—Review Article—

Small nonfunctional pancreatic neuroendocrine neoplasms: Time for a step-up treatment approach?

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ABSTRACT

Surgery has been regarded as the only curative treatment for patients with small nonfunctional pancreatic neuroendocrine neoplasms (NF-PNENs) less than 2 cm. Due to the significant adverse event rates of surgery, the European Neuroendocrine Tumor Society issued guidelines favoring surveillance for those patients lacking criteria suggestive of an aggressive disease. Despite the above recommendations, a significant proportion of small NF-PNEN patients still undergo surgery. Recently, several studies have reported the safety and effectiveness of EUS-guided radiofrequency ablation (RFA) for the treatment of small NF-PNENs. The experience with EUS-RFA is, however, limited, but published results indicate a potential role as a minimally invasive alternative treatment for these patients, in particular in those in whom further progression is more probable, before they reach the absolute need for surgery. A step-up approach with EUS-RFA followed by surgery for the failure cases can become a valid option to be validated in clinical studies.

Key words: EUS, Pancreatic neuroendocrine neoplasms, Non-functional, Radiofrequency ablation, Step-up treatment, Surgery

INTRODUCTION

Surgery, with both typical and atypical resections, has traditionally been the leading treatment of nonfunctional pancreatic neuroendocrine neoplasms (NF-PNENs), with a proven significant benefit in terms of survival.[1] However, substantial short- and long-term adverse events (AEs) occur, even in very expert hands. Indeed, in a recent systematic review of the literature including 62 studies, postoperative pancreatic fistula, delayed gastric emptying, hemorrhage, and inhospital mortality have been respectively reported in 14%–58%, 5%–18%, 1%–7%, and 3%–6% of the

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cases, depending on the surgical technique utilized.[2] In addition, long-term endocrine and exocrine pancreatic insufficiency following resection have been described to happen in up to 18% and 33% of the patients.[3,4]

STRATEGIES FOR SMALL NF-PNENs

Because of the high risk for AEs, in patients with a solitary NF-PNEN lesion <2 cm in diameter with negative lymph nodes or distant metastases at 68Ga-DOTATATE positron emission tomography, the European Neuroendocrine Tumor Society (ENETS) established guidelines demanding a less aggressive approach. Specifically, a watchful surveillance strategy was suggested for those patients with a Ki-67 index <5%, with tumor mostly but not only located in the head, with no symptoms, considering patient's age and preference, presence of comorbidities, and tumor stability over the first 6 months of follow-up.[5] This approach, however, is

Table 1. Summary of identified studies (all retrospective) reporting outcomes in small (≤20 mm) nonfunctional pancreatic neuroendocrine neoplasms undergoing active surveillance

Author, year	Total number of patients	Patients undergoing resection, *n* (%)	Patients in whom follow-up only was performed, *n* (%)	Outcomes in nonoperated patients	Follow-up period in nonoperated patients (median or mean)
Lee, 2012	75	0	75	Tumor size did not change throughout follow-up; no new local invasion, metastatic disease, or disease-specific mortality were reported	45 months (clinical) 35 months (radiological) (mean)
Cheema, 2012	NR	NR	2	None of the 2 patients had tumor growth	24 months (mean)
Gaujoux, 2013	46	8 (17.4)[$]	38 (82.6)	No distant or nodal metastases appeared on imaging in any of the patients; in 6 patients (13%), an increase in size of 20% or greater was observed on serial imaging	34 months (range, 24–52) (median)
Crippa, 2014	120	105 (87.5)	11 (9.2)	Tumor size did not change throughout follow-up	36 months (range, 18–66) (median)
Jung, 2015	145	72 (49.7)	73 (50.3)	In the 85 primarily followed patients (the ongoing followed up and the primarily followed, secondarily resected), only 3 patients (3.5%) had a meaningful tumor growth (of>20% or>5 mm)	31.1±22.1 months (mean)
Sadot, 2016	104	26 (25.0)[&]	78 (75.0)	Tumor size did not change during follow-up, and none of the patients developed evidence of metastases (locoregional or distant) on imaging	44 months (range, 4–223) (median)
Rosenberg, 2016	18	8 (44.4)	10 (55.6)	None of the followed up tumors had evidence of progression or metastasis	27.8 months (median)
Barenboim, 2019	44	2 (4.5)[@]	42 (95.5)	None of the patients developed distant metastases	52.5 months (mean)
Partelli, 2019	101	28 (28)[€]	73 (72)	There was no mortality and no evidence of distant metastases in the followed up patients; none underwent surgery; only 5 (6.8%) patients had a meaningful tumor growth>20%	40 months (median)
Assi, 2020	1014	890 (87.8)	124 (12.2)	5 years unadjusted overall survival of 77.4% in nonoperated *versus* 90.5% in operated patients[^]	25.1 months (median)
Powers, 2020	709	628 (88.6)	81 (11.4)	Cancer-specific survival probability was 98.2% for patients undergoing surgery *versus* 98.6% for patients who did not undergo surgery*	24 months (median)

