Review Article

EUS-guided radiofrequency ablation as an alternative to surgery for pancreatic neuroendocrine neoplasms: Who should we treat?

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ABSTRACT

Pancreatic neuroendocrine neoplasms (PanNENs) are rare tumors, but their incidental diagnosis has significantly increased due to the widespread use of imaging studies. Therefore, most PanNENs are now diagnosed when completely asymptomatic and in early stages. PanNENs are classified according to their grade (Ki-67 index) and can be functional (F-) or nonfunctional (NF-) depending on the presence or absence of a clinical, hormonal hypersecretion syndrome. The mainstay treatment of PanNENs is a surgery that is mostly curative but also associated with significant short- and long-term adverse events. Therefore, less invasive alternative locoregional treatment modalities are warranted. Recently, few case reports and two case series have described EUS-guided radiofrequency ablation (EUS-RFA) for the treatment of patients with both F-PanNENs and NF-PanNENs. If for F-PanNENs EUS-RFA can very easily become the standard of care, for NF-PanNENEs it is still controversial how to select patients for EUS-RFA. A balance between overtreatment (*i.e.*, RFA/surgery in patients who will not progress) and undertreatment (locoregional treatments in patients with undetected metastases) needs to be found based on solid data. The decision should also take into account patients' comorbidity and risk of postoperative death, life expectancy, tumor location, risk of postoperative fistula and postoperative morbidity, and risk of long-term exocrine and/or endocrine insufficiency. To answer the important question on which a patient should be treated with EUS-RFA, properly designed studies to evaluate the efficacy of this treatment in large cohorts of patients with NF-PanNENs and to establish prognostic factors associated with treatment response are urgently needed.

Key words: EUS, individualized therapy, pancreatic neuroendocrine neoplasms, radiofrequency ablation

Access this article online

Quick Response Code:

Website: www.eusjournal.com

DOI: 10.4103/eus.eus_28_19

How to cite this article: Larghi A, Rizzatti G, Rimbaş M, Crino SF, Gasbarrini A, Costamagna G. EUS-guided radiofrequency ablation as an alternative to surgery for pancreatic neuroendocrine neoplasms: Who should we treat? Endosc Ultrasound 2019;8:220-6.

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Received: 2018-10-25; **Accepted:** 2019-04-10; **Published online:** 2019-06-20

INTRODUCTION

Pancreatic neuroendocrine neoplasms (PanNENs) are rare, but their incidence has significantly increased in the last decades due to the widespread use of imaging studies.[1-3] This has led to the incidental diagnosis of a higher number of PanNENs completely asymptomatic and in early stages.[4,5] Although they represent ~1% of all pancreatic neoplasms, their prevalence is about 10%, mostly accounting for low-to-intermediate grade neuroendocrine tumors with a relatively "indolent" clinical course.[1,6] The WHO 2017 classification of PanNENs distinguishes between well-differentiated neuroendocrine tumors (PanNETs) and poorly differentiated neuroendocrine carcinomas (PanNECs). PanNETs are then divided according to a grading scheme based on Ki-67 index in PanNETs-G1 (Ki-67 index ≤3%) and PanNETs-G2 (Ki-67 index between 4% and 20%). PanNECs are all G3, with a Ki-67 index >20%.[7] PanNENs are classified as functional (F-) or nonfunctional (NF-) depending on the presence or absence of a clinical, hormonal hypersecretion syndrome, and the clinical management of these lesions is challenging. The mainstay treatment of PanNENs is surgery, which is associated with a significant benefit in terms of survival.[8] The surgical treatment of localized PanNENs includes both typical and atypical resections. Atypical surgeries, mostly used for well-demarcated and small-sized PanNENs, have been developed to decrease rates of long-term endocrine and/or exocrine impairment observed after typical resection.[9-11] Despite curative, pancreatic surgery is associated with significant short- and long-term adverse events (AEs). A recent systematic review of the literature, including 62 studies, evaluating the most common postoperative complications in PanNENs, has reported that pancreatic fistula occurred in 45% of the cases after tumor enucleation, in 14% after both distal pancreatectomy and pancreatoduodenectomy, and in 58% after central pancreatectomy.[12] Delayed gastric emptying was observed in 5% of the patients after both enucleation and distal pancreatectomy, in 18% after pancreatoduodenectomy, and in 15% after central pancreatectomy.[12] Overall, postoperative hemorrhage occurred in 6% of the cases, in particular in 1% after distal pancreatectomy, in 7% after pancreatoduodenectomy, and in 4% after central pancreatectomy. The overall pooled in-hospital mortality was 4% in distal pancreatectomy, 6% in pancreatoduodenectomy, and 4% in central pancreatectomy.[12] Based on the above data, less invasive alternative therapeutic interventions to avoid short- and long-term AEs of surgery are warranted.

