The course of pain and dysphagia after radiofrequency ablation for Barrett's esophagus-related neoplasia

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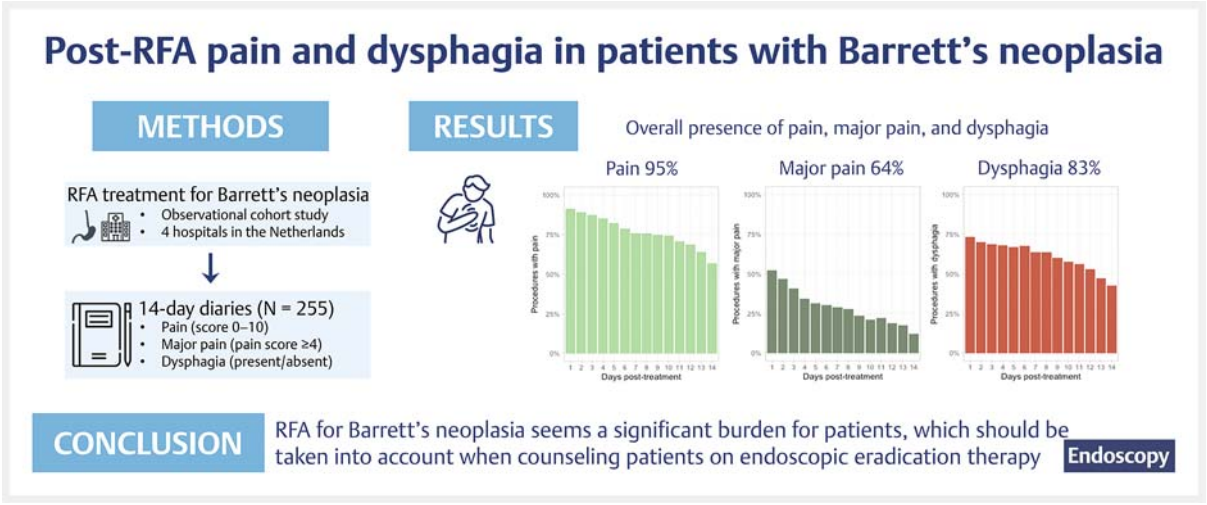

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ABSTRACT

Background Radiofrequency ablation (RFA) is effective for eradication of Barrett's esophagus (BE) neoplasia, but little is known on the course of pain and dysphagia after RFA. We aimed to describe the course of post-RFA symptoms and to identify possible associated risk factors.

Methods In this multicenter, observational cohort study, all RFA procedures registered in a prospective database were included. Patient and treatment characteristics were collected from medical records and patients self-registered post-procedural symptoms in electronic symptom diaries for 14 days. Mixed model regression was used for the analyses.

Results In total, 255 diaries were completed. Post-RFA pain was reported for 95 % (95 %CI 93–98) of procedures (median duration 14 days; 25th–75th percentiles [p25–p75] 11–14) and major pain for 64 % (95 %CI 58–69; median duration 8 days, p25–p75 3–13). Post-procedural pain significantly increased with BE length, younger age, and no prior ablation. Dysphagia was present after 83 % (95 %CI 79–88) of procedures (median duration 13 days, p25–p75 9–14). The risk of dysphagia decreased with age and increased when patients experienced more pain.

Conclusions RFA treatment for BE-related neoplasia seems a significant burden for patients, and post-procedural symptoms should be taken into account when counseling patients before starting endoscopic eradication therapy.

Introduction

Radiofrequency ablation (RFA) is the current standard-of-care ablation technique for Barrett's esophagus (BE)-related neoplasia neoplasia [1]. Numerous large prospective studies have shown this technique to be feasible, effective, and safe [2, 3]. Some of the potential adverse events of RFA have been systematically studied. In general, details on stricture formation, bleeding, and perforations are well reported in most studies [4]. By contrast, patient tolerability (e. g. pain and dysphagia) after RFA is not well studied despite it being clinically recognized that RFA can cause substantial post-procedural symptoms [4, 5].

