Surgery management for sporadic small (≤2 cm), non-functioning pancreatic neuroendocrine tumors: A consensus statement by the Chinese Study Group for Neuroendocrine Tumors (CSNET)

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Abstract. The incidence of small (≤2 cm), non-functioning pancreatic neuroendocrine tumors (NF-pNETs) increased in the last decades. Before making appropriate strategy for patients with NF-pNETs ≤2 cm, pathological confirmation is vital. Incidentally diagnosed, sporadic small NF-pNETs may bring aggressive behavior and poor prognosis, such as extrapancreatic extension, lymph nodal metastasis, distant metastasis and recurrence, even causing disease-related death. Understanding and formulating an appropriate strategy for the patients with sporadic small, non-functioning pancreatic neuroendocrine tumors have been controversial for some time. Although several studies have reported that patients with NF-pNETs ≤2 cm had less rate of malignant behavior compared with larger ones (>2 cm); and the surgery approach may leading to surgery-related pancreatic complications; but there is still a lack of level I evidence to convince surgeons to abandon all cases with sporadic small NF-pNETs. Based on an updated literature search and review, the members of the Chinese Study Group for Neuroendocrine Tumors (CSNET) from high-volume centers have reached a consensus on the issue of the management strategy for the sporadic small NF-pNETs. We recommend that, except for some selected patients with NF-pNETs <1 cm, incidentally discovered and unacceptable surgical risks, all others with NF-pNETs ≤2 cm should undergo tumor resection with lymph node dissection or at least lymph node sampling and careful postoperative surveillance.

Introduction

Pancreatic neuroendocrine tumors (pNETs), also named as islet cell tumors, are relatively rare, accounting for 1-2% of all pancreatic neoplasms (1,2). According to the hormonal symptoms, they are broadly divided into functioning (F-pNETs) and non-functioning pNETs (NF-pNETs). An estimated 66-91% of the pNETs were non-functioning and patients with NF-pNETs have been reported to have poorer outcomes than those with F-pNETs (3,4). With respect to recent studies and consensus statements, in F-pNETs and symptomatic or large (>2 cm) NF-pNETs, radical pancreatic resection is the only treatment capable of prolonging survival (5-7). However, in patients with sporadic small (≤2 cm) NF-pNETs, there are quite different views regarding the appropriate management strategy to adopt (8).

Many recent studies suggested that there is an increasing incidence of NF-pNETs, especially NF-pNETs (≤2 cm). An epidemiological survey conducted in Japan shows that the number of treated patients with pNETs in 2010 was ~1.2-times that in 2005 and the number of the new incidences of non-functioning pNETs in 2010 was ~1.7-times that in 2005 (9). Likewise, based on the first population-level analysis to exclusively characterize NF-pNETs ≤2 cm in a surgical population, the incidence of NF-pNETs ≤2 cm in the United States has increased by 710.4% over the 22-year study period with annual percentage change 12.8%; while the NF-pNETs ≤2 cm accounted for 20.2% of total pNET diagnoses in 2009, in contrast to 12.3% of that in 1988, which nearly doubled over the last 22 years (10). Whether this is the result of a true increase in incidence of the disease or result of increased detection is still speculative. However, we have reasons to believe that the more frequent use of cross-sectional imaging, especially the multiphasic computed tomography (CT) or magnetic resonance imaging (MRI) and endoscopic ultrasound (EUS) have played some important roles in this (2,3,10).

