NEW METHODS

EUS-guided radiofrequency ablation for management of pancreatic insulinoma by using a novel needle electrode (with videos)

Sundeep Lakhtakia, DM,1 Mohan Ramchandani, DM,1 Domenico Galasso, MD,2 Rajesh Gupta, DM,1 Sushma Venugopal, MD,3 Rakesh Kalpala, DNB,1 D. Nageshwar Reddy, DM1
Hyderabad, India; Rome, Italy; Brooklyn, New York, USA

Background and Aims: Insulinomas are one of the most common functional pancreatic neuroendocrine tumors. Surgical removal is the standard of care. Patients unfit for or refusing surgery need an alternative nonsurgical method to alleviate symptoms. EUS has been used to localize, aspirate, and tattoo insulinomas and to inject alcohol for local ablation. This study is aimed at assessing the feasibility of EUS-guided radiofrequency ablation (EUS-RFA) for managing patients with a symptomatic insulinoma by using a novel EUS-RFA needle electrode.

Methods: The EUS-RFA system used consists of a prototype 19-gauge needle electrode, generator, and internal cooling system. EUS-guided RFA is performed under real-time visualization at 50 W to ablate pancreatic insulinomas.

Results: In this observational human case series from a tertiary care center, 3 patients with a symptomatic pancreatic insulinoma, not eligible for surgery, underwent EUS-RFA by using an internally cooled prototype needle electrode. All had rapid symptom relief with biochemical improvement and remained symptom free at 11 to 12 months of follow-up. There were no procedure-related adverse events.

Conclusions: EUS-RFA with the novel device can be considered in select patients with a symptomatic pancreatic insulinoma based on preliminary findings of a beneficial effect without adverse events. Assessment of the safety profile requires larger prospective trials.

An insulinoma is the most common functional pancreatic neuroendocrine tumor (PNET), with the majority (90%) being small (<2 cm) and benign. The associated debilitation is related to hypoglycemia secondary to excessive uncontrolled insulin production. Whipple’s triad helps to identify insulinomas. Increased fasting serum insulin and C-peptide assist in the diagnosis.

Surgery is the standard of care for PNETs, with occasional adverse events including pancreatic fistulae and deep vein thrombosis leading to a pulmonary embolism. Patients unfit for or refusing surgery require alternative treatment.1 Medical therapy is costly and may have significant adverse effects. Embolization and ablation are options.2-25

BACKGROUND

Radiofrequency ablation (RFA) has been used to treat abdominal tumors, including hepatic tumors.2-4 However, pancreatic tissue is particularly sensitive to external insults, including heat, leading to slower adoption of RFA for pancreatic tumors.4-11 Reported adverse events with RFA (eg, pancreatitis or GI hemorrhage) are disputed.5,8,9,11 RFA with palliative surgery reportedly provided survival benefit in unresectable pancreatic cancer patients.5

EUS-guided RFA (EUS-RFA) in the pancreas of animals is feasible, with an acceptable incidence of pancreatitis.12-15
One study suggested EUS-RFA for managing small PNETs.12 Effective embolization of insulinomas was reported 3 decades ago.16-18 Recently, successful EUS-guided ablation by using ethanol injection was reported.19-21 RFA treatment of insulinomas has been administered percutaneously under CT guidance, intraoperatively, or endoscopically under EUS guidance.22-25 To the best of our knowledge, only 3 cases were reported to date in which EUS-RFA was used for the management of insulinomas,24,25 and this report presents the first clinical cases in which a novel EUS-RFA needle electrode was used in select patients with outcomes through 12 months.

Figure 1. A, Needle electrode (EUS-guided radiofrequency ablation). B, Close-up of the tip of the needle electrode showing the uncovered 1-cm tip. C, Needle electrode projecting from the echoendoscope tip. D, Handle of the needle electrode attached to the accessory channel of the echoendoscope. E, Viva Combo RFA generator, front view. F, Viva Combo RFA generator, side view. G, Viva pump.
METHODS

Patients

The observational study, approved by the institutional review board of the Asian Institute of Gastroenterology in January 2014, included patients with a pancreatic insulinoma refusing surgery or unfit for it after informed consent. To avoid any thermal injury to adjacent normal pancreatic tissue, lesions larger than 1 cm were preferred, so as to accommodate the entire 1-cm length of exposed needle electrode.

