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Progress Report

Study protocol for a multicenter randomized controlled trial to compare radiofrequency ablation with surgical resection for treatment of pancreatic insulinoma

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ABSTRACT

Background: Insulinoma is the most common functional pancreatic neuroendocrine tumor and treatment is required to address symptoms associated with insulin hypersecretion. Surgical resection is effective but burdened by high rate of adverse events (AEs). Endoscopic ultrasound-guided radiofrequency ablation (EUS-RFA) demonstrated encouraging results in terms of safety and efficacy for the management of these tumors. However, studies comparing surgery and EUS-RFA are lacking.

Aims: The primary aim is to compare EUS-RFA with surgery in term of safety (overall rate of AEs). Secondary endpoints include: (a) severe AEs rate; (b) clinical effectiveness; (c) patient's quality of life; (d) length of hospital stay; (e) rate of local/distance recurrence; (f) need of reintervention; (g) rate of endocrine and exocrine pancreatic insufficiency; (h) factors associated with EUS-RFA related AEs and clinical effectiveness.

Methods: ERASIN-RCT is an international randomized superiority ongoing trial in four countries. Sixty patients will be randomized in two arms (EUS-RFA vs surgery) and outcomes compared. Two EUS-RFA

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sessions will be allowed to achieve symptoms resolution. Randomization and data collection will be performed online.

Discussion: This study will ascertain if EUS-RFA can become the first-line therapy for management of small, sporadic, pancreatic insulinoma and be included in a step-up approach in case of clinical failure.

1. Rationale and aims

Pancreatic neuroendocrine tumors (PanNETs) are classified as functional (F-) or non-functional (NF-) [1]. F-PanNETs secrete hormones and typically present as a clinical syndrome secondary to hormonal hypersecretion. Insulinoma is the most common F-PanNET [2]. Insulinomas characteristically present between ages 40 and 45 years, 60% occur in females, and the symptoms are due to insulin hypersecretion. Insulin hypersecretion is associated with hypoglycemic neuroglycopenic and sympathetic-overstimulation symptoms [2,3]. Approximately 90% of insulinomas are single and benign, whereas multiple nodules are usually associated with multiple endocrine neoplasia type 1 (MEN-1) and malignant insulinomas, reported in approximately 5% of cases, are commonly larger than 2 cm [2,3]. Due to the early onset of clinical symptoms, insulinomas are usually small at diagnosis, with size ranging from 5 to 20 mm (82% < 2 cm, 47% < 1 cm) [3].

Treatment is required in all cases to address with insulin hypersecretion-related symptoms. The mainstay treatment of F-PanNETs is surgical resection, which is associated with a significant resolution of symptoms' [4]. Surgical treatment of localized insulinomas includes both typical and atypical resections. Atypical surgeries (e.g., enucleation, central pancreatectomy) are used for well demarcated and small size insulinomas and have been developed to decrease rates of long-term endocrine and/or exocrine impairment observed after typical resection [5,6]. Indeed, insulinomas do not often require large parenchymal resection and/or lymphadenectomy because of their benign nature.

Despite curative, pancreatic surgery is associated with significant short- and long-term adverse events (AEs). A recent systematic review of the literature, including 62 studies, reported postoperative pancreatic fistula to occur in 45% of cases after tumor enucleation, in 14% after both distal pancreatectomy and pancreatoduodenectomy, and in 58% after central pancreatectomy [7]. Enucleation and distal pancreatectomy were characterized by delayed gastric emptying in 5% of cases, in 18% after pancreatoduodenectomy, and in 15% after central pancreatectomy. Postoperative hemorrhage occurred in 6% of the cases, while overall pooled in-hospital mortality rates ranged between 3 and 6% [7].

Based on the above data, less invasive alternative therapeutic interventions to avoid surgical short- and long-term AEs have been introduced [8], with radiofrequency ablation under endoscopic ultrasound guidance (EUS-RFA) being the most widely utilized [9]. In published studies, EUS-RFA for insulinomas resulted safe and effective, with a few mild AEs and a complete regression of the clinical syndrome close to 100% [9]. The only available study comparing outcomes of EUS-RFA with surgical resection is a large retrospective propensity score-matched one, which demonstrated significantly lower rate of AEs in the EUS-RFA group versus the surgical group (18.0 vs 61.8%; $p < 0.0001$), with similar high clinical efficacy (95.5% vs 100%) [10].