RADIOFREQUENCY ABLATION FOR PanNENs AND CONCLUSIONS

Recently, few case reports and two case series have described radiofrequency ablation under EUS guidance (EUS-RFA) for the treatment of patients with both F-PanNENs and NF-PanNENs.[13-20]

Despite the limited number of published studies, interpretation of results is difficult due to the heterogeneity of these studies in terms of patients and outcome selection. Important variables to consider when evaluating patients for EUS-RFA are the type of PanNENs (functional or nonfunctional), number and dimension of the lesions, and grading and staging of the disease. Table 1 reports the main characteristics of available studies on EUS-RFA for PanNENs.

For F-PanNENs, the goal of treatment is to induce necrosis and death of the large majority of the neuroendocrine tumor cells to abate the hormonal hypersecretion with cessation of symptoms, without the need to obtain complete ablation of the tumor because of its very low malignant potential. Available studies, mostly case report and case series, report that all F-PanNENs were treated without any AEs and showed complete regression of the clinical syndrome.[17-20] In these studies, F-PanNENs were all single insulinomas with a diameter inferior to 20 mm. If the data on F-PanNENs will be replicated on a large cohort prospectively enrolled, EUS-RFA can become the standard of care for these patients, independently on patients and tumor's variables.

For NF-PanNENs, the decision-making process to determine which patients can benefit the most from RFA treatment is more complex than for F-PanNENs. A balance between overtreatment (*i.e.*, RFA/surgery in patients who will not progress) and undertreatment (locoregional treatment in patients with undetected metastases) needs to be found based on the available data. Some investigators, despite all the possible AEs of surgery, redundantly favor resecting all NF-PanNENs to avoid growth and progression.[28-32] On the other hand, several studies explored the safety and feasibility of a nonoperative management approach ("wait-and-see" strategy) for asymptomatic, incidentally discovered NF-PanNENs ≤2 cm[21-27] [Table 2].

Table 1. Characteristics of patients with nonfunctional pancreatic neuroendocrine neoplasms and outcome of their surveillance strategy

Author (year)	Number of Patients	Median follow up	Median tumor size at enrollment (mm)	Number of tumors with growth (%)	Patients with FN metastases	Patients with liver metastases	Patients who underwent surgery (%)	Reason for surgery
Lee *et al.*, 2012[21]	77	Mean 35 (3-153)	10 (3-32)	NS	0	0	2 (3)	1 MPD dilation 1 Unclear reason
Gaujoux *et al.*, 2013[22]	46	34 (IQR 24-53)	13 (9-15)	12 (26)	0	0	8 (17)	5 Patient's choice 3 Tumor growth
Crippa *et al.*, 2014[23]	12	36 (18-66)	14 (10-29)	0	0	0	None	
Kishi *et al.*, 2014[24]	19	45 (19-162)	12 (6-33)	4 (20)	0	0	1 (5)	Tumor growth
Rosenberg *et al.*, 2015[25]	15	NS	14 (8-110)	0	0	3 (20%)^	0	None
Jung *et al.*, 2015[26]	85	Mean 31.5	11.4 (4-20)	15 (17.6)	0	0	12 (14.1)	8 Tumor growth 3 Patient's choice 1 Development of symptoms
Sadot *et al.*, 2016[27]	104	44 (4-223)	12 (IQR 8-17)	53 (51)	0	0	26 (25)	10 Patient's choice 8 Tumor growth 7 Physician's choice 1 MPD dilatation

^Primary tumors were all >2 cm, NS: Not stated, MPD: Main pancreatic duct, IQR: Interquartile range