| TABLE 1. Patient and insulinoma characteristics and procedure details |
|-----------------|-----------------|-----------------|
| Age, y/sex      | 42/male         | 41/male         | 52/male         |
| Presentation    | Hypoglycemia with recurrent episodes of seizures for 4 y | Hypoglycemia with frequent eating and significant weight gain for 1 y | Hypoglycemia with recurrent episodes of syncope for 2 y |
| EUS-based lesion characteristics | Single hypoechoic PNET at the body; 14 x 12 mm; early signs of chronic pancreatitis | Single hypoechoic PNET at the genu; 17 x 12 mm | Multiple hypoechoic PNETs in the head, body, and tail; largest PNET (22 x 19 mm) in head is targeted for ablation |
| Reason for refusing surgery | Risk associated with poor cardiac status | Risk associated with obesity | Concern over major surgery |
| EUS-RFA         | Access route    | Transgastric    | Transgastric    | Transduodenal |
|                 | No. of needle electrode passes | 3              | 2              | 4              |
|                 | No. of ablation areas | 4              | 3              | 8              |
| Pre–EUS-RFA     | Blood sugar, mg/dL | 43             | 39             | 49             |
|                 | Fasting insulin, μIU/mL* | 41.1           | 51.2           | 36.2           |
|                 | C-peptide, ng/mL† | 4.0            | 5.8            | 5.5            |
|                 | Amylase, U/L     | 56             | 75             | 68             |
|                 | Lipase, U/L      | 34             | 27             | 48             |
| Immediate peri–EUS-RFA | Adverse events | None | None | None |
|                 | Amylase, U/L     | 92             | 102            | 93             |
|                 | Lipase, U/L      | 99             | 78             | 88             |
|                 | Symptoms         | None | None | None |
| 48-h post–EUS-RFA | Blood sugar, mg/dL | 72             | 87             | 91             |
|                 | Fasting insulin, μIU/mL* | 10.7           | 19.8           | 25.5           |
|                 | C-peptide†       | 2.4 ng/mL      | 3.6 ng/mL      | 4.0 ng/mL      |
| Mid-term post–EUS-RFA | Blood sugar, mg/dL | 3 mo | 70 | 88 | 90 |
|                 | Fasting insulin, μIU/mL, 11-12 mo* | 3-5 mo | 110 | 111 | 115 |
|                 | C-peptide, ng/mL, 11-12 mo* | 2.4 | 3.3 | 2.7 |
|                 | Symptoms         | 3 mo | None | None | None |
|                 | 5-6 mo | None | None | None |
|                 | 11-12 mo | None | None | None |

PNET, Pancreatic neuroendocrine tumor; EUS-RFA, EUS-guided radiofrequency ablation.

*Fasting serum insulin: normal range 2.6-24.9 μIU/mL.
†C-peptide: normal range 1.1-4.4 ng/mL.
Materials
The EUS-RFA system (Fig. 1) (STARmed, Seoul, South Korea) consists of the following:
1. A prototype needle electrode: 19-gauge, 140-cm long, covered with a sheath. The inner metal part is insulated over its entire length except for the terminal 1 cm with a sharp conical tip for energy delivery.
2. A generator (VIVA RF generator, STARmed) with variable wattage settings is connected to the handle of the needle electrode. Energy delivery is controlled by a foot switch.
3. An internal cooling system that has 2 tubes connected to the needle electrode handle. The inflow tube is connected via a pump to an external cold (0°C) saline solution bottle. Chilled saline solution circulates through the needle electrode during the RFA procedure. Warmed saline solution flows out through the outflow tube into an external container. This continuous cooling mechanism prevents charring of the surface of the electrode, improving accuracy of ablation.

Procedure
The needle electrode is passed under EUS guidance into the target lesion crossing a minimum of normal pancreatic tissue and avoiding pancreatic or bile duct. Puncture of interposing major vessels is avoided by using Doppler. The echogenic needle tip is positioned at the far end inside the lesion. The energy delivery (burn) was carefully applied only when the needle tip of the electrode was visualized within the margin of lesion on EUS.

Figure 2. A, Abdominal contrast-enhanced CT in the arterial phase shows an enhancing lesion (insulinoma) in the pancreatic genu (arrow). B, Well-defined hypoechoic oval-shaped lesion (insulinoma) in the pancreatic genu (arrow).

Figure 3. Post–EUS-guided radiofrequency ablation at 6 weeks. Contrast-enhanced CT shows a hypodense nonenhancing lesion in the genu of pancreas (arrow).

Figure 4. Post–EUS-guided radiofrequency ablation at 12 months. EUS shows a small residual hypoechoic lesion (arrow) with patchy echogenic areas.
The energy setting was 50 W. On pressing the foot pedal once, echogenic bubbles start appearing around the needle tip indicating completeness of RFA at the site. The generator is then switched off with the foot pedal. A coagulation necrosis area of approximately 10 to 12 mm is produced in approximately 10 to 15 seconds. If needed, the electrode is repositioned under EUS visualization to ablate another proximal area along the same trajectory. Additional passes by using a fanning technique can be used to further ablate the same lesion. Efforts are made to first ablate the most technically challenging segment of the lesion as visual artifacts may occur after applying RFA. The completeness of ablation is assessed endosonographically.

