Endoscopic Ultrasound-guided Radiofrequency Ablation Versus Surgical Resection for Treatment of Pancreatic Insulinoma

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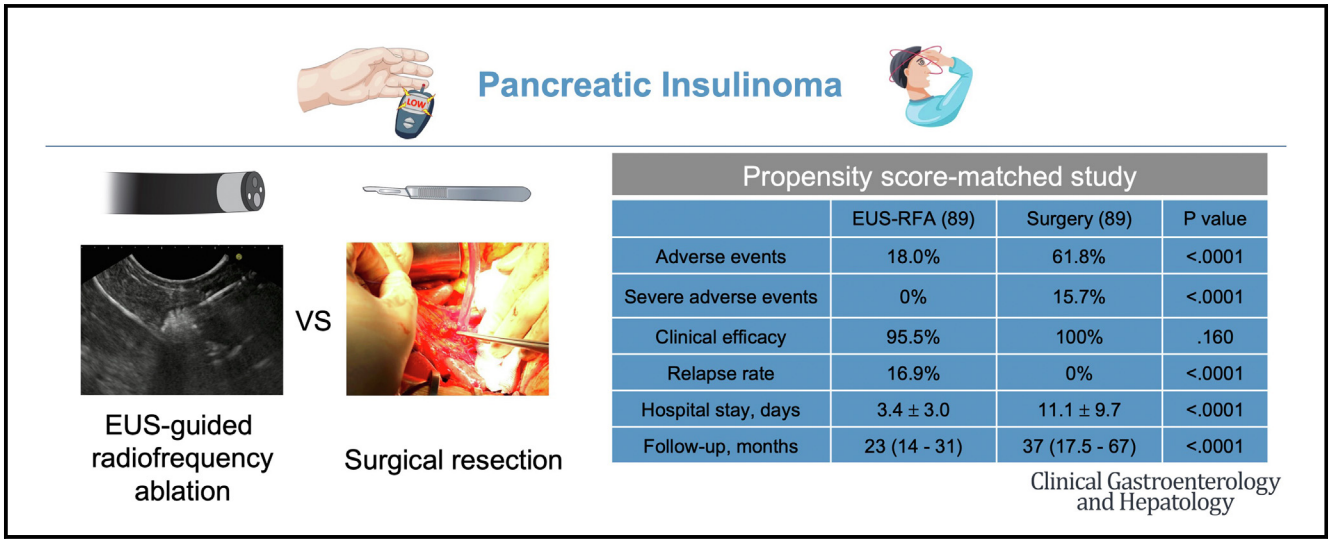

Abbreviations used in this paper: **AE, adverse event; AGREE, Adverse events in GastRointEstinal Endoscopy; ASA, American Society of Anesthesiologists; BMI, body mass index; CCI, Charlson comorbidity index; EUS-RFA, endoscopic ultrasound-guided radiofrequency ablation; IQR, interquartile range; MEN-1, multiple endocrine neoplasia type 1; panNETs, pancreatic neuroendocrine tumors; PI, pancreatic insulinoma; POPF, postoperative pancreatic fistula.**

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BACKGROUND & AIMS: **Endoscopic ultrasound-guided radiofrequency ablation (EUS-RFA) is emerging as a safe and effective treatment for pancreatic neuroendocrine tumors. We aimed to compare EUS-RFA and surgical resection for the treatment of pancreatic insulinoma (PI).**

METHODS: **Patients with sporadic PI who underwent EUS-RFA at 23 centers or surgical resection at 8 high-volume pancreatic surgery institutions between 2014 and 2022 were retrospectively identified and outcomes compared using a propensity-matching analysis. Primary outcome was safety. Secondary outcomes were clinical efficacy, hospital stay, and recurrence rate after EUS-RFA.**

RESULTS: **Using propensity score matching, 89 patients were allocated in each group (1:1), and were evenly distributed in terms of age, sex, Charlson comorbidity index, American Society of Anesthesiologists score, body mass index, distance between lesion and main pancreatic duct, lesion site, size, and grade. Adverse event (AE) rate was 18.0% and 61.8% after EUS-RFA and surgery, respectively ($P < .001$). No severe AEs were observed in the EUS-RFA group compared with 15.7% after surgery ($P < .0001$). Clinical efficacy was 100% after surgery and 95.5% after EUS-RFA ($P = .160$). However, the mean duration of follow-up time was shorter in the EUS-RFA group (median, 23 months; interquartile range, 14-31 months vs 37 months; interquartile range, 17.5-67 months in the surgical group; $P < .0001$). Hospital stay was significantly longer in the surgical group (11.1 ± 9.7 vs 3.0 ± 2.5 days in the EUS-RFA group; $P < .0001$). Fifteen lesions (16.9%) recurred after EUS-RFA and underwent a successful repeat EUS-RFA (11 patients) or surgical resection (4 patients).**

CONCLUSION: **EUS-RFA is safer than surgery and highly effective for the treatment of PI. If confirmed in a randomized study, EUS-RFA treatment can become first-line therapy for sporadic PI.**

Keywords: Hypoglycemia; Insulin; Neuroendocrine Tumor; Pancreatic Fistula; Acute pancreatitis.

