests with *P* values < 0.05 were considered statistically significant.

Results

Characteristics of NF-pNETs with tumor size 1–4cm in SEER database

Totally, 1828 NF-pNETs patients with tumor size 1–4cm were retrieved from SEER database from 2004 to 2015 (Table 1). Among all these patients, 1656 patients (90.6%) received surgery. Only 172 patients (9.4%) undertook observation, especially in elderly patients. 51.2% patients were over 70 years old. There was no difference between gender. More white patients were inclined to receive surgery. And for tumor located in the head, more patients tended to choose observation. Generally, tumor less than or equal to 2cm has been define to be small ones. In total, there are 821 patients with tumor less than or equal to 2cm in the SEER cohort. Most of these patients were conducted surgical resection. Only 8.2% patients undertook observation. However, there was no survival difference between the two groups (Figure 1A). For patients with tumor over 2cm, surgery did bring survival benefits to them (Figure 1B-C).

Clinicopathological characteristics of patients received surgery in SEER database

To investigate the possible prognostic features, we further analyze the clinicopathological characteristics in the surgery group (Table 2). We separated patients into three groups (small, median, large) according to the tumor size. For patients with tumor located in the head and tumor size 1–2cm, the proportion of surgery was relatively small. And the proportion of Grade I is as high as 85.2% in the small group. Besides, the rate of lymph node metastasis is only about 6% in the small group. In general, no matter surgery or observation, patients with tumor larger than 2cm had short survival time (Figure 2).

Clinicopathological characteristics of patients received surgery in our center

We also retrieved and analyzed the surgical data in our center form 2010 to 2018 (Table 3). In the small group, patients were younger than other group. No difference was found in gender distribution. In the small group, the proportion of G1 stage was as high as 72.6%. Similarly to the SEER data, the rate of

positive lymph node was only 4.8% in the small group. While in the large group, the rate turned to be 34.9%. Moreover, no distant metastasis was found in the small group.

Discussion

Recently, due to improved awareness of physical examination and wide use of cross-sectional imaging, NF-pNETs are being diagnosed increasingly at a small size. According to SEER, the incidence of pNETs with a ≤ 2 cm size has increased by 710.4% (with an annual 12.8% change) over the past 22 years [6]. However, the heterogeneity and uncertainty of pNETs biological behavior pose a dilemma to therapeutic decisions, especially for small tumors (≤ 2 cm). According to some publications, most of NF-pNETs ≤ 2 cm are likely to be benign or indolent. Therefore, in 2012, the European Neuroendocrine Tumor Society (ENETS) Guideline suggested that a observation approach could be advocated in selected cases for NF-pNETs ≤2 cm that are discovered incidentally [7]. Despite this, surveillance or surgery for pNETs ≤2 cm remains controversial. Initially, the concept of observation strategy in pNET was first introduced in the setting of MEN1 syndrome, in which a “field-defect” is thought to present throughout the pancreas and unless total pancreatectomy is performed, the pancreatic remnant is prone to develop new tumors latter[8]. Besides, the concept of surgery in small NF-pNETs is not without risk. Pancreatic surgery remains a high-risk procedure. Postoperative risk of morbidity and mortality is inevitable, especially for tumor located in pancreatic head[9]. Despite parenchyma-sparing pancreatectomy, such as central pancreatectomy and enucleation, could preserve more organ function and minimize long-term complication. However, non-anatomic resections may be associate with higher incidence of pancreatic fistula. Based on this, practices regarding decision for surgery or surveillance may vary differently between institutions depending on the cognition of both physician and patient.

Generally, tumor size has been consistently used to correlate with malignant potential and long-term prognosis. Currently, 2cm has often been suggested as a safe cutoff size to decide surgery or surveillance for NF-pNETs. However, some studies have concluded that small pNETs >0.5 cm already have a malignant potential[4,5]. Likewise, Gratian *et al* found a rate of lymph node metastases and distant metastases in pNETs of <2 cm of 29% and 10%, respectively[10]. Similarly, Haynes *et al* from Massachusetts General Hospital reviewed 139 patients with incidental NF-pNETs and reported a 7.7 % rate of distant metastases in resected pNETs <2 cm after a median follow-up of 34 months[11]. While in our study, we also found 4.8% rate of lymph node metastases in 3 out of 62 resected NF-pNETs. Therefore, small diameter at diagnosis (≤2 cm) is not an grantee of a benign or indolent behavior.

