Original research

Endoscopic radiofrequency ablation or surveillance in patients with Barrett's oesophagus with confirmed low-grade dysplasia: a multicentre randomised trial

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ABSTRACT

Objective Due to an annual progression rate of Barrett's oesophagus (BO) with low-grade dysplasia (LGD) between 9% and 13% per year endoscopic ablation therapy is preferred to surveillance. Since this recommendation is based on only one randomised trial, we aimed at checking these results by another multicentre randomised trial with a similar design.

Design A prospective randomised study was performed in 14 centres comparing radiofrequency ablation (RFA) (maximum of 4 sessions) to annual endoscopic surveillance, including patients with a confirmed diagnosis of BO with LGD. Primary outcome was the prevalence of LGD at 3 years. Secondary outcomes were the prevalence of LGD at 1 year, the complete eradication of intestinal metaplasia (CE-IM) at 3 years, the rate of neoplastic progression at 3 years and the treatment-related morbidity.

Results 125 patients were initially included, of whom 82 with confirmed LGD (76 men, mean age 62.3 years) were finally randomised, 40 patients in the RFA and 42 in the surveillance group. At 3 years, CE-IM rates were 35% vs 0% in the RFA and surveillance groups, respectively (p<0.001). At the same time, the prevalence LGD was 34.3% (95% CI 18.6 to 50.0) in the RFA group vs 58.1% (95% CI 40.7 to 75.4) in the surveillance group (OR=0.38 (95% CI 0.14 to 1.02), p=0.05). Neoplastic progression was found in 12.5% (RFA) vs 26.2% (surveillance; p=0.15). The complication rate was maximal after the first RFA treatment (16.9%).

Conclusion RFA modestly reduced the prevalence of LGD as well as progression risk at 3 years. The risk-benefit balance of endoscopic ablation therapy should therefore be carefully weighted against surveillance in patients with BO with confirmed LGD.

Trial registration number NCT01360541.

Summary Box

What is already known on this subject?
- The annual neoplastic progression rate of Barrett's oesophagus with low-grade dysplasia reaches 10%.
- Radiofrequency ablation (RFA) has been proposed as an alternative to surveillance based on two randomised controlled studies.

What are the new findings?
- RFA did not significantly reduce the prevalence of low-grade dysplasia on Barrett's oesophagus at 3 years.
- Spontaneous regression of confirmed low-grade dysplasia was observed in 31% of the patients in the endoscopic surveillance group.

How might it impact on clinical practice in the foreseeable future?
- The risk-benefit balance of endoscopic ablation therapy should be carefully weighted before offering this treatment to patients with Barrett's oesophagus with low-grade dysplasia.
- RFA for dysplastic Barrett's oesophagus should be performed in highly experienced centres.

INTRODUCTION

The rate of neoplastic progression of Barrett's oesophagus (BO) towards high-grade dysplasia (HGD) or adenocarcinoma does not exceed 2.6 cases per 1000 person-years (95% CI (2.2 to 3.1),[1] and justifies a simple endoscopic surveillance for most patients. Low-grade dysplasia (LGD) on BO has been reported in 5.6%–25.3% of patients with BO.[2] The management of HGD and early adenocarcinoma by endoscopic resection of visible lesions and endoscopic ablation of residual BO, most of the time performed by radiofrequency ablation (RFA) is currently consensual.[3–5] Conversely, the optimal management of BO containing LGD is still debated.[2 6] Indeed, the histopathological diagnosis of LGD is challenging, and the rate of neoplastic progression of BO with LGD has recently been reassessed from 21 cases per 1000 person-years (95%

CI 17.8 to 24.6)[7] to 91 cases per 1000 person-years (95% CI 58 to 136) or even 134 cases per 1000 person-years (95% CI 35 to 232).[8 9] This is explained by an improved definition of LGD, requiring a diagnostic confirmation by an expert pathologist, and allowing to downgrade the supposed LGD to non-dysplastic BO in up to 73% of cases.[10 11] These figures provide a rationale for the endoscopic therapy of BO with confirmed LGD. Since most patients with LGD do not display visible lesions, the preferred therapy is RFA,[4] given its high efficacy and good safety profile when compared with endoscopic resection.[12 13] Few studies have currently assessed endoscopic RFA for the treatment of BO with LGD.[14 15]

We conducted a multicentre randomised controlled trial comparing RFA with endoscopic surveillance, with the aim of assessing the efficacy of RFA for the endoscopic therapy of BO with LGD.

PATIENTS AND METHODS

Study design and patients

Fourteen French centres were selected based on their expertise in therapeutic endoscopy and BO management and > 10 cases of RFA performed annually. Patients aged 18–80 years were included if they had a histologically confirmed BO with at least 1 cm high circumferential extension and/or 3 cm high non-circumferential extension (ie, at least C1M1 or C0M3 according to the Prague classification[16]), with a confirmed diagnosis of LGD in the past 5 months, no visible lesion and LGD as worst histology (no concomitant HGD or early adenocarcinoma). Prior to enrolment, patients had an oesophagogastroduodenoscopy (OGD) performed by a senior endoscopist with a high definition endoscope, biopsies of all visible lesions and following the Seattle protocol.[17] All participating endoscopists were interventional endoscopists practising therapeutic endoscopy (endoscopic resections, biliopancreatic endoscopy), had followed a specific RFA training programme and had performed RFA procedures for at least a year. The diagnosis of LGD was accepted when established by two pathologists from the participating centre and further confirmed by central pathology review by the study's expert pathologist (BT). In case of a history of endoscopic resection for HGD or early adenocarcinoma, inclusion was only possible after 1-year follow-up and two series of biopsies according to the Seattle protocol, without HGD or cancer. Exclusion criteria were the presence of a BO with a C or M>12 cm length, presence of a visible lesion, contraindication to proton pump inhibitor (PPI) or anaesthesia, history of oesophageal or gastric surgical resection, oesophageal radiation therapy, oesophageal ablation therapy, oesophageal stricture, severe (Los Angeles grade C or D) peptic oesophagitis, oesophageal varices, systemic sclerosis and estimated life expectancy <2 years.

