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Technical Modifications for a One-Step Circumferential Endoscopic Mucosa Resection (CEMR) to Eradicate High-Grade Dysplasia and Mucosal Carcinoma in Barrett`s Esophagus. Preliminary Results

D i s s e r t a t i o n

Zur Erlangung des Grades eines Doktor der Medizin

dem Fachbereich Medizin der Universität Hamburg

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Angenommen vom Fachbereich Medizin

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Veröffentlicht mit Genehmigung des Fachbereichs Medizin der Universität Hamburg.

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Dedicated to my parents

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List of Abbreviations used in the Text

APC = Argon plasma coagulation

BE = Barrett`s Esophagus

CEMR = Circumferential endoscopic mucosa resection

EMR = Endoscopic mucosa resection

EUS = Endoscopic ultrasound

EUS-FNA = EUS-guided fine-needle aspiration

GERD = Gastroesophageal reflux disease

HGD = High-grade dysplasia

LES = Lower esophageal sphincter

LGD = Low-grade dysplasia

MBL-CEMR = Multiband-Ligator-CEMR

PDT = Photodynamic therapy

PPI = Proton pump inhibitor

SCC = Squamous cell carcinoma

SCE = Squamous cell epithelium

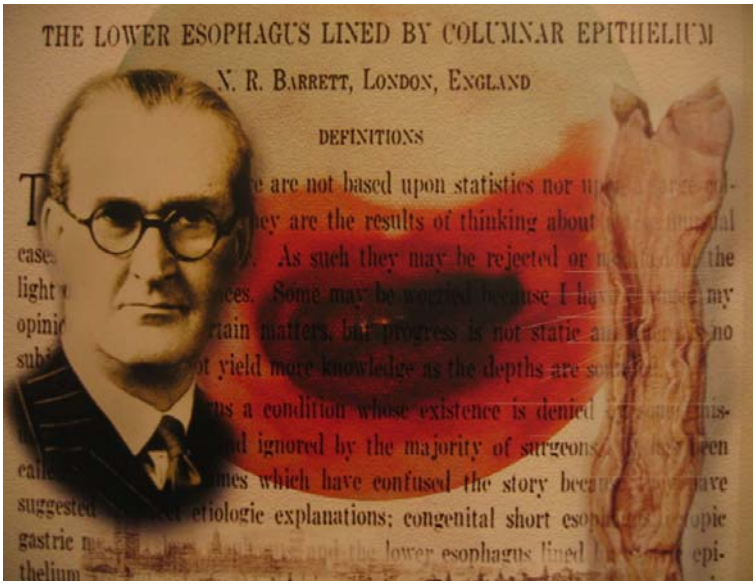


Figure 1: Portrait of Sir Norman R. Barrett *

*Norman Rupert Barrett (1903-1979), originally from Adelaide, Australia, studied in England and thereafter remained as a consultant surgeon at St. Thomas Hospital in London for the duration of his life. He developed novel concepts relating to subject of peptic esophagitis and the consideration of putative condition, which he referred to as a "short esophagus". His reflections on the subject of ectopic gastric mucosa (1957) "dented and dogma" of mid 20th century concepts of esophagitis, and have subsequently spawned a gastroenterological obsession that has led to the recognition of novel disease entity whose diagnosis and therapy has fixated contemporary gastroenterologist, surgeons and pathologists.

1. General

1.1 History, Definitions, Terminology

The first report about formal alterations and transformations of the distal esophageal epithelium was published in 1950 by Norman R. BARRETT[1] with complementary remarks by himself from 1956/1957 ***(Figure 1).*** The first publication did not find much echo, but during the following years there was already a collection of observations, mainly by surgeons, with different interpretations of what they found. Barrett himself came to some conclusions in a lecture at Mayo Hospital which

was published in 1957 where he summarized the situation of the last 6 years[2] . He started from observations of ulcers in the esophagus and interpreted a metaplastic distal mucosa as result of mechanic dislocation of gastric mucosa or as congenital short esophagus. A pathogenesis of the ulcers from heterotopic islands of gastric mucosa seemed unrealistic to him, because these dystopic lesions are mainly found in the proximal esophagus without any ulceration. He concluded his text with this statement: "*I submit that most of these cases are in truth examples of congenital short esophagus, in which there is neither general inflammation nor stricture formation, but in which a part of the stomach extends upwards into the mediastinum – or even to the neck – and that in this stomach a typical chronic gastric ulcer can form."*

Obviously a period of confusions continued a further couple of years, mainly because of inconsistent definitions and nomenclature. Barrett described the situation and the problem of confusions in his lecture at the Mayo Clinic, Rochester, in 1957: "*This paper concerns a condition whose existence is denied by some, misunderstood by others – and ignored by the majority of surgeons. It has been called a variety of names which have confused the story because they have suggested incorrect etiologic explanations; congenital short esophagus, ectopic gastric mucosa, short esophagus, and the lower esophagus lined by gastric epithelium are but a few. At the present time the most accurate description is that it is a state in which the lower end of the esophagus is lined by columnar epithelium. This does not commit us to ideas which could be wrong, but it carries certain implications which must be clarified. The literature about esophageal disorders is confused because common words have different meanings in the minds of different writers."*

But also this verbal intervention could not stop the confusion of definitions and nomenclatures. This is as more astonishing as Barrett pointed out very clearly that this atypical mucosa of the distal esophagus is not "Ectopic" from gastric mucosa but a completely different and new nosologic entity: "*These findings…suggest that the abnormal epithelium, despite it looks, does not function exactly as stomach and probably secretes little digestive juice."* And some lines further down: *"Surgeons who have studied the histology of specimen removed at operation have found that the greater part of the unusual epithelium consists of simple tubular glands which secrete mucus but which include few gastric elements."*

He furthermore emphasizes that this must be an acquired phenomenon and not embryonic resting tissue and he already assumed the correct hypothesis about pathogenesis, which has been ascertained later: *"One of the facts which are difficult to explain is why this deformity always involves the lower esophagus. No specimen has as yet been described in which the whole of the gullet is lined by columnar cells. The explanation could be that if the cardiac valve of a normal person were to become incompetent and of the lower esophagus were, as a result, to be bathed for a long time by digestive gastric juice, the squamous epithelium could be eaten away and totally replaced by more quickly growing columnar cells. This concept might explain the site of the deformity, the fact that many cases occur in patients who have an incompetent cardia due to sliding hiatal hernia, and the fact that many patients are elderly and have history of heartburn dating back many years."*

But even this later statement of 1957 about his discovery from the year 1950 lists a couple of errors, e.g. his hypotheses to stricture development,

of ulcerogenesis and of formal typing of carcinoma within the metaplastic segment.

During the following thirty years an intensified work about Barrett's phenomenon started and continued producing some more modifications of definitions and nomenclature [3, 4]. An important motivation for this growing interest was based on an increasing prevalence of reflux symptoms, reflux lesions and of adenocarcinoma of the esophagus [5, 6].

Finally, Reid et al [7] made a proposal for implementation of a generally accepted definition and classification. It is based on the presence of specialized intestinal metaplasia of the distal esophagus and on the extend of this changes of less than 3 cm (=short segment) or more than 3 cm (= long segment) proximal to the esophagogastric junction. A further differentiation of an additional ultrashort-segment BE with only focal metaplastic areas is not generally accepted and practiced [5].

Reflux- and time-associated consequences are observed as different intensities of dysplasia of the Barrett-epithelium. According to a proposal from Morson et al[8] they are differentiated to low-grade dysplasia (LGD) and high-grade dysplasia (HGD). Some authors supplemented an intermediate type, others tried to establish some sub-classifications, e.g. epithelium of fundic type, of junctional type or cardiac type[9, 10]. These intentions for modification could not be found in later publications and have obviously not been of general interest, because all alterations of Barrett's epithelium have their origin from specialized intestinal metaplasia.

