REVIEW ARTICLE

Radiofrequency ablation for the management of symptomatic pancreatic insulinomas

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Background and Aims: Insulinomas are among the most common types of functional pancreatic neuroendocrine tumors and can cause debilitating, recurrent, symptomatic hypoglycemia. Pancreatic resection can be curative, but many patients are not candidates for major pancreatic surgery. EUS-guided radiofrequency ablation (EUS-RFA) is a novel minimally invasive technique for ablation of pancreatic tumors.

Methods: In this article and accompanying video, we describe the EUS-RFA ablation device, provide instructions for device setup, and review outcomes of a case series of EUS-RFA for symptomatic insulinomas. We also review the current literature describing EUS-RFA for symptomatic pancreatic insulinomas.

Results: This series of patients in the United States, as well as studies performed in other countries, suggests normalization of insulin levels that appears to be sustained over months to years following the procedure. There has been a favorable adverse event profile in the case series reported to date.

Conclusions: EUS-RFA is emerging as a promising option for the management of symptomatic insulinomas, particularly for patients who are poor surgical candidates or who decline surgery. (VideoGIE 2024;9:45-50.)

INTRODUCTION

Insulinomas are among the most common types of functional pancreatic neuroendocrine tumors (pNETs) and can cause debilitating, recurrent, symptomatic hypoglycemia.[1] Surgical resection is the mainstay of treatment for symptomatic pNETs.[2] However, pancreatic resection can be associated with significant morbidity and mortality, and many patients are not good surgical candidates because of age and/or comorbidities.[3] Radiofrequency ablation uses thermal energy to induce cell death by coagulative necrosis and protein denaturation and is in widespread use for hepatocellular, renal, and lung cancers.[4] EUS-guided radiofrequency ablation (EUS-RFA) is a novel minimally invasive technique that enables real-time image guidance for ablation of pancreatic tumors.

Abbreviations: EUS-RFA, EUS-guided radiofrequency ablation; pNET, pancreatic neuroendocrine tumor.

2468-4481
https://doi.org/10.1016/j.vgie.2023.08.007

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Small case series of EUS-RFA for insulinomas performed outside of the United States have demonstrated promising results (Table 1).[5-10] Clinical success was defined as disappearance of clinical symptoms, and safety was defined as the absence of adverse events. A retrospective study of 3 patients with insulinomas in India demonstrated clinical improvement within 2 days of ablation, which was sustained over an 11- to 12-month follow-up period. No adverse events were noted.[5] A retrospective study in Israel on 7 patients with insulinomas found a clinical response in all patients that was sustained after a mean follow-up period of 10 months. No major adverse events were noted.[6] In a prospective study in Italy, 5 patients were successfully treated with EUS-RFA with a mean follow-up period of 12 months.[7] In France, clinical success with EUS-RFA was seen in 6 out of 7 patients with insulinomas with a mean follow-up period of 21 months. Adverse events included 1 patient with mild postprocedural abdominal pain, 1 with mild postprocedural pancreatitis managed conservatively, and 1 with fever and abdominal pain 7 days postprocedure treated with antibiotics. One older patient developed a retrogastric bleed 15 days after treatment and died 1 month after the procedure.[8] A retrospective study of 10 patients with insulinoma in Italy demonstrated clinical success in all patients 3 months after the procedure with 3 procedure-related early adverse

TABLE 1. Case series reporting the efficacy and safety of EUS-guided radiofrequency ablation for the treatment of symptomatic insulinomas by author and country

Study, year, country	Study design	No. of patients/ no. of insulinomas	Mean tumor size (mm)	Location	No. of radiofrequency ablation sessions/ nodules	Efficacy	Adverse events	Follow-up period (mo)
Lakhtakia et al, 2016, India[5]	Retrospective	3/3	19	Head	1	100	0	11.5
Oleinikov et al, 2019, Israel[6]	Retrospective	7/7	14.9	Head: 7 Tail: 2	1	100	0	9.7
De Nucci et al, 2020, Italy[7]	Prospective	5/5	12.8	Tail	1	100	0	12
Marx et al, 2022, France[8]	Retrospective	7/7	13.3	Head: 1 Tail: 6	1	85.7	4	21
Borrelli de Andreis et al, 2022, Italy[9]	Retrospective	10/10	11.9	Head: 3 Tail: 7	9:1, 1:2	100	3	3
Rossi et al, 2022, Italy[10]	Retrospective	3/3	12	Head: 1 Tail: 2	1:2, 2:1	100	1	24

All procedures were performed with a 19-gauge radiofrequency ablation trocar under echoendosonographic guidance.