As for determining the appropriate management for NF-pNETs ≤2 cm, surgery or surveillance, which one should be taken into consideration remained controversial. In 2012, the European Neuroendocrine Tumor Society (ENETS) Guideline suggested that a non-operative approach could be advocated in selected cases for NF-pNETs ≤2 cm that are discovered incidentally (6); for the reasons that most of NF-pNETs ≤2 cm are likely benign or intermediate-risk lesions and only 6% of NF-pNETs ≤2 cm are malignant when incidentally discovered (11). However, in 2016, the latest ENETS Guideline updated their views 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 (8). Moreover, during the surveillance time, if the tumor size increase >0.5 cm or to a size of >2 cm, surgery is necessary (8). However, according to the National Comprehensive Cancer Network (NCCN) Guideline Version 2.2016, patients with NF-pNETs ≤2 cm should undergo surgery (12). Observation can be considered in cases as follows: tumors <1 cm, incidentally discovered; while decision should be made based on estimated surgical risk, site of tumor and patient comorbidities (12). On the other hand, both in the ENETS and NCCN guidelines, only retrospective cohort studies and case series are included, due to the relative low incidence of NF-pNETs. Therefore, before a large and prospective randomized clinical trial with long-term follow-up come out, it still remains controversial whether surgery or surveillance should be carried out for the patients with NF-pNETs ≤2 cm.

To address the issue of whether surgery or surveillance should be under taken for the patients with NF-pNETs ≤2 cm, an expert panel from high-volume centers in China participated in a consensus conference hosted by the Chinese Study Group for Neuroendocrine Tumors (CSNET) in June 2016 to review the published literature and discuss the management strategies for the patients with NF-pNETs ≤2 cm. This Chinese expert consensus from the CSNET on pancreatic neuroendocrine tumors formulated a personalized proposal on the management strategies for the patients with NF-pNETs, which may add to the armamentarium available to pancreatic surgeons and physicians.

Materials and methods

For the consensus statement, a comprehensive search of medical literature was carried out using PubMed in April 2016. The PubMed search terms included 'non-functioning', 'non-functional', 'pancreas', 'pancreatic', 'islet', 'neuroendocrine tumor', 'neuroendocrine neoplasm', 'endocrine tumor', 'endocrine neoplasm', 'neuroendocrine', 'endocrine', 'tumor' and 'neoplasm' in various combinations. As the evidence level suggested by the Oxford Centre for Evidence-based Medicine, the reports were assessed and ranked. We excluded all case reports and non-English papers. Literature reporting data on MEN-1 syndrome were not included. A draft of the consensus statement was prepared by the CSNET members (G.Y. and C.H.S.), and then it was discussed, followed by an agreement by CSNET members at a conference held in June 2016 in Guangzhou, China.

Results and Consensus statements

It is vital to make pathological confirmation, before making the appropriate strategy for patients with NF-pNETs ≤2 cm. Recent studies have suggested the results that the incidence of NF-pNETs ≤2 cm have increased in the past few decades, on account of widely-used cross-sectional imaging, especially the multiphasic CT or MRI and nuclear medicine techniques (2,9,10).

Multiphasic CT and MRI are often used initially for the screening and staging of these lesions (13). The classic appearance is of a uniformly hypervascular, well-defined lesion that is most notably prominent on arterial phases of contrast enhancement (14). While nuclear medicine techniques can provide improved specificity and whole-body assessments for distant disease. The primary nuclear medicine imaging tool for pNET is somatostatin receptor scintigraphy (SRS) performed with a radiolabeled somatostatin analogue (15). Its overall sensitivity for pNET is ~70-90% but varies with tumor type and diminishes particularly for subcentimeter lesions (16,17). ^{18}Fluorine-FDG PET/CT is used as a complementary technique to SRS, which shows poor uptake in poorly differentiated tumors (16). Moreover, ^{68}Gallium PET/CT has been used extensively (18), other radioisotopes are under investigation for imaging of neuroendocrine tumors (13).

However, neither cross-sectional imaging or nuclear medicine techniques are able to obtain accurate preoperative pathology results. The seminal article by Rosch *et al* (19) in 1992 was the first to describe the important role of Endoscopic Ultrasound-Guided Fine-Needle Aspiration (EUS-FNA) in the detection of pNETs. Since then, EUS-FNA has been increasingly used and has become an integral part of the diagnosis of pNETs because of its high sensitivity for detecting, localizing and diagnosing pNETs for >20 years (20).