Since the existence of potential malignancy of small NF-pNET, observation strategy must be conducted cautiously. Based on a retrospective study, the cutoff of 2 cm of observation or surgery used for small NF-pNETs could be decreased to 1.7 cm to select patients more accurately[12]. Sadot reported a series of 104 patients who were recommended observation. After a median follow-up of 44 months, no patient developed metastases[8]. The observation group was significantly older and tended to shorter follow-up, which was inconsistent with our results. More than half patients in the observation group from SEER database were over 70 years old. According to a observational study of natural history of small sporadic

NF-pNETs, overall median tumor growth was 0.12mm per year [13]. Thus, observation strategy for older patients is reasonable.

Notably, in 2016, ENETS updated their Guideline that patients with NF-pNETs ≤2 cm have two options: i) It is recommended to have surveillance approach for the patients with G1 or low G2, asymptomatic, mainly with head lesion, no radiological signs suspicious for malignancy, as well as patient factors such as personal wishes, age, or with comorbidities; ii) while for the patients with G2, symptoms and patient wishes, surgery is recommended. Moreover, during the surveillance time, if the tumor size increase >0.5 cm or to a size of >2 cm, surgery is necessary[14].

Therefore, it is vital to determine pathological Ki67 index before making the appropriate strategy for patients with NF-pNETs ≤2 cm. In 1992, for the first time, endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) was reported to diagnose pNETs [15]. Since then, both its sensitivity and accuracy have improved greatly. Larghi *et al* reported that acquisition of tissue specimens with EUS-FNTA by using a 19-gauge needle is safe, feasible and highly accurate. Preoperative and postoperative Ki–67 proliferation indexes were 83.3% concordant in 10 patients [16]. More recently, Boutsen *et al* reported that, compared with preoperative grading, 21 of 22 (95%) pNETs <2 cm had the same grading after surgery [17].

Besides, molecular tests based on EUS-FNA may also be helpful to predict the biological behavior. By performing whole exome sequencing, Jiao et al found that 44 % of sporadic pNET harbored somatic inactivating mutations in MEN–1 and that mutations in the MEN1 gene implied a good prognosis [18]. In addition, loss of DAXX/ATRX proteins was reported to be associated with poor survival in patients with pNETs[19]. Thus, Ki67 combined with these molecular markers, may guide physicians to further subgroup distinct patients for observation or surgery.

In conclusion, for elderly patients with NF-pNETs ≤2cm with G1 or low G2, especially for tumor located in pancreatic head, observation strategy may be recommended. Meanwhile, close follow-up should be guaranteed to monitor the tumor dynamics.

Declarations

Acknowledgments

We thank Xiaoyan Sun for statistical analysis support.

Authors' contributions

JSR and LMQ contributed to the research design, data collection, data analysis, and manuscript writing. YZ, ZZ and XXW contributed to the data collection and manuscript writing. YXJ and ZQF contributed to the data analysis and manuscript editing. All authors read and approved the final manuscript.

Funding

This work was supported by the National Science Foundation for Distinguished Young Scholars of China [81625016].

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of our center (Fudan University Shanghai Cancer Center), in accordance with the Helsinki Declaration of 1975.

Consent for publication

Written informed consent was obtained from each participant.

Competing interests

The authors declare that they have no competing interests

Reference

1. Milena Ilic, Irena Ilic. Epidemiology of pancreatic cancer. World J Gastroenterol. 2016; 22: 9694-705.
2. Franko J, Feng W, Yip L, Genovese E, Moser AJ. Non-functional neuroendocrine carcinoma of the pancreas: incidence, tumor biology, and outcomes in 2,158 patients. J Gastrointest Surg. 2010;14:541-8.
3. Luo G, Javed A, Strosberg JR, Jin K, Zhang Y, Liu C, Xu J, Soares K, Weiss MJ, Zheng L, et al. Modified staging classification for pancreatic neuroendocrine tumors on the basis of the American joint committee on cancer and European neuroendocrine tumor society systems. J Clin Oncol. 2017;35:274-80.
4. Lewis RB, Lattin GE, Paal E. Pancreatic endocrine tumors: radiologic-clinicopathologic correlation. Radiographics. 2010;30:1445-64.
5. Kloppel G. Classifification and pathology of gastroenteropancreatic neuroendocrine neoplasms. Endocr Relat Cancer. 2011; 18:S1-16.
6. Kuo EJ, Salem RR. Population-level analysis of pancreatic neuroendocrine tumors 2 cm or less in size. Ann Surg Oncol. 2013; 20:2815-21.
7. Falconi M, Bartsch DK, Eriksson B, Klöppel G, Lopes JM, O'Connor JM, Salazar R, Taal BG, Vullierme MP, O'Toole D, et al. Barcelona Consensus Conference participants: ENETS Consensus Guidelines for the management of patients with digestive neuroendocrine neoplasms of the digestive system: Well-differentiated pancreatic non-functioning tumors. Neuroendocrinology. 2012;95:120-34.