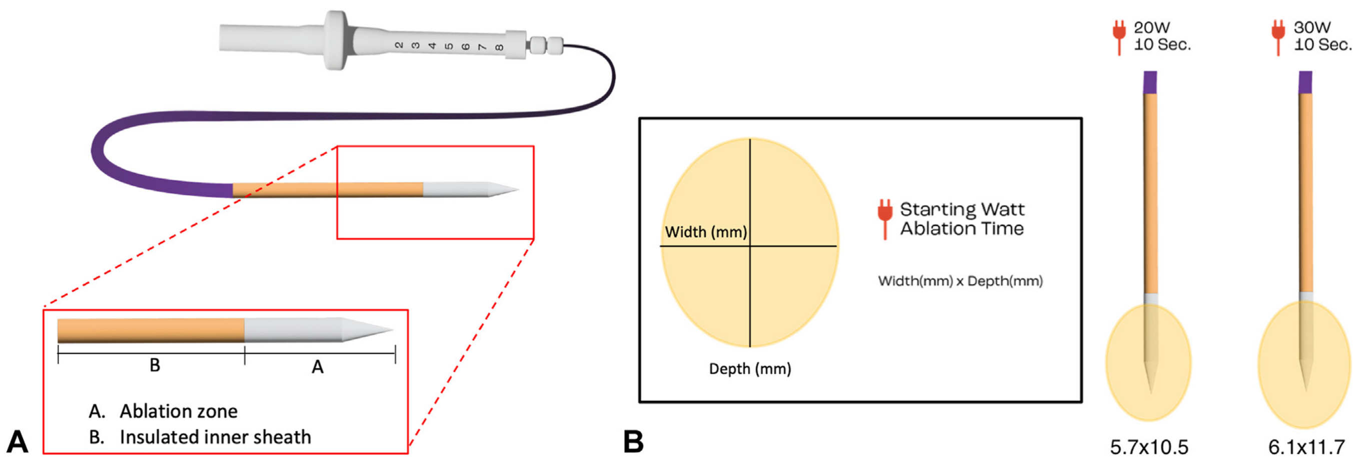

Figure 1. A, The EUS-guided radiofrequency ablation system consists of a 19-gauge monopolar electrode with an insulated trocar in several widths (5, 7, 10 mm) and an adjustable deploy length up to 8 cm. **B,** Ablation volume (width × depth in mm) depends on the length of the trocar, chosen energy, and ablation time.

events (2 cases of mild abdominal pain and 1 case of intraprocedural bleeding with spontaneous hemostasis).[9] One additional retrospective study in Italy of 3 patients with insulinoma reported clinical success in all patients sustained 2 years after the procedure. One patient developed intraprocedural bleeding, which was successfully treated endoscopically.[10]

In this article and accompanying video, we describe the EUS-RFA ablation system and device setup and review outcomes for 3 patients in the United States with symptomatic pancreatic insulinomas treated with EUS-RFA.

DESCRIPTION OF TECHNOLOGY

RFA causes direct tissue injury through targeted hyperthermia. A high-frequency alternating current generates temperatures between 60°C and 100°C to induce coagulative necrosis. Outside the core ablation zone, there is a transitional zone of sublethal hyperthermia. The surrounding tissue is unaffected.[11]

The device consists of a 19-gauge monopolar electrode with an insulated trocar in various lengths (5, 7, and 10 mm). There is a reach of up to 8 cm for focused and controlled ablation (Fig. 1A). A radiofrequency current generator controls power and impedance. A water pump circulates saline solution maintained at 32°F to cool the electrode to prevent injury to surrounding tissue. Ablation volume depends on the length of the trocar, energy setting, and duration of ablation. Based on bovine ex vivo studies, a 10-mm trocar at 20 W and 30 W for 10 seconds produces an ablation volume of approximately 5.7 × 10.5 mm and 6.1 × 11.7 mm, respectively (Fig. 1B).[12] In clinical practice, the ablation duration is also guided by

Figure 2. EUS-guided radiofrequency ablation device and setup. The 19-gauge trocar has been introduced into a linear echoendoscope. Catheters are seen connecting to the trocar to provide circulation of cold saline to prevent overheating of the device tip. EUS is used to locate the pancreatic mass and to guide the delivery of the radiofrequency energy.

the endosonographer—delivery of the ablation energy is stopped when the hyperechoic bubbling effect replaces the visualized region of tumor under endosonographic guidance.