Therefore, the aim of the current study was to describe the course of post-RFA symptoms in patients with BE-related neoplasia and to identify possible associated risk factors. The results of this study will help to adequately inform patients on the course of post-RFA symptoms and may be used to compare patient tolerability of newly developed ablation therapies in the future.

Methods

Patients

For this multicenter cohort study, all RFA procedures registered in a prospective database on patient tolerability after endoscopic treatment for BE-related neoplasia between January 2016 and September 2020 from four Dutch Barrett expert centers were included. This prospective registration was initiated to collect data on patient tolerability after endoscopic treatment, and comprises patient and treatment characteristics and electronic post-procedural symptom diaries. Patients with no access to email were excluded, as were completely empty diaries. Patients may be registered more than once within the registry as multiple, sequential RFA treatments are often required before all BE has been eradicated. A total of 26 RFA procedures included in the current study have been reported previously [5].

Endoscopic procedures

All RFA treatments were performed by dedicated BE endoscopists on an outpatient basis using sedation with midazolam or propofol. Prior to every RFA treatment, the BE segment was carefully inspected with both white-light endoscopy and narrow-band imaging or blue-light imaging, and the Prague score was documented. During every procedure, all visible BE was ablated using circumferential or focal RFA (Barrx; Medtronic, Minneapolis, Minnesota, USA). The ablation regimen depended on the device type. In cases of pain after RFA, patients were advised to use oral paracetamol (maximum 1 g three times per day) and to contact the clinical team to discuss additional therapy if needed. Furthermore, all patients were prescribed proton pump inhibitors twice daily after every procedure. Additionally, all patients were prescribed sucralfate solution, 1 g three times per day, and ranitidine 200 mg per day, for 2 weeks after RFA treatment. Additional medication to achieve optimal acid control could be added.

Post-procedural symptom diary

Patients self-registered post-procedural symptoms (pain, analgesics use, and dysphagia) in electronic symptom diaries for 14 days after every treatment, starting the day after RFA treatment. The daily survey consisted of four items: 1) pain score during meals, using a numeric rating scale of 0–10, with 0 indicating no pain and 10 the worst pain ever experienced; 2) pain score when not eating/at rest (same score as mentioned for 1); 3) use and type of analgesics; 4) post-procedural dysphagia using a validated score ranging from 0 to 4 [6], with 0 indicating no dysphagia, 1 minimal dysphagia (able to eat solid foods), 2 moderate dysphagia (need to crush or puree all foods), 3 severe dysphagia (passage of liquids only), and 4 indicating no passage at all.

Outcome parameters

As the electronic symptom diary included two questions on post-procedural pain (pain at rest and pain during meals), a composite pain score was used for all analyses, defined as the maximum value of both questions per patient per day (possible

value ranging from 0 to 10). Major pain was defined as a composite pain score ≥4, which is an arbitrary cutoff value based on a previous study that reported an acute postoperative pain score of ≥3.3 to be unacceptable [7]. Peak pain was defined as the maximum composite pain score reported after RFA. To analyze presence of dysphagia, dysphagia scores were dichotomized (≥1 vs. 0). Outcome parameters regarding pain were: 1) number of procedures with pain, major pain, and analgesics use (overall and per day of the diary); 2) number of days until pain, major pain, and analgesics use were no longer reported; 3) peak pain score per diary; 4) composite pain score throughout 14 days (overall and specified for different subgroups); and 5) risk factors for post-procedural pain. Outcomes parameters for dysphagia were: 1) number of procedures with dysphagia (overall and per day of the diary); 2) number of days until dysphagia was no longer reported; 3) association between pain and dysphagia; 4) presence of dysphagia throughout 14 days after RFA (overall and specified for different subgroups) and 5) risk factors for dysphagia.

