

5th Milan NET Conference

A live and web multimodal meeting among active Italian NET Centers

Wednesday June 12th, 2019

Safety and efficacy of endoscopic ultrasound-guided radiofrequency ablation for the treatment of functional and non-functional pancreatic neuroendocrine neoplasms: A Multicenter prospective study (NCT:03834701)



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RATIONALE (1)

- The mainstay treatment of PanNENs is surgery that, however, is associated significant short- and long-term adverse events
- A recent systematic review including 62 studies: fistula in 45% of the cases after enucleation, in 14% after both distal pancreatectomy and pancreatoduodenectomy, and in 58% after central pancreatectomy

Jilesen AP, et al, World J Surg 2016;40:729-48



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RATIONALE(2)

- Delayed gastric emptying (DGE) observed in 5% after both enucleation and distal pancreatectomy, in 18% after pancreatoduodenectomy and in 15% after central pancreatectomy
- Overall postoperative hemorrhage 6%
- Overall pooled in-hospital mortality 4.7%



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RATIONALE (3)



- Recently, 19 lesions in patients with F-PanNENs and 39 lesions in patients with NF-PanNENs have been treated with EUS-guided radiofrequency ablation (EUS-RFA), with high success rate and low AEs



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RFA for F-PanNENs (19 Lesions)



- All lesions were successfully treated with rapid disappearance of symptoms, without any AEs



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RFA for NF-PanNENs (39 lesions)

Author (yr)	No. of lesions	Mean diameter (mm, range)	6 mos. Follow up	12 mos. Follow up	Complications
Choi (2018)	7	20.3 (8-28)	Reduction diameter from 20 to 6.5mm	5 (71%) complete response	Acute pancreatitis (AP) (1) Abd pain (1)
Barthet (2019)	14	13.1 (10-20)	9 (71%) complete response	12 (86%) complete response	AP (1), MPD stenosis
Oleinikov (2019)	18	12.2 (4.5-29)	17 (94%)	N/A	Mild AP (2)

Choi JH, et al. Endoscopy 2018;50:1099-104.

Barthet M, et al. Endoscopy 2019:in press.

Leinikov K, et al. J Clin Endocrinol Metab 2019;2104:2637-47



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RATIONALE (4)



- The safety data, however, are still limited and it is still not clear how to select patients for EUS-RFA, in particular NF-PanNENs



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AIMS

Primary AIM

To evaluate the **safety** of EUS-RFA in large cohort of patients with F- and NF-PanNENs



Secondary AIMS

- a) To evaluate the **effectiveness** of EUS-RFA treatment
- b) To evaluate the rate of patients who will require **secondary surgery**
- c) To evaluate the **factors associated with response** to RFA treatment



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STUDY DESIGN

(11 Centers, 22 F- and 55-NF-PanNENs)

ENROLLMENT 12 months



EUS-RFA



FOLLOW UP

Minimum 12 months



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Inclusion criteria

For patients with F-PanNENs (almost all insulinomas)

- Size < 20mm

 For patients with NF-PanNENs

- Age ≥ 18 years and <80 years
- Diameter between 15mm and 25mm
- EUS-FNB proven NF-PanNENs, G1 or G2 $\leq 5\%$
- ^{68}Ga -DOTATATE PET/CT, CT, MRI negative for LN and other MTX
- Hyper- or Iso-enhancing pattern at MRI and/or CT, without calcifications
- Absence of symptoms



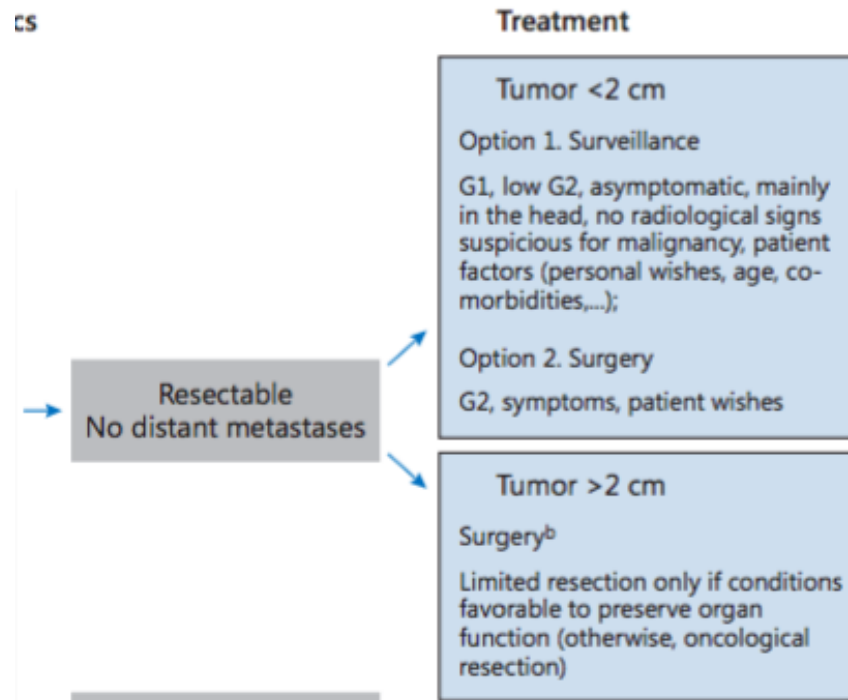
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Author (year)	Number of Patients	Median follow up	Median tumor size at enrollment (mm)	Number of tumors with growth (%)	Patients with FN metastases	Patients with liver metastases	Patients who underwent surgery (%)	Reason for surgery
Lee <i>et al.</i>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

Larghi A, et al. Endosc Ultrasound 2019; in press.