The most recent classification by expert consensus has been published and named in 2001 according to the place of the conference: Vienna Classification ***(Figure 2).***

Figure2: **The revised Vienna classification of gastrointestinal epithelial neoplasia**

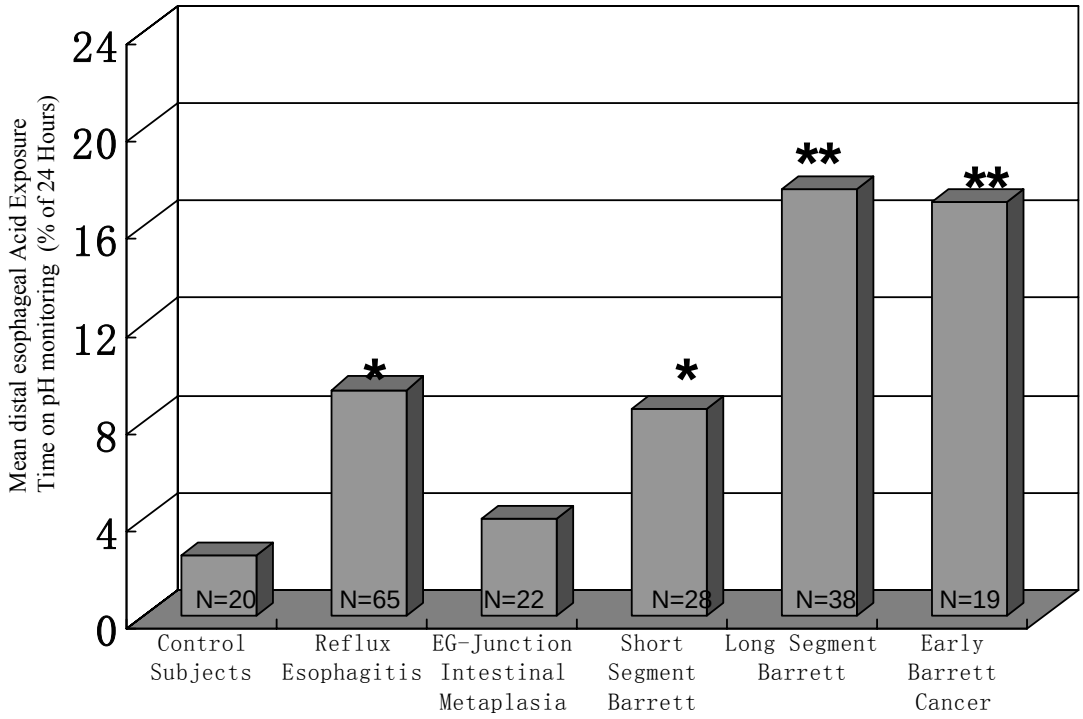
Category	Diagnosis	Clinically equivalent terms	clinical management
1	Negative for neoplasia		optional follow-up
2	indefinite for neoplasia		follow-up
3	Mucosal low-grade neoplasia	LGIN, low-grade adenoma/dysplasia	Endoscopic resection or follow-up*
4	Mucosal high-grade neoplasia	4.1 HGIN, high-grade adenoma/dysplasia 4.2 HGIN, non-invasive carcinoma(CIS) 4.3 Suspicious for invasive carcinoma 4.4 intramucosal carcinoma	Endoscopic or surgical local resection*
5	Submucosal or deeper invasion by carcinoma		Surgical resection*

LGIN, low-grade intraepithelial neoplasia; HGIN, high-grade intraepithelial neoplasia,including both categories 4.1 and 4.2; CIS, carcinoma in situ; intramucosal, invading into the lamina propria or muscularis mucosae.
*choice of treatment will depend on the size of the lesion, the depth of invasion as assessed endoscopically, radiologically, or ultrasonographically, the histological differentiation grade, and on general factors such as the patient's age and co-morbid conditions.

1.2 Pathogenesis, Epidemiology

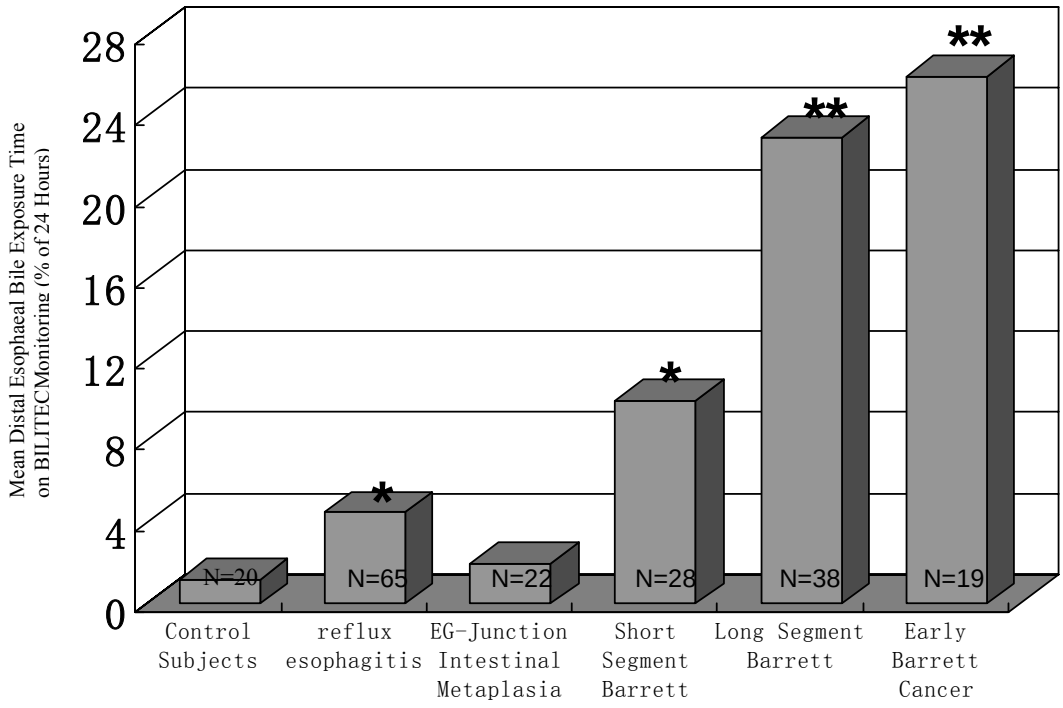
Metaplastic transformation of the epithelium correlates significantly with an increased reflux of acid and biliary-intestinal secretion, including intensity and duration of the exposition, as it has been supposed by Barrett in 1950[(1)] and proved by Stein et al[(5)]using detailed experiments (***Figures 3,4***).

Figure 3: BE and different complications correlated to acid exposition, calculated as percentage of 24-hours-period[5]



*P<0.01 vs control subjects. **P<0.01 vs control subjects and patients with reflux esophagitis.

Figure 4: BE and different complications and their correlation to exposition with biliary and intestinal reflux, calculated as percentage of a 24-hours-period[5]



*P<0.01 vs control subjects. **P<0.01 vs control subjects and patients with reflux esophagitis.

The influence of acid-free reflux on the development of metaplasia could be demonstrated very clearly by Meyer et al [11] in their report about totally gastrectomized patients. The significance of functional barriers by the lower esophageal sphincter, of cellular protection and of the molecular background of these processes still remains unclear.

Observed familiar accumulations of BE and probably also of Barrett's carcinoma need further genetic and molecular biologic analyses[12]

From observations of the progress to dysplasia it has been found that this process is generally not fast and not obligatory. Schnell et al[13] observed a sample of 1099 patients with BE out of a pool of 1125 totally for more

than 20 years. They found in 230 cases (=20.9%) constant metaplasia without alterations, in 738 cases (= 67.2%) a constant low-graded dysplasia and in 79 cases (= 7.2%) high-graded dysplasia. For the primary status they revealed pre-existent carcinoma in 42 cases (= 3.8%). During the observation period carcinoma developed from LGD in 10 patients (= 0.9%) and from HGD in 16 patients (= 1.5%). As result they concluded, that for the vast majority of patients i.e. 63 of 79 (= 85%) even HGD will not develop adenocarcinoma. This is different from the conclusions of Hameeteman et al[10] who suppose a continuous progression to different grades of dysplasia and out of an observation from 5 patients with Barrett's carcinoma they made risky extrapolations: *"Our data support the concept that a sequence of progression of dysplasia to carcinoma exists. The time it takes such development shows considerable variation, and high-grade dysplasia has been found to exist far as long as 3.5 yr without evidence of carcinomatous degeneration."*

By analysis using multivariate regressions for their large sample of patients with BE Schnell et al[13] found out, that there was only one significant correlation, namely between the length of Barrett's segment and the risk of carcinoma. According to the rules of probability this could be expected.