Adverse events were graded according to the French Public health code scale of the severity of adverse events in biomedical research (article R1123-54) (online supplemental table 1). A list of expected severe and non-severe adverse events was provided. Unexpected adverse events were considered severe when life threatening or leading to patient death, requiring unplanned hospital admission or a prolongation of the hospital admission or resulting in a permanent disability.

All serious adverse events were reviewed at the pharmacovigilance department of the Assistance Publique-Hôpitaux de Paris. The study was promoted by the Assistance Publique-Hôpitaux de Paris. The patients or the public were not involved in the design, or conduct, or reporting, or dissemination of our research. The trial was reported following the Consolidated Standards of Reporting Trials guideline[18] (online supplemental table 2).

Randomisation

The randomisation was achieved in a 1:1 ratio between the RFA and surveillance groups and stratified by centre. Randomisation lists (in fixed blocks of four) were performed by an independent DataManager and implemented on an online software (CleanWeb, Telemedicine Technologies, Boulogne-Billancourt, France) generating a 10-digit randomisation number sent to the investigator by email.

Ablation procedure

The first RFA procedure was performed within 3 months after randomisation, using the BarrX system (Medtronic, Minnesota, USA) under conscious sedation by propofol or general anaesthesia with endotracheal intubation, according to the anaesthesiologist's choice, with one to two nights' hospital admission. The balloon-based, circumferential and the focal, endoscope-attached RFA electrodes (HALO^{360} and HALO^{90}, respectively, Medtronic) were used depending on the circumferential extension of the BO. For circumferential RFA, a sizing balloon was introduced in the oesophagus over a guidewire to measure the inner diameter of the oesophagus. A HALO^{360} catheter of the adequate size, carrying a circumferential electrode, was placed in the oesophagus 1 cm above the proximal extent of the BO, under endoscopic guidance. Then, the balloon was inflated and the entire BO length was ablated at 12 J/cm^2. The ablation catheter was removed to clean the electrode, and the coagulated oesophageal mucosa was scraped out, using a soft distal attachment cap placed on the endoscope. The RFA catheter was then reintroduced, and a second ablation at 12 J/cm^2 was performed. For focal RFA, the HALO^{90} catheter, positioned at the distal end of the endoscope, was used to ablate residual tongues and islands of BO, using two consecutive ablations at 15 J/cm^2, followed by the scraping of the mucosal coagulum, and then by a second double 15 J/cm^2 ablation. Ablation regimen followed the settings recommended in 2013.[19 20] Up to four RFA procedures could be carried out, typically starting with a circumferential ablation, followed by focal ablations. The oesophagogastric junction was always ablated, although not always with a HALO^{90} catheter. Representative RFA treatment sequences and outcomes are presented in figures 1 and 2. Double-dose PPIs were prescribed during the month following the treatment, and then PPIs were resumed at the usual dose. After complete eradication of the BO or reaching the maximal number of four RFA sessions, a follow-up OGD with biopsies was scheduled at 12, 24 and 36 months after randomisation.

Control group

In the surveillance group, a second OGD was scheduled 12, 24 and 36 months after the randomisation, with the same modalities as the initial OGD.

Pathology

Oesophageal biopsy specimens were taken according to the Seattle protocol[17] and according to international guidelines[5]: quadrantic biopsies every 1 or 2 cm for short (<3 cm) or long (≥3 cm) segment BO, respectively. Biopsies were interpreted by two designated pathologists at each centre, with expertise in digestive pathology. For all biopsy samples with a diagnosis of LGD initially and on follow-up, two unstained pathology slides were sent for central pathology review at the Cochin University

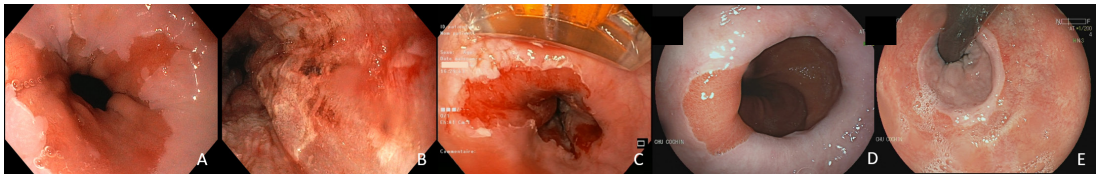

Figure 1 Representative endoscopic images of successful radiofrequency ablation treatment sequence in a patient aged 67 years with a C1M2 Barrett's oesophagus (BO) (panel A), treated with circumferential (panel B) and focal radiofrequency ablation (panel C), and complete eradication of dysplasia and intestinal metaplasia at 12 and 36 months, in direct (panel D) and retroflex view (panel E). The appearance of the oesophagogastric junction after radiofrequency ablation is typical, with a straight delineation between the neosquamous and gastric mucosa, and pseudoresidual tongues of BO, actually corresponding to normal gastric mucosa.