A conservative approach seemed to be safe as the majority of the observed tumors did not show any significant changes during the follow-up.[21-27] Tumor growth occurred in about one-fourth of the patients (84/358; 23.5%), while surgery was performed in only 49/358 (14.1%). Lymph node metastases were not detected in any patients, while distant liver metastases were detected in the study by Rosenberg *et al.*[25] in three of the 15 patients under surveillance. Based on all these data, the European Neuroendocrine Tumor Society (ENETS) developed guidelines recommending surveillance for the management of patients with lesions ≤2 cm.[34] However, with the exception of the study by Sadot *et al.*,[27] which is a well-designed matched case–control study, all the other studies are retrospective with a low level of evidence and with a short follow-up, which preclude drawing any definitive conclusions about tumor diameter cutoff to identify patients who could benefit from the "wait-and-see" approach *versus* upfront surgery.[35] Moreover, although the cutoff level of ≤2 cm has been widely adopted, other studies have found that larger NF-PanNENs size up to 3 cm did not correlate with behavior, and factors other than size are important.[36] Jiang *et al.*[37] found a correlation between radiologic diameter of 2.5 cm, high tumor grade, symptoms, and lymph nodes metastases. Salinen *et al.*[34] stratified NF-PanNENs into three groups: <2 cm, between 2 and 4 cm, and >4 cm and noted that size alone did not predict behavior. Finally, a study by Ricci *et al.*[38] retrospectively evaluating 102 surgically treated patients affected by NF-PanNENs found that some small tumors (≤2 cm) were T3–4 in 11% and G2–3 in 36.6% of cases. Moreover, lymph node and distant metastases were present in 31% and 8% of the cases, respectively.[38] Exclusion of lymph nodes, liver, and other distant metastases is of paramount importance to enroll a patient for RFA treatment. Regarding lymph nodes metastases, in a study on 181 patients who underwent surgical resection, 55 (30%) of them were found to have lymph nodes metastases.[39] At multivariate analysis, radiologically detected lymph nodes metastases and tumor grade (G2 vs. G1) were the independent risk factors associated with lymph nodes metastases. When tumor grade was excluded, radiologically detected lymph nodes metastases and tumor size larger than 4 cm were the independent risk factors associated with lymph nodes metastases.[39] Based on the ENETS guidelines, staging of patients with NF-PanNENs should be performed using a combination of multidetector computed tomography (CT), magnetic resonance imaging (MRI), and 68Ga-DOTATATE positron emission tomography (PET)-CT with overall good results.[40-43] All these imaging modalities should also be used during follow-up to monitor for disease recurrence at distant sites. Finally, risk stratification also involves the determination of tumor grade. Data on tumor grading in patients who underwent surveillance are limited and reflect the low reliability of cytological determination of Ki-67 on samples acquired under EUS examination. This is due to the heterogeneity of the distribution of Ki-67 within the tumor, making possible a underestimation of the grading of pancreatic sampling.[44,45] In the study by Jung *et al.*,[26] only four out of 77 patients (5.2%)

Table 2. Characteristics of available studies on EUS-radiofrequency ablation for pancreatic neuroendocrine neoplasms

Author (year)	Number of patients	F-PanNENs/ NF-PanNENs	NEN grade	Study type	Patients selection	RF device	Median follow-up (months)	Median tumor size (mm)	Outcome	Efficacy	Adverse events
Barthet *et al.*, 2018[33]	12 (14 NENs)	0/14	Grade 1	Prospective, multicenter	PanNEN <2 cm, unfit or refusing surgery	EUSRA RF electrode; STARmed, Koyang, Korea	12	13.1 (range 10-20)	Complete radiologic ablation	86% (12/14)	1 patient mild pancreatitis
Choi *et al.*, 2018[20]	8	1/7	NA	Prospective, single center	PanNEN <3 cm, unfit for surgery or high surgical risk (ASA III or IV)	EUSRA RF electrode; STARmed, Koyang, Korea	13 (range 8-30)	20 (range 8-28)	Complete radiologic ablation	75% (6/8)	1 patient with abdominal pain; 1 with pancreatitis
Bas-Cutrina *et al.*, 2017[19]	1	1/0	NA	Case report	Unfit for surgery	Habib™ EUS-RFA catheter, Emcision Ltd., London	10	10	Complete radiological ablation. Symptoms resolution	100% (1/1)	0
Waung *et al.*, 2016[17]	1	1/0	NA	Case report	Failure of medical therapy, unfit for surgery	Habib™ EUS-RFA catheter, Emcision Ltd., London	10	18	Complete radiological ablation. Symptoms resolution	100% (1/1)	0
Pai *et al.*, 2015[15]	2	0/2	NA	Prospective, multicenter	NA	Habib™ EUS-RFA catheter, Emcision Ltd., London	3-6	27.5	Change in vascularity and central necrosis	100% (2/2)	0
Armellini *et al.*, 2015[16]	1	0/1	Grade 2	Case report	Refusing surgery	EUSRA RF Electrode; STARmed, Koyang, Korea	1	20	Complete radiologic ablation	100% (1/1)	0
Lakhtakia *et al.*, 2015[18]	3	3/0	NA	Case series	Unfit for surgery	EUSRA RF Electrode; STARmed, Koyang, Korea	12	17.7 (range 14-22)	Symptoms resolution	100% (1/1)	0