Statistics

Statistical analyses were performed in R (Version 3.6.2 for Mac; R Foundation for Statistical Computing, Vienna, Austria) using packages lme4, rms, lmerTest, reshape2, ggplot, cowplot, gridExtra, and MuMIn. For baseline descriptive statistics, means were calculated with SDs for normally distributed variables and medians with 25th–75th percentiles (p25–p75) for variables with a skewed distribution. Categorical variables were presented as percentages of the total. Risk factors for pain and presence of dysphagia were analyzed, respectively, with linear mixed model and logistic regression analysis, which takes multiple diary entries per patient into account. Coefficients for pain were estimated using restricted maximum likelihood. The course of pain and dysphagia and differences therein for subgroups were analyzed by comparing multilevel longitudinal multivariable regression models with and without an interaction between time (restricted cubic spline with 5 knots) and different subgroups with a likelihood ratio test under maximum likelihood. Restricted cubic splines with 5 knots were also considered for evaluation of the effects of continuous covariates (age, BE segment length, and hiatal hernia length) and were included if they improved the model fit (lowering of the Akaike information criterion of more than 2). Missing data were dealt with by using mixed model regression; goodness of fit and assumptions were checked for all models [8]. A two-sided *P* value of <0.05 was considered significant and estimates are reported with 95%CIs.

Ethics

The Medical Ethics Committees United confirmed that the Medical Research Involving Human Subjects Act (WMO) did not apply for this study (reference number W15.100). Written informed consent, to send out an electronic symptom diary after endoscopic treatment and to use the data for medical research, was obtained from all patients. The manuscript was written in accordance with the strengthening the reporting of observational studies in epidemiology (STROBE) guidelines [9].

Results

Between January 2016 and September 2020, 272 diaries were sent out to patients following RFA for BE, of which 255 diaries were completed by 179 patients. Of these 255 diaries, 191 (75%) were completed in full for all 14 days and 238 (93%) were completed for more than 10 days (see **Fig. 1s** in the online-only Supplementary material). In total, 3570 daily questionnaires were expected for the 255 diaries included, but 217 pain scores (6%), 216 dysphagia scores (6%), and 215 analgesics use entries (6%) were missing.

RFA was performed with a circumferential device in 53 procedures (21%), with $1\times10\,J/cm^2$ – clean – $1\times10\,J/cm^2$ being the most frequently used dosimetry (83%), and a focal device in 202 procedures (79%), using a dosimetry of $3\times12\,J/cm^2$ – no cleaning in 93% of all focal treatments. Overall, 39% of procedures were performed on ablation-naïve esophageal tissue. The median BE length was C0 (p25–p75 0–0, range 0–13), M1 (p25–p75 0–4, range 0–14), and prior endoscopic resection was performed in 119 (47%) of procedures (**Table 1s**).