The problem of potential progression from dysplasia to carcinoma has also been evaluated by Shaheen et al[14]using meta-analysis of 25 suitable publications out of a pool of 554 publications, the majority of which with lacks of information. They evaluated a correlation between cancer risk and several factors: size of the study, the definition of BE, retrospective vs. prospective nature of the study, surveillance interval

and the effect of cancer detected in the first year of surveillance. In spite of several further unsolved problems, they came to the following conclusion: "*In conclusion, in studies reporting the incidence of adenocarcinoma of the esophagus in the setting of BE, there is a strong inverse relationship between the seize of the study and the reported cancer risk.....Publication bias, such smaller studies are published only if they feature high cancer risk, is a possible explanation for the observation"*

This problem of overestimating the risk to develop carcinoma was already pointed out by Hameeteman et al[10] and later by Spechler [15] in an editorial. The first group demonstrated the uncertainty for risk calculations for prevalence of Barrett's carcinoma showing large variations from 0% to 46.5% with a mean of 10%. For follow-up studies during longer periods they calculated incidences of carcinoma between 1 to 82 patient yrs and 1 to 441 patient years. This means a 30-40 fold risk to develop carcinoma in BE compared to normal population ***(Table 1-3***).

Table 1: Prevalence and estimated risk to develop carcinoma in different populations[16]

Author		Land	PJ/Ca	M (Ca)
Cameron et al	1985	USA	440	2
Robertson et al	1988	EB	56	3
Van der Veen et al	1989	NL	170	4
Hameeteman et al	1989	NL	52	5
Ovaska et al	1989	SF	55	3

PJ = patient's year

Table 2: Epidemiology and risk of carcinogenesis in BE calculated in incidences per patient year, showing a large range in observations[17]

Author		No. of patient-years	No. of cancers	Incidence (per patient-year)
Spechler*	1984	350	2	1 in 175
Sprung	1984	162	2	1 in 81
Cameron*	1985	884	2	1 in 441
Sampliner	1985	92	1	1 in 92
Achkar	1988	166	1	1 in 166
Robertson	1988	218	3	1 in 56
Van der Veen*	1989	681	4	1 in 170
Ovaska	1989	166	3	1 in 55
Hameeteman	1989	269	5	1 in 52
Skinner	1989	145	3	1 in 48
Williamson	1991	497	5	1 in 99

*means "by postal inquiry", all other studies are based on endoscopic and histopathologic examinations.

Table 3: Variations in calculated risk for carcinoma in BE during surveillance (10)

Study, year (ref)		case/patient-year follow-up
Skinner,	1989	1/48
Hameeteman,	1989	1/52
Robertson	1988	1/56
Present study		1/73
Williamson	1991	1/99
Van der Veen	1989	1/170
Spechler	1984	1/ 175
Mean		1/100

To find out the prevalence of BE for different ages, Cameron et al[18] analyzed the data of 51.311 patients from Olmsted County (Minnes) who contacted medical institutions for any reason. Their results show a close correlation of BE to the male population, to people of older ages and with longer history of reflux ***(Figure 5***).

Further epidemiologic data form 9 counties of the USA from 1979 to 1987 have been collected by Blot et al[19]. Analyzing the reports of 9406 patients with carcinoma of the esophagus, they found an increasing importance of BE because the frequencies of adenocarcinoma of the lower esophagus grew for more than 100% with special burden for the white male population and the age of 55 yr and more. These results are comparable to the conclusions of Falk[12] and the empiric results of Wright et al[17].

Figure 5: Prevalence of BE depending on the age of analized population. Results of epidemiologic research in Olmsted County (Minnes). During endoscopic procedure of 51,311 people contacting health care institutions. Clinical prevalence: 18/100,000 and Autopsy-prevalence: 376/1000, 000[18]

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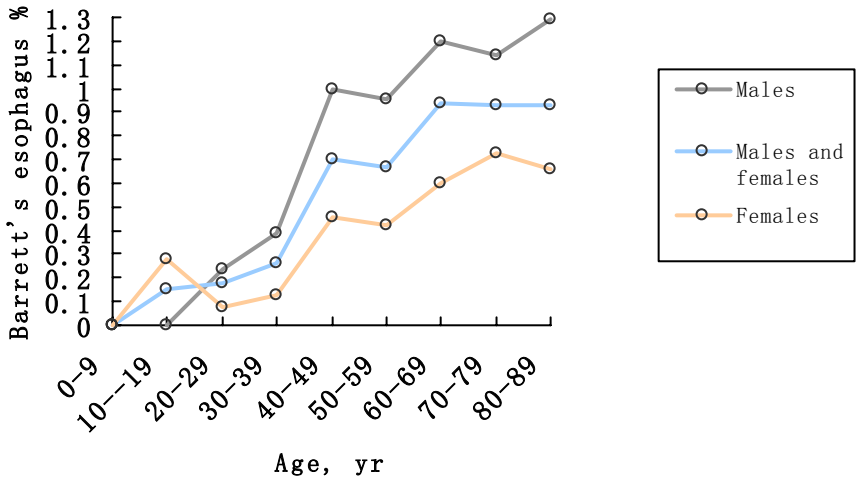


A similar reverse setting to evaluate the importance of BE for the development of adenocarcinoma was tried by Dulai et al[20]. They analyzed the literature about operated adenocarcinoma of the esophagus for references to BE. They found only 4.7% ± 2.9% documented diagnoses of BE as precursors and they concluded that the situation is

still open using this access of research. Their final statement lines out a different aspect for an explanation for this unexpected low rate of BE found in their study: "*These data thus provide a clear and compelling rationale for the development of effective screening strategies to identify patients with Barrett's esophagus.*"

Falk[12] points out that there is a close connection of prevalence of BE to the strictness of definition: in patients with reflux symptoms he described metaplasia in 12%, when the size of metaplastic area was not precisely documented and only in 5% when the size was precisely determined with 3 cm or more.

2. Diagnostic Procedures

2.1 Clinical Symptoms

There are no clear clinical criteria, symptoms or combinations of symptoms that can guide to the diagnosis of BE. Chronic reflux disease (GERD) and BE are similar in all essentials, (***Table 4***).

Table 4: Clinical symptoms in patients with BE. There is a close coincidention to the symptoms of reflux esophagitis[21]

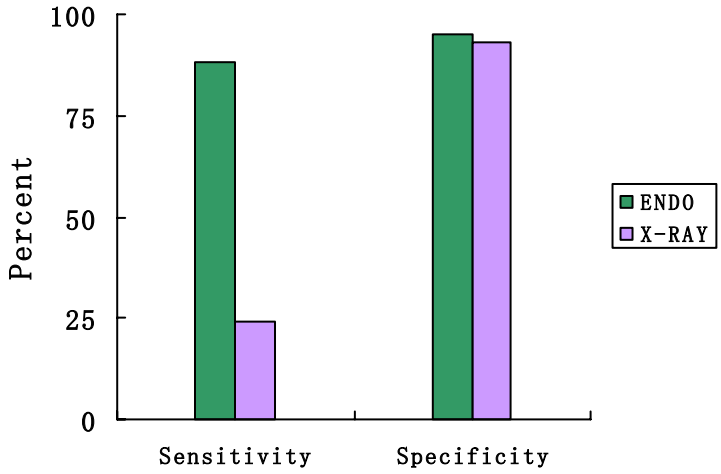
Symptoms	BE	Esophagitis	Total
Heartburn	137	172	309
Dysplasia	8	3	11
Vomiting/nausea	4	4	8
Asymptoms	19	26	45

2.2 Radiology

Conventional and advanced radiologic techniques are insufficient in detecting BE. Barrett (1957)[2] already mentioned these disappointing intentions: "*…unless a pathologic lesion is present in the esophagus, there is no special pattern caused by the columnar mucosal folds which suggest the diagnosis. The superficial lesions due to esophagitis cannot be seen and peristalsis is not abnormal.*"

Winters et al[4]investigated the quality of radiologic technique in a two-armed study on 118 patients from whom 33 had BE, 44 GERD and 41 normal histopathology. BE could be detected only in 13 out of 33 patients, the detailed date concerning the quality of the method are listed in ***Figure 6***. In available later publications there are no informations of improvements for radiologic techniques.

