Diplomarbeit

Radiofrequency Ablation of Barrett's Esophagus after Endoscopic Mucosa Resection of High Grade Intraepithelial Neoplasia and Early Cancer - A Medical Observation in Clinical Practice -

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Vorwort

Die vorliegende Arbeit widme ich meinen Eltern, denen ich für ihre stetige Unterstützung auf meinem bisherigen Weg danke.

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Table of Content

Abstract

Background: Barrett‘s esophagus (BE) is associated with an increased risk for developing dysplasia and adenocarcinoma. Current endoscopic treatment consists of endoscopic mucosal resection (EMR) for patients with high grade intraepithelial neoplasia (HGIN), early cancer (EC) and adjacent areas of BE followed by surveillance endoscopy. Thermal destruction by means of radiofrequency ablation is a promising new procedure for the treatment of BE which is also used in combination with EMR for relapse prevention. Recent studies are reporting on a very low number of major complications like perforation or stenosis.

Objective: Multicenter observation to assess the efficacy and safety of RFA in patients with HGIN/EC after EMR in common practice using the HALO® system.

Methods: Patients were enrolled for treatment of residual BE after EMR for HGIN/EC. Depending on the circumferential extent of BE, patients either received circumferential ablation using the balloon catheter ($HALO^{360}$) or focal ablation using the endoscope mounted catheter ($HALO^{90}$). After the intervention patients were treated with proton pump inhibitor twice daily (bid). Patients with residual BE at follow-up underwent repeat ablation.

Results: A total of 11 patients with HGIN (n=5) or EC (n=6) were included (all men; median age 72 years). All patients underwent at least one session of endoscopic mucosal resection. Worst histological grade after EMR was HGIN (n=1), low grade intestinal neoplasia (LGIN, n=4) and intestinal metaplasia (IM; n=6). After radiofrequency ablation (median 3 sessions, range 1-6) complete eradication of BE occurred in 6 patients (54.5%) while 3 patients had small isles of BE. In one patient HGIN was still detectable. For one patient biopsy results after RFA were not yet available. After a follow-up of median 6 months (range 2-18), available for 9 patients, no dysplasia had recurred . No major complications like perforation or stenosis occurred.

Limitations: Non-randomized, non-blinded study design, relative short-term follow-up.

Conclusion: Radiofrequency ablation after focal EMR for visible lesions in HGIN/EC patients appears to eradicate dysplasia (100%) and intestinal metaplasia (91%) without major complications like perforation and stenosis.

Zusammenfassung

Hintergrund: Barrett's Ösophagus (BE) ist mit einem erhöhten Risiko assoziiert, Gewebsdysplasien und Adenokarzinome zu entwickeln. Die aktuelle Therapie zur Behandlung von hochgradig intraepithelialen Neoplasien (HGIN) und Frühkarzinomen ist die endoskopische Mukosaresektion (EMR) mit anschließenden Kontrollgastroskopien. Radiofrequenzablation ist ein viel versprechendes neues Verfahren zur Behandlung von Barrett's Ösophagus, das auch kombiniert mit EMR als Rezidivprophylaxe durchgeführt werden kann. In bisherigen Studien traten kaum schwere Komplikationen wie Perforationen oder Stenosen auf.

Ziel: Multizentrische Beobachtung zur Beurteilung von Effizienz und Sicherheit der Radiofrequenzablation (HALO® System) im klinischen Alltag in der Behandlung von HGIN/Frühkarzinom-Patienten nach erfolgter EMR.

Methoden: Behandelt wurden Patienten mit verbliebenem BE nach Mukosaresektion von HGIN/Frühkarzinomen. Abhängig von Umfang und Größe des betroffenen Gewebes erhielten die Patienten entweder eine stufenweise circumferentielle Behandlung mit dem Ballonkathetersystem ($HALO^{360}$) oder eine fokale Ablation mit dem $HALO^{90}$ Aufsatz. Nach der Behandlung erhielten die Patienten Protonenpumpeninhibitoren zwei mal täglich für mindestens vier Wochen. Im Fällen von Rezidiven erhielten die Patienten eine wiederholte Ablation.

Ergebnisse: Eingeschlossen wurden 11 Patienten (alle männlich; Alter median 72 Jahre) mit HGIN (n=5) oder Frühkarzinom (n=6). Alle Patienten wurden zumindest einmalig mittels EMR behandelt. Die Histologie nach EMR ergab HGIN (n=1), LGIN (n=4) und intestinale Metaplasie (n=6). Nach RFA (median 3 Behandlungen, Min-Max: 1-6) trat eine komplette Eradikation von BE in sechs Patienten auf (54.5%), während bei drei Patienten noch kleine Inseln von BE nachweisbar waren. Bei einem Patienten wurde weiterhin HGIN nachgewiesen, für einen anderen lagen noch keine Ergebnisse nach RFA vor. Nach einem Follow-Up von median 6 Monaten (Min-Max: 2-18, 9 Patienten) kam es zu keiner Rückkehr von Dysplasien. Es traten keine schweren Komplikationen wie Perforationen oder Stenosen auf.

Einschränkungen: Nicht randomisiertes, nicht verblindetes Studiendesign, kurzes Follow-Up

Zusammenfassung: Radiofrequenzablation nach fokaler EMR von sichtbaren Läsionen in HGIN/Frühkarzinom Patienten scheint sowohl Dysplasien (100%) als auch intestinale Metaplasien (91%) erfolgreich zu eradizieren ohne dabei schwere Komplikationen wie Perforationen oder Stenosen hervorzurufen.

I Introduction

1 Barrett‘s Esophagus

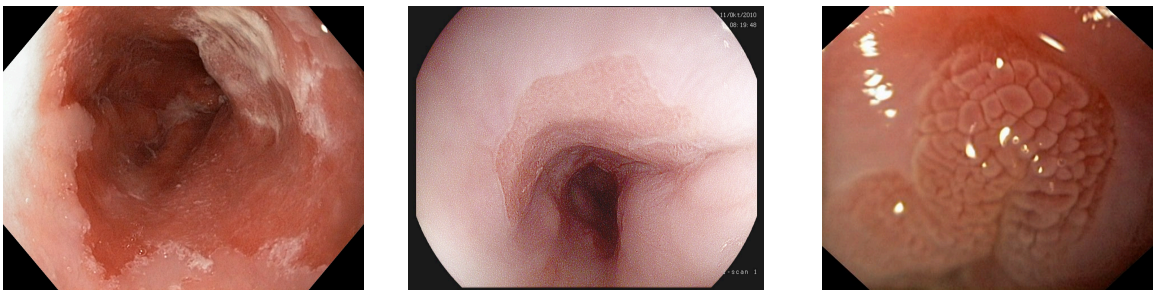
1.1 Definition

First described by Norman Rupert Barrett in 1950 as *chronic peptic ulcer disease of the esophagus*[1], Barrett’s esophagus (BE) is still commonly used. In the opinion of some experts the eponym BE should be replaced by the more informative term columnar lined esophagus (CLE).[2]

Barrett’s esophagus is a change in the distal esophageal epithelium of any length that can be recognized as a columnar type mucosa at endoscopy and is confirmed to have intestinal metaplasia by biopsy of the tubular esophagus.[3]

This working definition of BE mentioned in the updated guidelines 2008 for the diagnosis, surveillance and therapy of BE is mostly accepted in the clinical practice even though with some regional modifications or differences. The British Society of Gastroenterology for instance doesn‘t require intestinal metaplasia in the diagnosis of CLE[4] referring to Spechler et al. who recommended the differentiation of CLE with or without specialized intestinal metaplasia (SIM) regarding the different risks of developing adenocarcinoma.[5]

BE appears as a salmon-pink mucosa between the clean, pale-pink squamous mucosa and can be either circumferential, focal like islands or longer like tongues (Figure 1). The length can vary from only microscopically visible to a long segment intestinal metaplasia. There are reports that SIM may also appear in a normal looking esophagus.[6]



Circumferential | Tongue | Focal (Zoom)

Figure 1: Barrett‘s Esophagus

1.2 Classification

In the last decades many authors and working groups tried defining standards for a generally accepted classification system. One first effort was the description using the terms short and long segment Barrett‘s esophagus (SSBE; LSBE) whereas the limit of 3 cm is caused historically.[7] It‘s controversial if these terms are clinically relevant, especially since some studies showed that SSBE and even cardia intestinal metaplasia (CIM) may have some risk for progression to dysplasia and adenocarcinoma.[8, 9] In a long term follow-up of CIM however Morales et al. showed a low prevalence (0.0%) and incidence (1.4%/year) of dysplasia.[10] Ott et al. designed a demonstrative survey of a general classification based on modifications from JS Spechler that is extended by the term ultra short segment esophagus, which is shown in Table 1.[11]

In 2002 international endoscopists, surgeons and pathologists met in Paris to evaluate the Japanese endoscopic classification of superficial neoplastic lesions of the GI tract which resulted in the Paris Endoscopic Classification,[12] revised in 2003 (Table 2).[13]

Sharma et al. published in 2006 an alternative endoscopic classification system for BE that is named the Prague C & M Criteria.[14] This method allows the assessment of the circumferential (C) and maximum (M) extent of endoscopically visible BE. First presented by the IWGCO at the United European Gastroenterology Week meeting in Prague, Czech Republic in 2004, it was developed for the use in clinical practice and clinical trials. Endoscopic landmarks were defined as gastroesophageal junction (GEJ), squamo-columnar junction and diaphragmatic hiatus. First step is the identification of the proximal limit of the gastric mucosal folds as an independent marker of the GEJ. If present, hiatal hernia needs to be recognized. The circumferential extent of suspected BE is measured at the most proximal depth from the incisors. The measurement of the maximum extent of any Barrett‘s tongues is carried out likewise (Figure 2). The overall inter-observer reliability coefficient for the evaluation of the C & M Criteria was 0.95 and 0.94, respectively. Most recent studies used this system to evaluate the extent of BE.

Table 1: Classification of BE (Mod. from Spechler [5])
1. Columnar lined esophagus A) Evidence of specialized intestinal metaplasia (SIM) - Segment > 3 cm: long segment BE (LSBE) - Segment < 3 cm: short segment BE (SSBE) B) No evidence of SIM - Hernia - False negative biopsy 2. Endoscopic inconspicuous gastroesophageal junction (GEJ) with evidence of SIM - Ultra short segments of CLE

Table 2: Paris endoscopic classification[13]						
Type 0: Superficial lesion						
	0-I	polypoid				
	0-II	nonpolypoid - non excavated				
		0-Ia	slightly elevated			
		0-IIb	flat			
		0-IIc	depressed			
	0-III	excavated or ulcerative				
Type 1: Polypoid carcinomas, usually attached on a wide base						
Type 2: Ulcerated carcinomas with sharply demarcated and raised margins						
Type 3: Ulcerated, infiltrating carcinomas without definite limits						
Type 4: Non-ulcerated, diffusely infiltrating carcinomas						
Type 5: Unclassifiable advanced carcinomas						