Encouraged by the safety and efficacy data published so far and to overcome limitations of the retrospective propensity score matched study, we designed a multicenter, randomized study aimed to compare safety and efficacy of EUS-RFA versus surgical resection for treatment of pancreatic insulinomas.

2. Study design

This is a multicenter, international, randomized (1:1 ratio), parallel arms, unblinded trial. This study is carried out at 10 centers in Italy, Belgium, France, and India. The Ethics Committee of the provinces of Verona and Rovigo approved the study on 30 January 2023 (protocol number 6218). Before starting enrollment, we registered the protocol on Clinical Trial.gov (NCT05735912). This study will be conducted according to the principles and the recommendations of the 2013 Declaration of Helsinki. The CONSORT study flowchart is illustrated in Fig. 1.

2.1. Study population and eligibility

Consecutive patients diagnosed with pancreatic insulinoma will be assessed for eligibility.

Diagnosis of insulinoma will be performed according to guidelines [11]: "clinical symptoms are required for the diagnosis of insulinoma and the diagnosis of insulinoma will be established using the following six criteria: (1) documented blood glucose levels ≤2.2 mmol/l (≤40 mg/dl); (2) concomitant insulin levels ≥6 μU/ml (≥36 pmol/l; ≥3 U/l by ICMA); (3) C-peptide levels ≥200 pmol/l; (4) proinsulin levels ≥5 pmol/l; (5) β-hydroxybutyrate levels ≤2.7 mmol/l, and (6) absence of sulfonylurea (metabolites) in the plasma and/or urine. Further tests will include the 72-hour fast, which is the classical gold standard for establishing the diagnosis of insulinoma. Additionally, EUS-guided sampling demonstrating a neuroendocrine neoplasm with positive insulin immunohistochemistry will be possibly performed. As reported by guidelines [12], EUS-guided sampling is not mandatory, and it will left to the treating physician preference.

2.1.1. Inclusion criteria

- Age ≥18 years
- Diagnosis of pancreatic insulinoma [11]
- Presence of a visible single pancreatic nodule on imaging [computed tomography, and/or magnetic resonance imaging, and/or EUS].
- No evidence of distant localizations visualized on imaging
- Tumor ≤2 cm
- Informed consent provided by the patient or closest relative.

2.2. Exclusion criteria

- Grade 2 with Ki-67 >5% on histological examination at EUS-guided biopsy samples, when performed
- Distance between lesion and main pancreatic duct (MPD) ≤1 mm or MPD upstream dilation
- Diagnosis of MEN-1 according to guidelines [13]
- Unfit for surgery or high-risk surgical patients
- EUS not feasible for surgical altered anatomy
- Known bleeding disorder that cannot be corrected
- Use of anticoagulants that cannot be discontinued
- INR >1.5 or platelet count <50.000
- Pregnancy or breast feeding