*This study proves that although overall survival seems superior in surgically treated patients with stage I NF-PNENs, cancer-specific survival is not influenced, thus implying a treatment selection bias favoring surgery in healthier patients; [$]In only 3 patients, surgery was decided because of meaningful size increases over time; [&]Twenty-six patients initially allocated to the observation group underwent subsequent tumor resection for the following indications: Patient's preference in 38%, increasing tumor size in 31%, physician's preference in 27%, and development of pancreatic duct dilation 4%; [@]Two of the patients allocated to the observation group underwent resection due to tumor growth; [€]The main factors determining surgical resection were patient's preference (32%), positive ^{18}F-fluorodeoxyglucose PET-CT (21.5%), pancreatic ductal dilation (17.5%), cytologically determined G2 tumor (14.5%), and young age (14.5%); [^]This study presents data retrieved from National Cancer Database, where patients were identified using the diagnostic histology code associated with neuroendocrine tumors as per the International Classification of Diseases for Oncology; no explanation on why patients were operated or not were provided, such as comorbidity or functional status, or cause of death, if disease-related or not. NR: Not reported; NF-PNENs: Nonfunctional pancreatic neuroendocrine neoplasms; PET: Positron emission tomography; CT: Computed tomography

based mainly on retrospective studies with a low level of evidence and a short follow-up [Table 1].[6-16] In the only valid one, a well-designed matched case–control study by Sadot *et al.*,[11] among 104 patients who underwent surveillance, 25% were operated on, and overall, none developed metastases or died from disease after a median follow-up of 44 months.

The validity of the ENETS guidelines was further questioned by data from Ricci *et al.*[17] showing in small PNENs rates of N1 and M1 disease of 21.2% and 7.6%, respectively. However, a publication bias for M1 rate was found and the heterogeneity among studies for N status was only low–moderate. In addition, the study had several limitations, in particular lack of data on preoperative work-up, Ki-67 rates, and lesion morphology, which might all have a major impact on selection of patients to send to surgery, *i.e.* the ones with worse characteristics at higher risk for N and M disease. Conversely, in a more recent Italian multicenter retrospective study on 964 sporadic NF-PNENs, which in the large majority of cases (93.9%) underwent upfront resection, the prognosis of G1 tumors was excellent for all stages, suggesting that nonoperative management should be considered for stage I disease.[18]

In real life, however, despite the above controversies and the ENETS recommendations, a significant proportion of patients with NF-PNENs <2 cm undergo surgical resection. In a prospective German registry, 84 out of 287 (29.2%) of operated NF-PNEN patients had sporadic tumors ≤2 cm. Among them, only 22 (26.2%) had parenchyma-sparing resections, while postoperative relevant Grade III AEs, 30- and 90-day mortalities were reported in 32.2%, 2.4%, and 3.6%, respectively.[19] In these cases, among the 60 (72%) tumors classified as G1, and 24 (28%) as G2, lymph node metastases were detected postoperatively in only 6 (7.2%) patients, with lymphadenectomy being performed in 75.4%. The authors concluded that the attitude to operating NF-PNENs ≤2 cm, especially in elderly patients, seemed to be quite aggressive.[19]

Similarly, in an Italian retrospective cohort study on 101 patients with small NF-PNENs without nodal or distant metastases at baseline imaging studies, the same significant proportion (28%) were surgically treated.[4] High rate of postoperative complications (21/28, 75%; with 18% rate of Grade III AEs) occurred, with no proven benefit compared to the ones who underwent surveillance.[4] All of the 73 patients managed nonoperatively were alive, with no evidence of distant metastases, and none underwent surgery after a median follow-up of 40 months. Only 5 patients had a tumor growth >20%. The authors also concluded that surveillance of these patients seems warranted.[4]

