

Endoscopic ultrasound-guided radiofrequency ablation for intraductal papillary mucinous neoplasms with worrisome features: long-term outcomes in nonsurgical patients (with video)

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Background and Aims: Branch-duct intraductal papillary mucinous neoplasms (BD-IPMNs) are precancerous cystic lesions. Surgery is advised for high-risk stigmata (HRS) or multiple worrisome features (WFs), but it entails substantial morbidity, and many resections reveal only low-grade dysplasia. EUS-guided radiofrequency ablation (EUS-RFA) is a minimally invasive alternative, yet long-term data are limited.

Methods: We retrospectively analyzed a prospectively maintained cohort of consecutive patients who underwent EUS-RFA for BD-IPMNs with WFs/HRS at a tertiary referral center (2015-2024). Eligible patients were inoperable or declined surgery. Outcomes included technical success, adverse events (AEs), local control (defined as resolution of WFs/HRS with no cancer arising from the treated lesion), radiologic response, and pancreas-wide events.

Results: Fifty patients (62 procedures; 58 lesions) were treated. Mean follow-up was 4.1 ± 2.8 years after radiofrequency ablation. Technical success was 100%. AEs occurred in 27% of procedures, mostly mild abdominal pain; postprocedural pancreatitis occurred in 3 patients, including 1 case of necrotizing pancreatitis; there were no procedure-related deaths. Local control was achieved in 98% of lesions; 17% showed complete radiologic disappearance, and 86% decreased in size. No treated lesion progressed to cancer. Pancreas-wide disease control was maintained in 80% of patients; 4 (8%) patients developed pancreatic cancer remote from the treated cyst. Smaller cyst size and fewer WFs were associated with better outcomes.

Conclusions: EUS-RFA is feasible, safe, and provides durable local control of BD-IPMNs with WFs/HRS in patients who are unsuitable for surgery or who decline resection. These results support EUS-RFA as a promising therapeutic option in carefully selected patients. Larger prospective studies are needed to refine selection criteria and confirm long-term oncologic benefits. (Gastrointest Endosc 2026;■:1-8.)

BACKGROUND AND AIMS

Branch-duct intraductal papillary mucinous neoplasms (BD-IPMNs) are precancerous pancreatic cystic lesions with the potential to progress to invasive adenocarcinoma.¹ Their management relies on representing indirect clinical and radiologic markers of advanced dysplasia, categorized by international consensus as “worrisome features” (WFs) and “high-risk stigmata” (HRS).¹ According to current guidelines,

the presence of HRS constitutes a formal indication for surgical resection, although surgery may be considered in the presence of WFs and is usually recommended when ≥ 3 WFs coexist.¹

Pancreatic resection, however, carries substantial risks, with a perioperative mortality of around 5% and a morbidity rate of 20% to 40% (fistula, pancreatic insufficiency, and diabetes).² These findings highlight the problem of potential overtreatment in the management of BD-IPMNs. Despite

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these risks, over half of resected BD-IPMNs reveal only low-grade dysplasia, even when a mural nodule—the strongest radiologic predictor of high-grade dysplasia—is present.^{3,4} This underscores both the risk of overtreatment and the challenge of decision-making: surgery is guided by indirect markers of dysplasia, whose true grade is only confirmed after resection.^{1,3-5} In addition, up to half of pancreatic cancers in patients with intraductal papillary mucinous neoplasms (IPMNs) arise at a distance from the index cyst, further complicating the risk–benefit balance of surgery.⁶

EUS-guided ablation has been investigated as a minimally invasive alternative for pancreatic cysts, using ethanol, chemoablation, and, more recently, radiofrequency ablation (RFA). RFA induces thermal injury through direct tissue contact. When applied to cystic pancreatic lesions, cyst fluid aspiration is required to limit heat dissipation and bring the dysplastic epithelium into close proximity to the RFA probe. In this context, EUS-guided RFA (EUS-RFA) aims to reduce the dysplastic epithelial burden. Reported efficacy, defined as complete cyst ablation, varies between 30% and 80%, with adverse events (AEs) in 5% to 30% of cases, mostly pancreatitis.⁷⁻¹¹ These studies remain heterogeneous and have largely included BD-IPMNs with few or no WFs, limiting their generalizability as a substitute for surgery. In current practice, pancreatectomy is justified only when advanced dysplasia or carcinoma is strongly suspected, because resection of low-grade lesions exposes patients to major morbidity with limited benefit. Within this context, EUS-RFA emerges as a novel therapeutic tool: it offers a less invasive option for patients who are unfit for or who refuse surgery and may also attenuate the global carcinogenic potential of the pancreas by ablating advanced dysplastic lesions, thereby limiting protumoral intercellular signaling within the ductal–acinar network.^{12,13} This dual rationale—pragmatic in frail patients and potentially preventive at a biological level—positions RFA as a promising therapeutic alternative in the evolving management of BD-IPMNs. Nevertheless, data remain limited regarding technical success, AEs, clinical success, true long-term efficacy of RFA, and its ability to achieve durable local control or to modify the broader process of pancreatic carcinogenesis.