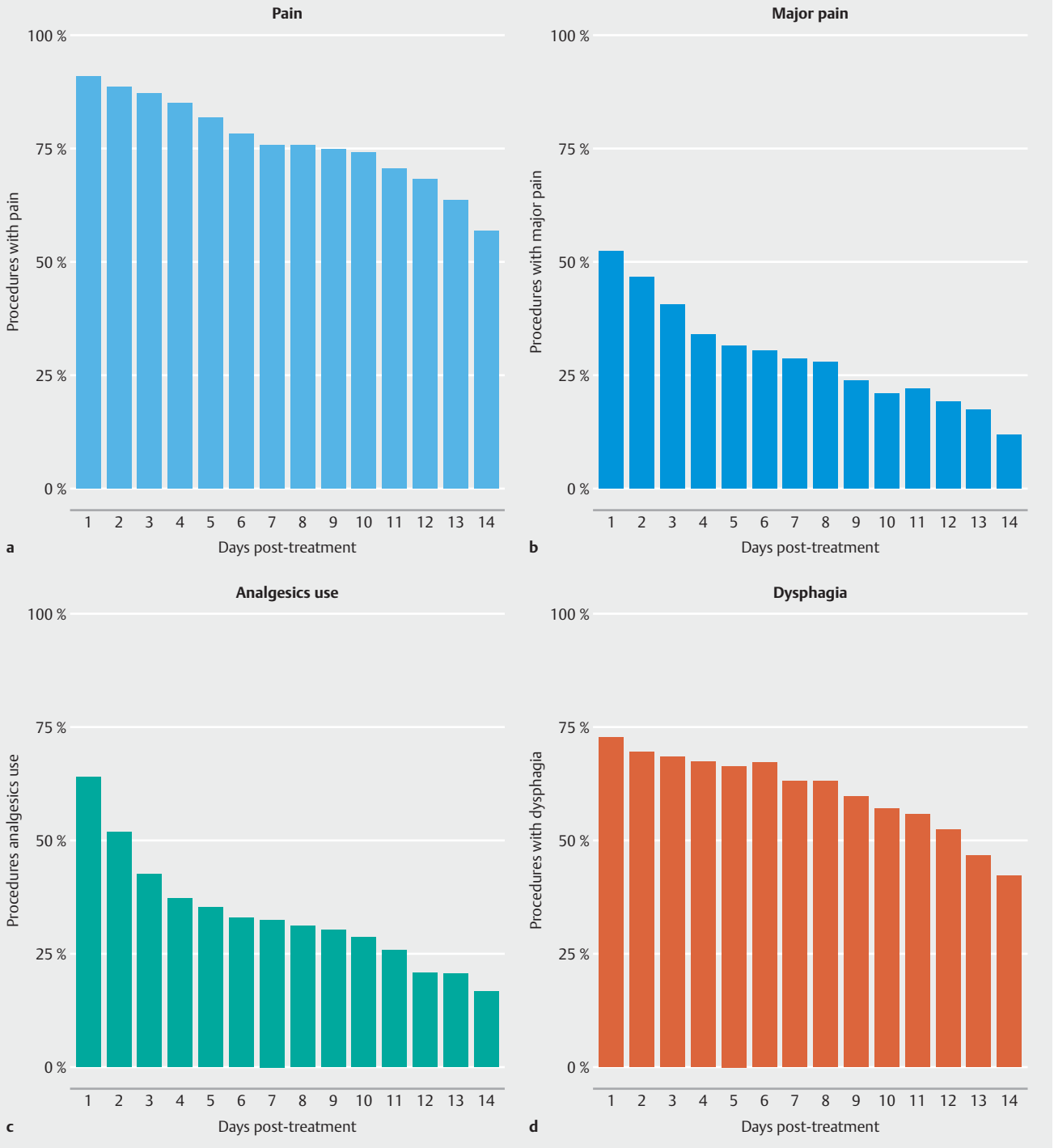
Post-procedural pain

Post-procedural pain was reported in 243 (95%; 95%CI 93–98) of 255 RFA procedures. After 109 procedures (43%), a pain score >5 was reported. The median duration until pain was no longer reported was 14 days (p25–p75 11–14) (▶ **Fig. 1a**). Major post-procedural pain was reported in 162 (64%; 95%CI 58–69) of RFA procedures. If present, the median duration until no major pain was reported was 8 days (p25–p75 3–13) (▶ **Fig. 1b**). In 28 procedures (11%), major pain was present throughout Day 14, the last day of the symptom diary. The median peak pain score per RFA procedure was 5 (p25–p75 3–7) and peak pain was reached after a median of 1 day (p25–p75 1–2.5). Analgesics use at any moment after RFA was reported for 186 procedures (73%; 95%CI 67–78). If analgesics were used after RFA, the median number of days until no analgesics were used was 8 (p25–p75 2–13) (▶ **Fig. 1c**). In 15% of procedures, analgesics use was still reported on Day 14. Paracetamol was the most widely used analgesic (**Fig. 2s, Table 2s**).

The overall course of the mean composite pain score throughout the 14 days after RFA treatment is depicted in **Fig. 3s a**. Age, BE segment length, sex, prior ablation, and RFA device type all resulted in a significantly different course of pain over time (all *P* <0.001) (**Fig. 3s b–h**). Post-procedural pain significantly increased with BE segment length, whereas pain after RFA significantly decreased with age and if ablation therapy had been performed previously (**Table 3s**). The percentage of variance of pain explained by the final model including time and both random and fixed effects was 74% (R2 conditional), and 18% including only fixed effects (R2 marginal).

