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**Endoscopic ultrasound radiofrequency ablation of pancreatic insulinoma in elderly patients: Three case reports**

Rossi G *et al.* EUS RFA of insulinoma

## **Abstract**

### **BACKGROUND**

Endoscopic ultrasound (EUS)-guided radiofrequency ablation (RFA) has been recently proposed as a local treatment for functional pancreatic neuroendocrine neoplasms (F-pNENs) unfit for surgery, in order to obtain clinical syndrome regression. Data about safety and long term effectiveness of this approach are scanty, and EUS-RFA procedures not standardized.

### **CASE SUMMARY**

The present case series reports on 3 elderly patients with a pancreatic insulinoma and comorbidities, locally treated by EUS-guided RFA with clinical success on hypoglycemic symptoms. RFA procedures were performed in deep sedation, under EUS control with a 19 G needle, an electrode 5-mm in size at a power of 30 W and multiple RFA applications during the same session in order to treat the whole area of the lesions. An immediate relief of symptoms was evident in 2 patients after the first EUS-RFA, while in the third patient a second endoscopic treatment was needed. All the 3 patients are symptoms-free without need of medications after 24 mo of follow-up with imaging follow-up showing no disease recurrence. As for adverse event, a single intraprocedural bleeding occurred, being endoscopically treated with success.

### **CONCLUSION**

EUS-RFA can represent an effective and safe alternative to surgery for the treatment of insulinomas in elderly patients at high surgical risk, but larger multicenter studies with longer follow-up are needed in order to better assess its safety and clinical success.

**Key Words:** Endoscopic ultrasound; Radiofrequency ablation; Insulinomas; Neuroendocrine neoplasms; Ablative therapies; Case report

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**Core Tip:** Endoscopic ultrasound (EUS)-guided radiofrequency ablation (RFA) has been proposed as a local treatment for functional pancreatic neuroendocrine neoplasms unfit for surgery but data about safety and long term effectiveness are scanty and procedures not standardized. The present case series reports on 3 elderly patients with comorbidities diagnosed with a pancreatic insulinoma that received local treatment by EUS-guided RFA with standardized protocol, with clinical success on hypoglycemic symptoms in a relatively long follow-up. Effective EUS-RFA can represent an alternative to surgery for the treatment of insulinoma in elderly patients at high surgical risk, but larger multicenter studies with longer follow-up are needed in order to assess safety and clinical success.

## **INTRODUCTION**

Pancreatic neuroendocrine neoplasms (p-NENs) incidence has increased over the last decades due to the advances in imaging methods<sup>[1]</sup>.

Non-functional p-NENs that were typically diagnosed at advanced stages when the volume of the lesions determined symptoms, are now often incidentally diagnosed as small (< 2 centimeters) lesions for which whether any treatment should be pursued is debatable<sup>[2]</sup>.

Functional p-NENs (F-pNENs) are usually recognized at early stages, due to the presence of a specific syndrome<sup>[3]</sup>. Surgery is always indicated in such symptomatic cases as a gold standard. However, given the high morbidity and mortality of pancreatic surgery, alternative treatments such as endoscopic ultrasound (EUS)-guided radiofrequency ablation (RFA) can be considered in order to obtain the resolution of the syndrome in elderly patients with comorbidities and high surgical risks.

The current literature<sup>[4]</sup> is scanty regarding data on EUS-RFA treatment of F-pNENs. Therefore, safety concerns remain and long-term data about the efficacy of the treatment are needed<sup>[5]</sup>. Moreover, specific RFA settings (particularly in terms of ablation power) are not standardized.

## **CASE PRESENTATION**

### ***Chief complaints***

This is a case series presenting data about feasibility, safety and clinical efficacy of EUS-guided RFA to induce the relief of clinical syndrome in 3 elderly patients with symptomatic pancreatic insulinomas at high surgical risk.

### ***History of present illness***

3 elderly patients with symptomatic pancreatic insulinomas underwent to a total of 4 EUS-RFA procedures performed after failure or limited control with medical treatments.