In this large series, our primary objective was to assess local control of BD-IPMNs after RFA treatment. Secondary objectives were to evaluate safety, overall ablation rate, the occurrence of pancreatic cancer at a distance from the treated lesion, and factors associated with response to RFA.

MATERIAL AND METHODS

Population

This retrospective analysis of a prospectively maintained database included all patients who underwent EUS-RFA for IPMNs with WFs/HRS at a tertiary referral center (North Hospital, Marseille) between December 2015 and November 2024.

Only patients with a definitive diagnosis of BD-IPMN were included, defined as a pancreatic cyst >5 mm in diameter communicating with the main pancreatic duct (MPD).¹ All patients with a definitive diagnosis of BD-IPMN with WFs or HRS who had an EUS-RFA were included. All these patients were discussed at a multidisciplinary tumor board including a surgical oncologist, gastroenterologist, and radiologist. Pretreatment evaluation consisted of magnetic resonance imaging, pancreatic protocol CT, and EUS to assess the presence of WFs or HRS. All included patients were unsuitable for surgery because of comorbidities or had declined surgical resection. Patients were informed that RFA was considered a nonstandard approach, with surgery remaining the conventional treatment.¹ Patients were initially followed at 3 months, 6 months, and 1 year, then every 6 months thereafter, with intervals subsequently extended based on clinical status. Follow-up imaging was primarily based on MRI, with EUS performed selectively when clinically indicated, such as in cases of persistent or recurrent WFs or equivocal MRI findings.

EUS-RFA procedure

All procedures were performed with the patient under general anesthesia with endotracheal intubation and volume-controlled ventilation. Three expert endoscopists performed all the procedures. IPMNs were identified by EUS, and cyst fluid was aspirated using a 19-gauge needle; the aspirated fluid was systematically sent for cytologic analysis. Cyst fluid aspiration was performed to reduce heat dissipation and to allow direct tissue contact between the RFA probe and the cyst wall or solid components.

Lesions were then punctured with a Taewoong (Taewoong Medical Co, Ltd, Gimpo-si, Gyeonggi-do, South Korea) EUSRA EUS-RFA radiofrequency needle, and a 50-W radiofrequency current was applied until an impedance of 100 Ω was reached. Energy delivery was continued until the appearance of echogenic white bubbles, indicating effective tissue heating, with each application lasting <1 minute. Mural nodules were systematically ablated, and depending on the size and morphology of the cyst, additional ablations were performed at 1 or 2 other sites within the IPMN. Up to 3 applications per lesion were performed. EUS-RFA procedural images for an IPMN with a mural nodule are shown in [Figure 1A](#); a procedural video is available as [Video 1](#), available online at www.giejournal.org.

Prophylaxis for acute pancreatitis was provided with nonsteroidal anti-inflammatory drugs (NSAIDs, intravenous ketoprofen 100 mg), unless contraindicated, in which case a hyperhydration protocol was used. Antibiotic prophylaxis with a single dose of a second-generation cephalosporin was also administered. After the procedure, patients were admitted for overnight observation in a standard ward and were allowed to resume oral intake the same day. For patients requiring multiple RFA sessions, each procedure was performed according to the same standardized protocol. See [Video 1](#), available online at www.giejournal.org.

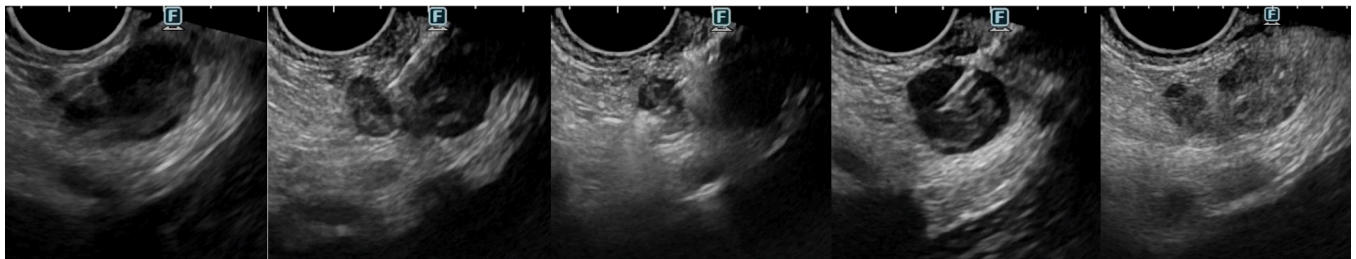


Figure 1. Chronological steps of EUS-guided radiofrequency ablation of an intraductal papillary mucinous neoplasm (IPMN), shown from left to right: IPMN before radiofrequency ablation, radiofrequency ablation of the mural nodule, appearance of the mural nodule at the end of ablation, radiofrequency ablation of the IPMN, and final appearance of the IPMN at the end of ablation.