Hospital. The same was done in case of discordance between local pathologists on follow-up biopsies.

Outcome measures

The primary outcome was the prevalence of LGD 3 years after randomisation. Secondary outcomes included the rate of neoplastic progression towards HGD or adenocarcinoma at 1 and 3 years, prevalence of LGD at 1 year, complete eradication of dysplasia (CE-D) and complete eradication of intestinal metaplasia (CE-IM)) at the end of the treatment and at the latest follow-up endoscopy and adverse events.

Initial CE-IM was defined as the absence of IM on the oesophageal biopsies at 1 year after randomisation, since all patients would have had, at this time point, a follow-up endoscopy after their last RFA treatment; durable CE-IM was defined as the absence of IM on the biopsies at the end of the follow-up. Similarly, we defined initial and durable CE-D.

Statistical analysis

We hypothesised that LGD would be eradicated in 80% of patients in the RFA group, and that a 40% spontaneous regression would occur in the surveillance group.[21] The randomisation of 68 patients (34 per group) was required to obtain a statistical power of 90%, with an α 0.05. Because of an anticipated dropout rate between 15% and 40%, and an absence of LGD confirmation by central pathology review in 35% of the patients, we decided to include 120 patients in order to randomise the required number of patients. The analysis of the primary outcome used the Fisher's exact test.

The analysis of the initially defined primary outcome ('prevalence of LGD 3 years after randomisation') required to introduce a modified intention-to-treat (mITT) population for the main outcome measurement, since all patients with neoplastic progression beyond LGD (ie, HGD and EAC) dropped out of the study and had to be excluded from the calculation of potential patients harbouring LGD. Thus, the mITT population was made of the randomised patient population, excluding patients with neoplastic progression during the study. Considering the possible benefit of RFA in LGD remission *and* the absence of neoplastic progression, we also reported the rates of CE-D and CE-IM, allowing to include all the study patients in the intention-to-treat (ITT) population.

In the ITT population, all patients with neoplastic progression or lost to follow-up were considered as treatment failures. Multivariate analysis used a logistic regression, and included RFA treatment, age, sex, maximal height of the BO at inclusion, time since diagnosis of BO, history of HGD or cancer, duration of GORD symptoms. Patients' characteristics were expressed as n (percentages) for categorical variables and compared using Fisher's exact test, and as mean±SD for quantitative variables, and compared using the Student's t-test or the Mann-Whitney U test. Survival was analysed using a Kaplan-Meier method, with a maximum 3-year follow-up, and compared using a log-rank test. The characteristics of the study patients with neoplastic progression were assessed by a semi-parametric Cox regression model. Statistical analysis was carried out using the SAS software V.9.4 (SAS Institute, Cary, North Carolina, USA). All tests are bilateral with a statistical significance at 5%.

All authors had access to the study data and reviewed and approved the final manuscript.

RESULTS

Patient characteristics

One hundred twenty-five patients were included in the study between 22 December 2010 and 17 December 2014, allowing for 82 patients to be randomised, 40 in the RFA group and 42 in the surveillance group. The study flow chart is presented in figure 3. After central pathology review, 26% of patients initially diagnosed with LGD in their centre were downgraded to non-dysplastic BO.

GORD symptoms were reported by 68.2% (56/82) of patients, for a mean±SD duration of 14.1±13.7 years. BO had been

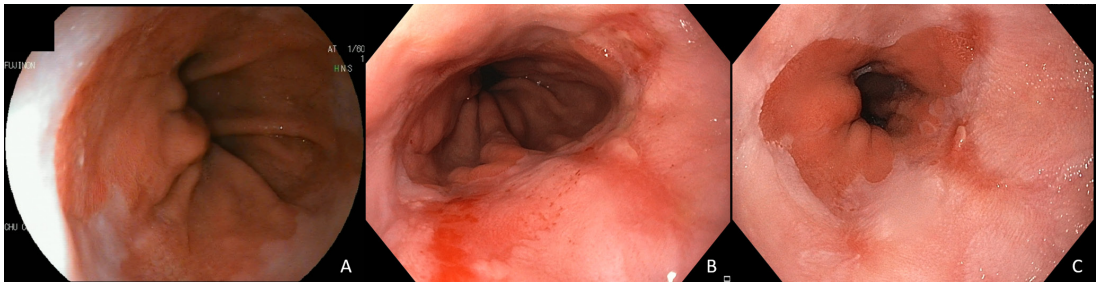

Figure 2 Representative endoscopic images of a failed radiofrequency ablation treatment sequence in a patient aged 73 years with a C2M4 Barrett's oesophagus (panel A), treated with 4 sessions of radiofrequency ablation with severe peptic oesophagitis at 12 months (panel B) and residual Barrett's oesophagus with low-grade dysplasia at 36 months (panel C).