NA: Not available, PanNENs: Pancreatic neuroendocrine neoplasms, NEN: Neuroendocrine neoplasms, RFA: Radiofrequency ablation

had Ki-67 detection available, which was G1 in three patients and G3 in one patient. In another study by Rosenberg *et al.*,[25] four out of 15 patients (26.7%) had available Ki-67 determination that showed G2 tumors in all of them. Finally, in the study by Lee *et al.*,[21] 14 of the 77 patients under surveillance had biopsy done that showed a Ki-67 <5% in all cases. At present, very scanty data are available comparing the reproducibility of the grading on biopsy samples acquired with EUS-guided tissue acquisition as compared with that of surgical specimens. One study by Larghi *et al.*[46] using a 19G fine-needle aspiration needle has reported a diagnostic accuracy of 93.3% and a capability of measuring Ki-67 expression in 86.6% and 92.9% of cases. Preoperative and postoperative Ki-67 proliferation indexes were concordant in 83.3% of the patients, whereas two patients were upstaged from G1 to G2 or downstaged from G2 to G1, respectively. Interestingly, when a cutoff of >5% to define G2 tumors, which seems to be more useful than the 3% value to stratify prognosis of patients with NF-PanNENs within the same disease stage,[47-49] was applied, a concordance was found in all cases. Newly developed needles, specifically designed to acquire tissue core biopsy, have been recently become available, which may result in a better performance.[50] Although Ki-67 determination cannot be completely reliable, it can be used together with all the other collected information to reach the final decision on which patients to set for RFA. Among other prognostic factors, incidentally discovered asymptomatic tumors have a greater 5-year progression-free survival than symptomatic tumors.[23,51] Moreover, the presence of calcifications and hypoenhancing tumors is both associated with a higher probability of lymph node and liver metastasis.[52-54]

Regarding EUS-RFA for NF-PanNENs, in a case series by Choi *et al.*,[20] seven patients with a median tumor diameter of 20 mm (range 8–28) were treated with 13 sessions of EUS-RFA. Complete response was achieved in five patients, while two had persistent PanNENs. Regarding AEs, one patient developed abdominal pain and one developed mild pancreatitis that resolved with conventional therapy. In a second series by Barthet *et al.*,[33] 12 patients with 13 NF-PanNEN lesions <2 cm (mean 13.1 mm, range 10–20) were treated with EUS-RFA. At 6 months, complete response was achieved in nine lesions (71%), a volume reduction of >50% diameter was observed in one case, while a decrease in diameter <50% in three and no changes in another one were noticed. At 1-year follow-up evaluation, 12 out of the 13 NF-PanNENs had complete disappearance or necrosis of the lesion (92.3%). AEs were observed in two patients, with one case of pancreatitis that was treated conservatively and one case of main pancreatic duct (MPD) stenosis 7 days after the procedure in a patient treated for a 12 mm NF-PNEN located in the pancreatic neck, 1 mm close to the MPD. Pancreatitis occurred at the first patient treated and made the authors to modify their protocol introducing prophylactic indomethacin 100 mg suppositories. No more cases of pancreatitis were observed thereafter.

Based on all the data presented above, it is still controversial how to select patients for EUS-RFA. This decision should also be balanced with patients comorbidity and risk of postoperative death, life expectancy, tumor location (pancreaticoduodenectomy carries a higher risk than distal resection), risk of postoperative fistula and postoperative morbidity, and risk of long-term exocrine and endocrine insufficiency. Moreover, it is important to remember that EUS-RFA treatment does not preclude subsequent surgery, which can be done in cases of failure. To answer the important question on which patient should be treated with EUS-RFA, properly designed studies to evaluate the efficacy of EUS-RFA treatment in large cohort of patients with NF-PanNENs and to establish prognostic factors associated with treatment response are urgently needed. These studies should be prospective, multicenter to reach a meaningful number of patients, with strict enrollment criteria decided upon a multidisciplinary discussion.

To fill in this gap, we have designed a large prospective study (registered at Clinical.Trials.gov NCT03834701) involving 11 centers (7 centers are ENETS Center of Excellence) with the following entry criteria:

- Distance from the MPD <2 mm
- Single lesion visualized at CT, and/or MRI, and/or EUS
- EUS-FNB-proven NF-PanNENs
- 68Ga-DOTATATE PET/CT positive for a pancreatic lesion and negative for lymph nodes, liver, and other distant metastases
- Hyper- or iso-enhancing pattern at MRI and/or CT with negative lymph nodes, liver, and other distant metastases and absence of inner calcifications
- G1 or G2 ≤5% on histological examination of EUS-guided biopsy samples utilizing FNB needles
- Diameter between 15 and 25 mm
- Absence of symptoms

- For F-PanNENs, a definitive diagnosis of a clinical syndrome related to excessive insulin secretion fasting test, insulin blood levels, C-peptide blood levels and size <20 mm.

Each patient fulfilling the entry criteria will be further evaluated in a multidisciplinary meeting to establish the definitive enrollment into the study.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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