Data collection and outcomes

Clinical, radiologic, and biological data were collected to assess treatment efficacy, local control of the IPMN, overall control of pancreatic carcinogenesis, and factors associated with response: demographic data (gender, age, and date of last report), preoperative IPMN characteristics (date of diagnosis, location, WFs, and HRS). All WFs (enhancing mural nodule <5 mm, main duct 5 to 9 mm, cyst ≥ 3 cm, thickened/enhancing wall, pancreatitis, abrupt duct change with distal atrophy, increased carbohydrate antigen 19-9, and rapid growth) and HRS (obstructive jaundice, enhancing mural nodule ≥ 5 mm, and main duct ≥ 10 mm) were recorded, and the total number of WFs was systematically counted for each patient and detailed preoperative characteristics of the IPMN.

Operative data recorded included cyst and mural nodule size at RFA and ablation parameters (power, impedance, and number of shots). Periprocedural and postprocedural AEs were classified according to the American Society for Gastrointestinal Endoscopy lexicon grading system.¹⁴ Follow-up data focused on local response (need for repeat RFA or surgery, cyst shrinkage or disappearance, persistence or recurrence of WFs/HRS) and oncologic outcomes, including the appearance of new IPMNs or pancreatic cancer either at the ablation site or elsewhere in the gland.

The primary end point was local control, defined as the sustained disappearance of WFs or HRS on follow-up imaging, with no invasive carcinoma arising from the treated IPMN. Secondary end points included technical success (defined as successful completion of the procedure since introduction of the RFA probe to induction of thermal current to the pancreatic lesions), procedural safety, and radiologic response (including complete disappearance of the treated IPMN). Pancreas-wide outcomes, defined as the occurrence of pancreatic cancer or the development of new IPMNs with WFs or HRS during follow-up, were assessed as exploratory outcomes.

Statistical analysis

A descriptive analysis was performed, with qualitative variables expressed as frequencies and percentages, quan-

titative variables with normal distribution as mean $\pm$ SD, and nonnormally distributed variables as median with range. Comparisons between groups of interests were carried out using the Fisher exact or χ^2 test for qualitative variables and the Mann-Whitney-Wilcoxon test for quantitative variables in univariate analyses. A P value $< .05$ was considered statistically significant. Because of the limited number of events, multivariate analysis was not performed, and predictors of outcome were explored using univariate analysis only. All analyses were performed using IBM SPSS Statistics software (IBM Corp, Armonk, NY, USA).

RESULTS

Population

A total of 50 patients (30 [60%] women; mean age, 70.8 $\pm$ 8.0 years; range, 52-82) underwent EUS-RFA for 58 IPMNs, including 8 patients treated for multiple lesions (2 lesions in 6 patients, 3 lesions in 1 patient). Four patients required 2 separate RFA sessions for the same lesion, resulting in a total of 62 procedures. At the time of RFA, IPMNs had been known for an average of 4.7 $\pm$ 4.2 years. Follow-up was available for 46 patients with 52 treated IPMNs: 2 (4%) patients died from nonpancreatic causes before a 1 year follow-up and 2 (4%) patients could not undergo CT, MRI, or EUS because of formal contraindications. The mean follow-up after RFA was 4.1 $\pm$ 2.8 years, and the median follow-up was 4.6 (IQR, 25-75 1.1-6.2) years.

Characteristics of IPMNs

At diagnosis, 33 (57%) patients presented with multifocal BD-IPMN, with an average of 2.73 $\pm$ 1.96 IPMNs per patient. Among the 58 BD-IPMNs treated, 24 (41%) were located in the pancreatic head, 8 (14%) in the uncinate process, 12 (21%) in the body, 10 (17%) in the tail, and 4 (7%) in the isthmus. The mean size of the treated lesions was 21.9 $\pm$ 9.7 mm (range, 7-50 mm), with 12 (20.7%) IPMNs measuring more than 30 mm. MPD diameter was 3.3 $\pm$ 0.9 mm on average; although no case reached ≥ 10 mm, 6 IPMNs (11.1%) showed moderate dilation (5-10 mm), and 2 (3.5%) displayed caliber change with upstream parenchymal atrophy.

TABLE 1. WFs/HRS at baseline and local control/complete response after EUS-guided radiofrequency ablation in BD-IPMN (N = 52)

WFs/HRS characteristics	Initial characteristics of treated IPMN (N = 52)	Local control of radiofrequency-treated BD-IPMN (N = 51/52)	Complete radiologic response (N = 9/52)
HRS			
Mural nodule ≥ 5 mm	22 (42%)	21/22	2/22
Obstructive jaundice	0 (0%)	0	0
Main pancreatic duct ≥ 10 mm	0 (0%)	0	0
WF			
Rapid growth (≥ 5 mm over 2 y)	24 (46%)	24/24	5/24
Mural nodule ≤ 5 mm	10 (19.2%)	10/10	0
Cyst ≥ 30 mm	12 (23%)	12/12	0
Pancreatitis caused by the IPMN	13 (25%)	12/13	0
Thickened/enhancing cyst wall	10 (19%)	10/10	1/10
Main duct size 5-9 mm	6 (11.5%)	6/6	0
Abrupt change in caliber of the main pancreatic duct with distal pancreatic atrophy	2 (4%)	2/2	1/2
New-onset diabetes at diagnosis	2 (4%)	2/2	0
No. of HRS and WFs per treated IPMN			
0	1	1/1	1/1
1	26	26/26	7/26
2	12	11/12	1/12
3	9	9/9	0/9
4	3	3/3	0/3
5	1	1/1	0/1

BD-IPMN, Branch-duct intraductal papillary mucinous neoplasm; HRS, high-risk stigmata; IPMN, intraductal papillary mucinous neoplasm; WF, worrisome feature.