Post-procedural dysphagia

Dysphagia was present after 83% (95%CI 79–88) of RFA procedures and, if present, the median duration until dysphagia was no longer reported was 13 days (p25–p75 9–14). In 39% of procedures, dysphagia was still present on Day 14, the last day of the symptom diary (▶ **Fig. 1d**).



▶ **Fig. 1** Percentage of procedures with pain, major pain, analgesics use, and dysphagia per day for 14 days after radiofrequency ablation (RFA) treatment. **a** Pain. **b** Major pain. **c** Analgesic use. **d** Dysphagia. The percentage of procedures that resulted in these symptoms all decreased over time. Major pain was defined as a composite pain score of 4 or higher (composite pain score was defined as the maximum value of two questions in the electronic symptom diary regarding pain at rest and pain when eating; scale 0–10, with 0 indicating no pain and 10 worst pain ever experienced).

The overall course of the presence of dysphagia over time is presented in **Fig. 4s a**. BE length ($P<0.001$), sedation ($P=0.02$), RFA device type ($P<0.001$), and prior ablation ($P=0.01$) all resulted in a significantly different course of dysphagia over time (**Fig. 4s b–h**). The risk of dysphagia decreased with age (multivariable odds ratio [OR] 0.87, 95 %CI 0.80–0.94; $P<0.001$) (**Table 4s**). The percentage of variance for dysphagia explained by the final model was 68 % (R2 Nagelkerke's modified statistic). The risk of dysphagia increased when patients experienced more post-procedural pain (**Fig. 5s**).

Discussion

This study showed that RFA treatment in patients with BE-related neoplasia causes considerable post-procedural symptoms of substantial duration in the vast majority of patients. The study also identified risk factors for post-procedural symptoms.

Almost all patients experienced pain after RFA. In more than 50 % of procedures, patients still reported pain on the last day of the symptom diary, with continued analgesics use in 15 % at Day 14. Major pain occurred after 64 % of RFA procedures. Dysphagia was also widely present after RFA (83 %), but was mostly transient. Most prior studies on RFA only reported pain if significant (i. e. requiring hospitalization or medical attention) [3, 10]. One study used post-RFA pain diaries and reported lower pain scores and shorter duration of pain than the current study [11]. Potential explanations lie in different ablation strategies (not regularly treating the gastroesophageal junction circumferentially when performing focal RFA and the use of different circumferential balloons), differences in symptom registration (non-electronic/electronic, visual analog scales vs. numeric rating scales), and differences in the use of analgesics. No previous studies on risk factors specifically for post-RFA symptoms have been performed, but our findings are in line with what could be expected based on related studies. The increase in pain after RFA along with BE length in our study fits previous associations between BE length and the prevalence of adverse events in general after RFA [4]. In addition, the decrease in pain after first RFA could well be explained by habituation to pain [12]. Finally, the decrease in pain when aging in our study is in line with the results of a systematic review and meta-analysis on aging and pain in general [13].

Our findings are relevant to clinical practice for a number of reasons. First, the findings will enable adequate counseling of patients with BE-related neoplasia with an indication for RFA on possible post-procedural symptoms and the risk factors associated with these symptoms. In addition to adequate counseling, these data can help in the decision on whether or not to perform ablation therapy. For individual patients, for example elderly patients or patients with severe comorbidity and only low grade dysplasia, close endoscopic surveillance remains a legitimate option. Recent long-term follow-up results of BE patients with low grade dysplasia under strict endoscopic surveillance revealed that all patients with progression could still be treated endoscopically [14]. This, in combination with the prophylactic aspect and post-procedural symptoms of RFA, raises the question of whether RFA is always directly indicated. The benefits of RFA should be carefully weighed against the risks and burden per individual patient. Finally, our data can help when deciding on the preferred ablation technique. Various new ablation therapies for BE-related neoplasia are currently being evaluated as alternatives to RFA, with some showing promising results [15]. As soon as newly developed ablation techniques match the efficacy and safety of RFA, patient tolerability might become decisive for selection of the preferred technique.