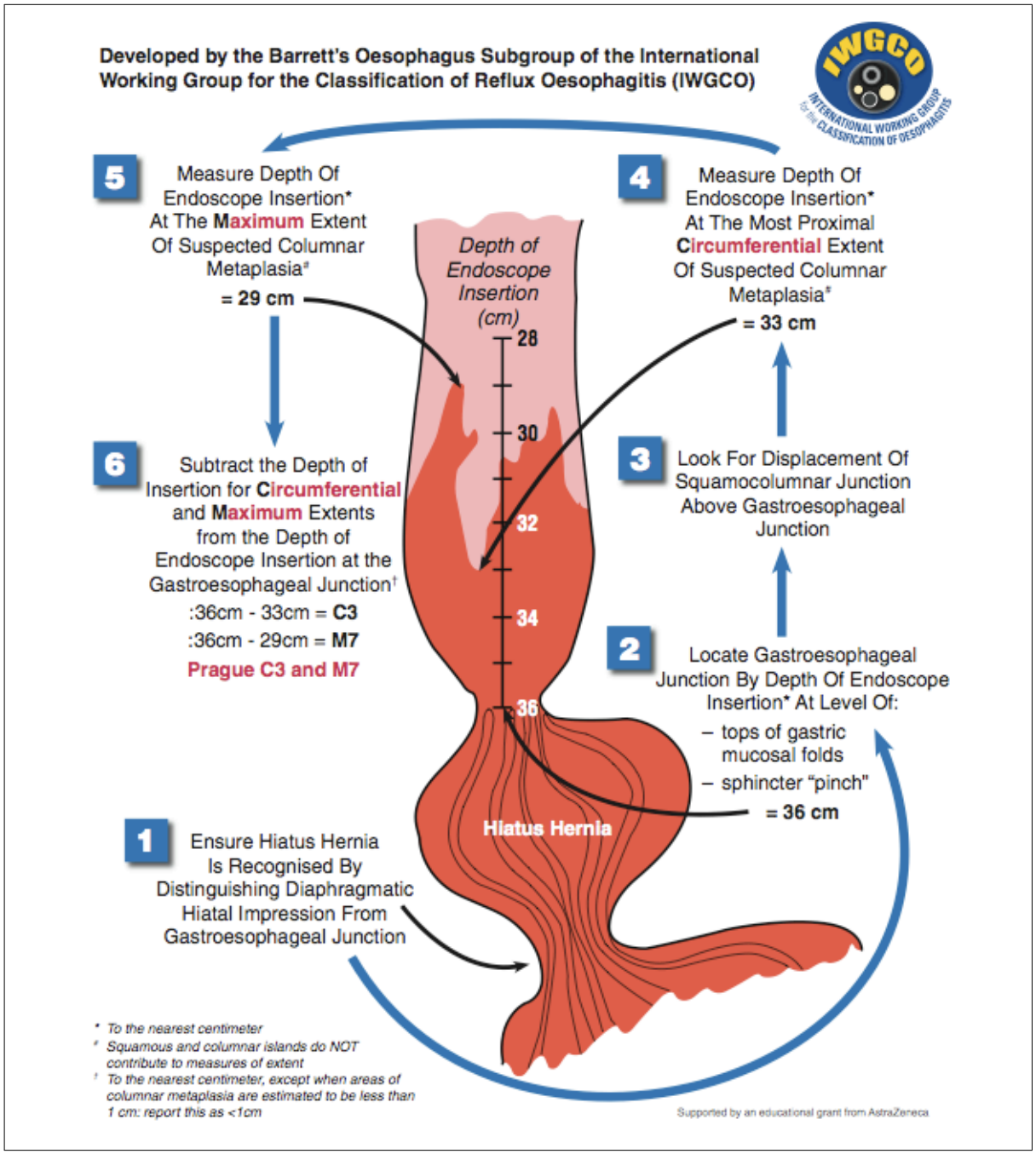


Figure 2: Prague C & M Criteria

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1.3 Histology

The normal esophagus is lined by squamous epithelium. Paull et al. described three different types of metaplastic columnar epithelium in the esophagus: (1) fundic-type; (2) junctional cardiac-type and (3) specialized columnar epithelium.[15] Fundic- and cardiac-type epithelia aren‘t distinguishable from normal gastric epithelium assuming therefor little malignant potential. Type 3 is called today specialized intestinal metaplasia and histological characterized by the presence of goblet cells. Recent studies however support the theory that squamous epithelium at first turns into non goblet columnar epithelium before goblet cells appear.[16]

BE includes epithelial and mesenchymal changes in the esophagus. Cells contain i.e. both stomach and intestinal tissue, produce mucous and show often a duplication of the muscularis mucosa.[17, 18] The double muscularis may complicate the analysis of the biopsy specimens from BE patients regarding the diagnosis dysplasia and adenocarcinoma.

1.4 Pathogenesis

A possible response to chronic inflammation in tissue is metaplasia. Barrett‘s metaplasia appears to be a protective process by conversion into a more resistant tissue as a response to prolonged injury which is caused mainly by acid and bile reflux.[19] Several components in the pathogenesis of BE are unclear or not analyzed so far. Many studies have shown that BE occurs as a complication of gastroesophageal reflux disease (GERD) whereas not every patient with GERD develops BE.[20, 21] Lieberman et al. found a strong association between the duration of GERD symptoms and the prevalence of BE.[22] Patients with symptoms between one to five years had an odds ratio for BE of 3.0 which increased to 6.4 in patients with more than 10 years of symptomatic GERD.

There is an increasing interest in the genetic changes that are causing this development. Souza et al. described two possible ways for a causal connection between GERD and BE regarding caudal homeobox genes like CDX-1 and -2 .[23] Gastroduodenal reflux components (i.e. bile salts and acid) or esophageal inflammation induce a higher CDX expression by esophageal epithelial cells. This increased expression of CDX might be an important step in the mediation of squamous to columnar cell metaplasia. Dvorak et al. showed that bile acids and a low pH induce oxidative stress and DNA damage in esophageal tissue which affects the genomic stability and signaling pathway.[24]

1.5 Epidemiology

1.5.1 Incidence and Prevalence

Epidemiological data about the prevalence and incidence of BE vary a lot. Ronkainen et al. showed that the prevalence of BE of the general swedish population was 1.6%.[25] Other results differ between 0.4% and 1,3%.[26, 27] Some reports included special risk populations and described therefore a higher prevalence of BE which ranged from 6,8 to 25%.[28, 29] For the Netherlands it has been reported that the incidence of BE increased from 14.3/100.000 person years in 1997 to 23.1/100.000 person years in 2002 whereas the number of upper gastrointestinal endoscopies decreased in the same period.[30] This development for the most part is independent of over-diagnosis and reclassification and represents a real augmentation in disease burden.[31] The incidence of BE differs in race, sex and age with the highest in non-hispanic white, male and older patients.[32]

1.5.2 Risk Factors

About 10% of patients with gastroesophageal reflux symptoms progress to Barrett‘s metaplasia.[22] Besides GERD as the main risk factor for BE there exist other parameters influencing the development of BE. Some occur independently, others correlate with GERD.

Hiatal hernia is an accepted risk factor for GERD and especially for BE.[33] Avidan et. al showed that Barrett‘s metaplasia versus non-erosive reflux disease is strongly associated with hiatal hernia and more frequent reflux episodes ($p < 0.001$).[34] Large amounts of cigaret and alcohol consume represented also risk factors for BE. Weston et al. identified the absence of a hiatal hernia ($p = 0.012$) as an important factor in the complete regression of Barrett‘s metaplasia.[35]

It is shown that overweight increases the risk developing BE. In a retrospective cross-sectional study in male veterans Stein et al. showed that overweight measured by the body mass index (BMI) increases the risk of BE.[36] There is evidence of a modest association between waist circumference and the risk of BE.[37]

Compared with GERD patients and normal subjects, patients with BE have lower pressures at the lower esophageal sphincter (LES), a higher grade of esophageal dysmotility and longer lasting reflux episodes.[38]

2 Dysplasia and Adenocarcinoma

Many factors argue for the impact of BE in the development of esophageal adenocarcinoma (EAC). There is a continuous and similar rising incidence of both BE and EAC in the last decades.[30] BE is very common as a former diagnosis in EAC patients.[39] A positive family history may play a role in the development of EAC but most genetic predispositions remain unclear up to now.[40] EAC is a multistep development often starting with GERD. The most important steps are summarized in the metaplasia-dysplasia-adenocarcinoma sequence.[41, 42] This model hasn‘t be the obligatory way to EAC shown by Kelty et al. in patients with glandular mucosa who might have a similar cancer risk as patients with SIM.[43]

Binato et al. reported on two promising markers in the progression from GERD to cancer.[44] The over-expression of p53 and increased Ki-67 might play an important role in the development of EAC in patients with GERD. These results support Polkowski et al. who published 1995 that p53 and Ki-67 may have a predictive value in the diagnosis of dysplasia and cancer.[45]

The risk of developing EAC in patients with BE is estimated at 0.5% per year.[46] Other results may be overestimated due to publication bias in the literature.[46] Regarding the length of Barrett‘s metaplasia the incidence rates can increase up to 1.6% per year in patients with LSBE.[47]

For the term dysplasia the Word Health Organization (WHO) recommended a change from low grade- and high grade dysplasia (LGD, HGD) to the terms low grade intraepithelial neoplasia (LGIN) and high grade intraepithelial neoplasia (HGIN).[48]

LGIN is a borderline condition. Sharma et al. showed that many patients regress to no dysplasia (66%) or persist in LGIN (21%) and that the incidence of cancer in LGIN with 0.6% per year may be similar to BE patients.[49] Based on that and a small number of patients, a relatively short follow-up period and and a high inter-observer variability among pathologists reported in the literature it‘s discussed if LGIN may be a poor marker of progression.[50] Otherwise Srivastava et al. reported that the extent of LGIN may increase the risk for EAC.[51] Weston et al. assessed some endoscopic and histological characteristics in order to evaluate the degeneration risk.[52] Predictive characteristics included the hiatal hernia size ($p < 0.02$, for hernia ≥ 3 cm), the length of BE ($p= 0.009$, > 2 cm) as well as the presence of dysplasia at diagnosis ($p < 0.0001$). Other clinical risk factors for the development of EAC are summarized in Table 3.

High grade intraepithelial neoplasia is a harder indicator for a high risk of developing EAC.[41] Data differ between 16% of HGIN patients developing EAC during a mean surveillance period of 7.3 years[53] and 26.7% during a follow-up of 17 to 35 month.[54] Rastogi et al. estimated in a recent meta-analysis a weighted incidence rate of 6.58 per 100 patient-years (95% CI, 4.97 - 8.19) which means an incidence of 6.6% per year.[55] Unifocal HGIN is on minor cancer risk than multifocal or diffuse HGIN.[56] Figure 3 shows the multistep model of the progression from BE to cancer with the main risk factors known so far.

Table 3: Distribution of clinical risk factors for EAC

Sex	Male	◣	Female	57
Race	White	◣	Black	57
Overweight	Obesity	◣	Normal Weight	58, 59
Symptomatic GERD	Severity/ Frequency/ Duration of symptoms			57, 62
Length of BE	LSBE > SSBE > SIM			9, 60
Hiatal hernia	Size			57
Helicobacter pylori	Absent	◣	Present	61
Smoking	Current smokers > former smokers > non smokers			63

GERD - Gastroesophageal Reflux Disease; BE - Barrett's Esophagus; LSBE, SSBE - Long-and Short Segment BE; SIM - Specialized Intestinal Metaplasia;

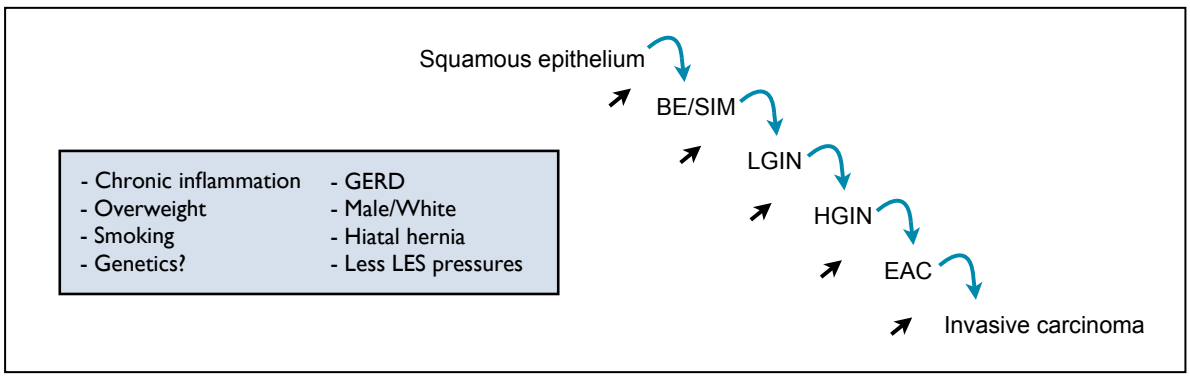


Figure 3: Risk factors for the development of BE and EAC

3 Guidelines for BE

Important guidelines for the diagnosis, surveillance and therapy of BE were published by the *American Collage of Gastroenterology* in 1998 and were updated in 2002 and 2008.[3] Recommended diagnostics include endoscopy and histological proof by a 4-quadrant biopsy. Surveillance is recommended for LGIN. In cases of HGIN the procedure has to be selected individually by patient and endoscopist and differs between surveillance, endoscopic ablation therapy or surgical resection.[3]

Besides these guidelines there exist other recommendations for the management of BE which vary within the different societies between Europe, America and even within America. Shaheen et al. compared different guidelines for the diagnosis, surveillance and therapy of BE with and without dysplasia of which two are listed in Table 4.[64] [65]

Table 4 Guidelines for the management of BE[64]

	American College of Gastroenterology [3]	**British Society of Gastroenterology** [4, 65]
Date	2008	2005
Diagnosis	Endoscopically with histological confirmation of SIM (**goblet cells**)	Endoscopically with histological confirmation of columnar metaplasia (**SIM isn't necessary**)
Biopsy	Four quadrant biopsies every 2 cm in CLE (1 cm in HGIN)	Four quadrant biopsies every 2 cm and biopsies of any visible lesion
Management		
No Dysplasia	Two EGDs with biopsy within **1** year and follow-up every **3** years	**Two** year surveillance
LGIN	- Highest Grade on repeat EGD with biopsies within 6 month - Expert pathologist confirmation - **1 year** interval until no dyslasia x 2	- Extensive re-biopsy after intensive acid suppression for 8 to 12 weeks - If persisting, surveillance every **6 month** - If regression on two consecutive examination, surveillance every 2 years
HGIN	- If mucosal irregularity than **EMR** - Repeat EGD with biopsies to rule out EAC within 3 month - Expert pathologist confirmation - Intensive surveillance every **3 month** or intervention based on results and patient (oesophagectomy or endoscopic ablation)	- If persisting after intensive acid suppression and if confirmed by two expert pathologists than **oesophagectomy** if fit for surgery - If unfit for surgery than EMR or endoscopic ablation
Screening	- General population: not recommended - Selective high risk: remains to be established, on that account it should be individualized	- Not for patients with chronic reflux symptoms (i.e. heartburn) - Yes for red flags like: dysphagia, recurrent vomiting, weight loss or anaemia
Imaging	New techniques (i.e. Chromoendoscopy (methylene blue), NBI or laser confocal microscopy) are not recommended yet for use on a routine clinical basis.	