Thirty-eight percent ($N = 21$) of BD-IPMNs had 1 HRS (mural nodule > 5 mm), and 98% ($N = 57$) had at least 1 WF. Overall, each IPMN exhibited an average of 1.7 ± 1.1 WFs or HRS (range, 0-5): 1 (1.5%) had none, 31 (45.6%) had 1, 12 (20.7%) had 2, 10 (17.2%) had 3, 3 (5.2%) had 4, and 1 (1.7%) had 5.

Primary end point: local control of RFA-treated BD-IPMN

Technical success was achieved in 100% of procedures. Local control of RFA-ablated IPMNs, defined as the sustained disappearance of WFs or HRS, was achieved in 98.1% of cases (51 of 52 lesions). Only 3 lesions required 2 RFA sessions to achieve WFs/HRS resolution. After a mean follow-up of 4.1 ± 2.8 years, 5 patients (9.6%) experienced reappearance of a WF in the treated lesion, which required a new RFA session. No cancer developed from any ablated IPMN.

None of the 9 IPMNs that achieved a complete radiologic response showed recurrence of WFs/HRS. Smaller BD-IPMN size was significantly associated with long-term improved local control ($P = .035$).

Table 1 presents the baseline WFs/HRS characteristics of the 52 lesions with available follow-up, together with the corresponding outcomes: local control and complete radiologic response in EUS-RFA-treated BD-IPMN.

Secondary end points

Radiofrequency endoscopic procedure and AEs.

Cytologic sampling for histopathologic analysis was performed in all cases, with the presence of dysplastic cells in 12 IPMNs (21% of all lesions). Among these, 11 (92%) showed low-grade dysplasia, and 1 (8%) showed high-grade dysplasia.

AEs occurred in 17 sessions (27.4%) (Table 2). Most were classified as AGREE I (13 cases, 21%), corresponding to mild, self-limited events requiring only nonopioid analgesics, primarily for abdominal pain. AGREE II AEs occurred in 3 cases (5%) and consisted mainly of edematous pancreatitis, managed with analgesics, short-term fasting (24-48 hours), and, in some cases, brief prolongation of hospitalization. Two events (3.2%) were classified as AGREE IIIa, including 1 case of necrotizing pancreatitis requiring endoscopic management and 1 biliary injury treated with radiologic intervention. Univariate analysis identified younger age ($P = .04$), a history of IPMN-related acute pancreatitis ($P = .002$), a smaller MPD diameter ($P = .031$), and repeat RFA sessions ($P = .014$) as significant predictors of AEs.

Radiologic response of RFA. A complete radiologic response of the radiofrequency-treated IPMN was observed in 9 lesions (17%). IPMNs located in technically challenging sites for puncture, such as the uncinate process ($n = 8$;

TABLE 2. Adverse events after EUS-guided radiofrequency ablation according to AGREE classification

AGREE grade	Procedure n (%)	Type of AEs	Management
AGREE I	13 (21%)	Abdominal pain	Nonopioid analgesics
AGREE II	3 (5%)	Edematous pancreatitis	Analgesics, fasting 24-48 hours, $\pm$ prolonged stay
AGREE IIIa	2 (3.2%)	Necrotizing pancreatitis (n = 1), biliary injury (n = 1)	Endoscopic/radiologic treatment
Total	17/62 (27.4%)	—	—

AE, Adverse event.

15%), showed no complete response ($P = .041$). The only factor significantly associated with complete response was a lower number of WFs/HRS ($P = .008$), whereas there was a trend toward better response in smaller IPMNs ($P = .055$). Two representative patient MRI scans before and after EUS-RFA are shown in [Figure 2](#).

In addition, 42 IPMNs (86%) decreased in size after RFA, with a mean reduction of 8.1 ± 7.9 mm. Among them, 10 lesions (19%) showed subsequent regrowth, generally without WFs or HRS. Only 1 case required a second RFA session because of rapid enlargement 22 months later.

Pancreas-wide outcomes during follow-up (exploratory). After a mean follow-up of 4.1 ± 2.8 years, pancreas-wide outcomes were assessed in 50 patients. Overall, 40 patients (80%) showed no pancreas-wide progression during follow-up.