8. Sadot E, Reidy-Lagunes DL, Tang LH, Do RK, Gonen M, D'Angelica MI, DeMatteo RP, Kingham TP, Koerkamp BG, Untch BR, et al. Observation versus resection for small asymptomatic pancreatic neuroendocrine tumors: a matched case-control study. Ann Surg Oncol. 2016;23:1361-70.
9. Mills L, Drymousis P, Vashist Y, Burdelski C, Prachalias A, Srinivasan P,MenonK, Cotoi C, Khan S, Cave J, et al. Tumour diameter is not reliable for management of non-secreting pancreatic neuroendocrine tumours. Endocr Connect. 2017;6:876-85.
10. Gratian L, Pura J, Dinan M, Roman S, Reed S, Sosa JA. Impact of extent of surgery on survival in patients with small nonfunctional pancreatic neuroendocrine tumors in the United States. Ann Surg Oncol. 2014;21:3515-21.
11. Haynes AB, Deshpande V, Ingkakul T, Vagefifi PA, Szymonifka J, Thayer SP, Ferrone CR, Wargo JA, Warshaw AL, Castillo CF. Implications of incidentally discovered, nonfunctioning pancreatic endocrine tumors: short-term and long-term patient outcomes. Arch Surg. 2011; 146:534-38.
12. Regenet N, Carrere N, Boulanger G, de Calan L, Humeau M, Arnault V, Kraimps JL, Mathonnet M, Pessaux P, Donatini G. Is the 2-cm size cutoff relevant for small nonfunctioning pancreatic neuroendocrine tumors:A French multicenter study. Surgery. 2016; 159:901-7.
13. Gaujoux S, Partelli S, Maire F, D'Onofrio M, Larroque B, Tamburrino D, Sauvanet A, Falconi M, Ruszniewski Observational study of natural history of small sporadic nonfunctioning pancreaticneuroendocrine tumors. J Clin Endocrinol Metab. 2013;98:4784-9.
14. Falconi M, Eriksson B, Kaltsas G, Bartsch DK, Capdevila J, Caplin M, Kos-Kudla B, Kwekkeboom D, Rindi G, Klöppel G, et al. Vienna Consensus Conference participants: ENETS Consensus Guidelines Update for the management of patients with functional pancreatic neuroendocrine tumors and non-functional pancreatic neuroendocrine tumors. Neuroendocrinology. 2016;103:153-171.
15. Rösch T, Lightdale CJ, Botet JF, Boyce GA, Sivak MV Jr, Yasuda K, Heyder N, Palazzo L, Dancygier H, Schusdziarra Localization of pancreatic endocrine tumors by endoscopic ultrasonography. N Engl J Med. 1992;326: 1721-26.
16. Larghi A, Capurso G, Carnuccio A, Ricci R, Alfieri S, Galasso D, Lugli F, Bianchi A, Panzuto F, Marinis LD. Ki-67 grading of nonfunctioning pancreatic neuroendocrine tumors on histologic samples obtained by EUS-guided fine-needle tissue acquisition: A prospective study. Gastrointest Endosc. 2012;76:570-7.
17. Boutsen L, Jouret-Mourin A, Borbath I, van Maanen A, Weynand B. Accuracy of Pancreatic Neuroendocrine Tumour Grading by Endoscopic Ultrasound-Guided Fine Needle Aspiration: Analysis of a Large Cohort and Perspectives for Improvement. Neuroendocrinology. 2018;106: 158-66.
18. Jiao Y, Shi C, Edil BH, de Wilde RF, Klimstra DS, Maitra A, Schulick RD, Tang LH, Wolfgang CL, Choti MA, et al. DAXX/ATRX, MEN1, and mTOR pathway genes are frequently altered in pancreatic neuroendocrine tumors. Science. 2011; 331:1199-203.
19. Marinoni I, Kurrer AS, Vassella E, Dettmer M, Rudolph T, Banz V, Hunger F, Pasquinelli S, Speel EJ, Perren A. Loss of DAXX and ATRX are associated with chromosome instability and

reduced survival of patients with pancreatic neuroendocrine tumors. Gastroenterology. 2014; 146:453–60.e455.