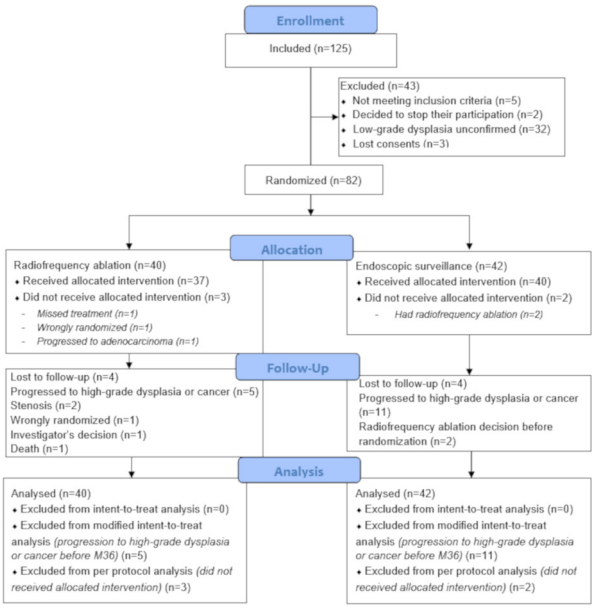

Figure 3 Study flow chart.

diagnosed for a mean±SD duration of 5.8±5.3 years, and LGD of 2.2±2.8 years. Antireflux surgery had been performed in 16 (19.5%) patients. Eight (9.8%) patients had a prior endoscopic resection for HGD or early adenocarcinoma. No patient had a history of endoscopic resection for a lesion harbouring LGD alone. Overall, 81 (98.8%) patients were on PPIs at inclusion, and 62 (75.6%) used other antireflux medications.

A hiatal hernia was observed by endoscopy in 48 (58.5%) patients, with a mean±SD size of 2.9±1.1 cm. The mean±SD size of the Barrett's segments were C=4.1±3.3 and M=5.8±2.9 cm. Two cases (2.4%) of peptic oesophagitis were recorded at baseline endoscopy, both Los Angeles grade A. The mean±SD follow-up was 30.0±13.4 months. The detailed values for each group of the study are presented in table 1.

Primary outcome: prevalence of BO with LGD at 3 years

Of the 40 patients randomised in the RFA group, 37 actually received the RFA treatment. Of these, 33 had a second RFA treatment session, 27 a third and 19 four RFA sessions. The median (p25–p75) number of RFA treatment session was 3 (2–4). The median (p25–p75) number of treated patient per centre was 4 (1.75–6) (online supplemental table 3).

The primary and secondary study outcomes are presented in table 2. In the mITT, the prevalence of BO with LGD 3 years after randomisation was 12/35 (34.3% (95% CI 18.6 to 50.0)) in the RFA-treated group vs 18/31 (58.1% (95% CI 40.7 to 75.4)) in the surveillance group, OR=0.38 (95% CI 0.14 to 1.02), p=0.05. In a multivariable analysis including RFA treatment or surveillance, age, sex, maximal height of the BO at inclusion, history of HGD or cancer, duration of gastro-oesophageal reflux symptoms, the reduction of the prevalence of BO with LGD at 3 years did not reach statistical significance, adjusted OR=0.34 (95% CI 0.10 to 1.20), p=0.10.

Secondary outcomes

Initial and durable complete eradication of dysplasia and intestinal metaplasia

In the ITT analysis, initial CE-D was 21/40 (52.5% (95% CI 37.0 to 68.0)) vs 11/42 (26.2% (95% CI 12.9 to 39.5)) in the RFA versus surveillance group, respectively (OR=3.12 (95% CI 1.23 to 7.87), p=0.015), and durable CE-D was 22/40 (55.0% (95% CI 39.6 to 70.4)) vs 10/42 (23.8% (95% CI 10.9 to 36.7)), in the RFA versus surveillance group, respectively (OR=3.91 (95% CI 1.52 to 10.06), p=0.004). Between 1 and 3 years after randomisation, dysplasia recurred in 3/40 (7.5%) patients vs 9/42 (21.4%), and regressed spontaneously in 4/40 (10%) vs 8/42 (19%) in the RFA versus surveillance group, respectively (p=0.07).

Initial CE-IM was 15/40 (37.5% (95% CI 22.5 to 52.5)) vs 0/42 (0) in the RFA versus surveillance group, respectively, (OR=51.68 (95% CI 2.86 to 932.62), p<0.001), while durable CE-IM was 14/40 (35.0% (95% CI 20.2 to 49.8)) vs 0/42 (0), in the RFA versus surveillance group, respectively (OR=46.52 (95% CI 2.57 to 841.25), p<0.001). Between 1 and 3 years, IM recurred in 4/40 (10%) patients of the RFA group.

Neoplastic progression rate

The neoplastic progression rate towards HGD or early adenocarcinoma at 3 years was 5/40 (12.5% (95% CI 5.0 to 26.6) vs 11/42 (26.2% (95% CI 15.2 to 41.2), p=0.15 in the RFA versus surveillance group, respectively, in the ITT analysis. Survival without neoplastic progression is illustrated on figure 4. Breaking down these cases, the rate of progression towards HGD was 3/40 (7.5%, 95% CI 1.2 to 20.6) vs 10/42 (23.8%, 95% CI 13.3 to 38.7), p=0.06 in the RFA versus surveillance group, respectively; meanwhile, the rate of progression towards early adenocarcinoma was 2/40 (5%, 95% CI 5.0 to 17.4) vs