Figure 6: Results of radiologic examination in detecting BE compared with endoscopy[4]



2.3 Endoscopy

It was again Barrett [2] who obviously already had a high estimation of endoscopy, despite the lack of modern instruments, when he stated: *"Esophagoscopy is an essential preoperative investigation in all patients suffering from diseases in the esophagus. The diagnosis should be suspected if the change-over of the mucous membrane is found at a high level. As the epithelial transition is sharp, there should be no difficulty in marking its point unless there is local inflammation. If there is a doubt, pinch biopsies will settle the matter."*

This situation did not change essentially during the time following: visible endoscopic criteria are not sufficient to identify BE from other alteration, sometimes even from normal squamous epithelium. Larger studies like that of Conio et al[21]about endoscopic macromorphology for the diagnosis of BE cannot show sufficient quality of conventional diagnostic criteria: sensitivity, specificity, accuracy and predictive values ***(Table 5***).

Table 5: Sensitivity and Specificity of endoscopic macroscopic diagnosis in BE. The results are not satisfying showing a sensitivity of 69.3%, a specificity of 63.1%, a pos. predictive value of 84%, a neg. predictive value of 62.7% and an accuracy of 66.5%[21]

Endoscopic diagnosis	Histological diagnosis		Total
	Metaplasia (BE)	Reflux esophagitis	
BE	142	62 (=30.4%)	204
Reflux grade II	26	58	84
Reflux grade III	10	26	36
Peptic stenosis	9	10	19
Peptic ulcers	6	4	10
More than 1 lesion	12	8	20
Total	205	168	373

The statement of Falk[12] is remarkable, when he cites observations from Spechler et al[22] about their diagnoses of BE without any visible alteration of the esophagus in 26 out of 142 patients (18%). Similar experiences with BE diagnosis in normal appearing mucosa of the lower esophagus were made by Nandukar et al[23], Johnston et al[24], Hirota et al[25],Voutilainen et al[26], Pereira et al[27], Trudgill et al[28] and by Ormsby et al[29]in autopsies.

By current definition BE is a specialized intestinal metaplasia of SCE of the distal esophagus. That means the diagnosis of BE is based on the results of histology of biopsy particles.

2.4 Biopsy, Histopathology

Biopsy does not show inherent reliability, even if all technical proposals for good quality had been taken into consideration: four quadrant biopsies in short distances, minimum 12 particles in suspected short segment BE and more in suspected long-segment BE.

The diagnostic safety can be improved by double-checks after short intervals. This design was used by Bonelli et al[16] in a multicenter study analyzing the results of 157 followed up patients from a pool of 405 patients. Second biopsies at one year follow-up revealed that 13.4% of the initial histologic findings were incorrect ***(Table 6).***

Table 6: Initial histologic diagnosis compared to the second one after one year. The data showing the histologic findings of 157 followed up patients from a sample of 405. In this group of 21 newly detected cases of metaplasia, two adenocarcinomas were found [16]

First examination	follow-up examination	
	BE	Negative
BE	100	13
Negative	21 (=15.4%)	23

The value of technical details during biopsy taking has been demonstrated by Reid et al[30] using a large-scaled study of histopathologic examinations of 48 patients with adenocarcinoma and 123 with HGD in BE. They found out that accuracy of the diagnosis could be improved by 100%, when they reduced the distances of biopsy-sites from 2 cm to 1 cm. In visible altered mucosa the error rate for 2 cm intervals was still 29%. It is also remarkable that even in resected specimens early mucosal carcinoma (n=36) could be detected only in 39% of the patients using conventional techniques of histopathologic sections. This error mainly (i.e. for 96%) concerned carcinoma restricted to the mucosa (T1m).

2.5 Complementary Optical Techniques

Additional staining techniques for targeted biopsies are obviously unable to improve the diagnostic results. Egger et al[6] investigated vital staining with methylene-blue and autofluorescence markers in 345 biopsy particles of 35 patients with BE. They found high specificity for the two techniques (91%) in differentiating metaplasia from HGD. But

the sensitivity rates of 21% for autofluorescence and 37% for methylene-blue staining were rather disappointing. Comparable results were found by Wo et al[31] whereas other groups saw some improvements using vital staining [32, 33].

Some new endoscopy-associated complementary optical techniques like fluorescence-spectroscopy or coherence-tomography are still in clinical experimental stage. A combination of different complementary techniques seems to show some improvement of diagnostic quality [34] . It remains unclear whether the use of all these additional techniques is more effective than improved technique of biopsy, particularly for the investigation of larger areas of BE.

2.6 **Accuracy of Histopathologic Diagnosis**

Differences in interpretations of pathologists regarding BE and dysplasia grades represent an additional problems. Falk[12] mentioned in an editorial that the interobserver agreement among 20 pathologists for the diagnosis of metaplasia without dysplasia was only 35%.

Reid et al[30] reported on interobserver variations among 9 pathologists from 4 institutions in classifying BE into five given subclasses. They found an agreement for HGD and mucosal carcinoma in 85% of the specimen and 87%, respectively, whereas the agreement for metaplaisa and LGD was only 72% ***(Table 7***).

Table 7: Interobserver variations in histologic diagnoses of BE, dysplasia and intramucosal carcinoma. The study was based on analysis of 70 biopsy specimens by 8 pathologists[35]

Round 2	Round 1
High-grade dysplasia + intramucosal carcinomar vs other	87%
85%	
Negative for dysplasia vs other	71%
72%	
Negative + indefinite vs other	75%
77%	
Negative vs indefinite + low-grade vs high-grade + intramucosal carcinoma	58%
61%	

Ormsby et al[29] concluded from their experiences in autopsies: "*Because different pathologists made many of the endoscopic and surgical pathology interpretations, it is also possible that interobserver variation in the diagnosis of intramucosal carcinoma contributed to the discrepancy.*"

Schnell et al[13] pointed out that this interobserver variability for the classification of metaplasia, LGD and HGD does really exist, but is not mentioned in the majority of all studies published. The group came to the following statement: "*However the few studies that report intraobserver and interobserver variation show the greatest agreement for higher grades of dysplasia. Agreement approached 85% for HGD and intramucosal adenocarcinoma.*" Hameeteman et al[10] also found a higher interobserver variability for specimens with low-grade and intermediate dysplasia.

2.7 Staging

The task of a reliable pretherapeutic staging is particularly regarding the identification of intramucosal carcinoma (T1m), in order to allow performing endoscopic mucosa resection (EMR) with lower mortality and morbidity. Only in this early stage of T1m the probability of lymph node involvement is negligible [36-38].

Endoscopic ultrasound (EUS) is currently the method of choice for staging of gastrointestinal tumors. For superficial tumors, high resolution radial EUS probes with 20 and 30 MHz transducers are used. Linear EUS-scopes with fine-needle aspiration (FNA) and colour-Doppler facilities are used for lymph node staging. However, the overall accuracy rate of EUS for T-staging of esophageal cancer is only 84% according to collected data from 21 studies recently reported by Shim et al[39]. Accuracy rate for T1 is 80.5%, for T2 76%, for T3 92% and for T4 86%. The overall accuracy rate of the N-staging is 77%, with 69% for N0, 89% for N1[40].With the aid of EUS-guided FNA the result of N-staging is significantly improved up to 87%[41].

Owing to the lack of reliable pretherapeutic tumor staging, EMR (see 3.3.2) has been recommended as a diagnostic tool. EMR provides better diagnostic tissues than biopsy. Superficial mucosal lesions with lifting sign after submucosal saline injection are resected endoscopically using diathermic snare. If histology of the specimen confirms that resection was complete and the tumor is confined to the mucosa, EMR can be considered curative therapy[42, 43].

3. Therapeutic Options

3.1 Conservative treatment, surveillance

For BE with and without LGD there is strong consensus for conservative treatment combined with different intervals for surveillance. LGD should be re-confirmed by expert pathologist within 6 months. Conservative treatment means: elimination of gastroesophageal reflux by reduction of body mass index (BMI) and administration of PPI. Under conservative treatment regression from metaplasia to normal SCE has been observed. But such improvement occurs rather infrequently. Surveillance endoscopy with four-quadrant biopsies in one-year interval is recommended for patients with BE and LGD. For BE without dysplasia, endoscopy surveillance with biopsy in 3-years interval is considered adequate. In cases with large hiatal hernia and incompetence of the LES surgical repair (laparoscopic fundoplication) may be considered. BE with HGD may be an indication for resective surgery.