The procedures to date have been performed with patients under general anesthesia; however, the ablations are of moderate duration and monitored anesthesia care might also provide suitable procedural sedation. Patients should have close periprocedural monitoring of the serum blood glucose. Highly symptomatic patients may already be hospitalized on a glucose infusion around the time of the ablation. While frequently administered for prevention of pancreatitis after ERCP[13] and given in one EUS-RFA study,[8] data on the role of rectal nonsteroidal anti-inflammatory drugs with EUS-RFA are limited and administration for prophylaxis is not routine at this time.

To begin, the sedated patient is placed in the left lateral position (Fig. 2). The 19-gauge trocar device is connected to a radiofrequency generator. A trocar is selected according to the size of the target tumor. Diagnostic EUS is performed to localize the lesion. The insulinomas are visualized from multiple locations—the second portion of the duodenum, the bulb, and the stomach. Color Doppler is used to exclude the presence of interposed vessels in the anticipated trajectory of the trocar. The trajectory is chosen such that the trocar does not pass through vessels or ductal structures. If possible, a trajectory that maintains 3 to 5 mm from vessels or ducts is recommended. With appropriate echoendoscopic technique, the trocar tip is readily visualized. The trocar is guided into the lesion using a linear echoendoscope. Ablations were performed at 20 W for 10 to 25 seconds each. After energy delivery, the trocar is reinserted into another aspect of the lesion until complete ablation of the tumor has been achieved. Smaller tumors (less than 3 cm) are more easily addressed with this approach. At the time of this publication, there is not a contraindication to the use of ablation near a vessel.

CASES

Case 1

A 90-year-old man with a medical history of coronary artery disease and atrial fibrillation presented with recurrent, highly symptomatic hypoglycemic episodes. Labs were significant for elevated C-peptide (6.3 ng/mL) and insulin (28 mIU/L) levels. A CT scan revealed a 1.8- × 1.0-cm pancreatic tail lesion. EUS with biopsy of the lesion revealed a well-differentiated pNET with Ki67 < 1%. The patient declined surgical management. EUS-RFA was performed at 20 W with 6 applications of energy to achieve complete visual ablation of the lesion by endosonographic appearance.

Case 2

A 46-year-old woman with a history of COVID-19 pneumonia complicated by spontaneous pneumothorax and portal vein thrombosis presented with recurrent, symptomatic hypoglycemic episodes for 3 years. Laboratory results were significant for elevated fasting C-peptide (4.3 ng/mL) and insulin (39.1 mIU/L) levels. A CT scan revealed a 9- × 8-mm mass in the uncinate process of the pancreas. EUS with biopsy of the lesion revealed a well-differentiated pNET with Ki67 1%. She declined surgical management. Because of the location of the mass deep in the uncinate process, it was noted to be mildly challenging to introduce the 19-gauge trocar. She underwent EUS-RFA with 10 applications of energy at 20 W to achieve complete visual ablation of the lesion by endosonographic appearance.

Case 3

A 66-year-old woman with a history of rheumatoid arthritis presented with recurrent, symptomatic hypoglycemic episodes for 10 years. She had experienced heavy weight gain from eating constantly to avoid hypoglycemia. She had undergone partial pancreatectomy at an outside hospital years prior; however, the tumor was not located, and she continued to have hypoglycemic episodes. Laboratory results were significant for elevated fasting C-peptide (4.8 ng/mL) and insulin (26.9 mIU/L) levels. A CT scan revealed a 13- × 15-mm mass in the head of the pancreas. EUS with biopsy of the lesion revealed a well-differentiated pNET with Ki67 < 1%. She was not a candidate for completion pancreatectomy. She was referred and underwent 4 applications of energy at 20 W in 1 EUS-RFA procedure to ablate the lesion by endosonographic appearance.

The accompanying video (Video 1, available online at www.videogie.org) and Table 2 compare the characteristics of the patients in this case series.