EGD - Esophagogastroduodenoscopy; NBI - Narrow band imaging

In recent cost-utility analyzes the screening and surveillance of BE patients is controversial. One time screening of 50 year old symptomatic men for BE and EAC may be cost-effective,[66] a surveillance interval of less than 5 years for BE patients without dysplasia is not.[67] Guidelines have to content with two other problems. Within practitioners the knowledge of the guidelines mostly is low and the abidance is consequently poor which leads to considerable variations in practice.[68, 69]

4 Diagnostics

4.1 Standard Endoscopy

At the moment white-light endoscopy is the most common method for the diagnosis of BE. This includes biopsies of all suspected areas and ideally a 4-quadrant biopsy every 2 cm. In a retrospective observation of 125 patients with BE Harrison et al. showed that a minimum of 8 biopsies (67.9% yield) had to be taken to diagnose benign IM.[70] The samples were analyzed with a conventional hematoxylin and eosin (H&E) staining. There was no significant additional use unless more than 16 biopsies (100% yield) were taken. The British Society of Gastroenterology does not require any IM to be identified.[4] It is assumed that if in the majority of patients with endoscopically suspected BE *a sufficient number of biopsies is taken over an adequate period of time, IM can usually be demonstrated*.[4] A major problem in the diagnostic of BE and/or dysplasia is the inter-observer reliability. The Munich Barrett follow-up study showed that only a third of the endoscopic and histological findings between the index and follow-up endoscopies obtained the same result.[71] In cases of confirmed BE the diagnosis remained on follow-up in 70%. Patient with erosive esophagitis (EE) or chronic reflux symptoms should take PPIs for acid suppression before screening for BE. The treatment period of PPI before undergoing endoscopy diversifies in the literature between at least 4 to 8 weeks.[64, 72, 73] Up to 12% of patients with EE after a mean PPI therapy of 11 weeks (range 8-16 weeks) had newly diagnosed BE in the follow-up endoscopy.[74]

4.2 Standard Histology

The standard procedure for the histological identification of IM with goblet cells is a conventional H&E staining. Often used in uncertain cases is alcian blue pH 2.5 (AB) staining which may increase the number of positive samples for IM but may not increase the number of positive diagnosis.[70] For that reason the AGA Chicago Workshop recommends the use of AB stain just in certain cases if only few goblet cells appear or pseudogoblet cells are suspected.[75]

According to the WHO the terms dysplasia, carcinoma in situ and atypia should be replaced by the new term intraepithelial neoplasia.[48] It is per definition *a lesion characterized by morphological changes that include altered architecture and abnormalities in cytology and differentiation. It results from clonal alterations in genes and carries a predisposition for progression to invasion and metastasis*.

Besides a different nomenclature, discrepancies have been also found in the diagnosis of either intraepithelial neoplasia/dysplasia or carcinoma. To develop a common terminology between western and japanese pathologists the Vienna Classification of gastrointestinal epithelial neoplasia was defined in 2000. This system is based on changes in cytology, architecture and the status of invasion which leads to a much better agreement among the experts.[76] Table 5 shows all categories and subcategories like described from Schlemper et al..

Table 5: Vienna Classification of Gastrointestinal Epithelial Neoplasia[76]

Category 1	Negative for neoplasia/dysplasia
Category 2	Indefinite for neoplasia/dysplasia
Category 3	Non-invasive low grade neoplasia (low-grade adenoma/dysplasia)
Category 4	Non-invasive high grade neoplasia 4.1 High grade adenoma/dysplasia 4.2 Non-invasive carcinoma (carcinoma in situ) 4.3 Suspicion of invasive carcinoma
Category 5	Invasive neoplasia 5.1 Intramucosal carcinoma (Invasion into the lamina propria or muscularis mucosa) 5.2 Submucosal carcinoma or beyond

Even with an uniform classification there is a significant inter-observer variability in the diagnosis of dysplasia.[77] The highest degree of this variability has been described within the top and the bottom end of the categories. This affects in particular the separation of no dysplasia (ND), indefinite for dysplasia (IND) and LGIN and the separation of HGIN and EAC with kappa values fewer than 0.5.[78, 79] A substantial reproducibility has been found in the differentiation between the group of ND/IND/LGIN and HGIN/EAC (kappa=0.61) which is important regarding the particular consequences in therapy and prognosis. Often used for the grading of dysplasia in BE are the Consensus Criteria of 1988[77] presented by Reid et al., modified at 2001.[80] Based on these Consensus Criteria, Table 6 shows the most common grading crite-

ria for dysplasia regarding other guidelines and reports (i.e. from the German Society for Pathology).[77, 78, 80-82]

Table 6: Grading Criteria for Dysplasia in BE

	Architecture	Surface maturation [1]	Cytology
ND	Normal	+	- Normal
IND	Normal	+	- Nuclear membrane irregularities - Inflammation
LGD/LGIN	Mild alterations (crypts mostly in good condition)	distorted [2]	- Nuclear membrane irregularities - Nuclear hyperchromasia (+) **- No loss of cell polarity**
HGD/HGIN	Marked alterations (budding and branching, crowded crypts)	-	- Prominent irregular nucleoli - Nuclear hyperchromasia (++) **- Loss of nuclear polarity** - Increased and atypical mitosis (++)
IMC	**Lamina propria** effected	-	- Dissociation of neoplastic cells

[1] Nuclear-cytoplasmatic ratio of surface cells is lower than of deeper glands; [2] Surface similar to deeper glands
ND - Negative for dysplasia, IND - Indefinite for dysplasia, IMC - Intramucosal carcinoma

The possible presence of a double muscularis mucosae in BE complicates a differentiation between intramucosal and submucosal adenocarcinoma since the border is defined as penetration through the deep muscularis mucosae.[18, 83] Westerterp et al. showed for patients with T1-adenocarcinoma (n = 107) that tumors infiltrating the „new“ more superficial muscularis mucosa and tumors invading the deep original muscularis had the same risk of lymphatic dissemination and recurrence after esophagectomy[84] which supports the theory that tumors not penetrating the deep muscularis mucosa should be considered as intramucosal adenocarcinomas.

4.3 Advanced Imaging and Techniques

4.3.1 Capsule Endoscopy

Capsule endoscopy is a new method in the noninvasive diagnostic of BE. The capsule takes up to 14 photographs using CCD chips at both ends during the natural passage through the esophagus. The data transfer operates via digital radio frequency. In a recent blinded prospective study of 94 patients undergoing screening and surveillance for BE the sensitivity/specificity for the identification of BE was 0.67/0.87.[85] These data confirm the results of Lin

et al. who published similar rates (sensibility 0.67/specificity 0.84).[86] No difference occurred between short and long segment BE. The evaluation of the GEJ was inadequate in both times which leads in both reports to the conclusion that the accuracy is limited and that it‘s use is not indicated for clinical routine.

4.3.2 Chromoendoscopy

Chromoendoscopy is the combination of magnifying endoscopy and the application of exogenous agents to the mucosal surface for a better recognition of mucosal changes. Mostly used are chemical agents reacting either intracellular (vital staining with methylene blue or Lugol‘s solution) or with mucosal surface components (contrast staining with acetic acid or indigo carmine).[64] Using a spray catheter the agents are applied to the surface of the esophagus. One first method was staining by methylene blue (MB). Binding to the mucosa containing intestinal metaplasia MB will not bind to HGIN or EAC.[87] Gossner et al. compared MB to 4-quadrant biopsies and diagnosed significantly more BE patients with intraepithelial neoplasia or early cancer by chromoendoscopy (80.9% vs. 26.4%, $p < 0.005$).[88] They also needed less biopsies with the new technique (6.5 vs. 14.1, $p < 0.001$). Nevertheless a recent meta-analysis of studies comparing chromoendoscopy to conventional 4-quadrant biopsies including 9 studies and a total of 450 BE patients did not found a clear advantage of MB detecting SIM and dysplasia.[89] Therefor recent studies concentrate on the diagnostic outcome of magnifying endoscopy combined with the local application of acetic acid. First used in gynecology to identify dysplasia at the uterine cervix, Guelrud et al. started using acetic acid in the diagnostic of SIM.[90] Hoffman et al. showed that biopsies guided by acetic acid had a significant better impact on the diagnosis of BE than random, 4-quadrant biopsies (78% vs. 57%).[91] The number to confirm BE was half as much compared to the 4-quadrant biopsies.

4.3.3 Narrow Band Imaging

Narrow band imaging (NBI) is an optical filter technology to improve the contrast of the tissue surface. NBI uses the particular depth of penetration of the different wavelength of light. Long wavelength leads to a deeper penetration. Blue light accentuates superficial capillary networks while green light is better absorbed by blood vessels in the submucosal layers. NBI combined with high resolution endoscopy may improve the accuracy identifying SIM, HGIN and superficial adenocarcinoma in BE.[92, 93] Sharma et al. showed a high sensitivity (100%), specificity (98,7%) and positive predictive value (95,3%) for the identification of HGIN

whereas the differentiation of IM from LGIN wasn‘t possible.[94] In the current literature authors don‘t use consistent characteristic patterns for non-dysplastic BE, HGIN or EAC which leads to different classification systems.[92, 95]

4.3.4 Confocal Laser Endomicroscopy

Endomicroscopy is the connection of a conventional endoscope and a confocal microscope providing in-vivo histology of the esophageal tissue.[96] „Confocal“ refers to the fact that illumination and detection happen in the same focal plane. Using a low power laser and exogenous fluorescence agents (i.e. acriflavine hydrochloride, fluorescein sodium) the reflecting light of the focused point is absorbed through a pinhole to the detection system. This new technique allows the evaluation of vascular and cellular structures up to 250µm below the surface during ongoing endoscopy. Kiesslich et al. showed in 63 BE patients that confocal laser endomicroscopy had an accuracy of 97.4% for detecting neoplasia.[97] In a study of 39 patients with BE including 16 patients with suspected neoplasia the reduction of biopsies was up to 60% for the diagnosis of neoplasia.[98]

However, as promising as most of these new techniques are, many authors recommend further studies for the confirmation of the clinical impact.[85, 98, 99]

5 Therapy

5.1 Medical Therapy and Antireflux Surgery

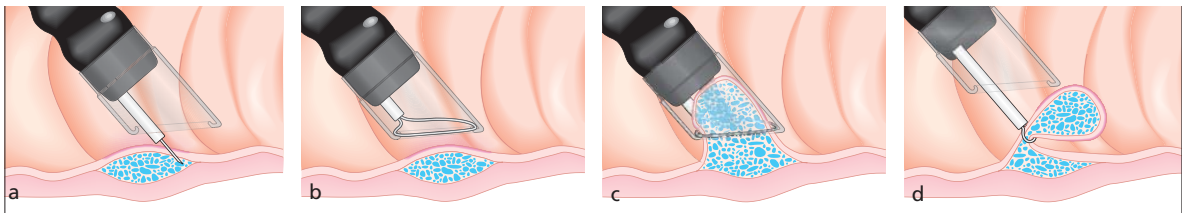
Long term proton pump inhibitors may reduce the risk of developing cancer in patients with BE.[100] The longer use of PPI was associated with an reduced incidence of dysplasia. Nguyen et al. reported apart from PPI on a possible risk reduction in developing EAC by using NSAID or statin therapy.[101] A recommended dosage is still discussed and depends in most studies between 20-40 mg two or three times a day.[64, 102] Antireflux surgery like fundoplication may control acid as well as biliopancreatic reflux and therefore eliminate the two biggest risk factors, which could be an advantage over the medical therapy.[103] It is mostly done when medical therapy doesn‘t have a lasting effect like an incomplete response or intolerance.[64] Corey et al. reported in a meta-analysis on a similar outcome of antireflux surgery and medical therapy.[104] They did not recommend antireflux surgery as an anti-neoplastic measure. There are publications about patients developing cancer years after surgery requiring nevertheless endoscopic surveillance consecutively.[105]