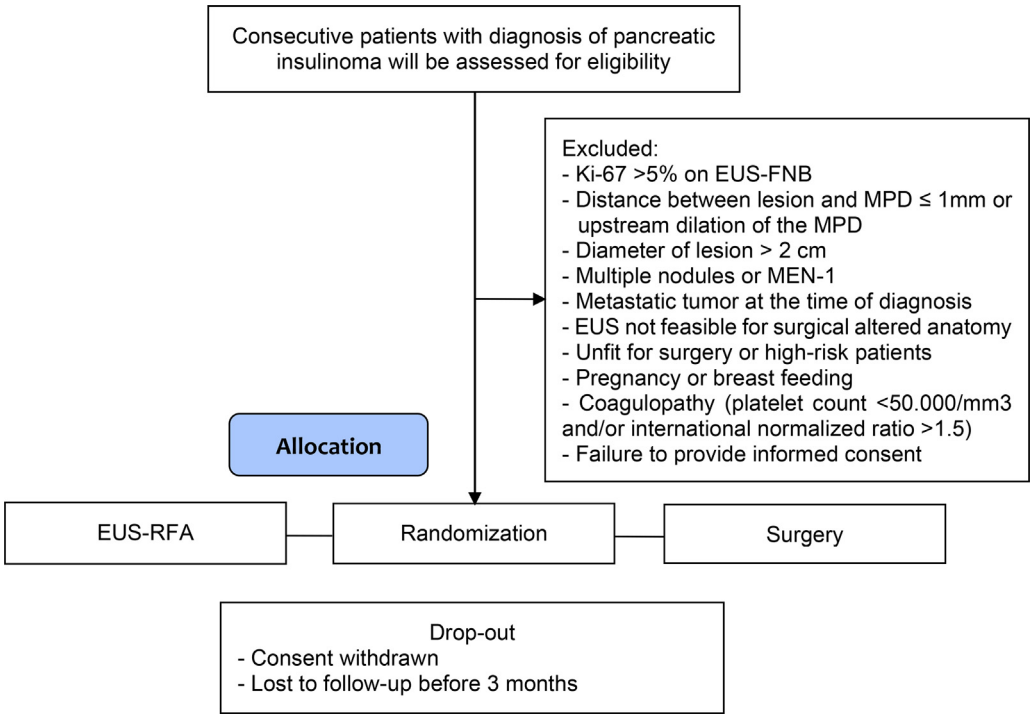

Fig. 1. CONSORT flow-chart of the study.

2.3. Objectives

2.3.1. Primary aim and endpoint

The primary aim of this study is to investigate the superiority of EUS-RFA vs surgical resection in terms of safety for treatment of pancreatic insulinoma. The primary endpoint is the rate of overall AEs (i.e., the ratio between the number of patients who will experience at least one treatment-related AE and the total number of patients who will receive the treatment). Because EUS-RFA is a repeatable procedure, in the EUS-RFA group a second treatment session in case of symptoms persistence or recurrence will be allowed. If two EUS-RFA sessions will be performed to complete the treatment, AEs related to both sessions will be considered. In case of clinical failure or recurrence, a different treatment will be proposed and AEs related to this treatment will be not considered in the analysis.

2.3.2. Key secondary aims and endpoints

(a) Rate of severe AEs. The severity of AEs will be classified according to the AGREE [14] and Clavien-Dindo [15] classifications for EUS-RFA and surgical arm, respectively. Severe AEs will be considered those classified as AGREE/Clavien-Dindo ≥3.
(b) Clinical effectiveness. Treatment effectiveness will be evaluated by comparing rate of patients with symptoms resolution. Symptoms will be investigated using specific questions for insulinoma included in the 10 EORTC PANNET module [16]. Treatment will be considered effective if all questions will be answered as “no”.

2.3.3. Other secondary aims

(c) Patient’s quality of life (QoL) evaluated using the EORTC QLQ-C30 questionnaire.
(d) Length of hospital stay calculated from the day of the procedure to the day of discharge from the hospital. In case of new admissions to perform a second session of EUS-RFA or to manage treatment-related AEs, the sum of the hospitalizations will be considered.
(e) Rate of local/distance recurrence, i.e., the rate of patients with the appearance on imaging of local solid mass, or lymph nodes, or distant metastases suspicious for disease recurrence.
(f) Reintervention rate defined as the percentage of patients requiring a new treatment for symptoms/disease persistence or recurrence (either third EUS-RFA or surgical resection).
(g) Rate of endocrine and exocrine pancreatic insufficiency.
(h) Evaluation of factors associated with EUS-RFA related AEs and clinical effectiveness.

2.4. Definitions

2.4.1. Adverse events

AEs are defined as any negative outcome for a patient that prevent completion of the planned procedure or cause any deviation from the standard postprocedural course [15,16]. Events that need no therapy or hospital prolongation, have no sequelae, or do not prevent the completion of the planned procedure are defined as “incidents” and will be not considered as AEs [17].

Possible common AEs after EUS-RFA or surgical resection are different. Specific definitions and timing of AEs will be based on the American Society of Gastrointestinal Endoscopy classification [17] for the EUS-RFA group and on international definitions for the surgical group [18–23], and are summarized in Table 1.

2.4.2. Clinical efficacy

Clinical efficacy is defined as complete disappearance of symptoms related to the hyper-hormonal secretion syndrome. Symptoms “persistence” is defined the irresolution of symptoms or their appearance within 6 months after treatment, whereas symptoms “recurrence” is defined the relapse of symptoms after a period of wellness of at least 6 months. After two EUS-RFA sessions, patients with symptoms persistence (even if mitigated), or requirement of

Table 1
Specific definitions of possible adverse events after surgery or endoscopic ultrasound-guided radiofrequency ablation (EUS-RFA) of pancreatic insulinoma. Definitions of adverse events are based on international lexicon or definitions [17–23].