It can be argued that both these studies analyzed patients' populations enrolled before the ENETS

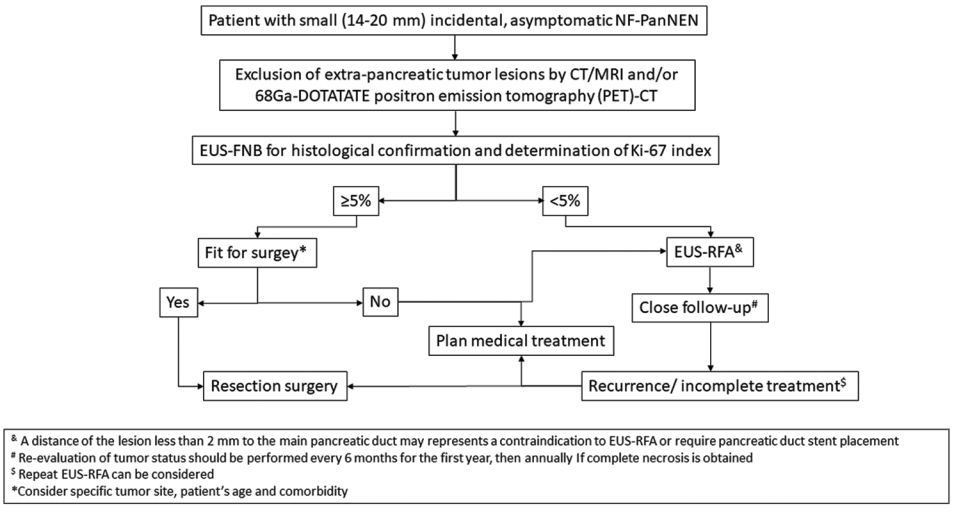

Figure 1. Algorithm proposing a novel strategy including EUS-guided RFA for small incidental pancreatic nonfunctional neuroendocrine neoplasms. *Consider specific tumor site, patient's age, and comorbidity; &A distance of the lesion less than 2 mm to the main pancreatic duct may represent a contraindication to EUS-RFA or require pancreatic duct stent placement; #Re-evaluation of tumor status should be performed every 6 months for the 1st year, then annually if complete necrosis is obtained; $Repeat EUS-RFA can be considered. NF-PNENs: Nonfunctional pancreatic neuroendocrine neoplasms; CT: Computer tomography; MRI: Magnetic resonance imaging; EUS-FNB: EUS-guided fine-needle biopsy; RFA: Radiofrequency ablation; EUS-RFA: EUS-guided RFA

guidelines on management of small NF-PNENs, issued in 2016, were implemented.[4,19] However, in a more recent interim analysis of a prospective international observational multicentric cohort study supported directly by ENETS (ASPEN study),[20] 79 (22%) from the 387 enrolled patients with PNENs <2 cm underwent surgical resection at diagnosis, with 5 more patients (3% of the 165 under surveillance after at least 1 year) being operated on within the 1st year of follow-up.[21] This result completely overlaps that from the previous two retrospective studies, suggesting that a significant fraction of these patients still undergo surgery despite ENETS guideline privileges a wait-and-see strategy. In our view, this phenomenon mostly occurs because every patient diagnosed with cancer is afraid of dying and perceives surgical treatment as the only chance for cure and long-term survival, as do some of the treating physicians. Consequently, NF-PNEN patients are usually referred to and seen by surgeons first, who have the power to direct patients' choices in their hands.

ALTERNATIVE MINIMALLY INVASIVE TREATMENT OPTIONS

Over the last decades, advances in ablative techniques performed under EUS guidance have provided alternatives to surgical resection. Ethanol injection inside PNENs has been reported first,[22] with multiple case reports and case series being published so far. The overall treatment success rate in NF-PNENs varied between 50% and 62.5%, with 20% of AEs mostly related to the amount of the injected ethanol that easily spreads into the surrounding normal pancreatic tissue.[23]

Recently for these patients, EUS-guided radiofrequency ablation (RFA) has become available as a minimally invasive alternative treatment, which acts by delivering thermal energy for producing coagulation necrosis of the tumoral lesion.[24] The available EUS-RFA device (EUSRA™, Taewoong Medical Co., Ltd., Gimpo-si, Gyeonggi-do, South Korea) is a 19-gauge needle that works with a dedicated generator (VIVA RF generator; Taewoong Medical). This is coupled with a cooling system in which a saline-chilled solution circulates within the needle, precluding tissue carbonization and limiting thermal effects outside the region of interest. EUS-RFA, however, is still considered experimental and, at least in Italy, is almost never proposed to patients as a possible management option.