Pancreatic neuroendocrine tumors (panNETs) are classified as functional or non-functional based on the presence or absence of a clinical hormonal hypersecretion syndrome. Insulinoma is the most common functional panNET.[1] Insulin hypersecretion is associated with hypoglycemic neuroglycopenic and sympathetic-overstimulation symptoms.[2] Due to the early onset of clinical symptoms, insulinomas are typically small at time of diagnosis, with size ranging from 5 to 20 mm (82% <2 cm, 47% <1 cm).[3] Approximately 90% of insulinomas are single and benign tumors, whereas multiple tumors are associated with multiple endocrine neoplasia type 1 (MEN-1), and malignant insulinomas were reported in approximately 5% of cases, with malignancy associated with larger size.[1,3]

The mainstay treatment of insulinomas is surgery,[1,4] which includes both typical and atypical parenchyma-sparing resections,[5] with enucleation performed in more than 50% of cases.[3,6] Despite being curative, pancreatic surgery is associated with significant short- and long-term adverse events (AEs).[7,8] A recent systematic review including 62 studies evaluating the most common postoperative AEs in panNETs, have reported postoperative pancreatic fistula (POPF) to occur in 14% to 58% of the cases, depending on the surgical resection, whereas delayed gastric emptying was observed in 5% to 18% of patients, and post-pancreatectomy hemorrhage occurred in 1% to 7% of cases.[8]

Based on the above data, less invasive alternative therapeutic interventions have been advocated and introduced in clinical practice.[9] Several case reports and 3 case series have recently evaluated radiofrequency ablation under endoscopic ultrasound guidance (EUS-RFA) for the treatment panNETs.[10-17] EUS-RFA of insulinomas appears to be safe and effective, with a few mild AEs and a complete regression of the clinical syndrome in nearly all cases.[18] However, there are no available studies comparing the outcome of EUS-RFA and surgery.

To fill in this gap, we performed a retrospective, propensity score-matched study, with the primary aim to compare safety of EUS-RFA vs surgical resection for treatment of pancreatic insulinomas (PIs). Secondary outcomes included clinical efficacy, length of hospital stay, and rate of symptoms recurrence necessitating additional treatment following EUS-RFA.

Methods

Patients

Institutional Review Board approval for this retrospective report was obtained (N. 3798CESC, 2022/05/23). Data of consecutive patients who underwent EUS-RFA at 23 endoscopic centers and surgical resection at 8 high-volume pancreatic surgical institutions were retrospectively collected. For this retrospective analysis, all patients were individually re-evaluated, including those previously described in case reports or case series. The study timeframe was from January 2014 to February

2022. Inclusion criteria were: (1) age ≥18 years; (2) diagnosis of insulinoma according to guidelines[19]; (3) underwent EUS-RFA or surgical resection. Exclusion criteria were: (1) multiple pancreatic nodules; (2) evidence of distant metastatic sites on imaging studies at the time of diagnosis; (3) diagnosis of MEN-1[20]; (4) less than 3 months of follow-up.

What You Need to Know

Background

Endoscopic-ultrasound radiofrequency ablation (EUS-RFA) is a promising technique for treatment of small pancreatic neoplasms. Whether EUS-RFA could replace surgery to treat pancreatic insulinomas is unknown.

Findings

EUS-RFA is safer than surgical resection. Clinical efficacy was comparable between the 2 groups, and in case of lesion recurrence following EUS-RFA, subsequent treatments can be performed, including surgery.

Implication for patient care

EUS-RFA could be offered as less invasive, first-line therapy for sporadic, small, pancreatic insulinoma.

Endpoints and Definitions

Primary endpoint. The primary endpoint was overall rate of AEs. In the EUS-RFA group, AEs were defined according to the American Society of Gastrointestinal Endoscopy classification,[21] and their severity was classified following the Adverse events in GastRointEstinal Endoscopy (AGREE) classification.[22] In particular, acute pancreatitis was defined by presence of typical pain with amylase/lipase at least >3 times normal.[21] Severe AEs were defined as those classified as AGREE ≥3. Events that did not require any therapy, had no sequelae, or did not prevent completion of the planned procedure were categorized as "incidents" and were not considered as AEs.[21]

In the surgical group, AEs were defined according to international definitions.[23-28] Severity of surgical AEs was assessed according to the Clavien-Dindo classification,[29] with those classified as Clavien-Dindo ≥3 deemed severe. The AGREE classification corresponds to the Clavien-Dindo classification adapted for endoscopy; thus, the severity of complications was very comparable between the 2 groups.

Positive 72-hour fasting test was defined as glucose blood level ≤55 mg/dL with concomitant insulin ≥3 mU/mL and C-peptide ≥0.6 ng/mL. For all endoscopic and surgical cases, AEs and clinical outcomes were individually re-evaluated at the time of the present study, graded by the investigators at the participating centers, and double-checked by the principal investigator (SFC) according to the information provided. Follow-up data were obtained from electronic charts/follow-up visits and from telephone contact performed at the time of data collection.

Secondary endpoints.

(a) Treatment effectiveness was defined as complete disappearance of symptoms related to insulin hypersecretion, with evidence of restored euglycemia (≥70 mg/dL). Improvement of symptoms without complete disappearance or continued requirement of medical therapy was considered as failure. In the EUS-RFA group, effectiveness was assessed at the end of treatment, which in some cases required multiple sessions. In the EUS-RFA group, post-treatment size of residual vascularized tissue was measured on cross-sectional imaging or contrast-enhanced EUS.