EUS-FNA is an excellent tool to establish the correct diagnosis of pancreatic lesions. Similar to other pancreatic lesions, NF-pNETs may be further evaluated by sampling these tumors by FNA performed during the EUS examination to optimize patient management (21). Studies have reported sensitivities of 61-84% and overall accuracy of up to 92.5% of EUS-FNA in establishing the diagnosis of pNETs (22-24). Alternative methods for obtaining tissue by EUS have been evaluated to overcome the limitations of FNA. The Endoscopic Ultrasound-Guided Trucut needle biopsy (EUS-FNTA) uses a 19-gauge needle to obtain core biopsies with the benefit of procuring larger and substantive amounts of tissue with conserved architecture that would enable histologic analysis (25). Larghi *et al* (26) reported that, among patients with NF-pNETs ≤2 cm, retrieval of tissue specimens with EUS-FNTA by using a 19-gauge needle is safe, feasible and highly accurate for both diagnosis and Ki-67 determination. In addition, the use of the Trucut needle has been limited by the technical difficulties of using this device, particularly with the duodenal approach (27).

In the updated ENETS guideline 2016, pathological classification should be confirmed before the treatment strategy can be decided among the patients with NF-pNETs ≤2 cm, because for those patients with G1 or low G2, it is safe to have the surveillance approach; while for those patients with G2, surgery is the other approach (8). However, due to the small tumor diameter (≤2 cm), a high-volume center and an experienced sonographer are required to improve the accuracy and reliability of the pathological confirmation.

Consensus statements. It is important for patients with suspected sporadic small NF-pNETs to have pathological confirmation before the appropriate treatment strategy is decided. While EUS-FNA has limitations in the pathological confirmation, EUS-FNTA is an excellent tool to establish the correct diagnosis. For the small-volume centers, due to the low sensitivities and poor accuracy, radiological signs suspicious for malignancy, such as CT, MRI, SRS, ^{68}Gallium or ^{18}Fluorine-FDG PET/CT, disease diagnosis can be made through serology results, such as chromogranin A (CgA) and pancreatic polypeptide (PP).

The recommended strategy for patients with NF-pNETs ≤2 cm. The appropriate treatment strategy for patients with NF-pNETs ≤2 cm remains controversial. Based on several studies the choice of radical surgery is advocated due to the risk of malignancy of ~9-27% in NF-pNETs ≤2 cm (10,28). On the other hand, a few studies suggested that such an aggressive surgical indication could expose some patients, with low pancreatic malignancies, to a high increased postoperative morbidity and mortality, depending on factors including age, presence of comorbidities, the sites of the tumor and the surgical approaches, but would not benefit patients' survival in the long term (29,30) (Fig. 1).

Incidentally diagnosed, sporadic NF-pNETs can display aggressive behavior, including extrapancreatic extension,