During follow-up, the number of IPMNs per patient tended to increase slightly to 3.12 ± 2.45 . Overall, 10 patients (19%) showed progression of global pancreatic disease after a mean of 4.4 ± 2.4 years after RFA: 3 developed concomitant pancreatic cancer at a site distant from the treated IPMN, 1 developed both a distant pancreatic cancer and a new BD-IPMN with WFs, and 6 experienced the appearance of 1 or more new WFs on IPMNs other than the RFA-treated lesion. One patient underwent surgery for HRS (MPD dilatation to 10 mm) and was found to have only low-grade dysplasia on the resection specimen. Finally, 4 patients (8%) developed pancreatic cancer after a mean follow-up of 5.0 years, but none originated from the RFA-treated IPMNs. All underwent surgical resection, and half remained in remission after a mean follow-up of 4.1 ± 2.8 years.

A contributive cytology result (low-grade dysplasia) from BD-IPMN fluid aspirated on the day of RFA showed a trend toward predicting the development of distant pancreatic cancer ($P = .065$). Similarly, a higher number of baseline BD-IPMNs tended to predict the emergence of new WFs on other lesions ($P = .067$).

Overall survival. After a mean follow-up of 8.8 ± 4.8 years from IPMN diagnosis and 4.1 ± 2.8 years from EUS-RFA for BD-IPMN with WFs/HRS, 5 patients died. Two deaths were caused by concomitant pancreatic cancer (at 3.3 and 5.1 years after EUS-RFA), whereas 3 patients died from other diseases or medical conditions within 2 years of EUS-RFA.

DISCUSSION

In this large single-center series, EUS-RFA for BD-IPMNs demonstrated excellent long-term local control (98%), with no cancer arising from treated lesions, a favorable safety profile, and an overall pancreatic disease control maintained in 80% of patients after more than 4 years of follow-up.

Importantly, all patients included in this study were either deemed unfit for surgical resection or declined surgery. Accordingly, these results are strictly limited to a selected high-risk, nonsurgical population and should not be extrapolated to surgically fit patients, in whom pancreatic resection remains the standard of care when indicated. In patients with HRS, EUS-RFA should therefore be considered only when surgical resection is contraindicated or declined, and not as an oncologic alternative to surgery.

In our series, EUS-RFA for BD-IPMNs was associated with an overall AE rate of 27%, mostly mild abdominal pain, with only 8% significant events (acute pancreatitis) and no procedure-related mortality. Most AEs were self-limited and required only conservative management, whereas clinically significant pancreatitis remained uncommon. Our results are consistent with published RFA series reporting AE rates between 11% and 29%.^{9,15,16} In the only study dedicated to BD-IPMNs, the AE rate was 9%, but only severe events were reported¹⁷; when focusing on serious AEs, our results are therefore comparable. Importantly, severe AEs remained rare despite the inclusion of patients with WFs or HRS. Compared with EUS-guided ethanol $\pm$ paclitaxel ablation, which has shown pooled AE rates around 18% in meta-analyses and up to 32% in studies with a higher proportion of IPMNs,^{7,18,19} the safety profile of EUS-RFA appears at least comparable. However, it is worth emphasizing that most of these studies excluded IPMNs with WFs or HRS and often selected cysts with a much lower malignant potential. In this sense, our population represents a higher-risk group, making the absence of excess morbidity particularly reassuring. This profile compares favorably to pancreatic surgery. It is also important to note that the morbidity of EUS-guided ablation remains lower than that of pancreatic surgery.¹¹ In this context, the risk of postprocedural pancreatitis represents the main safety concern of EUS-RFA and

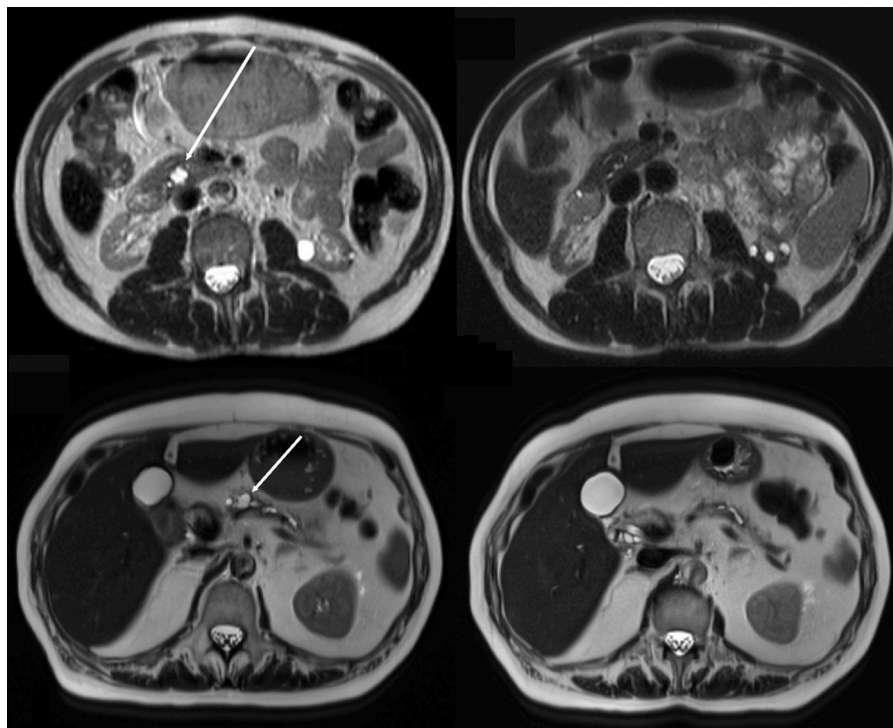


Figure 2. Representative MRI scans of branch-duct intraductal papillary mucinous neoplasms with worrisome features before EUS-guided radiofrequency ablation (*left*) and after treatment (*right*), illustrating radiologic response and local control. Top row and bottom row illustrate 2 representative

must be carefully weighed against potential benefits in nonsurgical patients.