(b) Hospitalization was assessed from the day of the procedure to the day of discharge. In the event of multiple EUS-RFA treatments, the sum of hospitalizations was considered the hospital stay.

(c) The percentage of patients with symptoms recurrence, requiring additional or new treatment (either new EUS-RFA or surgical resection) following EUS-RFA was evaluated.

EUS-RFA and Surgical Procedures

EUS-RFA was performed by experienced endosonographers (more than 5 years of experience with at least 300 pancreatobiliary EUS per year) with patients under deep sedation or general anesthesia, using an internally cooled 18- or 19-gauge needle electrode (EUSRA, Taewoong Medical, South Korea) attached to the specific radiofrequency current generator (VIVA RF generator; Taewoong) with wattage power ranging from 10 to 50W (**Video 1**). The majority of patients received rectal non-steroidal anti-inflammatory suppositories (83.4%) and antibiotic prophylaxis (68.5%). Technical details of EUS-RFA procedures are summarized in Supplementary Table 1. After the procedure, in the absence of AEs, patients were admitted for 1 night and underwent fasting glucose blood test the next morning.

Surgical resections, both typical and atypical parenchyma-sparing ones, were performed based on lesion characteristics (size, site, distance from main pancreatic duct) and each institutional policies/expertise. In a few cases, endoscopic retrograde cholangiopancreatography with pancreatic stenting was performed before EUS-RFA or surgical enucleation.

Sample Size Calculation

A sample size calculation was performed for the primary outcome. Reported AE rate after pancreatic surgery

for insulinomas was 46%.[3] A recent systematic review and a case series on EUS-RFA for pancreatic insulinomas revealed 23% (8/34) AEs.[16,18] A 2-tailed sample size calculation with type I error rate (a) set at 0.05 to attain 90% power for detecting a difference of 23% in AEs rate between the 2 treatments yielded a sample size of 88 patients per group.

Statistical Analysis

Patients' characteristics were summarized using conventional statistics, such as mean ± standard deviation or median with interquartile range (IQR) for continuous variables and absolute frequencies and percentages for categorical data.

To overcome biases owing to the different distributions of covariates among patients in the 2 groups, a 1-to-1 match was created using propensity score analysis. The propensity score represents the probability of each individual patient being assigned to a particular condition in a study given a set of known covariates. A multivariate logistic regression was performed to predict the probability of each individual patient being submitted to the 2 groups based on covariates that are known to be able to affect patient outcomes, namely age, sex, Charlson comorbidity index (CCI), American Society of Anesthesiologists (ASA) score, body mass index (BMI), location and size of the lesion, distance from main pancreatic duct, and tumor grading.

The predictive values were then used to obtain a 1-to-1 match by using nearest neighbor matching within a specified caliper distance. Thus, patients for whom the propensity score could not be matched due to greater caliper distance were excluded from further analyses. As suggested by Austin,[30] a caliper with a width equal to 0.2 of the standard deviation of the logit of the propensity score was used, as this value has been found to minimize the mean square error of the estimated treatment effect.

Categorical variables were compared either with the χ^2 test (with Yates' correction when appropriate) or the Fisher exact test. When comparing 2 groups, normally distributed continuous variables were analyzed using a 2-sample Student t test, whereas the Mann-Whitney U test was used for non-normally distributed variables. Univariate and multivariate analyses were performed to determine risk factor(s) associated with AEs. Recurrence-free survival was analyzed through the Kaplan-Meier method, and differences between groups were compared through log-rank test. A P-value $< .05$ was considered statistically significant.

Results

Study Population

Overall, 328 patients were identified, and 304 (109 males; mean age, 53.2 ± 16.5 years) fulfilled inclusion/exclusion criteria (Figure 1). All patients experienced hypoglycemic symptoms, with a mean blood glucose level of 46.9 ± 7.8 mg/dL. Diagnosis of insulinoma was based on 72-hour fasting test in 208 patients (68.4%), on EUS-guided sampling in 67 patients (22.0%), or typical imaging findings in 29 patients (9.5%). The majority of tumors were small (mean lesion size, 14.3 ± 6.1 mm) and well-differentiated (G1, G2, G3, and unknown in 221 [72.7%], 50 [16.4%], 1 [0.3%], and 32 [10.5%] cases, respectively). No patient developed distant metastases, and 8 patients died during follow-up (median, 26.5 months; IQR, 12−50 months) of unrelated causes.

Propensity Score Analysis

Propensity-score matching allocated 89 patients in each group (Supplementary Figure 1). There were 55 males and 123 females, with a mean age 54.9 ± 15.3 years. Insulinomas were in the head/uncinate in 69 cases (38.8%) and in the body/tail in 109 (61.2%). The mean lesion size was 13.5 ± 4.8 mm. Tumor grading remained unknown in 20 patients (11.2%), whereas it was identified in 158 cases as G1 in 145 (91.8%) and G2 in 13 (8.2%) cases. Age, sex, Charlson comorbidity index, ASA score, BMI, lesion size, location, and grading were comparable between the 2 groups. Table 1 summarizes the baselines characteristics of the overall population and the matched cohort.