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Inclusion criteria

- Ki-67 \leq 5%

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

Scarpa A, et al. Mod Pathol 2010;23:824-33.

Panzuto F, et al. J Clin Oncol 2011;29:2372-7.

Rindi G, et al. J Natl Cancer Inst 2012;104:764-77



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Definitive Enrollment



Each single patient fulfilling the inclusion criteria will be discussed in a multidisciplinary meeting to establish the definitive enrollment



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Main study parameter/endpoints

SAFETY: Rate of procedural and post-procedural AEs

EFFECTIVENESS:

F-PanNENs: complete disappearance of symptoms related to the hyper-hormonal secretion syndrome

NF-PNENs: 68Ga-DOTATATE PET/CT - DW-MRI - CT at 1 year

Complete response: No enhancing tissue, if questionable EUS-CH

Partial response: detectable pancreatic lesion with enhancing tissue $\leq 30\%$, negative lymph node and distant metastases

Absent response: detectable pancreatic lesion, enhancing tissue $>30\%$, with/without lymph node and distant metastases



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Main study parameter/endpoints

SECONDARY SURGERY

Need for surgery in patients with no response/failed or partial/recurrence to RFA treatment will be discussed in a multidisciplinary meeting

FACTORS ASSOCIATED WITH RESPONSE TO EUS-RFA TREATMENT IN NF-PanNENs

Univariate and multivariate analysis of demographic data, tumor data, and outcome data will be performed to determine factors associated with response to treatment

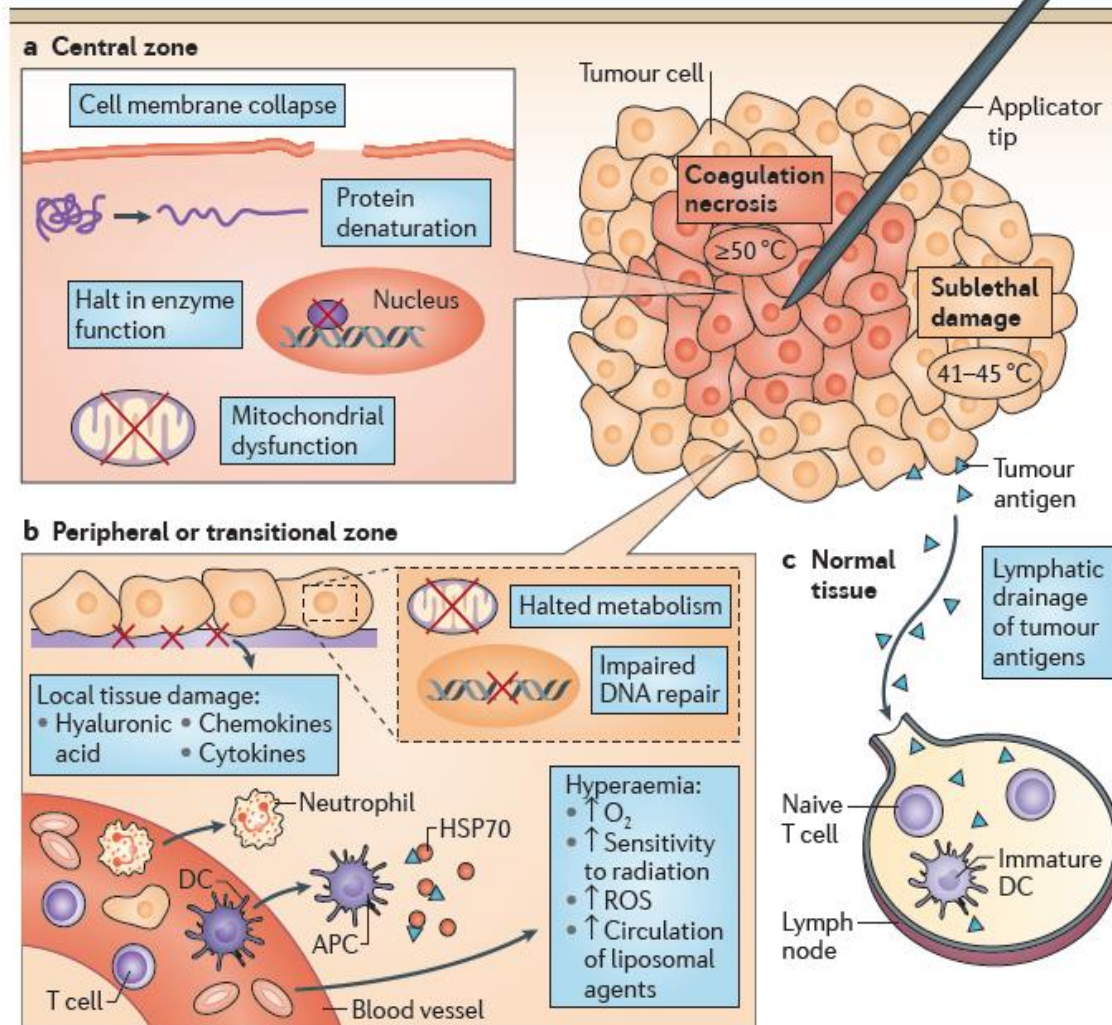


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Beyond Physics: RFA and Immunology





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Participating Centers

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Rome

Verona

Milan, Istituto dei Tumori

Milan, San Raffaele Hospital

Milan, Garbagnate Hospital

Turin

Middle East:

Jerusalem

Europe:

Rotterdam

Santiago di Compostela

Dublin

Leuven

Lyon

Newcastle

Stockolm





ENETS CoE Synergy Grant

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