**Case 1:** A 84 year-old male had repeated episodes of syncope since 3 years, associated with blood glucose < 20 mg/dL and neuroglycopenic symptoms with prompt relief of symptoms following the administration of glucose. Insulinoma diagnosis was supported by the next preoperative fasting test.

**Case 2:** A 82 year-old male patient, with 2 previous syncopal episodes with marked hypoglycemia (glucose = 38 and 32 mg/dL) was referred to our center. Fasting test confirmed diagnosis with glucose and C-peptide levels (glucose 40 mg/dL, C-peptide 0.7 ng/mL).

**Case 3:** A 84 year-old female patient was referred to our center after two years of symptomatic hypoglycemic episodes (glucose < 30 mg/dL). Fasting test was suggestive

for pancreatic insulinoma, with neuroglycopenic symptoms after fasting associated to glucose 30 mg/dL and C-peptide 0.9 ng/mL (normal values: 1.1-4.4 ng/mL).

### *History of past illness*

**Case 1:** The patient was suffering from a chronic renal failure and severe ischemic heart disease.

**Case 2 and Case 3:** Patients were affected by severe chronic obstructive pneumopathy disease.

### *Personal and family history*

No family history of NENs was present in all the cases.

### *Physical examination*

Case 1 presented a moderate grade of obesity. Other patients did not present particular signs at physical examination.

### *Laboratory examinations*

All the patients had consistent and constant neuro glycopenic symptoms and diagnosis was supported by blood elevated insulin, C-peptide and proinsulin blood levels at preoperative fasting test. The same plasma markers were used after EUS-guided RFA to support the relief of hypoglycemic symptoms and clinical syndrome.

### *Imaging examinations*

All the patients had consistent and constant neuro glycopenic symptoms and diagnosis was supported by blood elevated insulin, C-peptide and proinsulin blood levels at preoperative fasting test. The same plasma markers were used after EUS-guided RFA to support the relief of hypoglycemic symptoms and clinical syndrome.

### **MULTIDISCIPLINARY EXPERT CONSULTATION**

Patients were referred to our multidisciplinary neuroendocrine tumor board and due to the age and comorbidities, it was decided to treat the lesions with EUS-RFA at the Hospital Endosonography Unit.

### **FINAL DIAGNOSIS**

A cytological diagnosis of insulinoma was obtained with EUS-FNA in case 2. In case 1 and case 3 patients the clinical, biochemical and radiological scenario was considered typical for insulinoma and multidisciplinary evaluation considered the biopsy unnecessary as cited in international guidelines<sup>[2,6]</sup>.

### **TREATMENT**

During endoscopic procedures patients underwent to deep sedation and were placed in left lateral position. In each individual case RFA was delivered by a 19-Gauge needle (EUSRA; STARmedCo, Ltd; Koyang, Korea), with a 5 mm-active monopolar electrode on the distal part of the probe (delivering the ablation). Needle was inserted in the operative channel of a therapeutic EUS-scope (Pentax EG-3870UTK or Pentax 38J10UT), connected to an ultrasound platform (Hitachi Arietta 750 or Hitachi Arietta 850). Needle was also connected to a RFA generator (VIVA; STARmedCo, Ltd; Koyang, Korea) delivering the thermal energy to ablate the lesions and it was also connected to a peristaltic pump infusing cold saline solution (at 0 °C, to avoid tissue charring around the probe, maximizing the lesion ablation volume). Figure 1 describes RFA system. Generator was set at 30-W of power in all the procedures and treatment was applied for different times depending on tissue impedance (system was stopped at impedance > 500  $\Omega$ , resulting in an ineffective treatment), until a complete “cloud effect” has been obtained in the lesion area (multiple RFA applications were performed during the same endoscopic session).

Every patient underwent a computed tomography (CT)-scan after 24-72 h from RFA procedure, in order to assess the size of necrotic area inside the lesions and exclude complications.