In the last 2 years, four cohorts of patients with small NF-PNENs treated with EUS-RFA have been reported in the literature.[25-28] Overall, 41 patients with 51 lesions (mean diameter: 15.1 mm) have been treated with no severe AEs and a success rate of 86.3% [Table 2]. Interestingly, a self-limiting acute pancreatitis occurred in the first treated patient in the series by Barthet,[26] which led the authors to administer rectal NSAID prophylaxis with no additional acute pancreatitis cases. In another patient, a stenosis of the main pancreatic duct that was running very close to the treated lesion developed and was successfully treated with main pancreatic duct stenting.

Table 2. Case series published so far on EUS-guided radiofrequency ablation of nonfunctional pancreatic neuroendocrine neoplasms with 5 included patients or more

Author, year	Number of patients	Number of lesions	Lesion size (mm)	Needle gauge	Application power and duration		Number of endoscopic sessions	Rate of complete response (%)	Adverse events (*n*)	Follow-up (months)
Barthet, 2019[PS]	12	14	13.1	18	50 W	NR	1	12/14 (85.7)	Acute pancreatitis (1) MPD stenosis (1) Mild postprocedural pain (number unspecified)	12
Oleinikov, 2019[RS]	11	18	14.2	19	10-50 W	5-12 s	NR	17/18 (94.4)	Mild acute pancreatitis (2)	8
Choi, 2020[PS,§]	13	13	18.1	18, 19	50 W	NR	1.7	9/13 (69.2)	Acute pancreatitis (2, one moderate and one mild)	NR
de Nucci, 2020[RS]	5	6	16	19	20 W	10-25 s	1	6/6 (100)	Mild abdominal pain (2)	12

[§]This paper contains patients previously reported in the article by Choi *et al.*, Endoscopy 2018;50:1099-104; [PS]Prospective study; [RS]Retrospective study.
MPD: Main pancreatic duct; NR: Not reported

Remarkably, in a very recent meta-analysis on 51 NF-PNENs treated with EUS-RFA that showed a 93% effectiveness with no severe AEs, a positive response to EUS-RFA was associated with a lesion size ≤18 mm at EUS according to the receiver operating characteristic curve analysis,[29] which is very close to the 2-cm cutoff based on which to decide between surveillance and surgery in the ENETS guidelines.[5] This latter observation suggests that with this approach NF-PNENs might be better treated when small rather than bigger than this size.

Altogether, these results indicate a potential therapeutic role of EUS-RFA, especially for those patients in whom a watchful surveillance strategy should be applied by respecting the ENETS guidelines roles, in order to avoid further progression and to reach the absolute need for surgery. Clearly, proper patient selection should still be needed to prevent overtreatment, as in case of elderly patients with low progression probabilities and those with extremely small lesions. In this regard, two multicenter prospective studies, the RAPNEN study (NCT03834701) and the RFANET study (NCT04520932), are ongoing. These two trials differ in some inclusion criteria: (i) lesion size to enroll (between 15 and 25 mm for the RAPNEN study *versus* <20 mm in the RFANET study); (ii) Ki-67 ≤5% in the RAPNEN *versus* Ki-67 ≤3% in the RFANET; (iii) lesion >2 mm distant from the main pancreatic duct in the RAPNEN *versus* no mention of this variable in the RFANET; and (iv) absence of symptoms/inner calcification in the RAPNEN study *versus* no mention of these variables in the RFANET.

These studies will undoubtedly provide additional data on both safety and effectiveness on large patient populations. Nevertheless, skepticism exists among oncologists and surgeons because RFA does not allow the obtainment of a specimen, rendering impossible to verify the achievement of R0 ablative margins. However, a long-term follow-up (mean: 45.6 months) of the 12 patients with a successful response to EUS-RFA in the first paper published by Barthet,[26] showed recurrent disease after 42 months in only one case, with a biopsy proving G1 NF-PNEN.[30] The patient was scheduled to repeat RFA treatment, but refused.