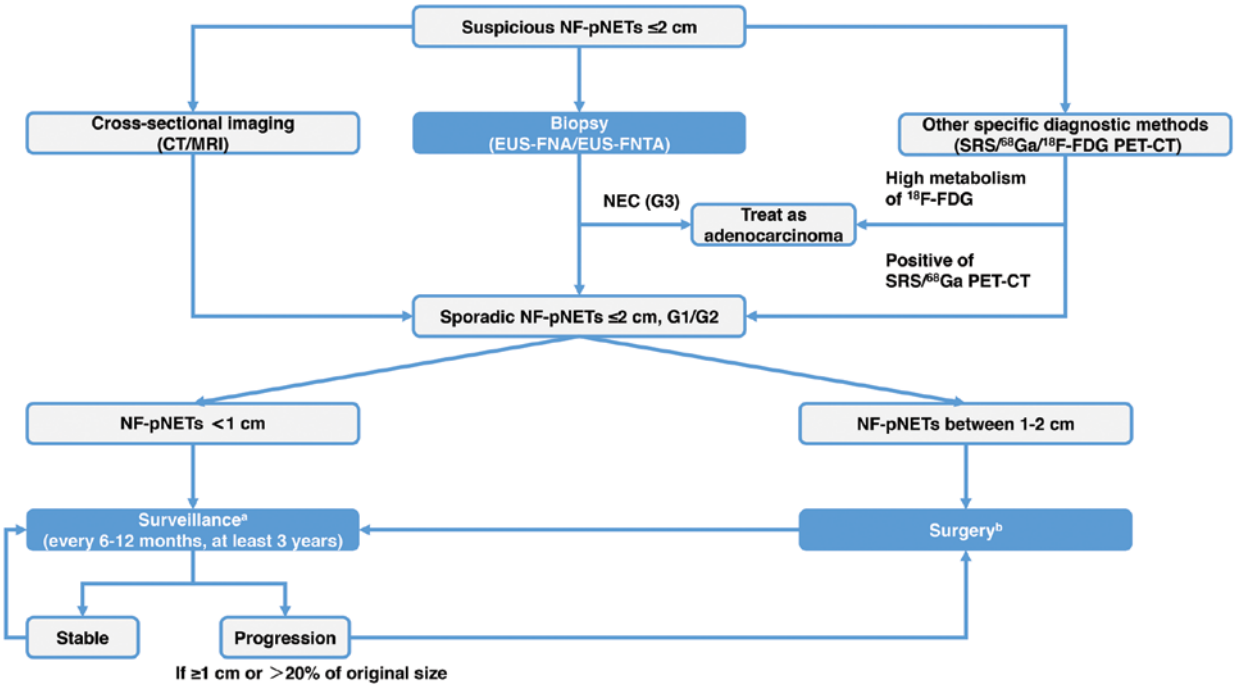

Figure 1. Treatment approach to sporadic small (≤2 cm), non-functioning pancreatic neuroendocrine tumors. a, ENETS guidelines surveillance schedule, EUS, MRI (or CT) every 6-12 months. b, Except for patients with G1 NF-pNETs between 1-2 cm, located in the head or the uncinate process or pancreas or with other contraindications.

lymph nodal metastasis, distant-organ metastasis, recurrence which may lead to disease-related death, even though the tumors are small (≤2 cm). With respect to the first population-level analysis to exclusively characterize NF-pNET ≤2 cm in a surgical population from the United States, rates of extrapancreatic extension, lymph nodal metastasis and distant metastasis in NF-pNETs ≤2 cm in the SEER database were 17.9, 27.3 and 9.1%, respectively (10). Haynes *et al* (31) also reported a case series of 39 patients with NF-pNETs ≤2 cm, where 3 had late metastases or recurrence after the resection. An Italian retrospective cohort study showed that, among 23 patients with NF-pNETs ≤2 cm, 4 (17.4%) had distant metastases before surgery; while in the other 19 patients without metastases before surgery, 4 had a local malignancy (lymph node metastasis or local infiltration) (28). Likewise, a study from Finland reported that among 24 patients with NF-pNETs ≤2 cm, 7 patients with small symptomatic NF-pNETs showed signs of malignant behavior: 4 had lymph nodal metastases, 1 had liver metastases before surgery, 3 developed liver metastases and 3 died of the disease (32). A retrospective cohort study from the United States showed that of the 56 patients with NF-pNETs ≤2 cm, 3 developed distant metastasis after resection, eventually resulting in 2 disease-related deaths (33).

On the contrary, several studies reported that the patients with NF-pNETs ≤2 cm had less rate of malignant behavior compared with larger ones (>2 cm); and the surgery approach may lead to pancreatic postoperative complications. A multicenter retrospective case series from Europe showed that among the 46 patients with NF-pNETs ≤2 cm followed up with serial imaging, distant or nodal metastases appeared on the imaging in none of the patients. Overall, 8 patients underwent surgery after a median time from the initial evaluation of 41 months; all resected lesions were ENETS T stage 1 (n=7) or 2 (n=1), grade 1, node negative, with neither vascular nor peripancreatic fat invasion (34). Likewise, another matched designed retrospective cohort study from the United States reported that, during a median follow-up of 44 months of the observation group, the median tumor size had not changed, and no patient had developed evidence of metastases; and no patient died of the disease (35). A recent study showed that small NF-PNETs (<2 cm) in either the operative or non-operative groups demonstrated no evidence of progression or metastasis; and morbidity in the operative group was 35% with pancreatic pseudocyst the most common (29). Lee *et al* (30) described that the surgery group patients had some type of complication, more than half due to a clinically significant pancreatic leak, while no recurrence or disease specific mortality was seen in the surgery group, including 5 patients with positive lymph nodes.