Primary Outcome

In the matched cohort, AEs were observed in 16/89 (18.0%) of the EUS-RFA treated patients and in 55/89 (61.8%) of those who underwent surgery, respectively ($P < .001$). In the surgical group, the most common AEs was postoperative pancreatic fistula (38/89; 42.7%; 17 biochemical leak, 20 grade B, and 1 grade C), and there was no difference in AEs rate between minimally invasive (ie, laparoscopic or robotic) and open treatment (32/50 [64.0%] and 23/39 [59.0%], respectively; $P = .628$), enucleation and formal resections (16/32 [50.0%] and 39/57 [68.4%]; $P = .112$), as well as pancreaticoduodenectomy and other surgery types (10/15 [66.7%] and 45/74 [60.8%]; $P = .775$).

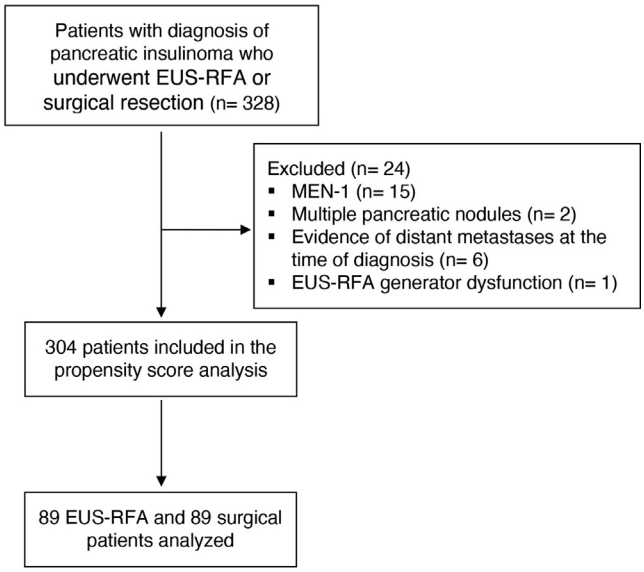
In the EUS-RFA group, the most common AE was acute pancreatitis (9/89; 10.1%), which occurred in lesions located in the head/uncinate, body, or tail in 3, 5, and 1 cases, respectively. Lesion size in patients who developed acute pancreatitis was significantly smaller than in those who did not show this AE (9.9 mm vs 13.8 mm; $P = .004$). Notably, in 8 of 9 patients (88.9%) with acute pancreatitis, the distance between lesion and main pancreatic duct was ≤2 mm (vs 16/65; 24.6% in other patients; $P = .0003$). In 3 of these cases, EUS-RFA was performed immediately after pancreatic stent placement.

Rate of severe AEs was significantly higher in the surgical group (15.7% vs 0%; $P < .0001$). Details of AEs

type, severity, and their management are summarized in Table 2. Univariate analysis revealed surgical treatment as the only factor associated with occurrence of AEs (odds ratio, 7.38; 95% confidence interval, 3.7−14.7; $P <$ .0001) (Supplementary Table 2). No treatment-related death was observed in both groups.

Secondary Outcomes

At the latest follow-up, 95.5% (85/89) in the EUS-RFA group and 100% (89/89) in the surgical group ($P = .160$) had clinical response, with mean glucose levels of 102.5 ± 27.9 md/dL. Fifteen of 89 patients (16.9%) treated with EUS-RFA experienced symptoms relapse (12 within 1 year). Four of these patients underwent uneventful patient-preferred surgical resection, whereas 11 were successfully re-treated with a new EUS-RFA session with complete symptom resolution lasting for an additional mean follow-up period of 23.0 months. Median recurrence-free survival was not reached. Figure 2 reports Kaplan-Meier estimates of recurrence-free survival that resulted significantly higher in patients treated with surgical resection ($P <$ .0001). The duration of follow-up was significantly longer in the surgical group than in the EUS-RFA group (median, 23 months; IQR 14−31 months vs 37 months; IQR, 17.5−67 months; $P <$ .0001). In the EUS-RFA group, complete disappearance of vascularized tissue (Figure 3) was obtained in 76 of 89 (85.4%). Evidence of residual vascularized tissue was more frequent in patients with symptoms recurrence (8/15; 53.3% vs 5/74; 6.8%, in patients with stable clinical response; $P <$ .0001).



EUS-RFA, endoscopic ultrasound-guided radiofrequency ablation
MEN-1, multiple endocrine neoplasia type 1

Figure 1. Study flowchart.

Importantly, patients treated with EUS-RFA had a significantly shorter length of hospital stay than those who underwent surgery (3.4 ± 3.0 vs 11.1 ± 9.7 days; $P <$ .0001).

Discussion

Considering promising results of EUS-RFA treatment of symptomatic pancreatic insulinomas reported in case series and systematic reviews,[13-18] we conducted a retrospective propensity score matched study comparing safety and efficacy of this therapeutic approach to surgical intervention. We found EUS-RFA to be associated with significantly lower overall and severe AE rates, but comparable efficacy to surgery.