Table 1 Patients' characteristics

	Radiofrequency ablation (n=40)	Surveillance (n=42)	P value*
Men—n (%)	36 (90.0)	40 (95.2)	0.36
Age, years—mean±SD	62.8±10.2	61.8 (9.9)	0.65
History of GORD symptoms, years—mean±SD	16.7±14.9	11.6±12.2	0.17
History of Barrett's oesophagus, years—mean±SD	6.1±5.6	5.5±5.0	0.61
History of LGD, years—mean±SD	2.2±3.2	2.2±2.4	1.00
Antireflux surgery—n (%)	7 (17.5)	9 (21.4)	0.65
Endoscopic resection for HGD or early adenocarcinoma—n (%)	2 (5)	6 (14.3)	0.33
PPI prescription—n (%)	40 (100)	41 (97.6)	1.00
C and M classification—mean±SD	4.0±2.9 and 5.6±2.7	4.2±3.7 and 6.0±3.1	0.77 and 0.56
Peptic oesophagitis—n (%)	1 (2.5)	1 (2.4)	0.97

*Student's t-test or χ^2 test as appropriate.
GORD, gastro-oesophageal reflux disease; HGD, high-grade dysplasia; LGD, low-grade dysplasia; PPI, proton pump inhibitor.

Table 2 Study outcomes

		RFA group n=40	Surveillance group n=42	OR (95% CI)	P value
Persistent LGD at 3 years—n (%)	mITT	12/35 (34.3%, 95% CI 18.6 to 50.0)	18/31 (58.1%, 95% CI 40.7 to 75.4)	0.38 (0.14 to 1.02)	0.05
	PP	15/37 (40.5%, 95% CI 24.7 to 56.4)	27/40 (67.5%, 95% CI 53.0 to 82.0)	0.33 (0.13 to 0.83)	0.02
Persistent LGD at 1 year—n (%)	mITT	12/35 (34.3%, 95% CI 18.6 to 50.0)	19/31 (61.3%, 95% CI 44.1 to 78.4)	0.33 (0.12 to 0.90)	0.03
	PP	11/37 (29.7%, 95% CI 15.0 to 44.5)	21/40 (52.5%, 95% CI 37.0 to 68.0)	0.38 (0.15 to 0.98)	0.04
CE-D at 3 years—n (%)	ITT	22/40 (55.0%, 95% CI 39.6 to 70.4)	10/42 (23.8%, 95% CI 10.9 to 36.7))	3.91 (1.52 to 10.06)	0.004
	PP	21/37 (56.8%, 95% CI 40.8 to 72.7)	10/40 (25.0%, 95% CI 11.6 to 38.4)	3.93 (1.50 to 10.36)	0.005
CE-D at 1 year—n (%)	ITT	21/40 (52.5%, 95% CI 37.0 to 68.0)	11/42 (26.2%, 95% CI 12.9 to 39.5)	3.12 (1.23 to 7.87)	0.015
	PP	20/37 (54.1%, 95% CI 38.0 to 70.1)	11/40 (27.5%, 95% CI 13.7 to 41.3)	3.10 (1.20 to 8.01)	0.018
CE-IM at 3 years—n (%)	ITT	14/40 (35.0%, 95% CI 20.2 to 49.8)	0/42 (0%)	46.52 (2.57 to 841.25)	<0.001
	PP	14/37 (37.8%, 95% CI 22.2 to 53.5)	0/40 (0%)	49.99 (2.75 to 909.33)	<0.001
CE-IM at 1 year—n (%)	ITT	15/40 (37.5%, 95% CI 22.5 to 52.5)	0/42 (0%)	51.68 (2.86 to 932.62)	<0.001
	PP	15/37 (40.5%, 95% CI 24.7 to 56.4)	0/40 (0%)	55.82 (3.07 to 999.99)	<0.001
Neoplastic progression rate at 3 years—n (%)	ITT	5/40 (12.5%, 95% CI 5.0 to 26.6)	11/42 (26.2% 95%CI 15.2 to 41.2)	–	0.15
	PP	4/37 (10.8%, 95% CI 0.81; 20.8)	11/40 (26.2% 95%CI 13.66; 41.3)	–	0.09
Treatment toxicity		7/37 (18.9%, 95% CI 9.2 to 34.5)	0/42 (0%, 95% CI 0 to 10)	–	0.004

ITT, intention-to-treat; LGD, low-grade dysplasia; mITT, modified intention-to-treat; PP, per protocol; RFA, radiofrequency ablation.

1/42 (2.4%, 95% CI 0.1 to 13.4), p=0.52 in the RFA versus surveillance group, respectively. The neoplastic progression rates in the per-protocol analysis were 4/37 (10.8%, 95% CI 3.7 to 25.3) vs 11/40 (27.5% 95% CI 16.0 to 43.0), p=0.09 in the RFA versus surveillance group, respectively. No advanced oesophageal adenocarcinoma requiring surgery was observed in either group.

Finally, excluding neoplastic progression, LGD was eradicated in (23/40) (57.5%, 95% CI 42.2 to 71.5) of patients treated with RFA, and regressed spontaneously in 13/42 (31.0%, 95% CI 19.1 to 46.0) of patients in the surveillance group, p=0.02.