Considering the survival prognosis, Massironi *et al* (36) showed that the 4-year survival rate was 100% in the surveillance group, while it was 90.5% among the surgery patients. On the other hand, a study based on the National Cancer Data Base (NCDB) from the United States showed that 380 patients with NF-pNETs ≤2 cm were divided into the surgery group (81%) and the surveillance group (19%); the 5-year overall survival (OS) rate was 82.2% for the surgery group and 34.3% for the surveillance group (37). Also, the SEER data presented that the disease-specific survival at 5, 10 and 15 years for NF-pNETs ≤2 cm was 91.5, 84.0 and 76.8% (10). Accordingly, based on later two relatively large population studies, we can see that the patients with NF-pNETs ≤2 cm had an overall survival advantage with resection compared to observation.

Some studies have suggested a more rational tumor size cut-off to distinguish the malignancy or not. Ende *et al* (38)

according to the receiver operating characteristic (ROC) analysis, found that using a cut-off point of 2.0 cm only led to a sensitivity of 85% in screening for metastases, while lowering the cut-off point to 1.8 cm allowed for a sensitivity of 95%. Likewise, a multi-center retrospective cohort study from France showed that on a ROC curve, and tumor size had a significant impact on malignancy. A tumor size cut-off was found on the ROC curve at 1.7 cm with a sensitivity of 92% and a specificity of 75% to predict malignancy (node or liver metastasis) (39). Also, a retrospective cohort study from the United States reported that an operation became a significant predictor of overall survival for tumors >1.5 cm but was not significant for tumors <1.5 cm, controlling for age-adjusted Charlson comorbidity index (40). Similarly, two Asian studies from Korea and Japan also take more aggressive approach to lower the tumor size cut-off to 1.5 cm for surgery (41,42).

Moreover, a recent abstract from the CSNET has been submitted and approved by the 13th Annual ENETS Conference Abstract Reviewing Committee 2016. In the multi-institutional clinical analysis in China, a total of 49 patients with NF-pNETs ≤2 cm who undertook surgery were included; postoperative pathological diagnosis showed that 14.3% were with positive regional lymph node metastasis, 12.2% perineuronal invasion and 4.1% vascular invasion; while at the last follow-up, 14.3% of the patients had recurrence and metastasis and 6.1% died of tumor metastasis. Our own clinical experience told us that, although NF-PNETs ≤2 cm usually exhibit minimal or no growth over many years, the minority will recur and metastasize. It suggests that these patients should receive surgical management or other active treatment and long-term follow-up (Ji M, Jin K and Zhang Y: 13th Annual ENETS Conference for the Diagnosis and Treatment of Neuroendocrine Tumor Disease: 272, 2016).

However, surgery decision should be made based on tumor location, the adjoin between the tumor and the vessels, and the patients' condition. Most importantly, for patients with G1 NF-pNETs between 1-2 cm located in the head or the uncinate process of pancreas, who need pancreaticoduodenectomy rather than parenchyma-preserving resection, surveillance is more suitable.