3.2 Surgery

The rational for recommending surgery in BE with HGD is the high coincidence of cancer detected in the surgical specimens. The coincidence rate has been reported in surgical literature to be as high as 40%. Some cancers had even already infiltrated the submucosal layer [44, 45]This problem particularly applies to long-segment BE because of the high incidence of multifocal lesions and the risk of missing these lesions endoscopically. Falk et al[46] reported that endoscopy and 4-quadrant biopsies at 2 cm intervals even with jumbo biopsy forceps missed cancer in 33% of the cases. Many of these lesions were invisible endoscopically.

The operative mortality of total esophagectomy is ranging between 1% and 10% depending on the skill of the surgeon with postoperative morbidity of 10% to 50% [44, 45].

Lack of knowledge about the risk and speed of progression of HGD to cancer has led to conducting follow-up studies. Schnell et al[13] reported that only 16% of a total of 75 patients with BE and HGD developed cancer during a mean of 7.3 years follow-up. During this follow-up period, endoscopy surveillance with biopsy was performed every three months. Patients who developed cancer and were compliant could be cured with surgical or ablative therapy.

Due to the relatively high risk of surgery, endoscopic interventional modalities have increasingly become popular in the therapy of BE with dysplasia. The spectrum includes different mucosal ablative and resection methods.

3.3 Endoscopic Treatment

3.3.1 Ablative methods

Endoscopic ablation of BE uses either thermal or photodynamic devices. The aim is to destroy the metaplastic and dysplastic epithelium allowing the restoration by SCE. Major drawback of this treatment is lack of histologic confirmation of complete eradication of BE. APC is currently the most commonly used method for ablation of BE.

3.3.1.1 Argon Plasma Coagulation (APC)

APC is a non-contact monopolar coagulation using argon gas as transmitter. The penetration depth of APC is less and the risk of perforation is therefore lower as compared to monopolar coagulation and Neodym-YAG Laser. The technique appears to be suitable for destruction of larger mucosa surface. Eradication rates reported in the literature range between 38% and 99%. Transient mild retrosternal discomfort and odynophagia were observed in most of the patients. Esophageal stricture and bleeding as more serious complications occurred in 0-7%[47-52]. Complication rate may increase if high power APC is used [53].

3.3.1.2 Photodynamic Therapy (PDT)

PDT is a physicochemical ablation treatment based on accumulation of photosensitizer in tissue. The principle of PDT is selective sensitization of precancerous or malignant lesions using a systemically applicable photosensitizer with subsequent endoscopically controlled, photochemically induced tissue ablation. Following exposure with light of an adjusted wave-length, zytotoxic reagents develop, mainly singlet oxygen, which then selectively destruct neoplastic tissue. The depth of treatment depends on the penetration of the Laser light and localization of the photosensitizer in the esophageal wall.

Photofrin, Porfimer sodium is the only photosensitizer that received US Food and Drug Administration approval for use in the esophagus. The light exposure is performed 2-3 days after intravenous application of the sensitizer under endoscopic control using a 1.5 to 2.5 cm cylindrical

diffuser or a windowed centering esophageal balloon[54]. The major problems of PDT are post-therapeutic stenosis and long-term skin photosensitization hypersensitivity for 60-90 days.

A new second-generation photosensitizer being used in trials is 5-Aminolaevulinic acid (5-ALA). It is administrated orally only 4-6 hours before light exposure and has the advantage of limiting skin photosensitization to 2 days. This method seems to be effective only for very superficial lesions up to 2 mm in depth[37].

3.3.1.3 Electrocoagulation

This contact thermal modality can also be used for ablation of BE. However, application through the probe is pinpointed and is therefore rather cumbersome and time consuming especially in long-segment BE. For mucosal ablation only bipolar electrocoagulation should be used because monopolar electrocoagulation is associated with higher perforation risk due to the relatively deep penetration. One multicenter study including a total of 58 patients with BE and no dysplasia reported a complete BE ablation of 78% at 6 months by using multipolar electrocoagulation. Transient mild chest pain and odynophagia occurred in 36% of the patients and esophageal stricture in 2% [55].

3.3.1.4 Laser Coagulation

Laser has the same disadvantage as electrocoagulation, namely pinpointed application and time consuming. The penetration depth of the energy is greater as compared with that of APC. Laser has therefore been completely replaced by APC in the gastrointestinal endoscopy. There have been only a few reports on the use of Nd:YAG-Laser and KTP-

Laser for BE ablation in rather small numbers of patients. The results are comparable with those of APC [56, 57].

3.3.2 Endoscopic Mucosa Resection (EMR)

This technique was first introduced in the seventies by Ottenjann[58] and Deyhle[59] as snare biopsy for obtaining large mucosa samples in the stomach. In 1976, Martin[60] first described the lift and cut biopsy technique using a double-channel endoscope for submucosal samplings. Tada et al[61]introduced the technique of "strip biopsy" using a double-channel endoscope. Since then, the technique of EMR has gained rapid popularity in Japan. Several technical modifications have been introduced mainly for the treatment of early malignant lesions in the esophagus and stomach (***Figure 7***).

Figure 7: Techniques of EMR

Lift and Cut using a double-channel endoscope
(Tada et al. ***Gastrointest Endosc*** 1984) [61]

Suck and Cut using an overtube
(Makuuchi et al. ***Jpn J Surg Gastroenterol*** 1991) [62]

Suck and Cut using a cap
(Inoue et al.***Surg Endosc*** 1990) [63]

Suck and Cut using band ligation device
(Chaves et al.***Gastrointest Endosc*** 1994) [64]

Simple Snare Resection without any addtional tool
(Soehendra et al. ***Endoscopy*** 1997) [65]

The principle of most EMR techniques is either “lift and cut” or “suck and cut”. Submucosal injection to lift the mucosa which was introduced by Deyhle et al[66] is generally considered as useful for reducing the risk of perforation. The “lift and cut” technique using a double-channel endoscope has been the most commonly used EMR method in Japan until 1998 (***Table 8***)[67]

Table 8: EMR methods for early gastric cancer used in Japan until 1998[67]

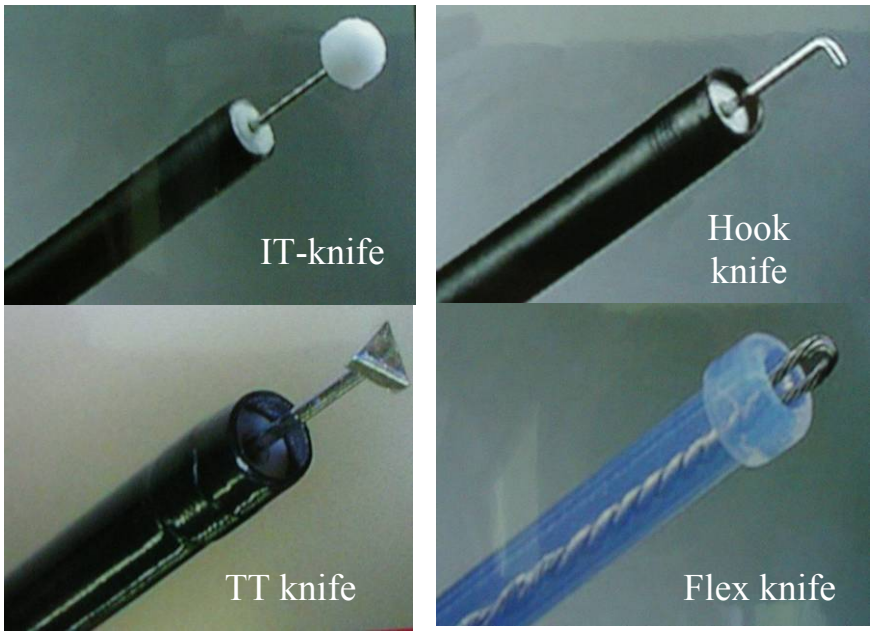
Author	n	Method				complete	incomplete
		2CS	1CS	EMRC	EMRL	EMR	
Tada	334	334	-	-	-	78%	22%
Takekoshi	308	308	-	-	-	74%	26%
O-izumi	256	256	-	-	-	91%	9%
Takahashi	140	140	-	-	-	77%	23%
Misaki	115	115	-	-	-	47%	53%
Atsumi	113	113	-	-	-	63%	37%
Honmyo	62	62	-	-	-	69%	31%
Hiki	48	48	-	-	-	71%	29%
Fujisaki	187	-	-	-	187	62%	38%
Chonan	123	46	31	46	-	70%	30%
Tani	86	-	-	86	-	98%	2%
Abe	60	25	35	-	-	62%	38%
Total	**1832**	**79%**	**4%**	**7%**	**10%**	**74%**	**26%**