We believe that a step-up approach, in which the less invasive procedure, *i.e.*, EUS-RFA, is performed first, leaving the more invasive one, *i.e.*, surgery for the failure cases, should be considered, given the indolent nature of these tumors. This treatment strategy has been previously utilized for other preneoplastic and early gastrointestinal cancers, such as gastric and colonic polyps/early carcinoma and low- and high-grade dysplasia and early cancer in Barrett's esophagus, in which endoscopic resection procedures have been a major breakthrough able to avoid more invasive surgeries, especially esophagectomy and gastrectomy.[31-33]

It is also true that at this point, EUS-RFA for NF-PNENs is still experimental and undoubtedly more data are needed to better define the potential and limits of this approach. This, however, will only be possible if EUS-RFA starts to be offered to properly selected NF-PNEN patients as part of the available treatment options [Table 3]. The selection of patients with PNENs for ablative treatments is still debated and a complex of factors are needed to be considered

Table 3. Proposed criteria for treatment decision between surveillance *versus* radiofrequency ablation *versus* surgery in patients with nonfunctioning pancreatic neuroendocrine neoplasms <2 cm and negative lymph nodes, liver, and other distant metastases identified on 68Ga-DOTATATE positron emission tomography/computed tomography

Considered criteria^	Favored strategy^		
	Surveillance	EUS-RFA	Surgical resection
Lesion location	All pancreas	All pancreas	Body/tail
Lesion diameter	≤13 mm	Between 14 and 20 mm	>20 mm
Pancreatic lesion-related symptoms	Absent	Absent	Present
Patient's age*	All ages	All ages	All ages
Significant comorbidities	Present	Present	Absent
MPD dilation	Absent	Absent	Present
Distance from the MPD	Irrelevant	>2 mm	Irrelevant
Lesion stability after the initial 6 monthly evaluation	Yes	No	No
Inner calcifications on cross-sectional imaging (CT/MRI)	Absent	Absent	Present
Ki-67 index evaluation on EUS-guided biopsy samples utilizing FNB needles (%)	≤5	≤5	>5

*Age of patients should be evaluated together with all the other criteria; ^Criteria should be discussed in a multidisciplinary meeting; ˇDifferent therapeutic strategies with pros and cons need to be discussed with patients. MPD: Main pancreatic duct; CT: Computed tomography; MRI: Magnetic resonance imaging; RFA: Radiofrequency ablation; FNB: Fine-needle biopsy

in the decision-making process, such as (i) lesion location since pancreaticoduodenectomy is associated with a significantly higher postoperative morbidity and mortality than distal resections; (ii) lesion size (we think it should be considered between 1.3/1.4 and 2 cm); (iii) presence of comorbidities and life expectancy; and (iv) risk of long-term exocrine and endocrine insufficiency derived from pancreatic resections.

At this stage, EUS-RFA treatment for NF-PNENs should be performed in multicentric research protocols, with clear-cut inclusion and exclusion criteria, after treatment standardization and collaboration between high-volume PNEN centers, in order to accomplish these desired tasks and potentially change the treatment paradigm of patients with NF-PNENs by sparing them from the mortality and morbidity of surgery. This approach will also require a strict follow-up by imaging studies followed by contrast-enhanced EUS, when necessary, to diagnose early recurrence and to fully establish its potential and limitations, and patients who can benefit the most from it.

Of course, we might be wrong and the future will prove that our proposed strategy has no advantages over what is presently recommended (wait-and-see *versus* surgical intervention). Nevertheless, if proven beneficial, EUS-RFA should become the treatment of choice for small NF-PNENs over surgery because of the less invasiveness and should be integrated into treatment algorithms, such as our proposed one [Figure 1], since a sum of variables need to be taken into consideration in case-by-case decision making.

CONCLUSION

EUS-guided RFA for small PNENs is here to stay. More data are needed to establish the proper role of this approach in the treatment algorithm of these patients and the criteria for patients who can benefit the most from it. We believe that time for a step-up approach with EUS-RFA followed by surgery when needed in these selected NF-PNEN patients has arrived. Risks of disease progression following EUS-RFA treatment and surgery-related morbidity and mortality need to be closely monitored and balanced to establish if our proposed approach is of value.

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Conflicts of interest

Alberto Larghi is a consultant for Boston Scientific Corp. and Pentax Medical. All the other authors disclose no financial relationships with a commercial entity producing health-care related products and/or services relevant to this article. Meanwhile, Alberto Larghi is an Editorial Board Member of the journal. This article was subject to the journal's standard procedures, with peer review handled independently of the editor and his research group.

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