Another interesting focus is the surgery management for G3 neuroendocrine neoplasms (NEN). According to the ENETS Guideline 2016, G3 NEN will probably be separated into G3 NET and G3 NEC in the future (43). But as for NF-pNETs ≤2 cm, the G3 NEN, including G3 NET and G3 NEC, are very rare neoplasms representing 1-2% (42,43). For the present, surgery with regional lymph node dissection is recommended for those patients who are diagnosed as G3 NET or G3 NEC of NF-pNETs ≤2 cm. Considering the survival is poor in G3 NEC (43), it should be treated as pancreatic ductal adenocarcinoma. Moreover, due to the low incidence of G3 NEN of NF-pNETs ≤2 cm, further studies are needed to clarify this issue.

Consensus statements. According to the afore-mentioned facts, currently the 2-cm cut-off is not suitable due to the wide use of cross-sectional imaging and endoscopic ultrasound; not to mention that this cut-off point is too high to omit some tumors with malignant behavior. Therefore, more aggressive approach is suggested to be taken, except for some selected patients with NF-pNETs <1 cm, incidentally discovered and unacceptable surgical risks, all others with NF-pNETs ≤2 cm should undergo tumor resection and careful postoperative surveillance. The follow-up for both surgery and surveillance patients should continue for at least 3 years, during which EUS, MRI/CT should be taken for every 6-12 months.

The surgery approaches for patients with NF-pNETs ≤2 cm. The surgery management for patients with NF-pNETs ≤2 cm has two parts: i) the choice of surgical techniques, which includes the typical and atypical techniques; and ii) the open or minimally invasive procedures.

The typical surgical techniques contain pancreaticoduodenectomy, distal pancreatectomy and total pancreatectomy; while the atypical surgical techniques include enucleation, middle pancreatectomy and middle-preserving pancreatectomy (44). All these surgical techniques can be performed by the open or minimally invasive methods, which include the laparoscopic approach and the robot-assisted surgical system. Therefore, the specific approach is decided by the tumor site, the tumor size and whether with or without lymphadenectomy.

Several studies have reported that parenchyma-preserving resections including enucleation and middle pancreatectomy are generally safe and effective procedures for treating small NF-pNETs (11,45,46). These procedures may be associated with some acceptable pancreas-related complications, mostly the pancreatic fistula, but an excellent postoperative pancreatic function for patients (45). Similarly, based on the largest single-institution series on laparoscopic resection for pNETs, it has been demonstrated that laparoscopic distal pancreatectomy, with or without splenectomy, and laparoscopic enucleation are safe and feasible in patients with small NF-pNETs located in the body and tail of the pancreas (47). However, both the open and the minimally invasive procedures, especially the enucleation, need to be integrated with the use of intraoperative ultrasonography to define correctly the surgical area with the main pancreatic duct to reduce the pancreatic fistula as much as possible (44).

Consensus statements. The specific surgery approach is decided by the tumor site, the tumor size, the age and the health condition. The typical and atypical surgical techniques, which are taken in the open or minimally invasive ways, are both suitable for NF-pNETs ≤2 cm, while the minimally invasive ways and parenchyma-preserving resection are recommended. For patients with NF-pNETs ≤2 cm, located on the head surface or in the body or tail of pancreas, parenchyma-preserving resection, especially enucleation, is safe and effective.

The lymphadenectomy strategy for patients with NF-pNETs ≤2 cm. According to the afore-mentioned facts, individual studies have shown a risk of lymph nodal metastases in NF-pNETs ≤2 cm between 12.9 and 27.3% (10,28,32,48). Although debate exists regarding the value of lymphadenectomy with surgery for small NF-pNETs (49), several studies have suggested a correlation between the lymph node metastases and the outcome. Another study based on the SEER data from the United States showed that the lymph nodal metastases were independently associated with the decreased disease-specific survival (50). Likewise, a retrospective cohort study from the United States reported that positive lymph

nodes rate of NF-pNETs <2 cm was 7.4%, but the negative lymph nodes were correlated with better survival on multivariate analysis (48).