5.2 Surgery

Occult carcinoma rates in HGIN patients after esophagectomy differ in surgical series in a wide range with an average of 37.4%.[106] Konda et al. used strict pathologic definitions to determine histology and found a significant overestimation of invasive carcinoma in former studies.[107] In a study of 60 HGIN patients with esophagectomy the complication rate was 29% and mortality rate 1.7%.[108] The five year survival was 88%. Complications during or after esophagectomy range from pneumonia and anastomotic leak to wound infection and ARDS.[106] The adjusted mortality rates of esophagectomy differs between very low volume hospitals and very high volume hospitals from 20.3 to 8.4 percent.[109]

5.3 Endoscopic Mucosal Resection

Endoscopic mucosal resection (EMR) uses the fact that the gastrointestinal tissue consists mainly of mucosa and muscle separated by the submucosa. Lifting the mucosa allows an easy and safe resection of the mucosal tissue without affecting the underlying layers. Several procedures are available for the endoscopic mucosal resection, i.e. the suck-and-cut technique, the lift-and-cut resection, band ligation mucosectomy, endoscopic submucosal dissection and cap assisted aspiration.[110] EMR is recently often performed using a cap to simplify the access to the lesions and avoid major complications like perforation (Fig. 4).[111] To prevent perforation it is important to inject a fair amount of saline into the submucosal layer to avoid muscle involvement. If en-bloc resection is not possible the procedure has to be performed stepwise in piecemeal-resection.



a) Injection b) Prelooping c) Aspiration of the target mucosa d) Resection outside the cap

Figure 4: Cap assisted Suck and Cut Technique
(Erbe Elektromedizin - Endo Cut® Broschüre)

EMR permits a more effective staging of the tissue by obtaining a larger tissue sample compared to standard biopsy, which allows a better evaluation of the invasion depth leading to a higher inter-observer agreement of BE related neoplasia.[112] In recent studies a complete re-

moval in patients with HGIN and/or early cancer treated with EMR was achieved in 81% and 87.5%.[113, 114] Major complications like perforation or severe hemorrhage were rare. Strictures occurred in 11% and 27% of patients and were successfully treated endoscopically. Chennat et al. found no significant relation between the appearance of strictures and the segment length of BE but there might be an association to the circumferential extent of the resection.[115] Therefor Pouw et al. changed the procedure from a one step circumferential resection to a stepwise manner.[116] Buried Barrett‘s mucosa meaning SIM beneath the neosquamous epithelium was reported in some studies whereas this risk might be reduced by a limited use of argon plasma coagulation (APC) for residual isles.[113, 114] Peters et al. evaluated retrospectively the histopathology of EMR specimens of Barrett‘s neoplasia. They compared the results with the endoscopic appearance to find characteristics for the indication of EMR.[117] In 293 procedures (IM in 57, LGIN in 52, HGIN in 104, T1m in 61, T1sm in 17, not assessable in 2 patients) they performed 150 EMRs for focal lesions using the Paris Endoscopic Classification system for evaluation. Most of the complete resections were 0-II, flat type and well differentiated (G1) whereas 0-I and 0-IIc lesions as well as moderately (G2) and poorly (G3) differentiated cancers were associated with a higher risk of submucosal infiltration.

5.4 Endoscopic Ablation Therapy

Endoscopic ablation therapy is performed by mechanical, chemical and thermal techniques normally including antireflux medication (i.e. PPI). The principle of this treatment is the elimination of metaplastic epithelium followed by the re-epithelialization with squamous mucosa through an induced an-acidic environment.

5.4.1 Photodynamic Therapy

Photodynamic therapy (PDT) is a technique using photo-sensitizer, a light activated drug, and laser light to achieve cell damage. Most frequently used photo-sensitizers are haematoporphyrin derivative (HpD), porfimer sodium (Photofrin) and 5-aminolaevulinic acid (5-ALA) whereas 5-ALA may have a lower incidence of strictures, a reduced duration of systemic photosensitivity and a higher affinity for epithelial tissues.[118]

The data regarding complete eradication of dysplasia vary between LGIN, HGIN and early cancer patients. Ackroyd et al. reports on 100% eradication of dysplasia over a median follow-up period of 53 month (range 18-68 month) in 40 patients with LGIN.[119] In a randomized, multicenter, international, pathologist-blinded HGIN trial of 208 patients PDT, using

porfimer sodium, plus omeprazole was significantly more effective regarding the complete eradication of HGIN than the therapy with omeprazole only (77% vs. 39%, $p < 0.001$).[120] EAC appeared significantly less in the PDT group (13% vs. 28%, $p < 0.006$). Treatment related side-effects occurred more often in patients treated with PDT (94% vs. 13%). Common PDT related effects were photosensitivity reactions (69%), strictures (36%) and vomiting (32%). After a follow-up of five years the results did not changed compared to the first two years of the study.[121] In 66 patients with HGIN/EAC divided in 2 groups (Group A: 35 patients with HGIN and group B: 31 patients with EAC) all treated with 5-ALA PDT complete response during a median follow-up of 37 month (range 23-55 month) was reached in 97% and 100%.[122] The estimated recurrence-free survival after 5 years was 89% in group A and 68% in group B. There was no report of major complications. Peters et al. evaluated the efficacy of PDT after EMR in patients with HGIN/EAC and divided 20 patients in 2 groups (A: 11 proven residual HGIN/EAC; B: 9 possible HGIN/EAC).[123] Successfully eradication was significantly different in both groups (55% vs. 100%, $p = 0.03$). In 4 patients (two each group) HGIN/EAC recurred after a median follow-up of 30 month (range 22-31 month). Most patients had residual Barrett‘s mucosa after treatment.

5.4.2 Argon Plasma Coagulation

Argon plasma coagulation (APC) is a treatment of non-contact electro coagulation using ionized argon gas and a high frequency surgical unit that provides a monopolar electric impulse to destroy abnormal cells.

In a recent prospective, randomized, controlled trial BE patients were selected either for an APC therapy (26 patients) or for surveillance (28 patients).[124] After 12 month of follow-up 14 of 23 APC patients had at least 95% regression and 9/23 (39%) had a complete eradication of BE. In the surveillance group none of the patients had more than 95% regression of BE. Kahaleh et al. reported in 37 BE patients (6x LGIN) after a follow-up of 48 month a relapse rate of 62% including to carcinomas (1 after 12 month of FU/ 1 after 18 month of FU).[125] Another study reported in patients with HGIN (n=7) or EAC (n=3) after a median follow-up of 24 month (range 12-36 month) a complete regression of HGIN/EAC in 8/10 patients.[126] In one patient HGIN persisted and in one HGIN progressed to an invasive carcinoma. Reports about buried glands after APC therapy are not uncommon and data differ between 0 and 44%.[127, 128] Byrne et al. reported also about major complications like perforation in 2/30 patients which included one case of death.

5.4.3 Radiofrequency Ablation

Thermal destruction by means of radiofrequency ablation (RFA) is a novel and promising technique for the treatment of BE. The HALO® system (BÂRRX Medical, Inc., Sunnyvale, CA, USA) is an FDA-approved and CE marked device created for the ablation of BE. After ablation the mucosa can regenerate in a non-acidic environment to a normal squamous epithelium (neosquamous epithelium, NSE).[18] First reports about esophagectomy studies evaluating the ablation setting in the porcine and human esophagus showed best results without injury of the submucosa or the muscularis propria at an energy density of 10J/cm^2 and 12J/cm^2.[129, 130]

The ablation of intestinal metaplasia (AIM) trial was one of the first published studies about RFA in BE patients.[131] This multicenter prospective clinical trial was divided in two serial phases. In a dosimetry phase 32 patients were enrolled for RFA with an energy density of 6,8,10 and 12J/cm^2 evaluating the dose-response and safety. In a second (effectiveness) phase 70 patients were treated with 10J/cm^2 twice (AIM II). All patients had nondysplastic BE. Complete remission of intestinal metaplasia (CR-IM) was observed in 70% at one year follow-up, counted after first ablation. No major complications were described. Recent results of the AIM-II trial at 2.5 years follow-up showed a complete eradication of intestinal metaplasia (IM) in 98% of BE patients.[132] No major complications like perforation or strictures were described and no buried glandular mucosa detected. Similar results were also published for the ablation of LGIN.[133, 134]

Shaheen et al. reported 2009 of a multicenter, sham-controlled and partial-randomized trial of RFA in patients with dysplastic BE.[135] Patients received in a 2:1 ratio either RFA or a sham procedure. CR-IM was achieved in 77.4% of the ablation group and in 2.3% of the control group. The complete remission of dysplasia (CR-D) depended on the grade of itself. Compared with the control group CR-D was achieved for HGIN in 81% (vs. 22.7%) and for LGIN in 90.5% (vs. 19%). RFA patients had less disease progression (3.6% vs. 16.3%, p=0.03) and developed fewer cancers (1.2% vs. 9.3%, p=0.045). Esophageal strictures were reported in 5 patients (6%).

A new approach is the combination of EMR and RFA. Pouw et al. presented at the DDW 2008 first results.[136] 31 of 44 patients received EMR before ablation (including EC, HGIN and LGIN). After a maximum number of ablation sessions (2x HALO^{360}, 3x HALO^{90}) and escape EMR (in three patients) CR-D and CR-M were achieved in 98%. No dysplasia oc-

curred after a median follow-up of 21 (IQR 10-27) months. Nontransmural laceration was found in three patients (7%). Stenoses occurred in four patients (9%), treated with a median of three (IQR 1-5) dilatations. Pouw et al. evaluated also the properties of the NSE in patients with HGIN or EC after RFA.[137] Measured parameters were the expression of Ki-67, p53 and genetic abnormalities. All patients showed abnormalities at baseline whereas all specimens after RFA were normal. No buried glandular were found.

Another study including 12 patients with HGIN or EC assessed possible effects of RFA on the esophageal inner diameter, compliance and motility.[138] They found no change of the esophageal diameter. The results of the esophageal manometry as well as the compliance measurement were not significantly changed by RFA. Table 7 shows a summary of current studies about radiofrequency ablation including important comparable parameters.

Table 7: Summary of the current studies about Radiofrequency Ablation in BE								
Authors	Design	Patients n	Histology	Ablations[1]	BE Length (cm)[2]	Follow-up[3] (month)	Results[4]	Adverse Events
Shaheen et al.	Multicenter, sham-control-led, randomized	127 (2:1)	HGIN LGIN	mean 3.5	5.3 (1-8) 4.6 (0.5 - 8)	12	CR-D 81% vs 22.7% CR-D 90.5% vs 19% CR-IM 77% vs 2.3% (total)	Upper GI hemorrhage (n=1)
Sharma et al.	Prospective Cohort	63	HGIN LGIN	C 1 (1-4) F 1 (0-2)	6 (1-12) 4 (1-13) 5 (1-13) (total)	21 (3-46)	CR-IM 67% - CR-D 79% CR-IM 87% - CR-D 95% CR-IM 79% - CR-D 89% (total)	Mild stricture (n=1)
Flei-scher et al.	Prospective multicenter clinical trial	70	IM	C 1.5 (1-2) F 1.9 (0-3)	3.2 (2-6)	12 30 (62 pat.)	CR-IM 70% CR-IM 98%	No major complications
Puow et al.	Prospective multicenter clinical trial	44	HGIN LGIN IM	C 1 (1-2) F 2 (1-2)	C5M7 (IQR C2-7; M4-9)	21 (IQR 10-27)	CR-IM-D 98%	Non transmural laceration (n=3; 7%) Stenosis (n=4; 9%)
Ganz et al.	Multicenter U.S. registry	142	HGIN	1 (1-2)	6 (IQR 3-8)	12 (8-15)	CR-D 80.4% CR-IM 54.3%	Asymptomatic stricture (n=1)
Sharma et al.	Prospective singlecenter trial	10	LGIN	C 1 (1-2) F 1 (0-1)	4.4 (3-6)	12	CR-D 100% CR-IM 90%	No major complications
Roorda et al.		13	HGIN LGIN IM	Total 1.4	6 (2-12)	12 (6-19)	CR-D 71% CR-M 46%	No major complications

[1] C (Circumferential Ablation), F (Focal Ablation); median (range)
[2] IQR (Interquartile Range); median (range)
[3] Median (range)
[4] CR-IM (Complete Remission of Intestinal Metaplasia) - CR-D (Complete Remission of Dysplasia)

II Patients and Methods

1 Patients Selection

1.1 Study Population

Genders eligible for study: both

1.2 Inclusion and Exclusion Criteria

Patients are selected meeting all following inclusion criteria:

1. Endoscopically diagnosed and histological verified BE after EMR of HGIN or stage I esophageal carcinoma (T1 N0 M0)
2. Age between 18 and 85 years

Patients are excluded if any one of the following exclusion criteria exists:

1. Pregnancy
2. Active esophagitis (LA Classification Grade C or D)
3. Absence of consent
4. > T1 esophageal carcinoma
5. Significant esophageal stenosis (not passable)
6. Any kind of esophageal varices

1.3 Ethic Commission

The study was approved by the Vienna AKH Ethic Commission Board.