TABLE 2. Comparison of 3 patients with symptomatic insulinoma who underwent EUS-guided radiofrequency ablation

Sex	Age (years)	Comorbidities	Tumor size (mm)	Location	Metastatic?	Pathology	Surgery offered/ accepted	No. of radiofrequency ablation sessions	Preablation insulin*	Preablation C-peptide*	Adverse events	Follow-up period (mo)
M	90	Coronary artery disease, atrial fibrillation	18 × 10	Pancreatic tail	No	Well-differentiated NET, Ki67 < 1%	Yes/no	6 at 20 W	28	6.3	None	21
F	46	Portal vein thrombosis	9 × 8	Uncinate process	No	Well-differentiated NET, Ki67 1%	Yes/no	10 at 20 W	39.1	4.3	Mild hematochezia, self-resolved	3
F	66	Rheumatoid arthritis, obesity	13 × 15	Pancreatic head	No	Well-differentiated NET, Ki67 < 1%	No/NA	4 at 20 W	26.9	4.8	None	14

F, Female; *M*, male; *NA*, not applicable; *NET*, neuroendocrine tumor.
*Insulin reference range, 1.9-23 mIU/L; C-peptide reference range, 0.5-3.3 ng/mL.

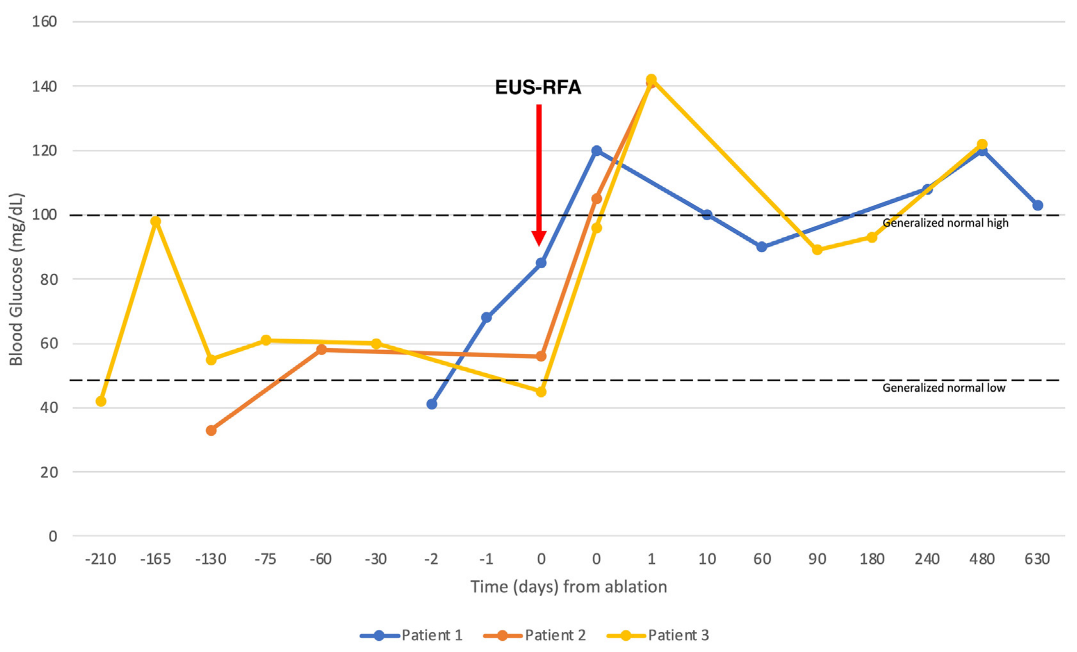

Figure 3. The patients' blood glucose trends throughout their hospital course and after discharge are displayed in relation to timing of EUS-guided radiofrequency ablation. All 3 patients had hypoglycemia in the preoperative area prior to their ablations. No hypoglycemia was seen during follow-up.

OUTCOMES

The patients tolerated the procedure well and experienced prompt resolution of their hypoglycemia. All 3 patients had planned admissions for observation and monitoring of the serum blood glucose levels during and following the EUS-RFA. Patients were monitored for 2 hours in the post-anesthesia care unit prior to admission and all were discharged within 24 to 48 hours following the procedure after medical clearance. There were no immediate adverse events. One patient reported melena 3 days postprocedure. She was readmitted and underwent EGD, which was unremarkable and without evidence of blood or upper GI tract injury. She was discharged the following day without further reported events.