An important strength of our study is the multicenter, prospective data collection with daily repeated symptom measurements for 14 days after RFA in a patient population that reflects clinical practice. RFA treatment for patients with BE-related neoplasia is centralized in BE expert centers in the Netherlands. Thus, all RFA treatments were performed by dedicated BE endoscopists in a standardized manner with comparable post-treatment instructions. The response rate for the post-procedural symptom diaries was high and the percentage of missing data low. Missing values were dealt with by using mixed model regression analysis, as were the multilevel data of procedures clustered within patients.

Limitations of this study mostly concern data registration in the post-procedural symptom diary. First, no pre-treatment baseline measurements of pain and dysphagia were registered. Thus, patients could have had symptoms before the start of treatment. Second, for a substantial proportion of procedures, pain and dysphagia were still reported on the last day of the diary. A prolonged period of symptom registration, 28 days for example, might have resulted in a more complete overview of post-procedural symptoms. However, patients also have to be willing to complete the diary and with a diary of 14 days the response rate was high. Another potential source of bias is the fact that not all patients received an electronic diary after RFA (20 % for the hospital with most inclusions), either because they had no access to email or due to logistic constraints. However, the characteristics of age and sex in our patient cohort were comparable with other large prospective cohorts [16, 17]. In addition, the most frequently used regimen for focal RFA in this study ($3\times12\,J/cm^2$ without cleaning) differs from the regimen in the instructions for use ($2\times12\,J/cm^2$ – clean – $2\times12\,J/cm^2$). A multicenter randomized controlled trial showed the simplified regimen of $3\times12\,J/cm^2$ without cleaning to be comparable in terms of safety and efficacy to a standard ablation regimen comprising a cleaning phase [18]. In this study, however, the standard regimen consisted of ablations of $15\,J/cm^2$ (i. e. $2\times15\,J/cm^2$ – clean – $2\times15\,J/cm^2$), which was the standard focal ablation regimen at the time in Europe, but higher than the regimen mentioned in the manufacturer's instructions for use. Furthermore, as pain after RFA in the current study was greater in patients without prior ablation, which represented only 39 % of the procedures, pain scores in this study might underestimate pain scores in a treatment-naïve cohort. Furthermore, it would have been interesting to evaluate the effect of socioeconomic status on post-RFA symptoms and to include the effect of post-procedural pain and dysphagia on the ability of patients to return to their normal daily and work activities; however, this information was not collected. In addition, the cutoff value of 4

to define major pain was arbitrary; however, for acute postoperative pain, a score of 3.3 or higher has been reported as an inacceptable symptom state [7]. Finally, future studies should also take patient preferences into account to focus on the tolerability outcome parameters patients consider most important.

In conclusion, RFA for BE-related neoplasia is a significant burden for patients. Almost all patients experienced pain after RFA, with 64 % of procedures resulting in major pain and 83 % in dysphagia. Patients with a younger age, larger BE segment, and not previously treated with ablation therapy experienced more pain after RFA treatment, whereas a younger age and more post-procedural pain were associated with post-procedural dysphagia. Post-procedural symptoms should be taken into account when counseling patients before starting endoscopic eradication therapy.

Competing interests

A. Overwater: reimbursement of study-related travel costs from Pentax Medical for an IRB-approved European, multicenter prospective study. E.J. Schoon: Speaker fee from Fujifilm, and financial support for research. J.J.G.H.M. Bergman: Unrestricted grants for research support from Medtronic, Pentax, Cernostics, Aqua Medical, Fractyl Laboratories, Endogenex, Digma Medical, Lucid, and CDx. R.E. Pouw: speaker fee from Medtronic, consultancy for MicroTech. B.L.A.M. Weusten: Financial support for research from Pentax Medical, C2Therapeutics, and Aqua Medical, and consultancy fee from Pentax Medical. S.G. Elias declares that he has no conflict of interest.

Clinical trial

Trial Registration: Netherlands National Trial Register | Registration number (trial ID): NL6672 | Type of study: Prospective, observational study

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