Adverse events

At least one adverse event was presented by 7/37 (18.9%) patients after RFA. The rate of adverse events decreased gradually along with the RFA treatment sessions, from 6/37 (16.2%) at the first treatment session, 2/33 (6.1%) at the second, 1/27 (3.7%) at the third to 1/19 (5.3%) at the fourth RFA session. Twenty-two adverse events were reported following RFA, of which chest pain in 9 (40.9%) cases, fever in 4 (18.2%), vomiting in 3 (13.6%), anaesthesia-related complications in 3 (13.6%) cases and dysphagia, bleeding or oesophageal stricture in 1 (4.5%) case each. No severe adverse event occurred, one was moderate and all others were mild. No adverse event was recorded in the surveillance group. One patient from the RFA group died during follow-up from of a cause unrelated to RFA, endoscopy or oesophageal adenocarcinoma (metastatic bladder carcinoma). The adverse events are presented in the table 3.

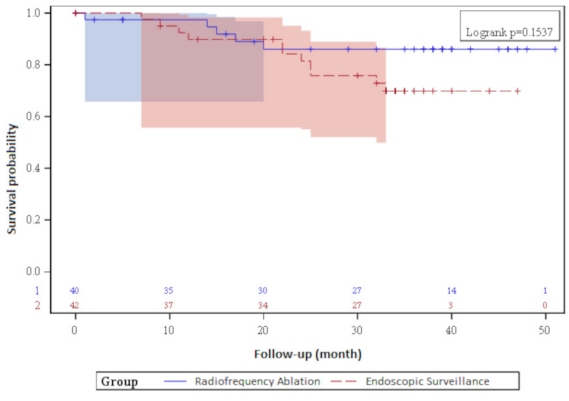

Figure 4 Survival without high-grade dysplasia or early adenocarcinoma, intention-to-treat analysis.

Post hoc analyses

Outcomes of RFA in low-volume versus high-volume centres

Of the 40 patients of the RFA group, 23 were treated in a low-volume centre (<30 RFA/year) and 17 in a high-volume centre (≥30 RFA procedures/year). CE-D at 3 years was 10/23 (43.5%, 95% CI 23.2 to 63.7) vs 13/17 (76.5%, 95% 56.3 to 96.6) in the low-volume versus high-volume centres, p=0.04. In addition, CE-IM at 3 years was 3/23 (13.0%, 95% CI 0.0 to 26.8) vs 8/17 (47.1%, 95% CI 23.3 to 70.8), in the low-volume versus high-volume centres, p=0.02.

Outcomes of RFA or surveillance in patients with or without prior endoscopic resection for HGD or early adenocarcinoma

Two out of the 40 patients of the RFA group and 6 of the 42 patients of the surveillance group had a history of endoscopic resection for HGD or early adenocarcinoma. Excluding these patients, persistent LGD (or neoplastic progression) at 3 years was 17/38 (44.7%, 95% CI 30.1 to 60.3) vs 23/36 (63.9%, 95%

Table 3 Main adverse events after radiofrequency ablation (RFA) of Barrett's oesophagus with low-grade dysplasia

Adverse events after the first RFA procedure—n (%)	5/37 (13.5%)
Fever	2/37 (5.4%)
Chest pain	2/37 (5.4%)
Cardiac arythmia	1/37 (2.7%)
Adverse events after the second RFA procedure—n (%)	4/33 (12.1%)
Vomiting	1/33 (3%)
Chest pain	1/33 (3%)
Upper GI bleeding	1/33 (3%)
Oesophageal stricture	1/33 (3%)
Adverse events after the third RFA procedure—n (%)	1/27 (3.7%)
Vomiting and chest pain	1/27 (3.7%)
Adverse events after the fourth RFA procedure—n (%)	1/19 (5.3%)
Vomiting and chest pain	1/19 (5.3%)

CI 47.5 to 77.6) in the RFA versus surveillance group, respectively, p=0.10. In addition, persistent BO at 3 years was observed in 29/38 (76.3%; 95% CI 60.6 to 87.2) vs 36/36 (100%) in the RFA versus surveillance group, respectively, p=0.02.

Outcomes of RFA in patients with long-standing LGD

Five patients in the RFA group had a diagnosis of LGD on BO for 5 years or more. Persistent LGD (or neoplastic progression) at 3 years was 3/5 (60.0%, 95% CI 17.1 to 100.0) vs 14/35 (40.0%, 95% CI 23.9 to 57.9), p=0.63, for patients with LGD for 5 years or more versus patients with LGD for 4 years or less, respectively. In addition, persistent BO at 3 years was observed in 5/5 (100%) vs 23/35 (65.7%, 95% CI 47.8 to 80.9) in the long-lasting versus short-lasting LGD patient groups, respectively, p=0.30.

DISCUSSION

As compared with an annual endoscopic surveillance programme, this randomised trial showed that although radiofrequency ablation significantly reduced the prevalence of LGD in BO at 1 year, this benefit was not maintained at 3 years.