### *Case 1*

One single endoscopic session was conducted with 4 subsequent EUS-RFA applications at 3 W for 12-16-12-10 s each with stop at impedance increase.

### *Case 2*

A first RFA procedure was performed, with 3 applications lasting 20, 15 and 15 s each with a power of 30 W. A complete relief of symptoms was not obtained, while a 72-h CT-scan showed a 7 mm hypodense necrotic area. Blood tests were consistent with the ablation failure.

A second EUS-RFA session was performed after 1 mo. 4 RFA applications were carried out for a respective time of 10, 8, 6, 8 s, until a complete covering of the pancreatic insulinoma by an hyperechoic cloud. Possibly due to the proximity between the lesion and gastroduodenal artery (Figure 2), an immediate post-procedural bleeding was endoscopically evidenced with a submucosal hematoma located at the superior duodenal genus, due to a side-branch artery injury. Bleeding was immediately treated by mechanical (metallic clip) and injective (adrenalin dilution: 1:10000) hemostatic therapy with success (Figure 3).

### *Case 3*

The procedure was performed by 3 applications lasting 6 s each at the standard power of 30 W.

## **OUTCOME AND FOLLOW-UP**

### *Case 1*



No immediate or late complications occurred and an immediate clinical success with syndrome relief was obtained. CT-scan performed 48-h after the procedure showed a 14 mm hypodense necrotic area in the context of pancreatic tail, as outcome of procedure. A subsequent diagnostic EUS performed after 3 mo, showed a total not-vascularized 12mm-area at contrast enhancement (Sonovue®, Bracco) in the site of previous RFA (Video). The patient is still asymptomatic (with mild hyperglycemia), after 27-mo of clinical follow up. No further radiological examinations were performed due to chronic renal failure and related-risks of CT or magnetic resonance imaging (MRI)-contrast medium administration.

### *Case 2*

Patient showed the relief of hypoglycemic symptoms immediately after the second procedure with normalization of glucose blood levels. A CT-scan performed 72 h after RFA revealed a 8-mm hypodense necrotic area at the site of the lesion, without evidence of bleeding signs (Figure 4). The patient refused further radiological follow-up nevertheless a complete symptoms relief persists at 24 mo with normalization of the biochemical tests.

### *Case 3*

CT-scan with contrast enhancement was performed 72 h after the RFA and confirmed the presence of a 13-mm necrotic area inside the lesion; a complete relief from hypoglycemic symptoms was obtained.

After 15 mo the patient remains asymptomatic without need of treatment. A contrast enhanced-MRI performed 14 mo after the procedure confirmed the complete disappearance of the treated lesion located in pancreatic body.

## **DISCUSSION**

EUS-RFA represents a potentially useful and safe option to treat insulinomas and related symptoms in patients at high surgical risk, especially in case of pancreatic head/neck lesions, requiring a Whipple resection.

EUS-RFA is relatively safe, although specific care needs to be paid regarding the bleeding risk of such hypervascularized lesions. Usually RFA-related complications can be readily endoscopically treated by a high-experienced endoscopist. In the present series, EUS-RFA led to symptoms relief during a relatively long follow-up, with the need of a single endoscopic session in 2 patients and of 2 endoscopic sessions in another. Notably, while most of the published case series on this topic<sup>[7-10]</sup> did not present specific and standardized ablation settings, in the present study we have standardized the setting of the ablation power in line with previous *ex-vivo* animal<sup>[11]</sup> and human studies (unpublished data), with the application of 30 W and stopping the energy delivery at the increase of tissue impedance. All the 3 patients are symptoms-free after more than 12 mo of clinical and biochemical follow-up and the lesion is no longer visible after 14 mo in one of the patients who underwent radiological examination.

## **CONCLUSION**

Larger multicenter studies with a longer and standardized follow-up are needed in order to confirm the actual safety and protracted clinical success of EUS-RFA in this scenario. In this view, the results of a large multicenter study endorsed by the European Neuroendocrine Tumour Society that is ongoing are eagerly awaited (ClinicalTrials.gov Identifier: NCT03834701).

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