Blood glucose monitoring demonstrated episodes of hypoglycemia preprocedure in all 3 patients and no episodes of hypoglycemia over their postprocedure monitoring. This was sustained for the 3 patients over 21-, 3-, and 14-month postprocedure follow-up, respectively (Fig. 3). Insulin and C-peptide levels were elevated in all 3 patients preprocedure and were noted to normalize 1 day following the ablation (Fig. 4). Radiographic improvement was also noted (Fig. 5).

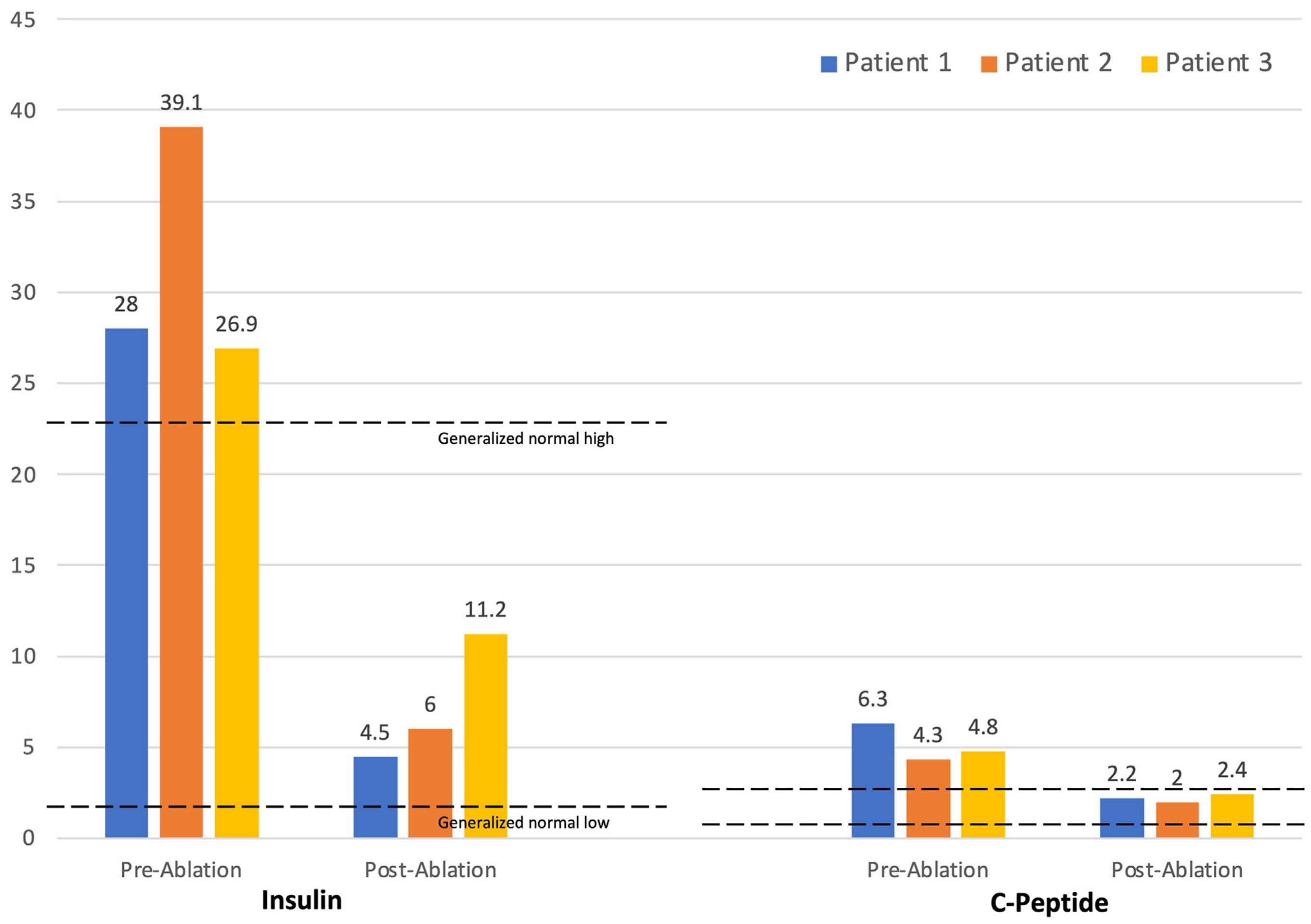

Figure 4. Insulin and C-peptide levels before and 1 day after ablation. All 3 patients had elevated levels of insulin and C-peptide preprocedure. The insulin and C-peptide levels normalized after ablation.