EUS-RFA		Surgery	
Adverse event	Definition	Adverse event	Definition
Acute pancreatitis	Typical pain with amylase/lipase >3 times normal	Post-operative pancreatic fistula	A drain output of any measurable volume of fluid with amylase level greater than 3 times the upper Institutional normal serum amylase level
Perforation	Evidence of air or luminal contents outside the gastrointestinal tract	Post-pancreatectomy hemorrhage	Post-operative episode of hemorrhage with severity based on the amount of blood loss or transfusion requirements
Bleeding	Hematemesis and/or melena or hemoglobin drop >2 g	Delayed gastric emptying	Inability to return to a standard diet by the end of the first postoperative week
Infection (pancreatic)	>38 °C, >24 h with collection	Chyle leak	Output of milky-colored fluid from a drain, drain site, or wound on or after postoperative day 3, with a triglyceride content ≥ 110 mg/dL
Abdominal pain	Not caused by pancreatitis or perforation	Post-operative pancreatitis	Biochemical evidence for pancreatic inflammation (urinary trypsinogen-2 >50 ug/L or serum amylase/lipase > upper limit of normal)

EUS-RFA, endoscopic ultrasound-guided radiofrequency ablation.

medical therapy, or recurrence will be considered as treatment failure (metachronous lesion(s) will need to be excluded).

2.4.3. Technical success

In the EUS-RFA arm, technical success is achieved if the needle will be inserted inside the lesion and at least one application of RFA current will be released until raising of the impedance. In the surgical group, technical success is defined as the surgical resection properly completed.

If the allocated treatment will be deemed not technically feasible at the time of the intervention, the other treatment will be considered and performed after informed consent will be obtained from the patient. For example, the nodule could be not visible at EUS or EUS-RFA considered not feasible because of interposed vessels or interposed MPD. In such cases, surgical resection will be proposed to the patient and performed after informed consent obtained, and data recorded in the electronic case record form.

2.4.4. Endocrine and exocrine insufficiency

New onset (not pre-existing) diabetes after EUS-RFA or surgery will be considered as treatment-related endocrine pancreatic insufficiency. Exocrine pancreatic insufficiency will be defined, diagnosed, and managed according to current guidelines [24].

2.5. EUS-RFA and surgical procedures

2.5.1. EUS-RFA

EUS-RFA will be performed with the patient hospitalized. Rectal indomethacin or diclofenac 100 mg suppository will be given before the procedure for acute pancreatitis prophylaxis. Antibiotics to prevent infection will also be administered according to the local protocol.

EUS-RFA will be performed using the EUSRA system (Taewoong, Seoul, Korea) consisting of a 19-gage inner cooled needle electrode and a radiofrequency current generator (VIVA RF generator; Taewoong). The inner metal part of the needle is insulated over its entire length, except for the terminal 5–20 mm for energy delivery. The generator allows the control of physical power and impedance parameters [25].

Considering the size criteria of insulinoma to be included into the study (≤20 mm), a 5–15 mm exposed tip will be chosen according to the size of the tumor. After standard EUS scanning and Doppler examination to exclude interposed vessels, the electrode needle will be inserted into the lesion under direct EUS guidance. Radiofrequency power will be decided by the endoscopists according to the tumor size, shape, and needle active tip length. A slowly increasing hyperechoic zone will be visualized during the EUS-RFA procedure. The radiofrequency generator will be stopped if the hyperechoic area will sufficiently cover the tumor, or a few seconds after an increase in the impedance value is indicated by the generator. If necessary, the procedure will be repeated by reinserting the needle in another portion of the lesion until obtaining the largest possible ablation of the tumor.

It will be possible to perform contrast-enhanced EUS [26] by 4.8-mL intravenous injection of SonoVue™ (Bracco Imaging, Milan, Italy) before and/or after EUS-RFA to evaluate tumor margins and residual tissue to be ablated.

2.5.2. Surgical resection

Surgical resection will be performed in an inpatient setting. The type and extension of surgical resection, as well as need for lymphadenectomy, will be decided by the treating surgeons according to the tumor position, distance from the MPD, and local expertise.