Nevertheless, a Chinese study reported that lymphadenectomy in small (≤2.5 cm) NF-PNETs is not routinely necessary, for the reason that incidentally discovered NF-pNETs ≤2.5 cm were associated with a low-risk of lymph nodal metastases (7.7%) and excellent survival (51). Another large population, including total of 1854 patients with NF-pNETs ≤2 cm, based on NCDB data from the United States showed that, among tumors ≤0.5 cm, 33% presented with regional lymph nodal metastases and 11% with distant metastases. In addition, the 5-year OS rate for patients not undergoing surgery was 27.6 vs. 83.0% for partial pancreatectomy, 72.3% for pancreaticoduodenectomy and 86.0% for total pancreatectomy. While the multivariate analysis demonstrated no difference in OS based on the type of surgery or the addition of regional lymphadenectomy (52).

Consensus statements. There is a relatively certain incidence of lymph nodal metastases in the patients with NF-pNETs ≤2 cm, but the correlation between the lymph node metastases and the overall survival remain controversial. To avoid misunderstaging, here we also recommend that lymph node dissection for patients with NF-pNETs >1 cm, and lymph node sampling should be carried out for tumors <1 cm. For experienced surgeons during minimally invasive resections, we highly recommend lymph node dissection or lymph node sampling.

Discussion

Pancreatic neuroendocrine tumors are relatively rare, which mostly tend to be sporadic or non-functioning. Based on the SEER and NCDB Databases, the incidence of NF-pNETs ≤2 cm has increased by 2- or 3-fold in the last decades (10,52). It is still speculative whether this is the result of a true increase in incidence of disease or the result of increased detection. However, we have reasons to believe that the more frequent use of cross-sectional imaging, especially the multiphasic CT or MRI and EUS has played an important role in this.

Although the involvement of aggressive behavior of small NF-pNETs, such as extrapancreatic extension, lymph nodal metastasis, distant metastasis, recurrence and even sometimes disease-related death, are indicated by numerous individual studies (10,28,31-33), level I evidence or sizeable, multiple center, prospective, controlled trials still appear insufficient. At the same time, other series argued that, small NF-pNETs usually exhibit minimal or no growth over many years, and nonoperative management may be advocated when serial imaging demonstrates minimal or no growth without suspicious features (29,30,34,35,53). Considering this, a very interesting study from Italian scholars have reported that they have developed a Markov model to investigate whether the patients with NF-pNETs ≤2 cm should directly undergo pancreatic surgery or should be followed longitudinally to detect growth and malignancy. This model was sensitive to diagnostic age and length of follow-up; in particular, for patients >65 years of age, the two strategies provided similar results but the surveillance strategy was more cost-effective than the surgery strategy (54).

Also, several studies have shown that surgery is safe and can be advocated for the patients with NF-pNETs ≤2 cm (11,45,46). Considering the risks of lymph nodal metastases involvement in the patients with NF-pNETs ≤2 cm, lymph node dissection or at least lymph node sampling is highly recommended for patients with small NF-pNETs. Consequently, most patients with NF-pNETs ≤2 cm should undergo tumor resection and careful postoperative surveillance, except for some selected cases with NF-pNETs <1 cm, incidentally discovered and unacceptable surgical risks.

The current consensus concerning the issue of the management strategy for patients with sporadic small, non-functioning pancreatic neuroendocrine tumors is supported and unanimously approved by CSNET members from several high-volume pancreas centers in China and suggests that surgery should be taken for most patients with small NF-pNETs, except for some selected ones with NF-pNETs <1 cm, incidentally discovered and unacceptable surgical risks. The specific surgery management is decided based on the tumor site, the tumor size, age and the health condition. Although the dissection of lymph nodes is recommended by the CSNET in most cases, multiple center, prospective and controlled trials are still needed to confirm the correlation between the lymph nodal metastases and the outcome.

Limitation and future directions. Due to the relative low incidence of NF-pNETs, all the included studies are retrospective cohort studies or case series. Therefore, the appropriate strategy for patients with NF-pNETs ≤2 cm remains controversial before a large and prospective randomized clinical trial with long-term follow-up is carried out. At the same time, considering the yearly high incidence of NF-pNETs, international cooperation is also recommended.

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