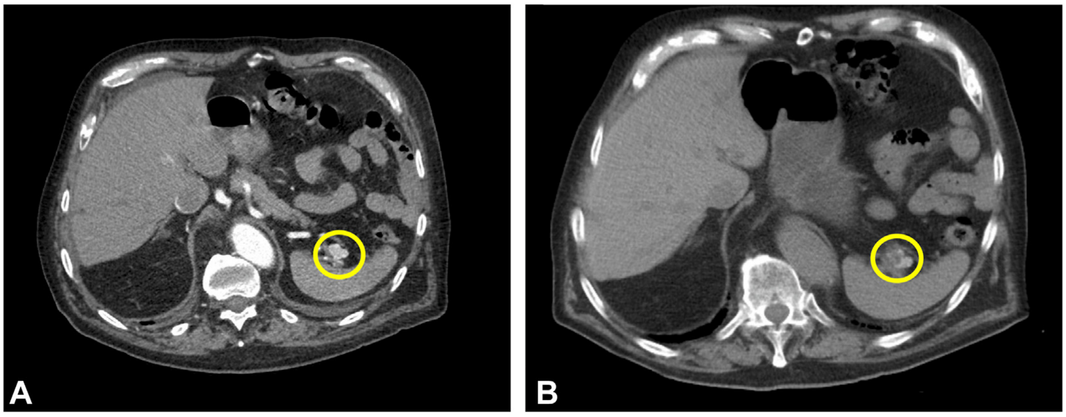

Figure 5. Abdominal CT scan **(A)** before and **(B)** 2 months after EUS-guided radiofrequency ablation (patient 1).

CONCLUSIONS

EUS-RFA appears to offer a safe, well-tolerated, and less invasive management option for symptomatic insulinomas. This series of patients in the United States, as well as studies performed in other countries (Table 1), suggests normalization of insulin levels that appears to be sustained over months to years following the procedure with a favorable adverse event profile. For patients with recurrence of symptoms, it may be possible to repeat the EUS ablation to eradicate residual or recurrent tumors. The role of prophylactic pancreatic duct stenting is unclear at this time, and ERCP with pancreatic duct stenting could paradoxically increase the incidence of pancreatitis by manipulation and stent placement.[8,14] We do not routinely place pancreatic duct stents prior to ablation at this time. Larger trials may clarify the risk of pancreatitis (which was not seen in this study).

In prior studies, metastatic lesions, asymptomatic patients, vascular invasion, and coagulation disorders have been contraindications.[15] Discussion and monitoring may be indicated for patients with cardiac pacemakers. Note, however, that particularly for nonsurgical candidates, the hypoglycemic episodes themselves can produce serious and in rare cases fatal outcomes, and as such, contraindications are felt to be relative and ablation may be recommended in multidisciplinary discussion despite comorbidities and anatomical considerations.

The procedure requires significant experience in interpretation of endosonographic imaging to detect what are often small and subtle isoechoic lesions in the pancreatic parenchyma. The trocar is 19-gauge stainless steel and there is no sheath, thus the introduction of the device into the lesion can be somewhat challenging, particularly for lesions in the uncinate process. In our experience, despite the trocar being 19-gauge, the tip is solid and passage is more akin to advancement of a 22-gauge FNA needle. Additionally, multidisciplinary discussion and/or presentation in an institutional tumor board is strongly recommended as there are other treatment options such as pancreatic surgical resection. Finally, establishing the hyperinsulinemic hypoglycemia and managing the patients preablation is suited to centers with expertise in endocrinology. Thus, these cases may be best addressed by high-volume endosonographers in centers with multidisciplinary expertise in radiology, endocrinology, and pancreatic surgery. Patients should be counseled on the novel nature of the procedure, and that expectations for outcomes are derived from limited, though promising, data.

Overall, EUS-RFA appears to offer a high success rate and a very favorable side effect profile over the relatively short-term follow-up period reported to date. It is emerging as a promising option for the management of symptomatic insulinomas and has potential to be a first-line therapy pending studies on the efficacy and long-term outcomes. At present, we recommend discussion in a multidisciplinary manner and/or review in a formal tumor board setting for consensus recommendations on treatment allocation.

DISCLOSURE

This research received funding to the institution from PCI Biotech, Cook Medical, CSA Medical/Steris, Boston Scientific, and Cancer Prevention Pharmaceuticals. The authors did not disclose any financial relationships.

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