2CS=two channel scope; 1CS=one channel scope; EMRC=EMR with cap; EMRL=EMR with ligation

The “en bloc” resection method using IT- (insulation-tipped diathermic), flex, triangle or hook knife has been recently proposed to achieve higher rate of complete removal of gastric cancer, hence reduction of the

recurrence rate (***Figure 8***)[68-70]. Gotoda et al had shown a significant reduction of recurrence rate from 5 % to 0% as compared to previous piece-meal resection technique[71].

Figure 8: Different instruments for "en bloc" resection: IT knife, TT knife, flex knife and hook knife.

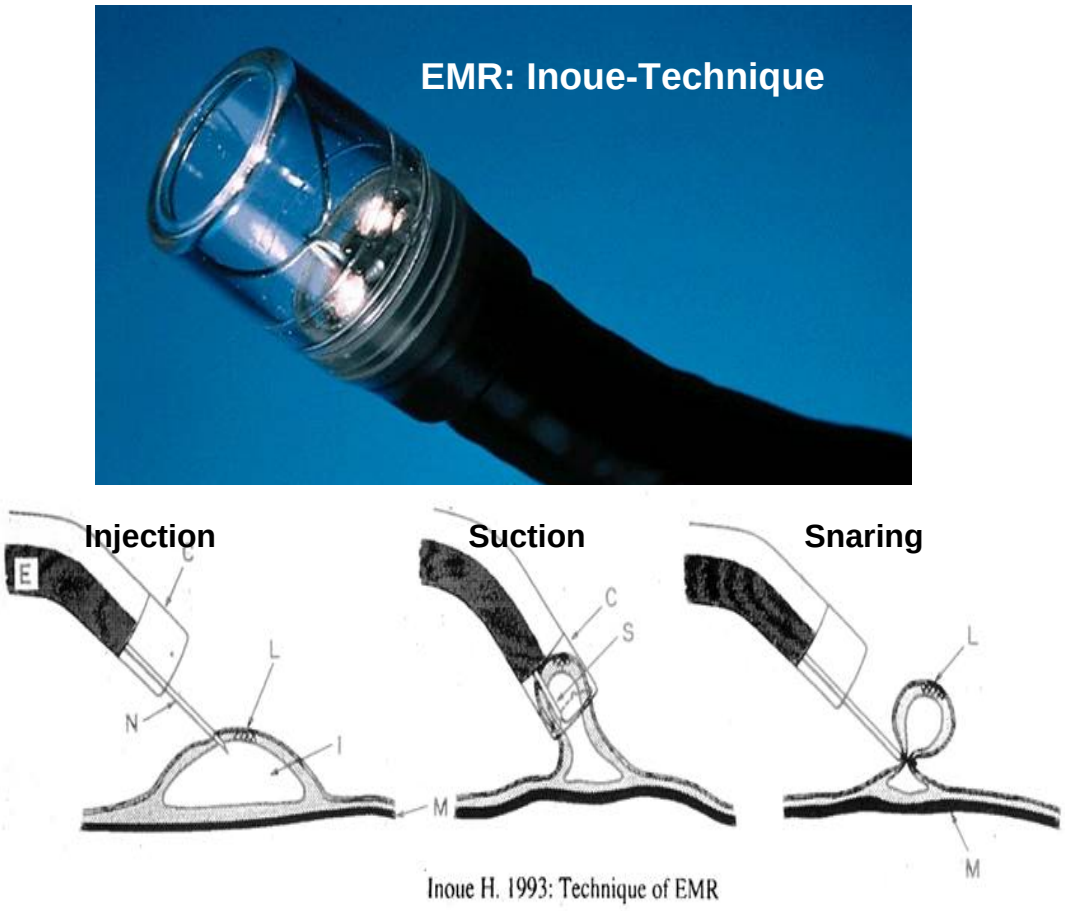


However, "en bloc" EMR is associated with a higher complication rate. Perforations occurred in 5% in a large series but were endoscopically manageable in 98% of the cases. The en-bloc EMR technique[68] is best suitable for the stomach. For the esophagus with smaller lumen, this technique is rather cumbersome.

In Europe, EMR is playing an increasing role in the treatment of early malignant mucosal changes (HGIN and T1m) in BE, as the number of this type of cancer is rising rapidly. The most commonly practiced method in the esophagus is the "suck and cut" technique which was popularized by Inoue et al[72]. A special transparent plastic cap is

mounted to the distal end of the endoscope. Submucosal injection of 20-30 ml saline solution is performed prior to resection. A special asymmetric soft snare made of braided wire is used as it can be properly placed in the inner gutter at the distal end of the cap. The tumor bearing mucosa is first sucked into the cap and then snared. The resected specimen is then sucked into the cap and retrieved by withdrawing the endoscope (***Figure 9***). The soft snare is easily deformed and therefore usually suitable for single use only. Another "suck and cut" technique uses the single rubber band ligator to create a pseudopolyp enabling snare polypectomy of flat mucosal lesions[73, 74].

Figure 9: "Suck and cut" EMR technique using a cap[63]



C=cap; N=needle; L=lesion; I=injection; M=muscle propria; S=snare

3.3.3 Endoscopic eradication of BE

EMR performed in BE has been localized resections restricted to the mucosa bearing malignant changes. Depending on the length of follow-up periods, recurrence rate of tumor rises from 14 % up to 30 %[37, 75]. Most of these recurrences occurred as metachronous lesions which emerged from the remaining BE. However, multifocal early malignant changes are known to exist especially in long-segment BE suggesting that some of the recurrences may be from preexisting synchronous lesions. In fact, HGD or HGIN in BE represents a diagnostic problem. Endoscopic recognition of these lesions even with the aid of methylene blue staining and other currently available imaging techniques has not been perfected as yet. Four quadrant random biopsies are not sufficient enough in detecting all the early malignant changes[6, 31, 46]. To avoid development of cancer, endoscopic treatment of BE has been proposed. Although several studies have shown encouraging results of thermal ablation of BE, there still remain some uncertainties due to incomplete removal and evidence of buried subepithelial BE glands after treatment. [48-50, 76, 77]. The Department of Interdisciplinary Endoscopy at the University Hospital Hamburg-Eppendorf has therefore recommended circumferential EMR for complete removal of BE containing HGD or IMC. Simple snare resection technique was performed to completely remove BE in “piece-meal” fashion[78]. Since this technique and other “suck and cut” techniques using a cap or band ligation device are quite cumbersome in removing long-segment BE, we have recently modified the multiband variceal ligator (MBL) to facilitate multiple, extensive mucosal resections.

Conio et al[79] first published the feasibility of circumferential EMR in an animal study. The group from the Department of Interdisciplinary Endoscopy at the University Hospital of Hamburg-Eppendorf reported the first clinical results of circumferential EMR in BE using the simple snare technique. EMR in this small series (n=12) was performed in 3-4 week intervals.

4. Present Study

4.1. Aims of the Study

The aim of this study is to evaluate the feasibility and safety of the novel "band and cut" technique in BE using the modified variceal multiband ligating (MBL) device and to report on our preliminary clinical experience with the modified MBL device used for circumferential EMR of BE containing HGD and/or IMC.

4.2 Study Design, Criteria for Enrolling and Exclusion

In this uncontrolled prospective study, consecutive patients with BE and HGD and/or IMC referred to EMR during the first 10 months of 2004 were included. The trial has a fixed start point and open end. It followed the regulations of the Declaration of Helsinki (1964) for biomedical research in human in the revised versions of 1975 and 1983 and the Recommendations for Good Clinical Practice (GCP) of the FDA.