1.4 Participating Centers

AKH Wien
Universitätsklinik für Innere Medizin III
Abteilung für Gastroenterologie & Hepatologie
Währinger Gürtel 18-20, 1090 Wien

KH der Elisabethinen Linz
4. Interne Abteilung
Fadingerstr. 1, 4020 Linz

2 Endoscopic Preliminary

After the endoscopic and histological diagnosis of HGIN/EC all patients were treated with EMR. All EMR procedures were performed using the endoscopic cap assisted method or the endoscopic snare mucosectomy technique. If en-bloc resection was not possible the procedure was performed stepwise in peace-meal technique. EMR specimens were pinned down on paraffin and immediately fixed in formalin. Standard hematoxylin and eosin staining was performed by experienced gastrointestinal pathologists.

After EMR except of one patient all patients underwent at least one high resolution endoscopy before RFA. Biopsies were taken from all visible lesions detected by white light endoscopy or advanced imaging techniques (i.e. NBI). Random multiple biopsies were taken of the remaining BE segment.

3 Study Devices

3.1 Circumferential Radiofrequency Ablation System

Circumferential RFA was performed using the HALO^{360} ablation system consisting of a sizing balloon catheter (max. outer diameter 33,7 mm), a number of ablation catheters and a high-power generator (Fig. 5).

The sizing balloon measures the inner diameter of the esophagus by pressure-regulated inflation within the BE segment (4 psi). The electrode array of the ablation catheter measures 3 cm in its length and is composed of multiple slender copper bands (each 250 μm wide and alternating in electrical polarity). All bands encircle the balloon in a distance of 250 μm among each other. The balloon is available in five outer diameter sizes upon full inflation (22, 25, 28, 31 and 34 mm). The RF energy generator provides an ultra-short impulse (<1 sec) with a preset amount of energy (300 W).

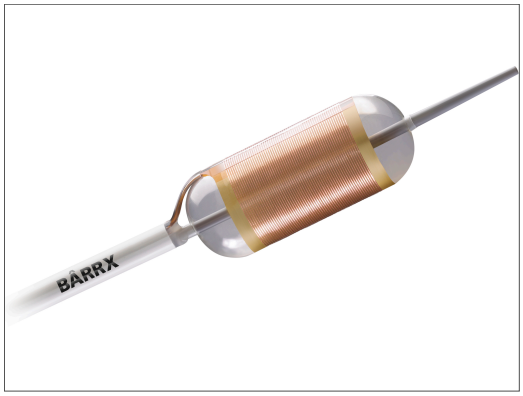
3.2 Focal Radiofrequency Ablation System

Focal RFA was performed using the HALO^{90} ablation system consisting of an endoscope-mounted electrode and a high-power generator (Fig. 5). The HALO^{90} device fits on the distal end of a flexible endoscope (range from 8,6 to 12,8 mm). Its upper surface consists of an articulated platform covered by an active electrode array (20 mm x 13 mm) using the same electrode pattern as HALO^{360}. The platform moves in 2-D (left-right, front-back) to ensure tissue

contact. By deflecting the endoscope upwards the electrodes adjust to the target tissue. In both study devices activating the footswitch starts the ablation procedure.

HALO^{360} Generator

HALO^{90} Generator



HALO^{360} Ablation Catheter

HALO^{90} Ablation Catheter

Figure 5: HALO® Ablation System
(Barrx Medical Product Folder - http://www.barrx.com/HALO_Technology/Content/HALOPresentationFolder.pdf)

4 Ablation Procedure

4.1 Medication and Endoscopic Approach

Before intervention patients received Lidocain (Xylocain®) spray. Endoscopy was performed under conscious sedation with Propofol (Diprivan®), sometimes in combination with midazolam, as routinely performed at the attending departments. After intervention patients were observed for several hours and discharged when no signs of complications occurred. Patients were treated with proton pump inhibitors b.i.d. as a maintenance dosage. Patients got prescribed metamizole sodium 3x20gtt a day for prophylactic pain therapy.

4.2 Circumferential Ablation Technique

First upper endoscopy was used for identification of special landmarks: the top of the IM and the top of gastric folds are described. The location was recorded depending on the individual distance to the incisors. For a better visualization and more efficient delivery of energy the mucous was removed by irrigating the esophagus with 1% N-acetylcysteine in plain water. Afterwards a guide wire was placed and the endoscope removed. The sizing balloon catheter was positioned over the guide wire above the proximal edge of the BE. Via the RF generator the balloon was inflated. Using a pressure/volume algorithm the generator calculated and displayed the inner diameter of the esophagus. Repeating this procedure the balloon was moved distally in 1 cm intervals to the end of the esophagus and beginning of the gastric cardia. After removing the sizing balloon catheter the first step was completed.

Depending on the diameter an adequate ablation catheter was chosen and introduced over the guide wire. The endoscope was reintroduced beside the ablation catheter to ablate under visual control. Including islands now the proximal edge of the ablation catheter was positioned 1 cm above the proximal end of the IM and the balloon got inflated. Following air aspiration for a better contact the ablation was accomplished within < 1 second. Depending on the extents and the grade of IM, the esophagus was treated with 10 or 12 J/cm^2. After deflation the balloon was moved distally (~3 cm) until a small overlap still persisted and the esophagus was ablated as described before. This procedure was repeated until reaching the gastric folds. The ablation catheter including the guide wire and the endoscope were removed consecutively. The ablation catheter was cleaned from adherent tissue like mucous and denatured proteins while the endoscope was reintroduced for cleaning the ablation zone. Using an EMR cap and irrigation with tap water the surface of the esophagus was cleaned of ablated tissue to improve

the efficacy of the second ablation. The ablation procedure was repeated until all IM tissue received two energy applications. Figure 6 demonstrates the singular steps.

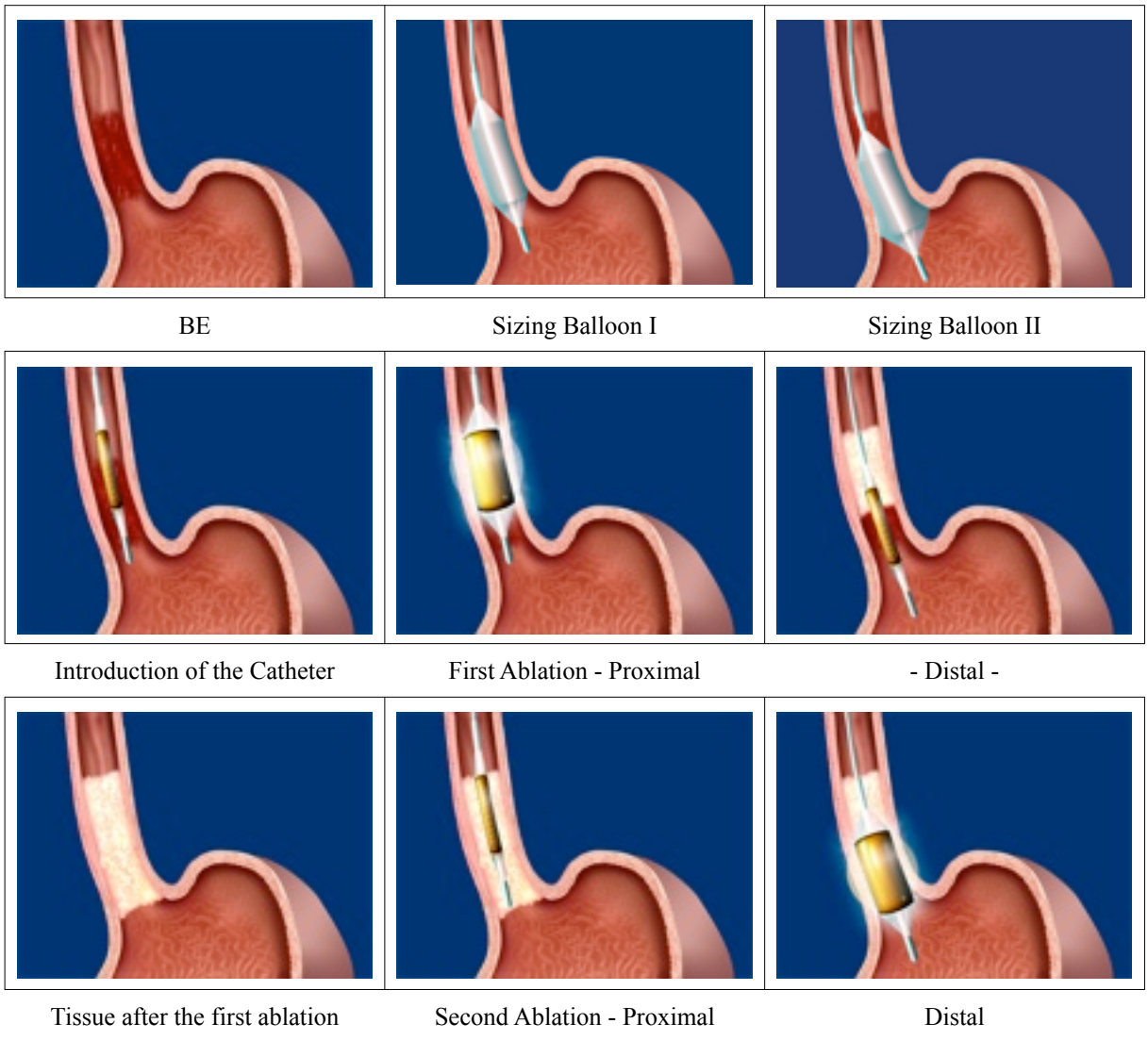


Figure 6: Circumferential Ablation Procedure
(Barrx Medical Product Folder - http://www.barrx.com/HALO_Technology/Content/HALOPresentationFolder.pdf)

4.3 Focal Ablation Technique

As mentioned above first upper endoscopy was performed to assess local conditions and excluding any presence of strictures or bleedings. Afterwards the esophagus was flushed with 1% N-acetylcysteine in plain water for a better visualization. Then the electrode was mounted on the tip of the endoscope oriented at the 12 o'clock position in the video image and reintroduced into the esophagus. By deflecting upwards the electrode surface got attached plane to the target tissue and energy was applied under air aspiration twice in an automated manner. This procedure was repeated until all BE was treated. By using the leading edge of the catheter the esophagus was cleaned of all ablated tissue as mentioned above. Endoscope and device were removed to clean the electrode surface and reintroduced to repeat the procedure. Finally all IM tissue received four energy applications.

5 Pathologic Evaluation

The baseline diagnosis was made by at least one experienced pathologist. Biopsies from the gastric corpus were not included in the results.

6 Study Protocol

All patients who agreed to participate in the study underwent RFA after EMR of HGIN or EC. Patients had the right to leave the study at any time for any reason. Endoscopic procedures were performed using a standard gastroscope (i.e. GIF H180; Olympus, Tokyo, Japan) under conscious sedation with propofol, sometimes combined with midazolam. Two months after RFA multiple biopsies were taken and the biopsy specimens were processed for routine histology. Serial sections were stained with Haematoxylin & Eosin, as well as PAS stain. The procedure was repeated until no dysplasia/BE was found. Patients underwent follow-up including multiple biopsies at 6 and 12 month after the last treatment (Fig. 7).