EUS-RFA was initially used to treat insulinomas in patients deemed unfit or at high-risk for pancreatic surgery,[10,31,32] an approach also suggested by the European Neuroendocrine Tumor Society guidelines.[4] With time, however, the use of EUS-RFA has become more prevalent and has been reported in various case series,[15,16] which have clearly demonstrated its promising safety profile and with high effectiveness. Based on these results, the natural subsequent question was how EUS-RFA compares with the standard of care (ie, surgical resection). To answer this question, we collected data from a large number of patients affected by pancreatic insulinoma who underwent EUS-RFA or pancreatic resection. To reduce the risk of selection biases, propensity score analysis was used to balance general characteristics influencing surgical risk (eg, CCI, ASA score, BMI, location of the lesion) and the safety and efficacy of EUS-RFA (lesion size, distance from main pancreatic duct).

The EUS-RFA treatment was found to be significantly superior to surgery in terms of AE rates (18% vs 61.8%), with no occurrence of severe AEs. The AEs rate found in our study is slightly higher than the 14% reported in a recent meta-analysis,[33] which, however, also included patients with non-functional panNETs who underwent EUS-RFA. Overestimation of risk of AEs in our population can be related to the performance of endoscopic retrograde cholangiopancreatography with pancreatic stenting before EUS-RFA in 4 of the 16 patients who experienced an AE.[34] In these patients, it was impossible to determine if acute pancreatitis was related to one of the procedures or a combination of both.

The robustness of our results was further confirmed in univariate analysis, which revealed surgical treatment as the only factor associated with the occurrence of AEs with an odds ratio of 7.38 (95% confidence interval, 3.7−14.7). Of note, a trend toward significance ($P = .06$) was observed for a ≤2 mm distance between the lesion and the main pancreatic duct. Proximity to the pancreatic duct is known to be associated with an increased risk of AEs for both EUS-RFA[15] and surgical enucleation.[35] Therefore, despite the fact that, in the present study, a

Table 1. Baseline Features Before and After Propensity Score Matching

	Overall population (N = 304)			Matched population (n= 178)		
Variable	EUS-RFA (n = 111)	Surgery (n = 193)	*P* value	EUS-RFA (n = 89)	Surgery (n = 89)	*P* value
Male	33 (29.7)	76 (39.4)	.106	27 (30)	28 (31)	1
Age, *y*	59.0 ± 17.1	49.9 ± 15.3	**< .0001**	55.1 ± 16.0	54.7 ± 14.6	.853
CCI			.08			.513
2	39 (35.1)	98 (50.7)		40 (44.9)	36 (40.4)	
3	23 (20.7)	39 (20.2)		19 (21.3)	19 (21.3)	
4	13 (11.7)	24 (12.4)		8 (9.0)	15 (16.9)	
5	14 (12.6)	19 (9.8)		11 (12.4)	13 (14.6)	
6	6 (5.4)	5 (2.6)		4 (4.5)	5 (5.6)	
7	3 (2.7)	2 (1.0)		2 (2.2)	0 (0)	
8	2 (1.8)	1 (0.5)		2 (2.2)	1 (1.1)	
9	2 (1.8)	0 (0)		1 (1.1)	0 (0)	
10	2 (1.8)	0 (0)		2 (2.2)	0 (0)	
Missing	7 (6.3)	5 (2.6)		0 (0)	0 (0)	
ASA score			.20			.80
1	35 (31.5)	62 (32.1)		33 (37.1)	25 (28.1)	
2	52 (46.8)	95 (49.2)		39 (43.8)	44 (49.4)	
3	24 (21.6)	36 (18.6)		17 (19.1)	20 (22.5)	
4	0	0		0	0	
BMI, kg/m^2	27.3 ± 5.5	26.5 ± 4.7	.188	27.2 ± 4.7	27.2 ± 5.2	.876
Lesion size, *mm*	13.2 ± 4.2	15.0 ± 7.0	**.015**	13.4 ± 3.9	13.7 ± 5.9	.520
Lesion site			**< .001**			.08
Head/uncinate	50 (45.1)	61 (31.6)		34 (38.2)	35 (39.4)	
Body	45 (40.5)	62 (32.1)		39 (43.8)	27 (30.3)	
Tail	16 (14.4)	70 (36.3)		16 (18.0)	27 (30.3)	
Lesion grade			**.005**			.150
G1	80 (72.1)	145 (75.1)		66 (74.2)	79 (88.8)	
G2	4 (3.6)	47 (24.4)		3 (3.4)	10 (11.2)	
G3	0 (0)	1 (0.5)		0 (0)	0 (0)	
Unknown	27 (24.3)	0 (0)		20 (22.4)	0 (0)	
Ki-67, %	1.7 ± 0.8	2.5 ± 3.6	**.048**	1.7 ± 0.8	2.1 ± 1.6	.129
MPD caliber, *mm*	2.1 ± 0.8	2.0 ± 0.7	.612	2.1 0.7	2.1 0.7	.635
Upstream MPD dilation	4 (3.6)	2 (1.8)	.196	3 (3.4)	1 (1.1)	.620
Distance lesion to MPD, *mm*			.776			.850
>2	64 (57.7)	99 (51.3)		53 (59.5)	47 (52.8)	
≤2	28 (25.2)	48 (24.5)		21 (23.6)	17 (19.1)	
Unknown	19 (17.1)	69 (35.2)		15 (16.8)	25 (28.1)	
Time of follow-up, *months*	23 (14-30)	37 (18-66)	**< .0001**	23 (14-31)	37 (17.5-67)	**< .0001**
Type of surgery	–		–	–		–
Pancreatoduodenectomy		22 (11.4)			15 (16.8)	
Distal pancreatectomy		79 (40.9)			38 (42.7)	
Central pancreatectomy		12 (6.2)			4 (4.5)	
Enucleation		80 (41.5)			32 (36.0)	

Note: Data are presented as number (%), mean ± standard deviation, or median (interquartile range).
ASA, American Society of Anesthesiologists; BMI, body mass index; CCI, Charlson comorbidity index; EUS-RFA, endoscopic ultrasound-guided radiofrequency ablation; MPD, main pancreatic duct.

significance was not reached, in our opinion, this factor should be evaluated before treatment planning. Similarly, the use of rectal non-steroidal anti-inflammatory drugs to prevent post-RFA pancreatitis should be considered until further evidence becomes available.