Proven that the indication is given, informed consent was obtained orally and written prior to treatment.

Criteria for **inclusion** were:

- BE regardless the length;
- Verified HGD and IMC by two pathologist;
- No suspicious regional lymph node in EUS;
- Consent of the patient;
- Limited number of inclusions to 10-15 patients for the first calculations regarding efficiency and safety.

Exclusion criteria were:

- BE without Dysplasia or with LGD;
- Indefinite EUS finding in excluding involvement of the submucosal layer and regional lymph nodes;
- No consent of the patient;
- General clinical risk with critical parameters according to NYHA III and higher preventing safe endoscopy under propofol anesthesia.

4.3. Methods and Instruments

All patients were clinically examined to evaluate their individual risk profile, especially to rule out coagulopathy.
If there were no calculable risks - i.e. for otherwise healthy patients-, the treatment was planned as outpatient procedure with observation for 6-8 hours in the department. All other patients were hospitalized.
Endoscopy and EMR were performed under conscious sedation using i.v. propofol according to the individual need given by an assisting physician experienced in intensive care treatment. Oxygen saturation and pulse

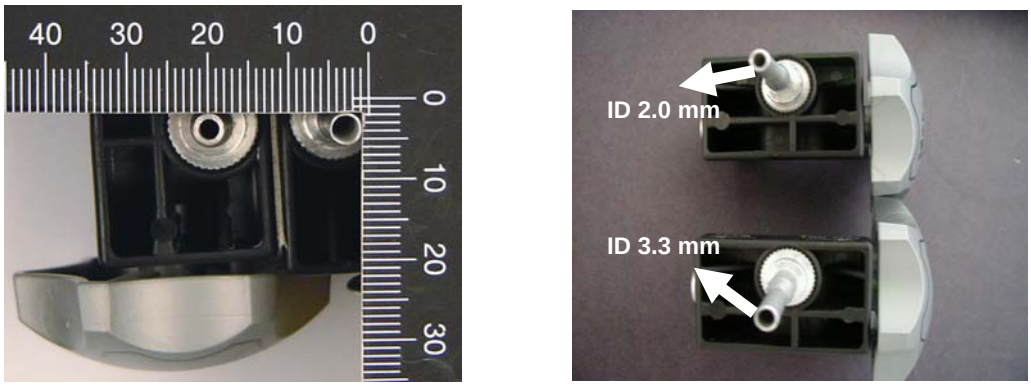
rate were continuously monitored using pulse oxymeter during the endoscopic treatment and the post treatment observation.
The entire EMR procedure was recorded on mini disk and important images were additionally stored in the computer.

4.3.1. Instruments

Therapeutic electronic endoscopes with 3.7 mm working channel were used (GIF-1T 140/160, Olympus Co. Tokyo, Japan). Banding for creating pseudopolyp was performed with a modified Six Shooter MBL (Wilson-Cook, Winston-Salem, NC, USA) which allows for six banding procedures. The modification of MBL (Wilson-Cook, Winston-Salem, NC, USA) consists simply in widening the threading channel of the cranking device from 2 mm to 3.2 mm (***Figure 10***). This allows for the insertion of a 7 French catheter through the threading channel of the cranking device into the 3.7 mm working channel of the endoscope. Band ligation can be performed with the polypectomy snare still within the working channel without any increased friction during winding of the thread. This enables sequential banding and snare resection of esophageal mucosa without the need to change the endoscope. With this modified MBL, extensive or circumferential EMR can be accomplished usng only a single endoscope within a relatively short time. Other 7 French accessories, such as argon plasma coagulation (APC) probe, clipping device or hot biopsy forceps can also be introduced if required without the need to retrieve the endoscope and the MBL device.
For resection, mini hexagonal polypectomy snare sized 1.5 x 2.5 cm made of braided wire (AcuSnare SASMH-1, Wilson-Cook, Winston-

Salem, NC, USA) is used. This snare can be reused in the same session for several resections owing to its shape's stability.

Figure 10: Design of the modified cranking device of the multiband-ligator (MBL) used for performing one-step CEMR. The threading channel is widened from 2.0 mm to 3.2 mm.



4.3.2. Circumferential EMR

The Barrett's mucosa is first sucked into the ligating barrel and the rubber band is deployed in the same manner like variceal ligation creating a pseudopolyp. No submucosal saline injection prior to ligation is required. The polypoid bleb is then immediately resected using pure coagulating current (output 60 watt, setting 3). It does not matter whether the snare is placed above or below the band. In most of the cases, however, the snare will automatically lie below the rubber band. Following each resection, the specimen and the detached rubber band are pushed into the stomach by using the tip of the snare's catheter or flushed down by a water jet from a pump machine connected to the accessory channel of the endoscope. The second ligation is performed by sucking the adjacent mucosa with a bit overlapping ensuring that no Barrett's remnant remains. The procedure is started from the gastro-

esophageal junction and accomplished circumferentially until the entire Barrett's mucosa is completely removed (***Figure 11 a-h***).

Figure 11a-h: Endoscopic images. Procedure and result of MBL-CEMR.
a. 5 cm long-segment BE with a IMC (nodule).
b. Six-shooter MBL is targeted to the nodule.
c. The IMC bearing mucosa area is sucked into the barrel and a pseudopolyp is created by ligating it.
d. The polypectomy snare is placed around the pseudopolyp.
e. The first resection is performed. The next pseudopolyp is being created by sucking the adjacent mucosa area with slight overlapping.
f. After two sequentially performed resections no remnant of BE is seen in the resected area.
g. The final endoscopic image after the CEMR has been accomplished.
h. Endoscopic image at 6 month follow-up showing complete restoration of the BE with no recurrence.