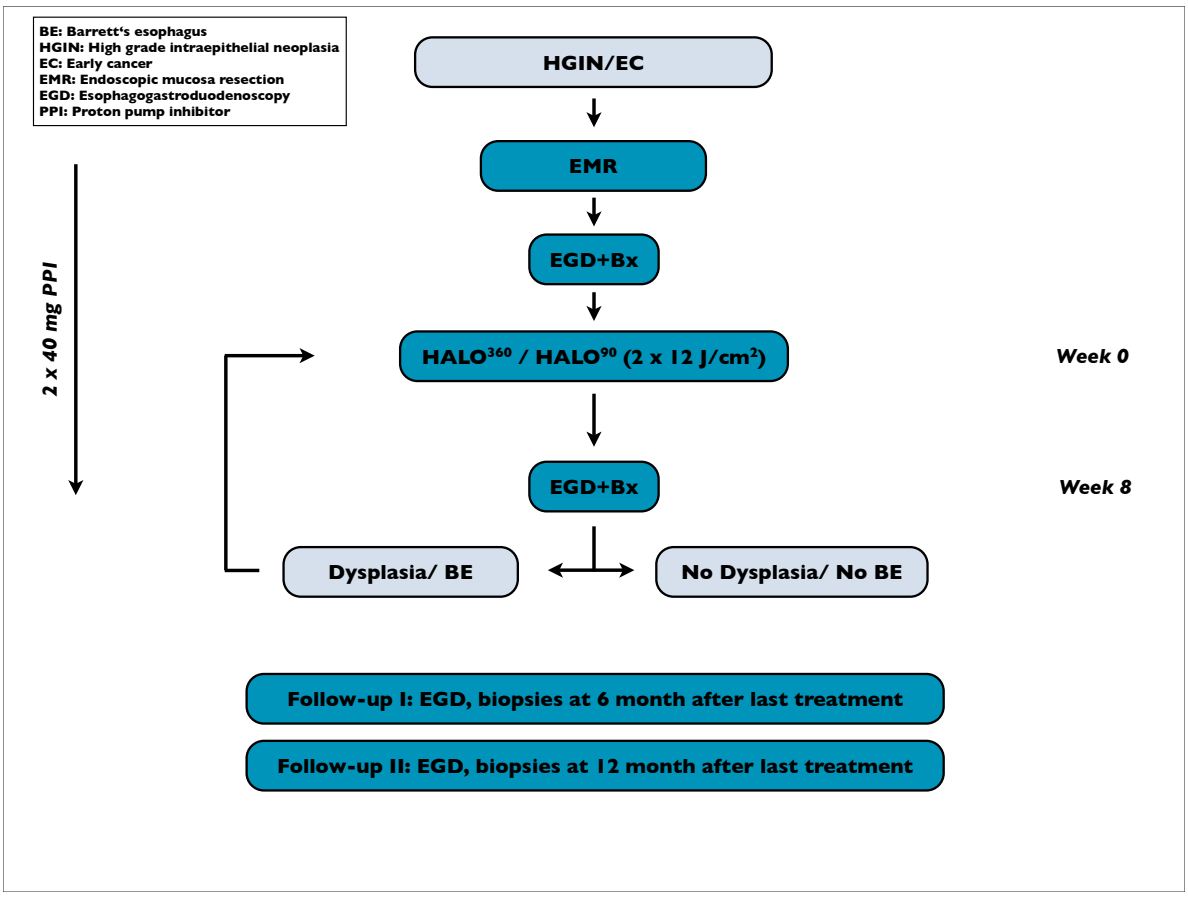


Figure 7: Study Protocol

7 Risk/Benefit Assessment

HGIN as a high risk factor of EAC should be treated safely and efficiently. The combination of EMR with RFA may lead to a better strategy in the treatment of Barrett‘s esophagus with HGIN and early cancer. The confirmation of the hypothesis may change the current strategy of circumferential resection to radiofrequency ablation after EMR of focal lesions in HGIN and EC patients decreasing the complication rates.

8 Data Analysis and Statistics

Date are shown in median with range from minimum to maximum values. Different values in patients before and after treatment were analyzed, where appropriate, by Student‘s paired t-test, by the paired Wilcoxon rank sum test, by the Friedman test or the Mann-Whitney-U test. Statistical significance was defined for all outcomes as a two sided P value of less than 0.05 (α-level). All analyzes were calculated with the PASW statistics software, version 18.0 (SPSS Company). Sample size for our investigation was calculated with PS - Power and Sample Size Program[139] with a power=0.80, effect size=80% and an α-level of 0.05 and resulted in 15 patients.

III Results

All 11 patients included in this study were male and caucasian. The median age was 72 years (range 59 - 81 years). In six patients diagnosis before treatment was BE with HGIN and in six patients diagnosis was BE with EC (Table 8).

Table 8: Patients Characteristics (n = 11)			
Median Age (range)	72 years (59 - 81)	Pre-EMR Diagnosis	
		Patients with HGIN	5 (45.5%)
Men: Women	11 : 0	Patients with EC	6 (54.5%)

1 EMR Results

All 11 patients underwent endoscopic mucosal resection. APC was used during piece-meal EMR to ablate the resection margins. ER specimens showed complete resection at the deep resection margin in all six EC patients. The median length of BE after EMR measured after Prague C & M criteria was 3 cm in circumference (range 0-6) and 5 cm in maximum extent (range 2-9). Histological grade after EMR was HGIN in one patient, LGIN in four and IM in six patients. Patients characteristics after EMR are also shown in Table 9.

One case of perforation during an EMR session was treated successfully endoscopically with clips and prophylactic antibiotics (Tazonam i.v.). There was no other major complication like stenosis, perforation or major bleeding. Minor bleedings were easily treated with APC.

Table 9: Patients Characteristics after EMR			
Median Length (cm; range)		Post-EMR Diagnosis	
Circumferential extent	3 (0 - 6)	Patients with BE	6 (54.5%)
Maximum extent	5 (2 - 9)	Patients with LGIN	4 (36.4%)
		Patients with HGIN	1 (9.1%)

2 Ablation Results

All patients tolerated ablation therapy well under conscious sedation. Median frequency of RFA was three (range 1-6) per patient. Five patients were treated once. Within this group four patients were ablated with HALO^{360} and one with HALO^{90}. The other six patients were treated with a minimum of three ablation sessions (median 3.5; range 2 - 6) whereas the type of ablation was depending on the extent of BE. Repeated ablation was performed in 8 weeks intervals.

After the last session of ablation six patients had no sign of any BE. Three patients had still Barrett‘s isles near the GEJ which were not ablated anymore. We found no circumferential Barrett‘s epithelia in any patient after RFA. In one patient isles of HGIN were still found after the first RFA session. Complete eradication of Barrett‘s epithelia was achieved in 6/11 patients (54.5%) up to now (Table 10). The mean endoscopic regression was 93 %.

Table 10: Patients Characteristics after RFA

Median Number of Ablation Sessions (range)	3 (1 - 6)
If more than once (median; range)	3.5 (3 - 6)
HALO^{360} (median; range)	2 (1 - 4)
HALO^{90} (median; range)	1.5 (0 - 4)
Median Length (cm; range)	
Circumferential extent	0 (0)
Maximum extent	0 (0 - 2)
Post-RFA Diagnosis	
Patients without BE	6 (54.5%)
Patients with BE	4 (36.4%)
LGIN/HGIN	1 (9.1%)
Outstanding	1 (9.1%)

The diagnosis at baseline, after EMR and RFA is demonstrated in Figure 8. Statistics are shown in Table 11.

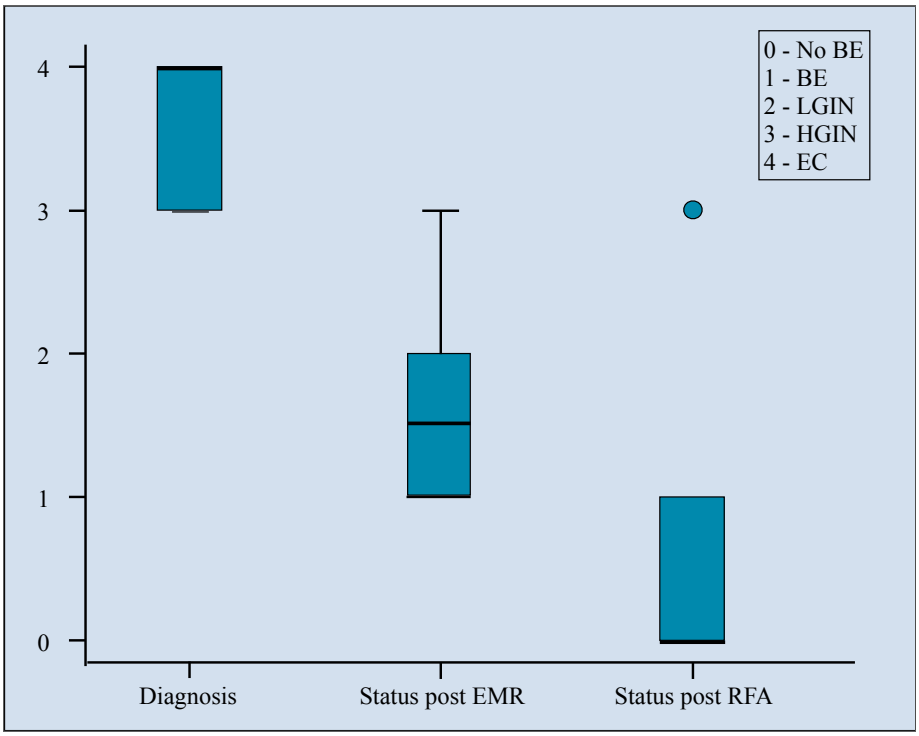


Figure 8: Boxplot - Diagnosis over the course ($p < 0.001$)

Table 11: Statistics for Diagnosis at different points of therapy (p-values)			
	Baseline - St. p. EMR	St. p. EMR - St. p. RFA	Baseline - St. p. RFA
Student‘s t-test	< 0.001	= 0.004	< 0.001
Wilcoxon test	= 0.003	= 0.015	= 0.004
	Baseline - St. p. EMR - St. p. RFA		
Friedman test	< 0.001		

The length of BE before and after RFA is demonstrated in Figure 9. Statistics are shown in Table 12.

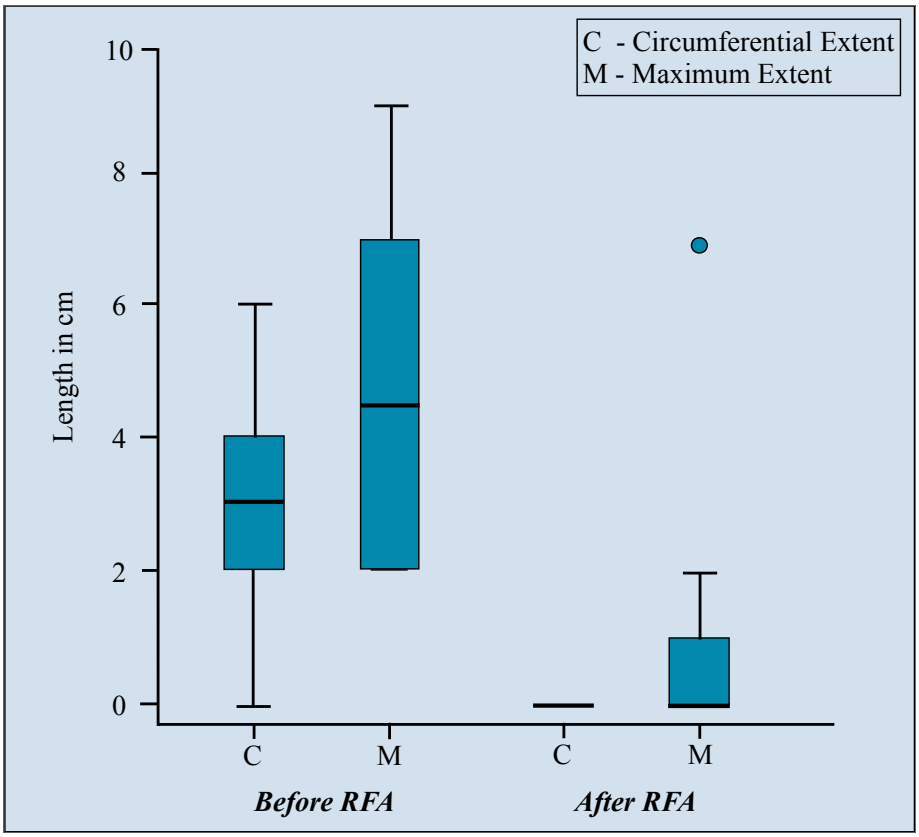


Figure 9: Boxplot - Length over the course ($p \leq 0.001$)

Table 12: Statistics for the Prague C&M Classification before and after RFA (p-values)		
	Prague C - Before vs After RFA	Prague M - Before vs After RFA
Student‘s t-test	= 0.001	< 0.001
Wilcoxon test	= 0.007	= 0.005

3 Adverse Events

After two applications of 12J/cm^2 in each ablation session no major complication like perforation, stenosis or major bleeding occurred. However one patient reported severe pain in the esophagus several days after treatment. He was admitted for observation. After an esophagus x-ray with contrast followed by an endoscopic examination no stenosis or perforation was found.