In the surgical group, the most common AE was the development of pancreatic fistula. In prior literature, the rate of AEs after pancreatic surgery varies widely, particularly with respect to volume and institutional expertise. However, our results are comparable to those

Table 2. Details of AEs and Their Management in the Matched Cohort

EUS-RFA						Surgery					
	Severity[a] (grade)						Severity[a] (grade)				
AE	I	II	III	IV	Management	AE	I	II	III	IV	Management
Acute pancreatitis, 9 (10.1)	3	6	–	–	Medical treatment (9)	POPF, 38 (42.7)	18	13	7	–	Conservative management (18), Antibiotics/IV nutrition (13), endoscopic intervention (3), radiological intervention (3), surgical intervention (1)
Abdominal pain, 5 (5.6)	4	1	–	–	Conservative management (4), Antibiotics (1)	DGE, 3 (3.4)		2	1		Total parenteral nutrition (2), endoscopic intervention (1)
Spleen hematoma, 1 (1.1)	–	1	–	–	Hospital admission >24 hours (1)	Abdominal fluid collection, 2 (2.2)	1	–	1	–	Conservative management (1), surgical intervention (1)
Diabetes, 1 (1.1)	–	1	–	–	Medical treatment (1)	Postoperative hemorrhage, 2 (2.2)	–	1	1	–	Blood transfusion (1), surgical intervention (1)
						Biliary fistula, 2 (2.2)	–	–	2	–	Radiological intervention (2)
						Others,[b] 8 (9.0)	1	5	2	–	Conservative management (1), antibiotics (3), antibiotics + nasojejunal feeding (1), radiological intervention (1), Medical treatment (1), Surgical intervention (1)
Total, 16 (18.0)	7 (43.8)	9 (10.1)				Total, 55 (61.8)	20 (36.4)	21 (38.2)	14 (15.7)		

Note: In patients with multiple adverse events, the most severe is reported.
Note: Data are presented as number or number (%).
AE, Adverse event; DGE, delayed gastric emptying; EUS-RFA, endoscopic ultrasound-guided radiofrequency ablation; IV, intravenous; POPF, postoperative pancreatic fistula.
[a]According to the AGREE[20] and Clavien-Dindo[27] classifications.
[b]Others include: surgical site infection (1), pulmonary embolism (1), symptomatic abdominal hernia in the site of trocar (1), bilio-enteric anastomotic stricture (1), pleural effusion (1), postoperative pancreatitis (1), urinary tract infection (1), pneumonia (1).

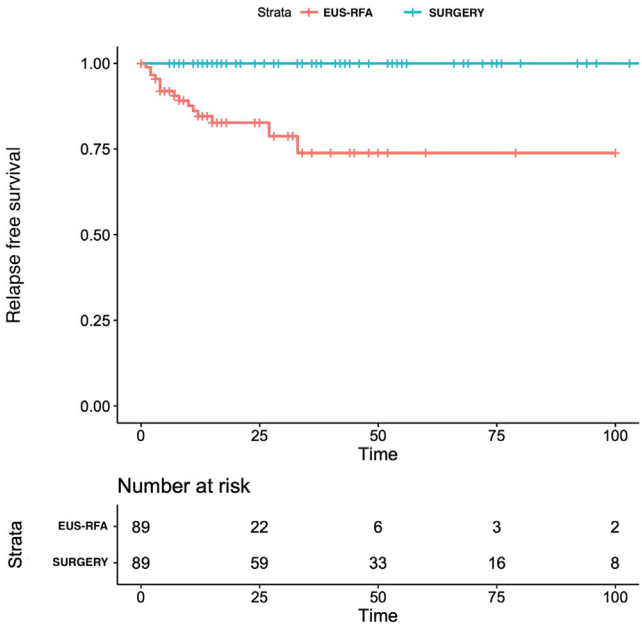


Figure 2. Kaplan-Meier estimates of recurrence free survival in patients with pancreatic insulinoma who underwent EUS-RFA or surgical resection.

of a prospective registry of surgical resection for panNETs in which AE rates occurred in 56.1% of the cases, 28.1% of which were severe.[7] We also graded the severity of AEs and found surgical AEs to be more often severe compared with AEs following EUS-RFA (7.8% vs 0%), necessitating endoscopic, radiological, or surgical management in 15.7% of cases. Notably, no fatalities occurred in both groups.