These results are noticeably inferior to those reported in the literature: the first large multicentre trial assessing RFA versus sham procedure included 64 patients with LGD.[14] In this study, Shaheen *et al* obtained a 90.5% clearance of LGD in the RFA-treated group vs 22.7% in the surveillance group (p<0.001) at 1 year, and a CE-IM in 81% vs 4%, p<0.001 in the RFA and sham groups, respectively. However, the 3-year outcomes, suggesting a 100% persistent clearance of LGD and a 91% complete remission of IM (CR-IM), included less than half of the patients initially treated for LGD.[22] The latest follow-up of this patient cohort reported a 29.7% (95% CI 16.5 to 43.0) cumulative incidence of recurrent IM and/or dysplasia after a mean follow-up of 3.6 years per patient.[23] Of note, the vast majority of the patients of our study reached the 36 months follow-up. Phoa *et al* published in 2014 the first randomised trial on RFA in BO containing LGD,[15] with the neoplastic progression rate towards HGD or adenocarcinoma as a primary outcome: the authors included 140 patient with BO and confirmed LGD, and observed a 25% reduction of the neoplastic progression risk, and a complete clearance of LGD in 98.4% in the RFA-treated patients vs 27.9% in the control group, p<0.001. Half of the patients had not reached the 3 years follow-up by the time the results were published, due to an early termination of the trial justified by the superiority of RFA for the primary outcome. The latest follow-up data of this cohort found a complete clearance of dysplasia and IM in 90% of the patients, 6 years after the inclusion in the study.[24]

A first explanation for these discrepancies with our results is the 31.0% rate of spontaneous clearance of LGD in our study, slightly higher than the 22.7% and 27.9% clearance rates observed in the other studies.[14 15] Of note, higher rates of spontaneous regression of LGD at 3 years, ranging from 34% to 75%, have been reported.[21 25 26] One can question the possibility of a true spontaneous regression of LGD as opposed to a sampling error: however, the sampling bias is limited by the repeated follow-up endoscopies with biopsies. For gastroenterologists, LGD mainly refers to elevated lesions of the GI tract (adenomas), that we hold to have a malignant potential, and never spontaneously regress. However, flat LGD in other locations of the human body, such as the uterine cervix (CIN 1 lesions), regress in over 50% of cases.[27] Also, these data raise the question of the reliability of the pathological diagnosis of LGD on BO[28]: indeed, while the diagnosis of LGD may reach an agreement, provided a sufficient number of expert pathologists is involved (56%–69% agreement with two pathologists,[29 30] up to 84% with three pathologists[10]), its reliability remains questionable, with κ values of 0.14–0.45[10 29 30]: what we call spontaneous regression of LGD could be a—consensual—initial misclassification. Finally, the patients with LGD of our study have comparable spontaneous regression rates and neoplastic progression rates as the Dutch patients with LGD. Therefore, it seems that we do refer to the same disease as our colleagues when we talk about LGD on BO. This is probably the most important point to determine the indication of a treatment or surveillance. Of note, the number of centres needed to include the study population underlines that BO with confirmed LGD is actually a rare disease.

The 26% downstaging rate of the initial diagnoses of LGD towards non-dysplastic IM is in agreement with the 32% reported by Wani *et al*,[29] even though it is much lower than the 52%–73% reported by others.[10 30] Although the 65% LGD confirmation rate assumed in the sample size calculation might seem far from the 27%–45% confirmation rate reported by others,[10 30] we need to take into consideration that these LGD diagnoses were made by pathologists from tertiary endoscopy centres, already specialised in digestive pathology. Finally, the 75% confirmation rate of LGD observed in our work confirmed this hypothesis.

A second explanation is the limited rate of CE-IM in our study. Shaheen *et al*[14] performed a mean of 3.5 RFA sessions, and Phoa *et al*[15] performed a median number of 3 RFA sessions per patient, and further escape resection or ablation procedures in a fourth of the patients. It is likely that the limited number of four RFA sessions, the absence of systematic ablation of the oesophagogastric junction using a focal catheter, and the absence of escape resections account for the low rate of CE-IM in our study. A recently published randomised study from the UK comparing RFA and argon plasma coagulation for dysplastic BO only achieved CE-IM in 55.9% of patients after four sessions of RFA, despite the initial endoscopic resection.[31] The rates of CR-IM and complete remission of dysplasia (CR-dysplasia) of the randomised and large prospective studies on BO with LGD are presented in table 4. These data, ours, and those of smaller centres,[32 33] suggest that a very specific expertise is needed to achieve the 90% CE-IM rate obtained in the Surveillance vs Radiofrequency Ablation (SURF) trial.[15] Additionally, a learning curve effect on the efficacy of RFA was documented in a 2015 study by Pasricha *et al*,[34] showing that the number of RFA sessions needed to obtain CE-IM reached a steady state after 30 patients treated with RFA at a given centre; this case load was not a prerequisite for the selection of the centres participating in our study in 2010. Of note, while the rate of CR-dysplasia dropped from 68.5% at 1 year to 57.5% at 3 years, the CE-IM rate of 27.5% remained stable at 3 years, suggesting that IM did not recur in any of our study patients. CE-IM may however be a disappointing end point for the treatment of dysplastic BO, since IM can recur at a rate of 8.6% per year,[35] justifying continued endoscopic surveillance even after obtaining CE-IM.[5 36]

As previously mentioned, the absence of escape therapy limited the rates of CE-IM, and allows us to conclude on the efficacy of RFA alone rather than on the efficacy of a multimodal endoscopic therapy for BO with LGD. We did not collect information on PPI dosage or observance to PPI treatment: it is possible that this insufficient acid suppression, compared with the long-term double dose PPI+14 days anti H2 and sucralfate therapy that is now widely adopted,[37] partly accounts for the poor rates of CE-IM observed in the study. Finally, the caseload

Table 4 Outcomes of radiofrequency ablation (RFA) for Barrett's oesophagus (BO) containing low-grade dysplasia (LGD) in the literature