All patients reported retrosternal pain after ablation. Within one week under metamizole sodium 3x20 gtt a day the patients were free of symptoms. All patients remained asymptomatic and no further therapy was necessary.

4 Follow-up

After a median follow-up of 6 months (range 2-18 month) in 9 patients no dysplasia occurred (100%). In six patients (66.6%) no sign of BE was found. In three patients small isles of BE remained at the GEJ. Up to now one patient is still in therapy after several sessions of EMR without effective eradication of HGIN tissue and one RFA session. In one patient control endoscopy after RFA was not yet realized (Table 11).

Table 11: Patients Characteristics during follow-up

Median follow-up (months)	6 (2-18)
Follow-up Diagnosis	
Patients without dysplasia	9 (100%)
Patients without BE	6 (66.6%)
Patients with BE	3 (33.3%)
Outstanding or still in therapy	2

IV Discussion

The incidence of BE and EAC has been rising for the last decades in most western countries. It is widely accepted that the metaplasia-dysplasia-carcinoma sequence plays the major role in the development of EAC. Nevertheless, in clinical practice it is controversial if BE per se requires early treatment instead of surveillance endoscopy. Anderson et al. reports of a quite similar mortality rate in patients with BE compared to the general population observed between 1993 and 1999 in Northern Ireland.[140] The risk of cancer is rising with the grade of dysplasia but the high inter-observer variability in the histological diagnosis of LGIN complicates in the clinical practice its real estimation.[141] In our study, we therefore included only high risk patients with a history of HGIN and early esophageal cancer. Recent Guidelines (i.e. from the American College of Gastroenterology) are vague when it comes to recommendations how to handle patients with HGIN. Implying a 30 % risk of cancer development, the recommended individualized treatment ranges from careful intensive surveillance and ablation therapy to esophagectomy.[3] PDT and APC are new techniques for endoscopic ablation therapy showing some good results but also unwanted side effects. The intention has to be a treatment procedure that guarantees a minimum of complications and a maximum of effectiveness. There are some indicators that RFA especially in combination with EMR might be such a therapy.

In this study we assessed if RFA after EMR of focal lesions and EC is an effective and safe method to remove the remaining Barrett‘s epithelia and prevent the recurrence of any dysplasia. We found no recurrence of dysplasia or carcinoma after a median follow-up of 6 months. 6 of 9 patients had no recurrence of IM during the follow-up and the median reduction of IM in the remaining 3 patients was 91%. No severe adverse events like perforation or stenosis occurred during or after RFA. One patient was admitted for observation after reporting severe pain in the esophagus but no perforation or stenosis was found. One patient had not yet completed therapy. This patient was treated with RFA after several procedures of EMR without a successful eradication of all dysplastic tissue. We still found HGIN in his biopsies and he will receive rescue EMR. One patient had just finished his first session of RFA, therefore, no data for the histological evaluation are available up to now.

Despite the target of 100% eradication of BE we decided not to ablate patients with small isles of BE near the GEJ. This may be debatable and one may argue that these patients were not treated completely. Considering the low incidence of HGIN/EAC in patients with adequately treated BE[47], the fact that IM of the cardia appears to have a low risk in progressing to cancer[10] and the fact that all patients will remain under endoscopic surveillance, in our view makes further treatment unnecessary. Also, this reflects current guidelines which do not recommend further ablation in these patients.
Our data support recently published results of a european multicenter study including 23 patients with HGIN or EC. After EMR and RFA neoplasia and intestinal metaplasia was eradicated in 95% and 88% of all patients. After a median follow-up of 22 (IQR 17.2-23.8) months no neoplasia recurred. Adverse events were melaena (n=1) and dysphagia (n=1). In line with these results we recommend a longer follow-up to evaluate the long-term efficacy and safety of RFA after endoscopic resection.

Limitations of the study include a non-randomized, non-blinded design without any control group. This is planned for a future project but would exceed the dimensions of this thesis. The present results reflect the first experiences of RFA in the treatment of HGIN and EC in Austria. Regarding the easy use and the safety of RFA we continue the treatment of HGIN and EC in combination with EMR. Objective for the future is also a longer-term follow-up of 5 and 10 years in order to evaluate the long-term efficacy.

A basic objective in the management of BE should be the development of a preventive treatment strategy like established in the prevention of the colon carcinoma. To justify preventive treatment patients have to be on higher risk for cancer and the interventions have to be safe. The treatment option of *RFA after EMR for HGIN* may fulfill these conditions for the interventional arm. In the diagnosis the finding of an effective method to identify more high risk patients with BE will be one major challenge in the future. Endomicroscopy (EM) may be one step in this direction. Improving the targeted biopsy EM may help recognize dysplasia earlier than it is possible today.

In conclusion, radiofrequency ablation after focal EMR of visible lesions in patients with HGIN and EC appears to be an effective and safe method in the eradication of dysplasia

(100%) and IM (91%). A long term follow-up is needed to assess its value as a preventive treatment strategy for esophageal cancer.

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VI Abbreviations

5-ALA	5-Aminolaevulinic
AB	Alcian Blue
AIM	Ablation of Intestinal Metaplasia
APC	Argon Plasma Coagulation
BE	Barrett‘s Esophagus
BMI	Body Mass Index
CIM	Cardia Intestinal Metaplasia
CLE	Columnar Lined Esophagus
CR-D	Complete Remission of Dysplasia
CR-IM	Complete Remission of Intestinal Metaplasia
EAC	Esophageal Adenocarcinoma
EC	Early Cancer
EE	Erosive Esophagitis
EMR	Endoscopic Mucosal Resection
GEJ	Gastroesophageal Junction
GERD	Gastroesophageal Reflux Disease
H&E	Hematoxylin & Eosin
HGD	High Grade Dysplasia
HGIN	High Grade Intestinal Neoplasia
IM	Intestinal Metaplasia
IMC	Intramucosal Carcinoma
IND	Indefinite for Dysplasia
IQR	Interquartile Range
LES	Lower Esophageal Sphincter
LGD	Low Grade Dysplasia
LGIN	Low Grade Intestinal Metaplasia
LSBE	Long Segment Barrett‘s Esophagus

MB	Methylene Blue
NBI	Narrow Band Imaging
ND	No Dysplasia
NSE	Neosquamous Epithelium
PAS	Periodic Acid Schiff
PDT	Photodynamic Therapy
PPI	Proton Pump Inhibitor
RFA	Radiofrequency Ablation
SIM	Specialized Intestinal Metaplasia
SSBE	Short Segment Barrett‘s Esophagus
WHO	World Health Organisation
WHR	Waist-to-hip Ratio

VII Statutory Declaration

I declare that I have authored this thesis with the title *„Radiofrequency Ablation of Barrett's Esophagus after Endoscopic Mucosa Resection of High Grade Intraepithelial Neoplasia and Early Cancer - A Medical Observation in Clinical Practice -"* independently and without any unauthorized help. I have not used other than the declared sources/resources, and I have explicitly marked all material including tables and figures which has been quoted either literally or by content from the used sources.

This thesis has been neither presented to any institution for evaluation nor previously published.

Vienna, 22.10.2010 Stefan Traussnigg

VIII Addendum

1 TNM Classification

TNM Classification System[48]	
T - Primary Tumor	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor invades lamina propria or submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades adventitia
T4	Tumor invades adjacent structures
N - Regional Lymph Nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
M - Distant Metastasis	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

For tumors of the lower thoracic esophagus

M1a Metastasis in coeliac lymph nodes

M1b Other

For tumors of the upper thoracic esophagus

M1a Metastasis in cervical lymph nodes

M1b Other

For tumors of the mid-thoracic esophagus

M1a Not applicable

M1b Non-regional lymph node or other

Stage Grouping			
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage IIA	T2, T3	N0	M0
Stage IIB	T1, T2	N1	M0
Stage III	T3	N1	M0
	T4	Any N	M0
Stage IV	Any T	Any N	M1
Stage IV A	Any T	Any N	M1a
Stage IV B	Any T	Any N	M1b

2 Statistical Results

Friedman-Test

Deskriptive Statistiken					
	N	Mittel-wert	Standard-abweichung	Mini-mum	Maxi-mum
Diagnosis	10	3,60	0,516	3	4
Diagnosis Status post EMR	10	1,60	0,699	1	3
Diagnose Status post HALO	10	0,60	0,966	0	3

Ränge	
	Mittlerer Rang
Diagnosis	3,00
Diagnosis Status post EMR	1,85
Diagnose Status post HALO	1,15

Statistik für Test[a]	
N	10
Chi-Quadrat	18,865
df	2
Asymptotische Signifikanz	0,000
a. Friedman-Test	

Test bei gepaarten Stichproben									
	Gepaarte Differenzen								
		Mittelwert	Standard-abweichung	Standardfehler des Mittelwertes	95% Konfidenzintervall der Differenz		T	df	Sig. (2-seitig)
					Untere	Obere			
Paaren 1	Prague C - FU Prague C	2,900	1,792	0,567	1,618	4,182	5,118	9	**0,001**
Paaren 2	Prague M - FU Prague M	3,700	2,058	0,651	2,228	5,172	5,687	9	**0,000**
Paaren 3	Diagnosis - Diagnosis Status p.EMR	2,000	0,632	0,191	1,575	2,425	10,488	10	**0,000**
Paaren 4	Diagnosis Status p. EMR - Diagnose Status p. HALO	1,000	0,816	0,258	0,416	1,584	3,873	9	**0,004**
Paaren 5	Diagnosis - Diagnose Status p. HALO	3,000	0,943	0,298	2,326	3,674	10,062	9	**0,000**

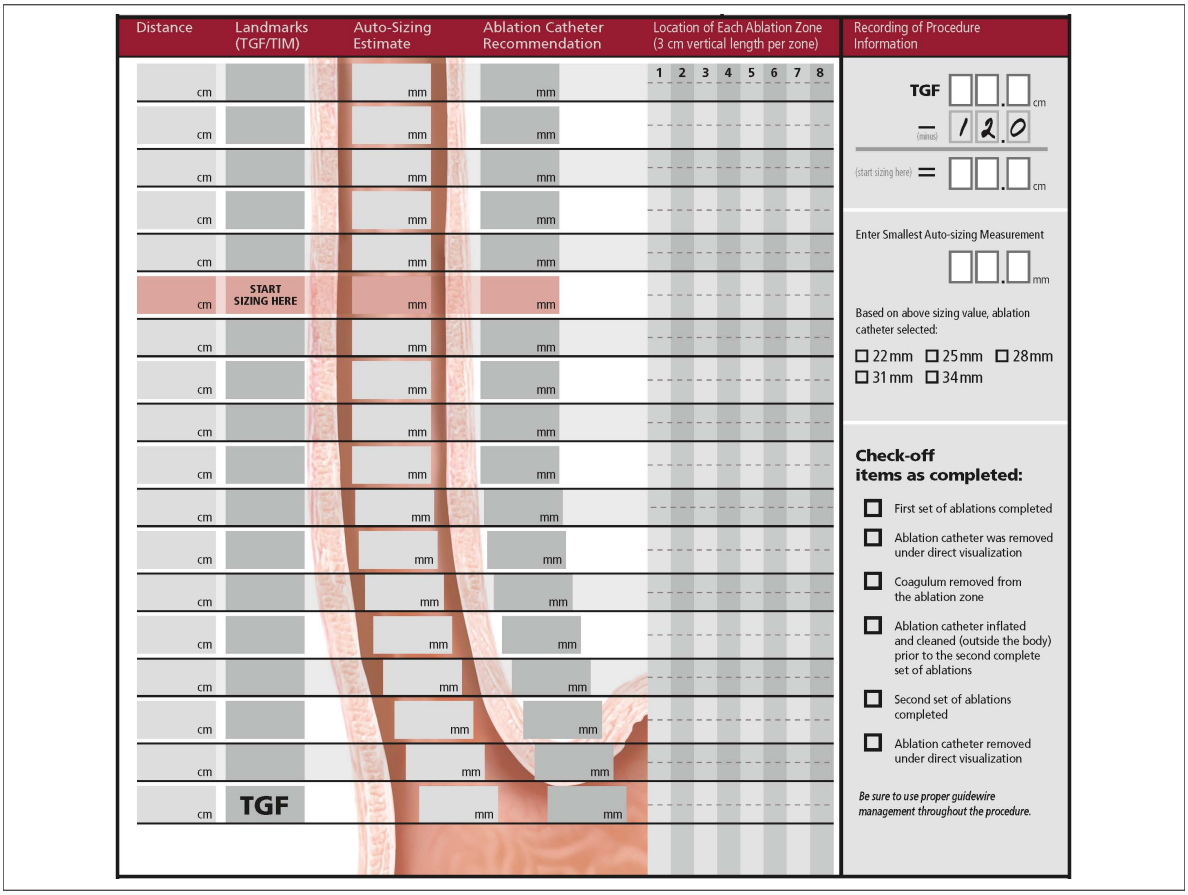
Wilcoxon-Test

Ränge				
	N	Mittlerer	Rangsumme	
FU Prague C - Prague C	Negative Ränge	9[a]	5,00	45,00
	Positive Ränge	0[b]	0,00	0,00
	Bindungen	1[c]		
	Gesamt	10		
FU Prague M - Prague M	Negative Ränge	10[d]	5,50	55,00
	Positive Ränge	0[e]	0,00	0,00
	Bindungen	0[f]		
	Gesamt	10		
Diagnosis Status post EMR - Diagnosis	Negative Ränge	11[g]	6,00	66,00
	Positive Ränge	0[h]	0,00	0,00
	Bindungen	0[i]		
	Gesamt	11		
Diagnose Status post HALO - Diagnosis Status post EMR	Negative Ränge	7[j]	4,00	28,00
	Positive Ränge	0[k]	0,00	0,00
	Bindungen	3[l]		
	Gesamt	10		
Diagnose Status post HALO - Diagnosis	Negative Ränge	10[m]	5,50	55,00
	Positive Ränge	0[n]	0,00	0,00
	Bindungen	0[o]		
	Gesamt	10		