Technical success was achieved in all procedures, in line with published series of EUS-RFA for cystic and solid pancreatic lesions.^{9,15-17,20} This confirms that, once cyst evacuation is complete, EUS-RFA is technically feasible and comparable to other EUS-guided ablation modalities such as ethanol or ethanol–paclitaxel injection, which also report near-universal technical success.^{19,21,22} Nonetheless, the lack of complete radiologic responses in lesions located in anatomically challenging sites such as the uncinate or isthmus suggests that local heat delivery may be less effective in these regions, possibly limiting ablation efficiency despite procedural success.

Our series demonstrates excellent local control of BD-IPMNs with EUS-RFA, reaching 98% at a mean 4-year follow-up, even in patients presenting with multiple WFs. Although complete radiologic disappearance was achieved in only 20% of cases, the majority of residual lesions remained stable or regressed in size, suggesting that full cyst eradication may not be necessary to ensure oncologic safety, provided that WFs/HRS are controlled. Radiologic cyst size reduction after EUS-RFA should be interpreted with caution. Although cyst size ≥ 30 mm is a recognized WF, cyst shrinkage may reflect necrosis, fibrosis, or mucin reduction rather than true eradication of dysplastic epithelium. Accordingly, size reduction was considered a descriptive radiologic outcome and not a primary oncologic end point, supporting our choice of “local control” as a clinically rele-

vant surrogate in nonsurgical patients. Our results are consistent with other dedicated series about cyst ablation, which reported a 17% complete disappearance rate and 78% $\geq 50\%$ volume reduction after 2 systematic RFA sessions, although with shorter follow-up.^{17,20} Comparisons with ethanol- or paclitaxel-based ablation are more difficult given heterogeneous protocols and lower-risk populations, but complete resolution rates in IPMN-focused cohorts ranged from 9% to 74%, with at least 1 report of pancreatic adenocarcinoma developing from a treated cyst.^{7,18,19} Direct comparison with ethanol- or ethanol–paclitaxel-based ablation is not appropriate, because those cohorts largely enrolled lower-risk IPMNs (typically without WFs/HRS or with size alone as the trigger), used heterogeneous protocols, and had shorter follow-up. Consequently, safety and efficacy should be interpreted within the context of each study’s selection criteria and methodology.

In our series, overall pancreatic disease control was maintained in 80% of patients after a mean 4-year follow-up, with 8% developing pancreatic cancer, all at a distance from the treated IPMN. Importantly, no cancer arose from an RFA-ablated lesion. This finding is consistent with the concept that EUS-RFA may achieve durable local control by reducing the dysplastic epithelial burden within the treated cyst. However, because our study is not comparative, it remains difficult to determine whether these rates reflect a true protective effect of RFA or the natural history of BD-IPMNs. In Oyama’s cohort,⁶ the cumulative risk of pancreatic ductal adenocarcinoma (PDAC) reached about 15% at 15 years

after IPMN diagnosis, whereas our patients were followed for a mean of 9 years from initial diagnosis (including 4 years after RFA), precluding direct comparison. Importantly, our results should not be interpreted as evidence that local ablation of a single BD-IPMN modifies the natural history of the entire pancreas. Accordingly, long-term surveillance of the entire pancreas remains mandatory after EUS-RFA, regardless of local radiologic response.

Even though no formal evidence currently demonstrates that local treatment of a single BD-IPMN can modify the natural history of the entire pancreas, several pathophysiological hypotheses may help contextualize the observed absence of malignant transformation within radiofrequency-ablated lesions. First, controlling the index IPMN reduces the global neoplastic burden and may limit intercellular signaling cascades that favor progression. Indeed, Wehrle et al¹² reported a very low rate of PDAC (~2%) when pancreatectomy was performed at the appearance of the first WF, suggesting that removing the IPMN resets the ductal-acinar environment and interrupts protumor pathways (transforming growth factor beta, Wnt, Hippo, and Ras). Second, by ablating mucin-producing lesions, RFA may relieve ductal hypertension while also eliminating the proinflammatory and protumoral effects of mucin stasis.²³⁻²⁵ Persistent mucin accumulation is known to drive fibrosis, epithelial stress, and carcinogenic signaling, all of which may be attenuated by local ablation.^{23,25} Third, although still speculative, an immune-mediated mechanism cannot be excluded. Experimental data suggest that RFA may trigger an abscopal-like effect through immunogenic cell death, releasing tumor antigens and danger signals that activate dendritic cells and stimulate CD8⁺ T-cell responses.²⁶⁻²⁸ Such immune priming has been demonstrated in pancreatic cancer models, particularly when combined with immunomodulators, and could enhance systemic surveillance, thereby suppressing the emergence of new high-risk IPMNs or distant PDAC.²⁶⁻²⁸ Importantly, no signal suggesting RFA-induced malignant progression was observed in our cohort; however, as with any local ablative therapy, a theoretical risk related to incomplete ablation cannot be entirely excluded. This underscores the importance of careful patient selection and the need for ongoing surveillance after treatment.