2.6. Enrollment and drop-out

Enrollment will be competitive between centers and will extend for a maximum period of 3 years after local Ethic Committee/IRB approval. A minimum 3-year follow-up period will be required to assess late AEs and symptoms recurrence. Patients will be considered dropped-out in case of consent withdrawn or if lost before 3 months of follow-up.

2.7. Randomization and blinding

Once eligibility to the trial will be verified, patients will be randomized in a 1:1 ratio into one of two study arms based on a computer-generated randomized blocks sequence (block size of 4/6). To ensure the integrity of the study, considering the potential impact of lesion site to the primary outcome, a stratification according to lesion sites (head/uncinate or body/tail) will be performed. The randomization list will be electronically determined and updated on the REDCap platform by the Clinic Research Unit at the University of Verona.

2.8. Data collection

Case record forms of demographics (such as age, sex, ASA score, Charlson comorbidity index, body mass index), tumor diagnosis, lesion features, EUS-RFA or surgical treatment, treatment-related AEs, clinical efficacy, symptoms relapse, disease recurrence, endocrine/exocrine pancreatic insufficiency, and QoL will be recorded

Table 2
Study timetable.

Procedures/ Assessment	Screening	In-hospital Period	After discharge			
Contact	Contact 1	Contact 2	Contact 3	Contact 4	Repeated Contacts	Last Contact
Timing	0	Duration of hospital stay	Week 2	Week 4	Every 6 months	End of the study*
Procedure		Daily evaluation by treating physician	Telephone call or follow-up visit	Telephone call or follow-up visit	Telephone call or follow-up visit	Telephone call or follow-up visit
Informed consent	X					
Inclusion / Exclusion criteria	X					
Demographics	X					
Medical, Surgical history	X					
Physical examination	X					
lesion features	x					
randomization	x					
Adverse event assessment		X	X	X	X	X
Clinical efficacy		X	X	X	X	X
Quality of Life			X	X	X	X
Days of hospitalization(s)		X	X	X	X	X
Need for reintervention		X	X	X	X	X
Disease recurrence			X	X	X	X
Endocrine/exocrine pancreatic insufficiency		X	X	X	X	X

* The study will end three years after the enrollment of the last patient.

online. Study outcomes will be evaluated during the hospital stay period, after two weeks, one month, and every six months after treatment until the end of the study (three years after enrollment of the last patient). The study timetable is reported in Table 2.

2.9. Sample size calculation

A sample size calculation was performed for the primary outcome. In a recent propensity score-matched study comparing EUS-RFA and surgery for the treatment of pancreatic insulinoma, rate of AEs was 61.8% and 18% after surgery and EUS-RFA, respectively. A 2- tailed two Proportions Fisher's Exact Test sample size calculation with type I error α set at 0.05 to attain 90% power for detecting a difference of 43.8% in AEs rate between the two treatments resulted in a sample size of 29 patients per group. Considering a drop-out rate of approximately 4%, a total of 60 patients will be enrolled (30 patient per group). The expected distribution in different part of the pancreas (and body/tail) is 43% in the head/uncinate and 57% in the body/tail [3]. Therefore, 26 lesions in the head/uncinated and 34 in the body/tail will be included.

2.10. Statistical analysis

Patients' characteristics will be summarized using conventional statistics, like mean ± standard deviation or median and interquartile range for continuous variables and absolute frequencies and percentages for categorical data.

The primary endpoint (rate of overall AEs) will be evaluated with Fisher's exact test. The rate of severe AEs, clinical efficacy, local or distant recurrence, additional treatment, and endocrine and/or exocrine pancreatic insufficiency will be evaluated with the chi-square test (with Yates' correction when appropriate) or the Fisher's exact test in case of low frequencies. QoL (analyzed as mean scores during follow-up) and the time of hospitalization will be compared using a two-sample Student's *t*-test or the Mann-Whitney *U* test in case of not normally distributed variable.

Univariate and multivariate analyzes will be performed by the Cox regression model to evaluate significant predictors of EUS-RFA AEs and treatment response.

A *p*-value <0.05 will be considered statistically significant.

2.10.1. Analysis population

Different analysis sets are defined. The intent-to-treat analysis set (ITT) contains all randomized patients grouped according to the allocated treatment. The modified intent-to-treat analysis set (mITT) contains all randomized patients but grouped according to their received treatment and excluding dropped-out patients. The per-protocol (PP) analysis set contains all randomized patients who received the allocated treatment. The main analyzes will be performed on the mITT analysis set. Results on the other analysis sets will be reported additionally.