Study	Number of patients	Design	Setting	RFA sessions	Escape therapy	CE dysplasia	CE intestinal metaplasia	Annual neoplastic progression rate
Shaheen *et al*[14]	42 vs 22	RCT RFA vs surveillance	BO with LGD	Up to 4	Not stated	**90.5%** vs 22.7%, p<0.001	**81%** vs 4%, p<0.001	5% vs 14%, p=0.33
Phoa *et al*[15]	68 vs 68	RCT RFA vs surveillance	BO with LGD	Up to 5	ER=7.4% APC=17.6%	**98.4%** vs 27.9%, p<0.001	**90%** vs 0%, p<0.001	Not stated vs 11.8% – 1.5% vs 26.5% p<0.001 after a 36 months median FU
Current study	40 vs 42	RCT RFA vs surveillance	BO with LGD	Up to 4	No	**55%** vs 23.8%, p=0.004	**35%** vs 0%, p<0.001	4.2% vs 8.7% – 12.5% vs 26.2%, p=0.15 at three years
Peerally *et al*[31]	36 vs 40	RCT RFA vs APC	BO with dysplasia	Up to 4	No	**79.4%** vs 83.8%	**55.8%** vs 48.3%, p=NS	Not stated
Vliebergh *et al*[39]	295	Prospective	BO with dysplasia	Median 2 (p25–p75 1–3)	ER or APC in 13%	**87%**	**82%**	Not stated
Krajciova *et al*[40]	170	Prospective	Bo with dysplasia	Median 2 (range 1–6)	Not stated	**98.5%**	**77.9%**	0%
Ganz *et al*[41]	92	Prospective	BO with dysplasia	Median 1 (p25–p75 1–2)	Not stated	**80.4%**	**54.3%**	Not stated
Hauge *et al*[32]	86	Prospective	BO with dysplasia	Mean 1.4 (range 0–4)	Not stated	**50%**	Not stated	4.5%
Komanduri *et al*[42]	221	Prospective	BO with dysplasia	3	No	Not stated	**71%**	Not stated
Haidry *et al*[43]	266*	Prospective	BO with dysplasia	Mean 2.6 (range 1–5)	ER=13%	**77%**	**57%**	3.4%

*Patients treated between 2008 and 2010.
APC, argon plasma coagulation; CE, complete eradication; ER, endoscopic resection; FU, follow-up; RCT, randomised controlled trial.;

was heterogeneous throughout the centres, and significantly different eradication rates of dysplasia and IM were observed between low-volume and high-volume centres.

We could not demonstrate a statistically significant impact of the RFA treatment on the neoplastic progression rate of BO with LGD. Although the 8.8% annual neoplastic progression rate was in accordance with the latest data on LGD confirmed by expert pathologists,[9] the risk of neoplastic progression remained high in the RFA treatment group, at 4.2% annually, much higher than the 1.5% rate at 3 years observed by Phoa *et al*.[15] This 13.7% absolute risk reduction, corresponding to a 47.7% relative risk reduction, might not have reached statistical significance because the study was not adequately powered to study this end point, and again possibly because of the low rate of CE-IM in our study. Of note, while the neoplastic progression rate at 3 years was diminished from 26.5% to 1.5% in the study by Phoa *et al*.[15] RFA treatment lowered the neoplastic progression rate from 14% to 5% only in the study from Shaheen *et al*.[14]

Our data question the validity of the RFA treatment for BO with LGD. First, because of the spontaneous regression of LGD in almost a third of the patients. Second, because the low rate of CE-IM we achieved after up to four treatment sessions did not result in a statistically significant difference in the prevalence of LGD or the neoplastic progression rate between the RFA and surveillance groups at 3 years. Third, because 18.9% of the patients in the RFA group experienced at least one adverse event after RFA in our study, a higher rate than the mean 11.3% reported in other prospective studies,[13] although we need to acknowledge that mild adverse events due to the hospital admission of the patients after the RFA procedures were recorded. Fourth, the RFA increases treatment cost by US$8593 per patient, even when the cost of the endoscopic treatment of progression is taken into account.[38]

Our study is the second to address the specific question of the impact of RFA for patients with a BO and LGD. The strengths of our study are its prospective and randomised design, the central pathology review and the long-term follow-up. The limitations include a large number of centres, with a relatively small number of patients treated at each centre; the heterogeneity of the patients, with treatment-naïve patients and patients with prior early adenocarcinoma or HGD treated endoscopically, although their outcomes were not significantly different in the RFA group and the low rate of CE-IM, possibly accounting for the limited contribution of the RFA, although difficult to quantify in the absence of a precise morphological analysis of the remaining BO. Including patients who underwent endoscopic resection for HGD or early adenocarcinoma instead of only patients with flat LGD might have brought heterogeneity to the analysed cohort. However, these patients accounted for 9.7% (8/82) of the study population, were over-represented in the surveillance group and were included only after 1-year follow-up and two series of biopsies without HGD or adenocarcinoma.

In conclusion, in this multicentre randomised study in patients with BO and a confirmed diagnosis of LGD, RFA alone did not significantly reduce the prevalence of LGD or the rate of neoplastic progression at 3 years. The risk-benefit balance of endoscopic ablation therapy should therefore be carefully weighted before offering this treatment to patients with LGD.

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