This study has several limitations. First, its retrospective, single-center design and the absence of a control group (surgery or surveillance alone) prevent definitive conclusions regarding comparative efficacy. Second, although this represents the largest published series of EUS-RFA in IPMNs to date, the cohort size (62 lesions) remains modest. Third, histologic confirmation of complete eradication cannot be obtained with ablative techniques; residual microscopic disease, therefore, cannot be fully excluded, because radiologic resolution or cyst size reduction does not equate to histologic eradication of dysplasia. Because surgical resection was not performed in this nonsurgical population, the true pathologic cure rate cannot be assessed and should not be inferred from our results, even though no malignant progression was

observed in treated lesions after a mean 4-year follow-up after RFA. Accordingly, the primary end point of “local control” should be interpreted as a clinical and radiologic surrogate, indicating the absence of progression toward criteria that would otherwise mandate surgery, rather than as evidence of complete dysplasia elimination.

Finally, although the mean follow-up in our cohort reached 9 years from IPMN diagnosis (4 years post-RFA), which is relatively long compared with prior reports, it may still be insufficient to fully capture the lifelong malignant potential of these lesions, whose natural history often exceeds a decade. This limitation should, however, be interpreted with caution, because many of our patients were elderly and comorbid, making very prolonged surveillance less clinically relevant in practice. Nonetheless, this series significantly advances the field by providing real-world evidence on the feasibility, safety, and oncologic efficacy of EUS-RFA in frail patients with worrisome or high-risk IPMNs—patients for whom pancreatic surgery carries substantial morbidity and even mortality despite harboring only low-grade dysplasia in many cases.

CONCLUSIONS

In this largest series reported, EUS-RFA achieved excellent local control of BD-IPMNs with WFs/HRS, with no cancer arising from treated lesions and an acceptable safety profile. This minimally invasive approach offers a valuable alternative for frail patients unfit for surgery, in whom therapeutic options are limited. EUS-RFA may thus represent an important component of a risk-adapted management strategy for IPMNs. Prospective multicenter studies are needed to confirm these results and clarify its place in the management of BD-IPMNs.

PATIENT CONSENT

All participants provided informed consent and permission for the procedure, data collection, and use of their data. The study received approval from the local Institutional Review Board (IRB) of Assistance Publique–Hôpitaux de Marseille (APHM) (ethics approval reference: FYYTGY).

DISCLOSURE

The following authors disclosed financial relationships: J. Michel Gonzalez: Consultant for Taewoong (outside the submitted work). M. Barthet: Consultant for Boston Scientific and Taewoong; research support from Taewoong (outside the submitted work). All other authors disclosed no financial relationships.

DIVERSITY, EQUITY, AND INCLUSION

While citing references scientifically relevant for this work, we actively worked to promote gender balance in

our reference list. The author list of this paper includes contributors from the location where the research was conducted who participated in the data collection, design, analysis, and/or interpretation of the work.