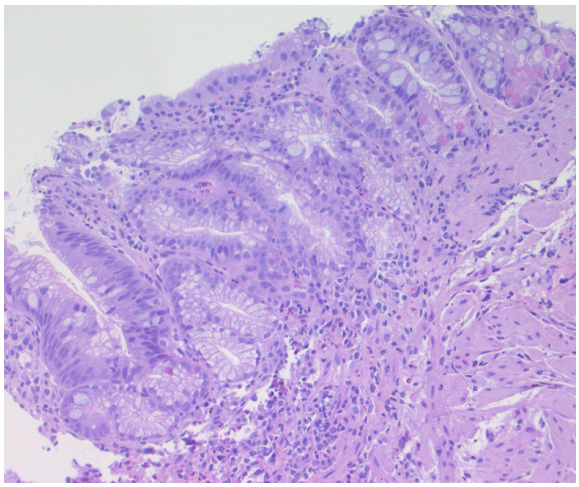
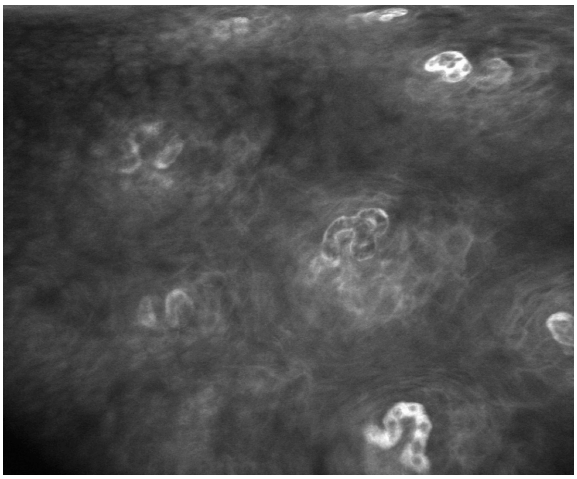
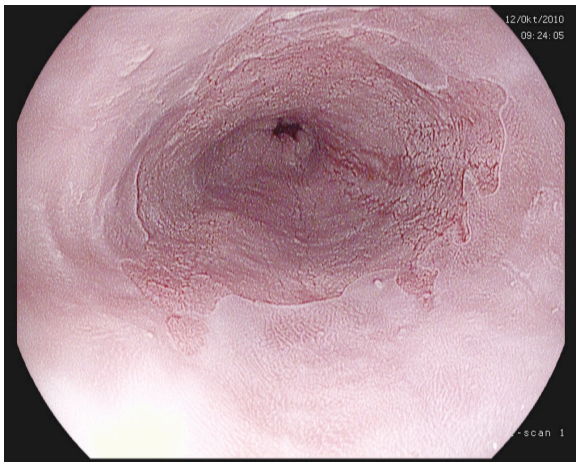
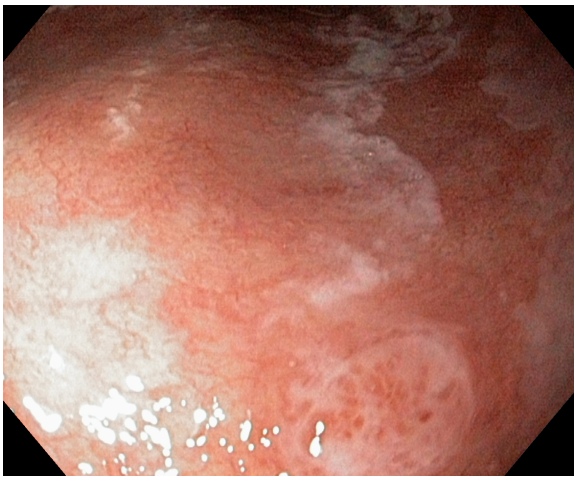
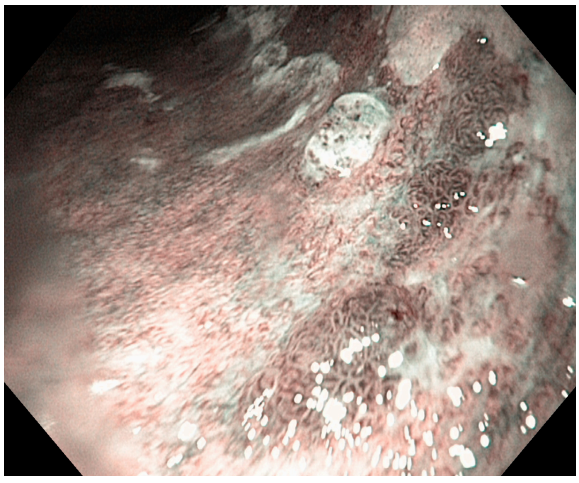
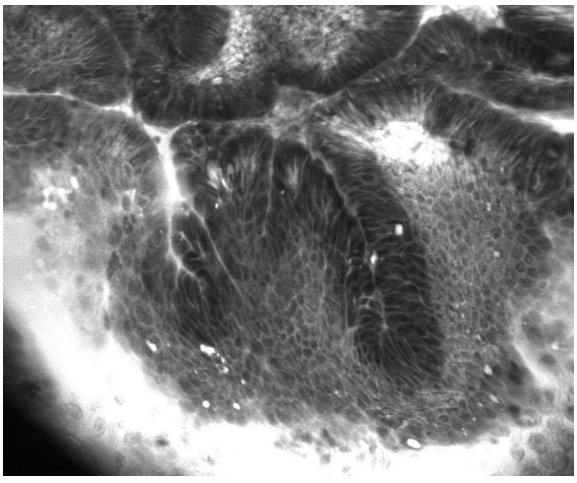
a. FU_Prague_C < Prague_C
b. FU_Prague_C > Prague_C
c. FU_Prague_C = Prague_C
d. FU_Prague_M < Prague_M
e. FU_Prague_M > Prague_M
f. FU_Prague_M = Prague_M
g. Diagnosis.St.p._EMR < Diagnosis
h. Diagnosis.St.p._EMR > Diagnosis
i. Diagnosis.St.p._EMR = Diagnosis
j. Diagnose_St.p._HALO < Diagnosis.St.p._EMR
k. Diagnose_St.p._HALO > Diagnosis.St.p._EMR
l. Diagnose_St.p._HALO = Diagnosis.St.p._EMR
m. Diagnose_St.p._HALO < Diagnosis
n. Diagnose_St.p._HALO > Diagnosis
o. Diagnose_St.p._HALO = Diagnosis

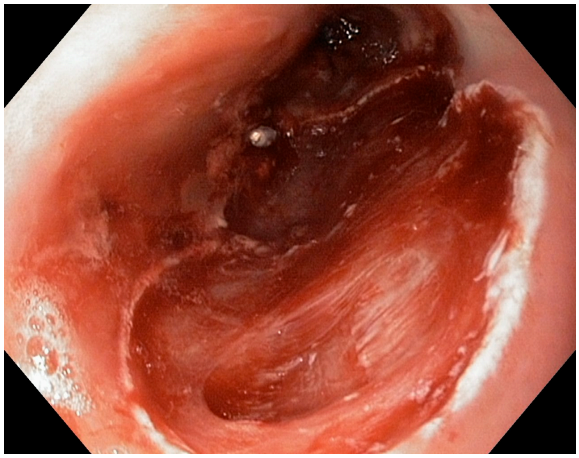
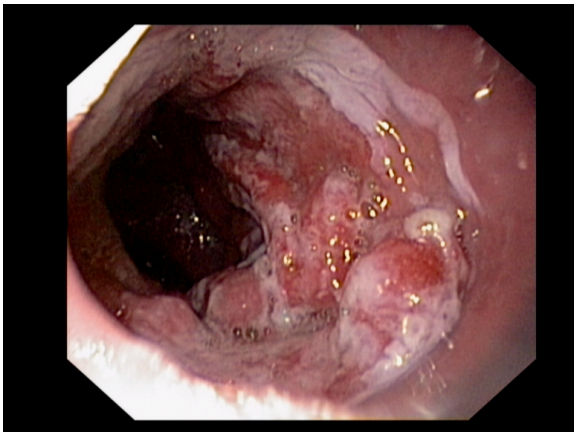
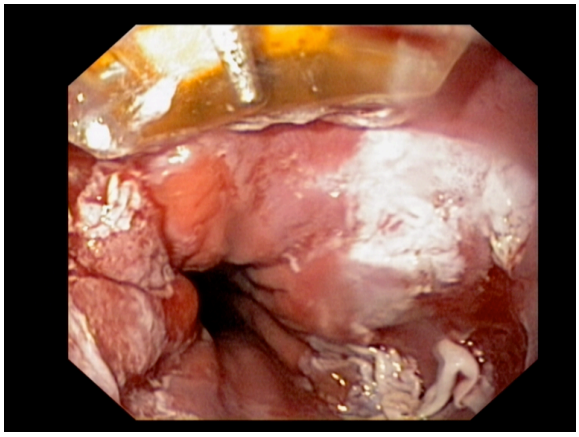
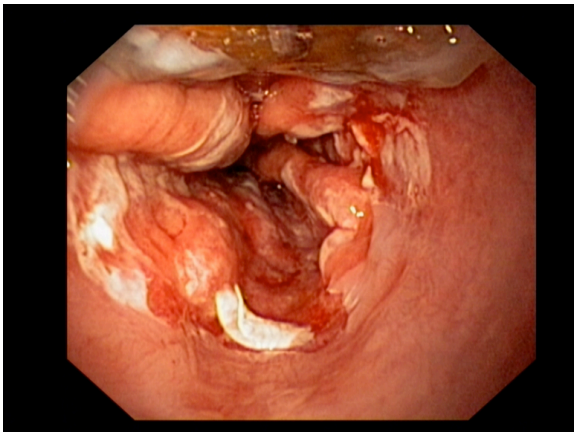
Statistik für Test[b]					
	FU Prague C - Prague C	FU Prague M - Prague M	Diagnosis Status post EMR - Diagnosis	Diagnose Status post HALO - Diagnosis Status post EMR	Diagnose Status post HALO - Diagnosis
Z	-2,677[a]	-2,820[a]	-3,022[a]	-2,428[a]	-2,848[a]
Asymptotische Signifikanz (2-seitig)	**0,007**	**0,005**	**0,003**	**0,015**	**0,004**
a. Basiert auf positiven Rängen.					
b. Wilcoxon-Test					

3 HALO® Ablation Sheet



4 Pictures

	
Specialized Intestinal Metaplasia	BE (Endomicroscopy)
	
LSBE (Acetic acid)	Barrett‘s Ca
	
Barrett‘s Ca (NBI)	Barrett‘s Ca (Endomicrocopy)

	
HGIN after EMR	St.p.first HALO^{360} Ablation
	
HALO^{90}	HALO^{90}

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