Reviewer #1:

The following statements need clarification from the authors.

1. The authors claim "immediate" clinical success with syndrome relief. There is no pre-operative and post operative biochemical data to support this claim.In the history of present illness the article says that patients 1 and 3 had repeated syncopal or hypoglycemic episodes (Frequency not given) and patient 2 had only two episodes. If that is the case the claim that symptoms disappeared immediately after surgery is untenable. The article also has contradicting statement in the laboratory examinations heading: where it is stated that all patients had consistent and constant neuro glycopenic symptoms.
   Reply: We appreciate the remark and we revised all the histories of the patients adding in "History of present illness" and "Laboratory examinations" any clarifications.
2. The revision says that these patients were subjected to repeat CECT scan 24 to 72 hours after EUS treatment, to assess presence of necrosis at treatment site even after the so called immediate clinical success. This information could have been achieved with US itself non-invasively. The CECT has not changed the management protocol in these patients even in the patient with CKD.
   Reply: Thank you for your comment. We decided to use CECT scan for experting in our center and to assess necrosis after radiofrequency treatment as in previous clinical randomized controlled trial of pancreatic lesions ablation (Testoni SGG, Petrone MC, Reni M, et al. Efficacy of Endoscopic Ultrasound-Guided Ablation with the HybridTherm Probe in Locally Advanced or Borderline Resectable Pancreatic Cancer: A Phase II Randomized Controlled Trial. Cancers (Basel) 2021;13(18):4512). Moreover, patient 1 presented a moderate grade of obesity and abdominal US could be not useful to follow up the pancreas gland.
3. It may be beyond the scope of this case series to quote that most of the published reports do not provide specific and standardized EUS ablation settings.
   Reply: We very appreciate the comment. However we believe that a discussion in a setting of clinical cases report about the standardization of EUS-RFA is fundamental being the insulinoma relatively rare disease, in order to reach the optimal setting.
4. So also the statement "pancreatic surgery is associated with high morbidity and mortality" may not hold water.
   Reply: It is known that pancreatic surgery has a relatively high morbidity and mortality, especially in low-medium rate of pancreatic center expertizing. So also a optimal standardization of EUS-RFA procedure is fundamental in this scenario.

Reviewer #2:

The optional end points namely procedural success, optimum result and complications make EUS guided RFA a successful modality in management of pancreatic insulinoma and the authors concur with the published reports. In this case report the authors describe EUS Guided RFA not as an alternative to "surgery" which is the Gold standard, but as modality in those who are unfit for surgery, find good results in a small number of patients and conclude that it is an alternate to surgery in those elderly patients. EUS guided RFA is described as "local treatment" by the authors, loco regional may be more appropriate In the discussion the authors indicate that EUS guided RFA described in the literatures are "not standardized", though same settings that is used in the cited references were used by the authors.

All 3 patients are considered as high risk patients but co morbidities like DM , SHT are indicated. It is quoted that there was immediate clinical success after the procedure but what symptoms were alleviated is not described nor there is a periprocedure blood glucose mapping to indicate the response to treatment. Is

neuro glycopenic symptoms consistant or episodic in insulinoma? Role of plasma insulin, C peptide and proinsulin levels in diagnosis, treatment evaluation and follow up are not alluded to.

Reply: We thank the reviewer for the constructive criticisms and useful comments and suggestions. We actually employed plasma insulin, C-peptide and proinsulin levels both for the diagnosis and follow-up to support data of symptoms relief. We added this comments in manuscript file.

No standardized follow up protocols, like specific time frame for follow up imaging/ are indicated in the study.

Reply: The reviewer is correct, and, indeed, as a case series we did not have a standardized protocol for the three patients but every patient underwent to a CT-scan at 24-72 hours after the endoscopic procedure, in order to assess the eventual necrotic core inside the insulinoma as effect of radiofrequency ablation. We added the comment in text file. The follow-up examinations also depended on the patients' general conditions, and being them elderly and with comorbidities were not standardized.

The bleeding in the II case, if from gastro duodenal artery, was managed by endoscopic clipping rather than embolization is not explained in detail.

Reply: We thank the reviewer for the opportunity to clarify. The bleeding in case 2 was probably due to a side-branch vessel injury and not to a direct injury of gastroduodenal artery and for this reason a gastroduodenal artery embolization was not necessary. Alsopatient symptoms and blood tests and the CT-scan after 72 hours did not show further bleeding signs.

Though the lesion was in contact with main pancreatic duct in the 2nd case, the role of pancreatic stent in prevention of post procedure complications is not discussed by the authors. If description is added, the video will be more useful.

Reply: Thanks for the important comment. We have now clarified in the text that we did not position a pancreatic stent due to the proximity (1-2 millimeters) of the lesion respect to the main pancreatic duct (MPD). Moreover,it was already reported in the text that the MPD was not dilated and the patient had no abdominal pain. We added the clarification in the text.

Reviewer #3:

This is case series study of EUS-RFA. This is a very interesting subject for an endosonographer, and I have a number of queries for the authors.

1) Case1 and case3 have not been histologically diagnosed. Please describe the reason.

Reply: We thank the reviewer for the opportunity to clarify further. Indeed, it is reported in specific guidelines (*Jensen RT et al. ENETS Consensus Guidelines for the Management of Patients with Digestive Neuroendocrine Neoplasms: Functional Pancreatic Endocrine Tumor Syndromes. Neuroendocrinology 2012;95:98–119. Falconi M et al. Consensus guidelines update for the management of functional p-NETs (F-p-NETs) and non-functional p-NETs (NF-p-NETs). Neuroendocrinoloy 2016; ; 103(2): 153–171.)* that insulinoma diagnosis is based on clinical symptoms and blood tests evidence, as cited: "The diagnosis of all

functional p-NETs requires the demonstration of an inappropriate elevation of the appropriate, specific serum hormonal marker (i.e. gastrin in ZES, insulin in insulinomas, etc.) combined with clinical/laboratory evidence of oversecretion of the appropriate hormone (such as gastric acid hypersecretion in ZES, hypoglycemia in insulinomas, etc.)(table 1) [1– 3, 57, 66] . The diagnosis of functional p-NET requires clinical evidence of hormonal overexpression (table 1) and is not based only on immunohistochemical results" (*Jensen RT et al. ENETS Consensus Guidelines for the Management of Patients with Digestive Neuroendocrine Neoplasms: Functional Pancreatic Endocrine Tumor Syndromes. Neuroendocrinology 2012;95:98–119*). As in these cases the clinical, biochemical and radiological scenario was considered typical, we considered the biopsy unnecessary.

2) Describe the cauterization range in the EUS-RFA settings described in Materials and methods. If there are any results from animal experiments, please describe them.

Reply: Thanks for the comment. We did not use a range of ablation but we set in every patient a power of 30 Watts on the generator. As reported in discussion session, due to the scanty data in literature about this radiofrequency ablation system standardization, in the present study we have standardized setting of the ablation power in line with our previous ex-vivo animal [11] and human studies (unpublished data), with the application of 30 W and stopping the energy delivery at the increase of tissue impedance.

3) Insert an arrow into the lesion in Figure.4.

Reply: Thank you for the suggestion. We inserted the arrow in order to highlight the necrotic area.