RESULTS

Three patients with symptomatic insulinomas were treated by using EUS-RFA and followed for 11 to 12 months (February 2014 to January 2015). Table 1 provides patient and lesion characteristics and procedure details. Table 1 also summarizes key outcomes.

There were no adverse events related to the procedure. Hypoglycemia with elevated fasting insulin and C-peptide levels was documented before EUS-RFA in all cases. Hypoglycemia relief was rapid, with blood sugar levels at 80 to 100 mg/dL within 24 hours. The patients remained euglycemic and asymptomatic at all visits through 11 to 12 months after insulinoma ablation.

Case 1

A 42-year-old man with significant alcohol intake and cardiomyopathy presented with a 4-year history of recurrent seizures. Abdominal contrast-enhanced CT (CECT) failed to detect any pancreatic lesions. EUS showed a well-defined pancreatic body lesion and early chronic pancreatitis in adjacent parenchyma. On the first needle electrode pass, 2 areas in the same trajectory were ablated from the far to the near end. On the second pass, a more distal aspect of the lesion was targeted (Video 1, available online at www.giejournal.org) to achieve complete tumor ablation. The patient had rapid relief of hypoglycemia with maintained normal blood sugar on serial monitoring. At 48 hours, serum insulin and C-peptide levels were reduced. CECT and EUS at 8 months after RFA did not show any visible pancreatic mass lesion. He remained asymptomatic throughout 12 months.

Case 2

A 41-year-old man presented with recurrent hypoglycemia for 1 year, leading to frequent eating, including at night, causing weight gain and an increased body mass index of 46.8 kg/m². Abdominal CECT showed an enhancing pancreatic genu lesion (Fig. 2A) confirmed on EUS (Fig. 2B). He underwent EUS-RFA of the insulinoma with resolution of hypoglycemia on the same day. During the next 48 hours of hospital stay, he remained euglycemic without excessive hunger and significant reduction of fasting insulin and C-peptide levels. At 6 weeks, CECT showed a hypodense nonenhancing lesion in the genu of the pancreas (Fig. 3). At 6 months, fasting serum insulin and C-peptide levels were 29.3 μU/mL and 4.1 ng/mL, respectively. At 12 months, he remains asymptomatic with an 18-kg weight loss and a small residual lesion on EUS (Fig. 4).

Case 3

A 52-year-old man presented with a 2-year history of recurrent syncope from hypoglycemia. Abdominal CECT showed enhancing lesions in the head and body of the pancreas. (Fig. 6).
pancreas (Fig. 5). EUS showed a large hypoechoic lesion (22 x 19 mm) in the head of pancreas close to and inferior to the prepapillary pancreatic duct, with additional lesions in the uncinate (5 mm), body (12 x 10 mm), and tail (8 mm) (Video 2, available online at www.giejournal.org). EUS-FNA cytology from the larger lesion suggested benign PNET. Presuming the pancreatic head lesion to be the principal culprit, transduodenal EUS-RFA was performed in the short echoendoscope position. The needle electrode became deformed at completion of the procedure, which was presumed to be due to a combination of factors: transduodenal access route, the target PNET location in the head of the pancreas, and the need for 4 needle passes. He had no further hypoglycemia. At 48 hours, fasting insulin and C-peptide levels were normal, and CECT showed peripheral rim enhancement. At 3 months, fasting serum insulin was 11.1 μU/mL. Abdominal CECT still showed a pancreatic head lesion with rim enhancement and a central nonenhancing hypodense area (Fig. 6). EUS showed a peripheral hypoechoic lesion with irregular anechoic and echogenic areas. He is asymptomatic at 11 months.

**DISCUSSION**

Our series provides early illustration of the feasibility of EUS-RFA for the treatment of symptomatic insulinomas by using a novel EUS-RFA needle electrode. Excellent beneficial effects seem immediate and were maintained for several months with no adverse events. In selected patients for whom surgery is not an option or who refuse surgery, EUS-RFA seems a promising option. The novel EUS-RFA system used in this case series appears to provide very good procedural control. Procedural optimization, and ultimately standardization, will require multicenter experience. In addition, although no adverse events were observed in this small case series, this constitutes insufficient assessment of the safety profile, which will need to be addressed in a larger prospective trial.

The obvious drawback of this ablative method is its palliative nature given the possibility of growth of the remnant tumor. However, in patients unfit for or unwilling to undergo surgery but with clinically debilitating symptoms, EUS-RFA may offer an excellent management option. Multicenter studies involving larger numbers of patients with longer follow-up are needed to establish the efficacy of this novel treatment method.

**REFERENCES**