3. Discussion

In every field of medicine, disease treatment should be balanced according to invasiveness and effectiveness and based on disease aggressiveness. Insulinoma is a peculiar disease. On one hand, they are small and with a very low oncological risk. On the other hand, insulinomas determine dramatic symptoms requiring treatment in all cases. Up to now, surgery was the only approach to deal with these tumors with undoubted effectiveness in eliminating symptoms. Unfortunately, even the less demolitive resection (i.e., enucleation) is burdened by not negligible AE rates.

Recently, an internally cooled electrode needle for EUS-RFA has become available for treatment of pancreatic tumors. Considering the abovementioned features of insulinomas, a less invasive management seems preferable to surgery. The goal of minimally invasive treatment in F-PanNETs is to induce necrosis and death of the large majority of the neuroendocrine tumor cells to abate hormonal hypersecretion with cessation of symptoms, without the need to obtain complete ablation because of very low malignant potential of this tumor [27]. The first case series of EUS-RFA for the treatment of pancreatic insulinomas has been published in 2016 [28]. Afterwards, retrospective case series and meta-analyzes have reported encouraging results using EUS-RFA for treatment of patients with both F-PanNETs and NF-PanNETs [9,29–32]. These data have been confirmed by preliminary results of a longitudinal prospective multicenter study investigating safety and efficacy of EUS-RFA in F-PanNETs and NF-PanNETs [33]. Among 24 F-PanNETs (all insulinomas) only three (12.5%) mild adverse events were observed, all treated conservatively. Effectiveness was 100% (18/18) at 6-months and 1 year (9/9) [33]. Similarly, another prospective observational study including 13 insulinomas and other pancre-

atic neoplasms, reported mild AEs in 22% of cases, with a complete symptom's resolution in all patients with insulinoma [34]. Moreover, a recent propensity score-matched study comparing outcomes of EUS-RFA with surgical resection has been published [10]. By means of propensity score analysis, 89 patients were allocated in each group after matching for age, sex, Charlson comorbidity index, body mass index, size and site of the lesion, tumor grade, and lesion distance from the MPD. This study demonstrated a significant lower rate of AEs in the EUS-RFA group with similar high clinical efficacy. Interestingly, in 15/89 (16.9%) cases symptoms recurred after EUS-RFA after a mean time of 9.5 months and were successfully re-treated by EUS-RFA in 11 cases or underwent surgical resection in 4 cases. No patient experienced tumor metastases [10]. As a results, while initially EUS-RFA was reserved for poor surgical candidates or for patients who refused surgery, currently EUS-RFA could be considered as a treatment option in all cases. However, in the propensity score-matched study [10], the follow-up time was significantly shorter in the EUS-RFA group, thus leading the possibility of recurrence rate underestimation. Moreover, given the retrospective nature of the study, a percentage of AEs could be missed. Therefore, to produce most robust evidence with well-balanced follow-up and prospective patients' monitoring, we designed a randomized controlled trial to compare EUS-RFA and surgery for the treatment of pancreatic insulinomas. If our hypothesis is correct, EUS-RFA can become the first-line treatment modality for all insulinoma patients, or at least to be considered as a treatment option depending on patient characteristics, patient preference, surgical risk, presence of comorbidities, and location of the tumor.

Some limitations exist in the present study design. First, all involved centers are pancreatic referral institutions, thus results of this study might not be applicable in a community hospital setting. Second, EUS-RFA and surgical techniques are not standardized. Each operator will decide the preferred method according to his experience and based on patient's and lesion features. Therefore, technique-related confounding factors could impact on the results. On the other hand, this design reflects real life where each surgeon or endoscopist can operate unconstrained by pre-established rules. Third, we will not include patients with multiple nodules or MEN-1 because management of such cases depends on several factors and randomization could be difficult to be proposed. Forth, the sample size was established on the safety outcome. Therefore, efficacy will be evaluated on an underpowered sample. Finally, reaching the anticipated sample size will require a strong collaborative effort because many patients could accept only surgery as salvage therapy after unsuccessful RFA, and it is possible that some of them could withdraw their consent after being randomized.

Conflict of interest

None declared.

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