Tables

Due to technical limitations, Tables 1 - 3 are only available for download from Supplementary Files section.

Figures

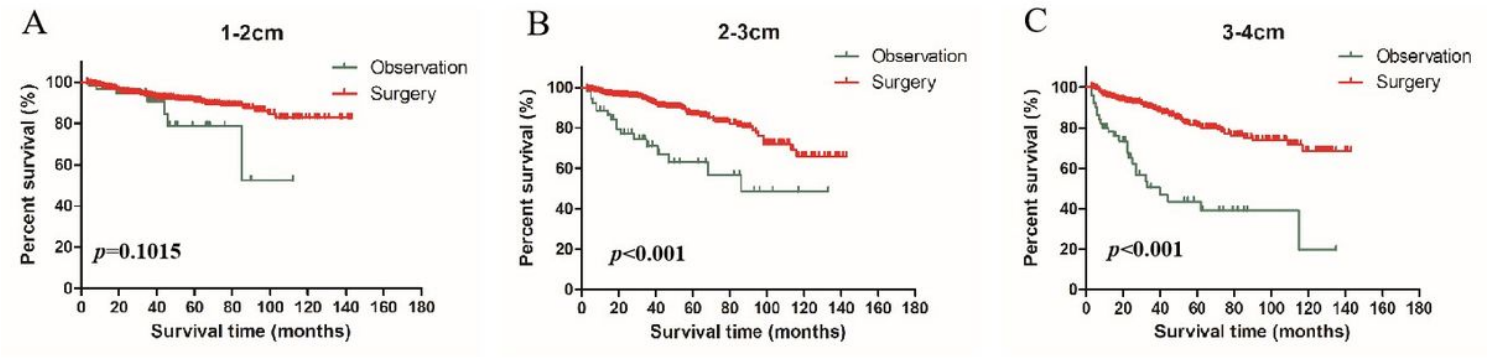

Figure 1

Overall survival (OS) of patients who have undergone observation or surgery. (A) Tumor size 1-2cm; (B)Tumor size 2-3cm; (C)Tumor size 3-4cm.

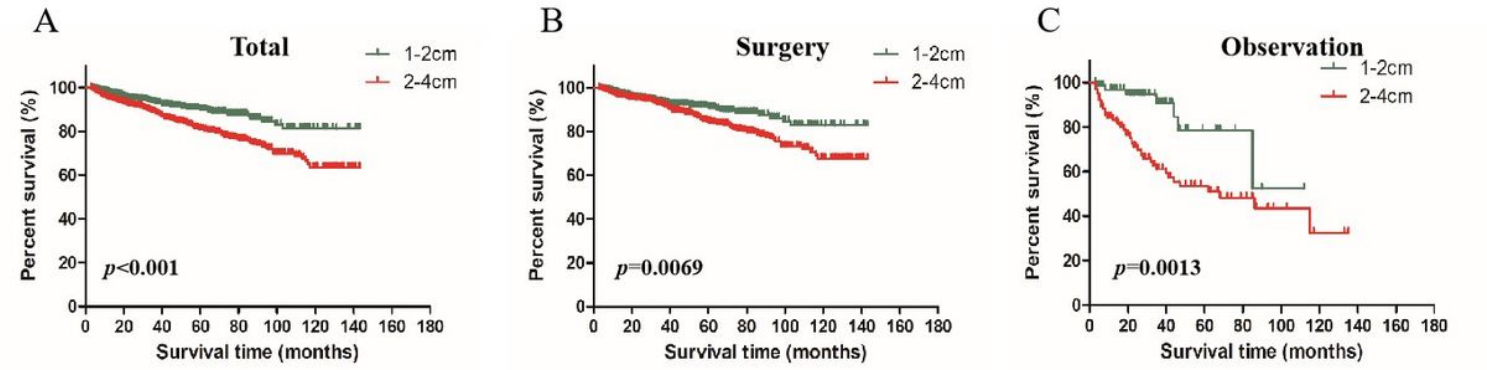

Figure 2

Overall survival (OS) of patients based on tumor size. (A) Total; (B)Surgery group; (C) Observation group.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table2.docx

- Table3.docx
- Table1.docx