Clinical effectiveness of EUS-RFA was found to be comparable to surgical resection (95.5% vs 100%). Overall, symptoms recurrence was observed in 15 cases (16.9%) after a mean of 9.5 months. In 11 patients, a second EUS-RFA session was performed and was associated with symptom relief during a follow up of 23.0 months. Thus EUS-RFA was considered as successful treatment, even though a second procedure was required. In the 4 additional cases of symptom recurrence, patients opted for surgical resection, and these cases were deemed treatment failures. Recurrence of insulinoma-related symptoms might be attributed to the lack of a standardized ablation protocol, in which repeat EUS-RFA should be contemplated. Indeed, symptom recurrence can be expected after EUS-RFA if not enough tissue has been ablated. Ablation typically begins from the central portion of the lesion to avoid AEs and might not be sufficient. However, in functional panNETs, the goal of treatment is to ensure the disappearance of symptoms, which could be achieved even in case of residual small amount of vital tissue. For this reason, endosonographers concentrate the ablation treatment in the center of the lesion, sometimes resulting in sparing the borders and the surrounding normal pancreatic tissue. This allows EUS-RFA to be highly safe and effective, but at the expense of a small risk of relapses.

Finally, the length of hospital stay was significantly shorter for EUS-RFA vs surgical resection (3.4 vs 11.1 days). We believe that with the growing of the experience, the length of hospital stay after EUS-RFA can be further shortened, and the procedure even offered on an outpatient basis, with hospitalization reserved for patients with post-procedural symptoms.

Our study results strongly suggest that EUS-RFA could be offered as first-line treatment for all cases of sporadic, small PIs for different reasons. First, insulinoma is generally benign, and does not require formal oncological resection with lymphadenectomy, as demonstrated by the fact that the most common surgical procedure is enucleation.[3] Theoretically, EUS-RFA could replace surgical enucleation, with the added benefit of being applicable in cases where surgical enucleation is technically impossible and formal pancreatic resection is required. Second, it is possible to develop a step-up approach where EUS-RFA can be followed by a second ablation treatment or surgical resection, if needed. Third, besides a lower rate of AEs, a shorted length of hospital stay, and a comparable clinical efficacy, EUS-RFA could reduce the risk of surgical-related endocrine/exocrine pancreatic insufficiency that occurs in 27% to 58% of patients after formal resection.[36] However, before EUS-RFA can become the standard of care, our conclusions should be investigated further in a randomized controlled trial with long and balanced follow-up between the 2 treatment modalities. Indeed, in the present study, the mean duration of follow-up was shorter in the EUS-RFA group.

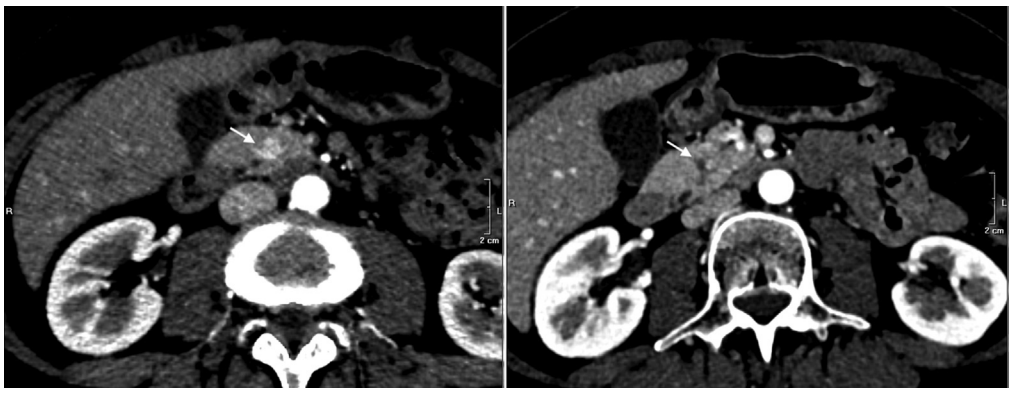


Figure 3. Computed tomography scan before and after EUS-RFA of PI. A 9-mm hypervascular nodule is documented in the pancreatic head (*left panel, white arrow*). After ablation, a slightly smaller hypovascular area is visible without residual hypervascular tissue (*right panel, white arrow*).

We acknowledge several limitations in our study. First, due to the retrospective design, there is a risk of selection bias associated with the preference for EUS-RFA in older patients with a high surgical risk. Nevertheless, we attempted to limit this bias by employing the propensity score analysis and balancing the 2 groups for numerous factors associated with AEs and clinical success. Second, the duration of follow-up varied significantly between the 2 groups. This was expected because EUS-RFA has become widespread more recently, and, despite the mean follow-up in the EUS-RFA group being 2 years, we cannot exclude higher relapse rate over a longer observational period. Third, our data come from experienced centers and operators and might not be reproducible in other settings. Fourth, both surgical and EUS-RFA techniques are not standardized, and there is heterogeneity in technical aspects. However, this is reflective of real world, where technical decisions widely vary in different institutions and are left to the preference and experience of the operator.

In conclusion, our study demonstrated better safety profile and a comparable clinical effectiveness of EUS-RFA compared with surgical resection for the treatment of small, sporadic PIs. EUS-RFA did not preclude subsequent treatments if required, including surgery. If our results are confirmed in a randomized controlled trial with long and well-balanced follow-up, EUS-RFA could be offered as first-line treatment for these tumors.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2023.02.022.