REFERENCES

- Ohtsuka T, Fernandez-del Castillo C, Furukawa T, et al. International evidence-based Kyoto guidelines for the management of intraductal papillary mucinous neoplasm of the pancreas. *Pancreatology* 2024;24:255-70.
- Farges O, Bendersky N, Truant S, et al. The theory and practice of pancreatic surgery in France. *Ann Surg* 2017;266:797-804.
- Jang JY, Kim SW, Lee SE, et al. Treatment guidelines for branch duct type intraductal papillary mucinous neoplasms of the pancreas: when can we operate or observe? *Ann Surg Oncol* 2008;15:199-205.
- Lorenzo D, Aguilera Munoz L, Vedie AL, et al. Mural nodules and prevalence of high-grade dysplasia in branch duct intraductal papillary mucinous neoplasm of the pancreas undergoing resection. *Br J Surg* 2024;111:znae292.
- Zelga P, Hernandez-Barco YG, Qadan M, et al. Number of worrisome features and risk of malignancy in intraductal papillary mucinous neoplasm. *J Am Coll Surg* 2022;234:1021-30.
- Oyama H, Tada M, Takagi K, et al. Long-term risk of malignancy in branch-duct intraductal papillary mucinous neoplasms. *Gastroenterology* 2020;158:226-37.e5.
- Song YJ, Huh G, Kim EH, et al. Comparison of outcomes of EUS-guided ablation and surveillance only for pancreatic cystic lesions: a propensity score-matching study (with videos). *Gastrointest Endosc* 2023;98:585-96.e3.
- Ardeshtna DR, Woods E, Tsung A, et al. An update on EUS-guided ablation techniques for pancreatic cystic lesions. *Endoscopic Ultrasound* 2022;11:432-41.
- Barthet M, Giovannini M, Lesavre N, et al. Endoscopic ultrasound-guided radiofrequency ablation for pancreatic neuroendocrine tumors and pancreatic cystic neoplasms: a prospective multicenter study. *Endoscopy* 2019;51:836-42.
- Barthet M, Giovannini M, Gasmi M, et al. Long-term outcome after EUS-guided radiofrequency ablation: prospective results in pancreatic neuroendocrine tumors and pancreatic cystic neoplasms. *Endosc Int Open* 2021;9:E1178-85.
- Cho SH, Seo DW, Oh D, et al. Long-term outcomes of endoscopic ultrasound-guided ablation vs surgery for pancreatic cystic tumors. *Clin Gastroenterol Hepatol* 2024;22:1628-36.e4.
- Wehrle CJ, Hossain MS, Perlmutter B, et al. Consequences of a surveillance strategy for side-branch intraductal pancreatic mucinous neoplasms: long-term follow-up of one thousand cysts. *Ann Surg* 2024;280:683-92.
- McCleary-Wheeler AL, McWilliams R, Fernandez-Zapico ME. Aberrant signaling pathways in pancreatic cancer: a two compartment view. *Mol Carcinog* 2012;51:25-39.
- Nass KJ, Zwager LW, van der Vlugt M, et al. Novel classification for adverse events in GI endoscopy: the AGREE classification. *Gastrointest Endosc* 2022;95:1078-85.e8.
- Pai M. Endoscopic ultrasound guided radiofrequency ablation, for pancreatic cystic neoplasms and neuroendocrine tumors. *WJGS* 2015;7:52.
- Choi JH, Seo DW, Song TJ, et al. Endoscopic ultrasound-guided radiofrequency ablation for management of benign solid pancreatic tumors. *Endoscopy* 2018;50:1099-104.
- Patel V, Shah ZK, Hart P, et al. S4 safety and efficacy of endoscopic ultrasound-guided radiofrequency ablation for branch duct-intraductal papillary mucinous neoplasms: a single arm clinical trial. *Am J Gastroenterol* 2024;119:S2.
- DeWitt J, McGreevy K, Schmidt CM, et al. EUS-guided ethanol versus saline solution lavage for pancreatic cysts: a randomized, double-blind study. *Gastrointest Endosc* 2009;70:710-23.
- Gómez V, Takahashi N, Levy MJ, et al. EUS-guided ethanol lavage does not reliably ablate pancreatic cystic neoplasms (with video). *Gastrointest Endosc* 2016;83:914-20.
- Younis F, Ben-Ami Shor D, Lubezky N, et al. Endoscopic ultrasound-guided radiofrequency ablation of premalignant pancreatic-cystic neoplasms and neuroendocrine tumors: prospective study. *Eur J Gastroenterol Hepatol* 2022;34:1111.
- Oh HC, Seo DW, Song TJ, et al. Endoscopic ultrasonography-guided ethanol lavage with paclitaxel injection treats patients with pancreatic cysts. *Gastroenterology* 2011;140:172-9.
- Attila T, Adsay V, Faigel DO. The efficacy and safety of endoscopic ultrasound-guided ablation of pancreatic cysts with alcohol and paclitaxel: a systematic review. *Eur J Gastroenterol Hepatol* 2019;31:1-9.
- Shockley KE, To B, Chen W, et al. The role of genetic, metabolic, inflammatory, and immunologic mediators in the progression of intraductal papillary mucinous neoplasms to pancreatic adenocarcinoma. *Cancers* 2023;15:1722.
- Suh H, Pillai K, Morris DL. Mucins in pancreatic cancer: biological role, implications in carcinogenesis and applications in diagnosis and therapy. *Am J Cancer Res* 2017;7:1372-83.
- Ponnusamy MP, Seshacharyulu P, Lakshmanan I, et al. Emerging role of mucins in epithelial to mesenchymal transition. *Curr Cancer Drug Targets* 2013;13:945-56.
- Rodríguez-Ruiz ME, Vanpouille-Box C, Melero I, et al. Immunological mechanisms responsible for radiation-induced abscopal effect. *Trends Immunol* 2018;39:644-55.
- Zerbini A, Pilli M, Penna A, et al. Radiofrequency thermal ablation of hepatocellular carcinoma liver nodules can activate and enhance tumor-specific T-cell responses. *Cancer Res* 2006;66:1139-46.
- Lambin T, Lafon C, Drainville RA, et al. Locoregional therapies and their effects on the tumoral microenvironment of pancreatic ductal adenocarcinoma. *World J Gastroenterol* 2022;28:1288-303.

Abbreviations: AE, adverse event; BD-IPMN, branch-duct intraductal papillary mucinous neoplasms; EUS-RFA, EUS-guided radiofrequency ablation; HRS, high-risk stigmata; MPD, main pancreatic duct; RFA, radiofrequency ablation; WF, worrisome feature.

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