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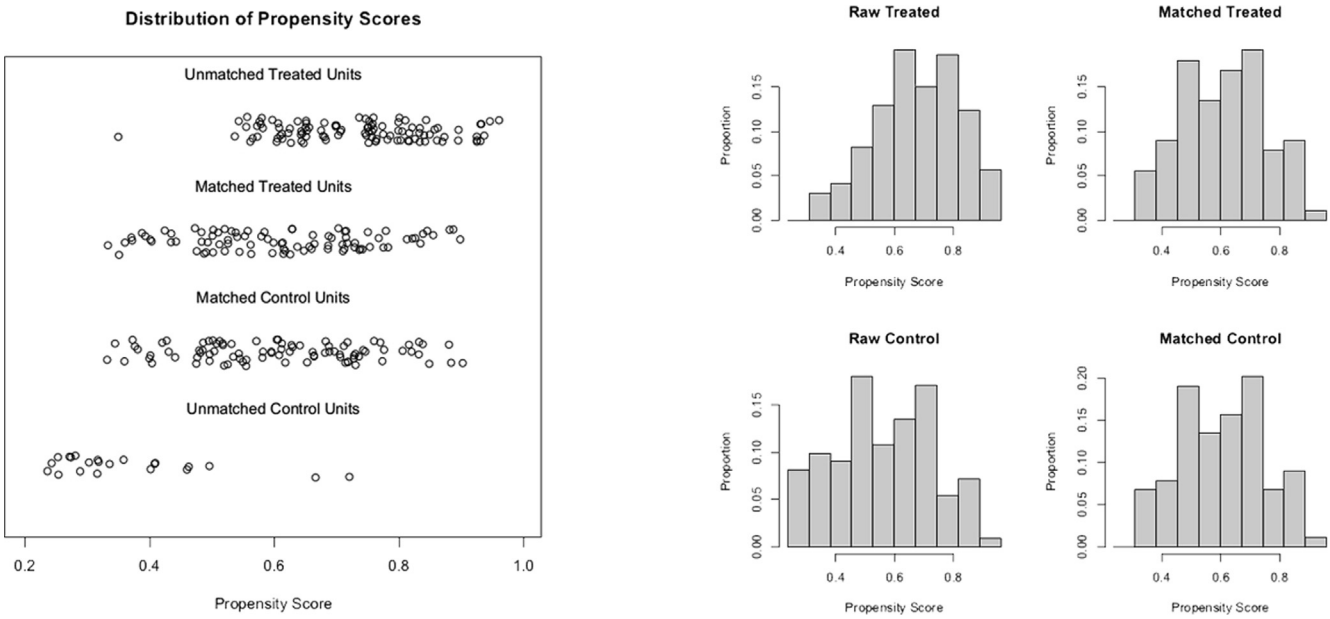
Conflicts of interest
All the authors disclose no conflicts.



Supplementary Figure 1. Of the initial 304 patients, after 1-to-1 propensity score caliper matching, 178 patients were selected for comparison: 89 patients treated with EUS-RAF and 89 patients treated with surgery. (*A*) Propensity score matching jitter plot. (*B*) Propensity score matching histogram.

Supplementary Table 1. Technical Aspects of EUS-RAF in 89 Patients With PI

	N (%)
Prophylaxis[a]	
Rectal indomethacin	53 (59.6)
Rectal diclofenac	23 (25.8)
Pancreatic stenting	10 (11.2)
Antibiotics	61 (68.5)
Needle electrode	
19 gauge	84 (94.4)
18 gauge	5 (5.6)
Exposed active tip, *mm*	
5	19 (21.3)
10	70 (78.7)
Wattage	
10	3 (3.4)
20	1 (1.1)
30	29 (32.6)
50	56 (62.9)
Number of RFA applications	
1	4 (4.5)
2	22 (24.7)
3	33 (37.1)
4	17 (19.1)
5	10 (11.2)
6	3 (3.4)
Site of puncture	
Stomach	52 (58.4)
Duodenal bulb	17 (19.1)
Descending duodenum	20 (22.5)

EUS-RFA, Endoscopic ultrasound radiofrequency ablation; PI, pancreatic insulinoma; RFA, radiofrequency ablation.
[a]More than one possible.

Supplementary Table 2. Univariate Analysis of Factors Associated With AEs

Variable	OR (95% CI)	*P* value
Age, *y* (ref. 55)	0.95 (0.52–1.73)	.87
Sex (ref. male)	0.79 (0.41–1.52)	.49
CCI (ref. 1)	1.26 (0.67–2.36)	.46
ASA score (ref. 1)	1.06 (0.71–1.58)	.77
BMI, kg/m^2 (ref. $<$ 27.4)	1.26 (0.99–2.41)	.07
Size, *mm* (ref. $<$13.5)	0.99 (0.93–1.05)	.77
Site (ref. head/uncinate)	1.16 (0.62–2.15)	.63
Distance lesion to MPD, *mm* (ref. $\leq$2)	0.49 (0.23–1.04)	.06
Treatment (ref. EUS-RFA)	7.38 (3.70–14.70)	$<$ .0001

AE, Adverse event; ASA, American Society of Anesthesiologists; BMI, body mass index; CCI, Charlson comorbidity index; CI, confidence interval; EUS-RFA, endoscopic ultrasound-guided radiofrequency ablation; MPD, main pancreatic duct; OR, odds ratio; ref, reference.