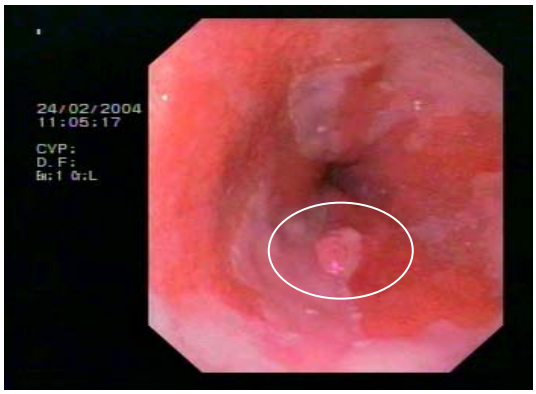


Figure 17a

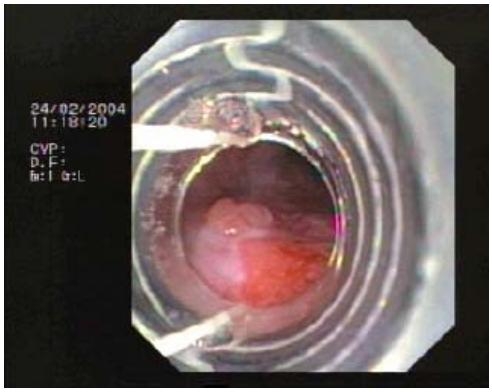


Figure 17b

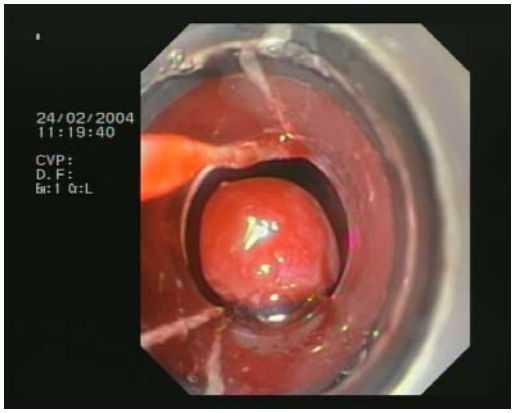


Figure 17c

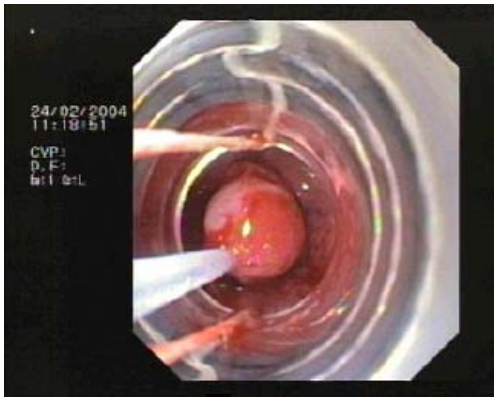


Figure 17d

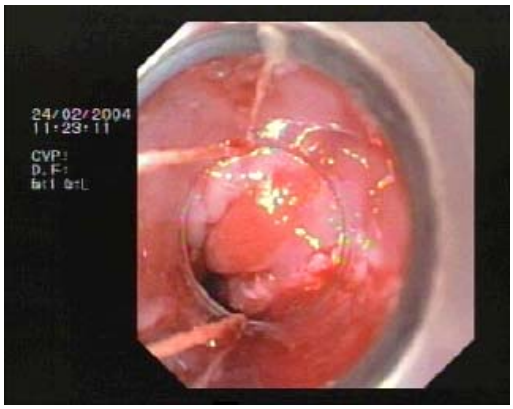


Figure 17e

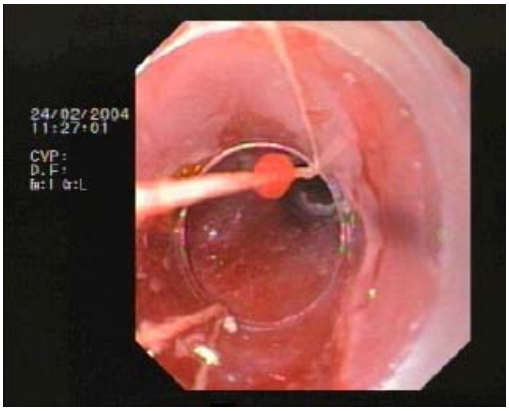


Figure 17f

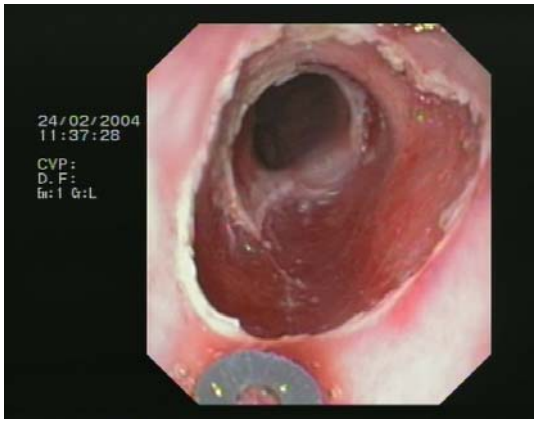


Figure 17g

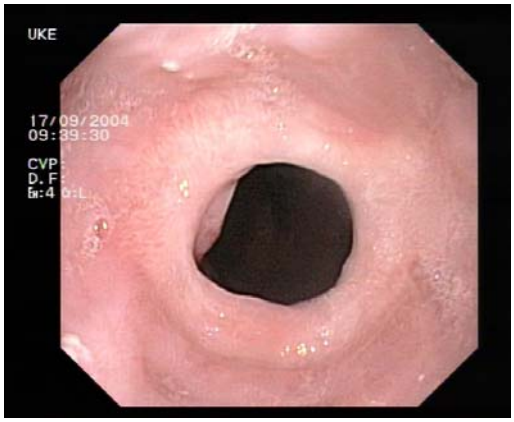
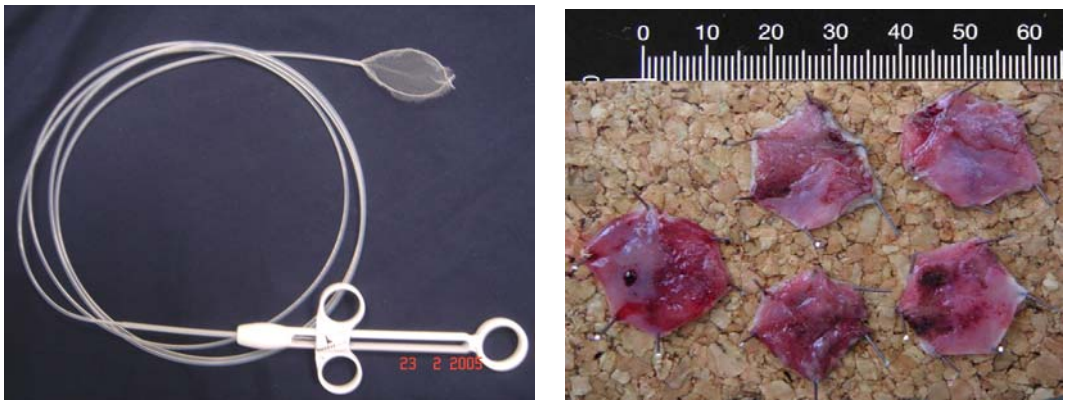


Figure 17h

At the end of the procedure all resected specimens are collected in the stomach by using the Roth's retrieval net basket (US endoscopy, Mentor, OH, USA), and spread over a cork plate. Each of the specimens is measured individually prior to formalin fixation (***Figure 12)***.

Figure 12: Disposable 2.5mm Roth net basket for collecting the resected mucosa specimens (left). Resected specimens and measuring on a cork plate (right).



Following EMR, patients were put on proton-pump inhibitor (at least 40 mg/day) and pureed diet was recommended. The first endoscopic follow-up was performed three weeks later on out-patient basis. Repeated EMR sessions for cases of extensive Barrett's segment were then carried out in 3-4 weeks interval. If dysphagia occurred, patients were advised to come back immediately. In case of stricture, bougienage was performed using 27-38 French Savary-Gilliard dilators (Wilson-Cook) depending on the stricture's grade.

4.3.3 Statistical Analysis

The data management was descriptive. For the study of correlations the following non-parametric tests were used: Fisher's exact test for independent and the McNemar test for dependent samples using 5% significance levels.

5. Results

During a period of ten months total of 14 consecutive patients were treated with the new MBL-EMR technique. There were 12 men and 2 women with a median age of 64 years (range 43-82yrs). All patients had circumferential Barrett's segment with a length of 2-10 cm (median 4 cm). 9 patients had long-segment BE (≥ 3 cm) and 5 short-Segment BE (< 3 cm). In the initial biopsy prior to EMR, IMC was found in 11 and HGD in 3 cases, respectively. No multifocal lesions were diagnosed.

In 5 of 14 patients, complete circumferential EMR was accomplished in one session using 3-18 bands (median: 6). Six patients required a total of 2 sessions, one patient 4 sessions, and one patient 5 sessions until the entire BE was removed. One patient having multifocal HGD and/or IMC in 24 of a total of 49 specimens was finally recommended to surgery because of technical difficulties caused by mural thickening after 4 sessions. The median number of EMR sessions was 2 (range 1-5). The mean size of EMR specimens measured prior to formalin fixation was 14.2 ± 4.1 mm (range 7-22 mm).

Histology of the EMR specimens confirmed IMC in 8 and HGD in 3 cases, LGD in 2. In one patient, no dysplasia in BE could be detected. In 5 patients with long-segment BE, multifocal lesions were found (In cases with multifocal lesions, the highest degree of dysplasia or malignant changes was selected). In a total of 217 EMR specimens, 40 IMC and 43 HGD were detected histologically.

Rubber bands were deployed successfully in 217 of a total 236 shootings. Deployment failure occurred in patients with mural thickening or scar formation from previous EMR due to lack of compliance of the tissue to suction.

Minor bleeding occurred in 4 patients which were controlled in all at the end of the EMR procedure, employing only 1-3 clip in each patient. In one patient with liver cirrhosis, additional bleeding from a submucosal collateral vein was controlled by immediate obliteration using a total of 2 cc of cyanoacrylate/Lipiodol mixture (ratio 0.5:0.8 cc). 0.5 cc of the mixture was administered per injection. Detailed description of our technique of cyanoacrylate glue injection has already been described[21]. Hemorrhages occurred equally in 2 patients with short-segment and 2 with long-segment BE.

Esophageal strictures occurred in 10 patients (71%), all following the first circumferential EMR after a median of 7 days (range: 5-10) which concur with the onset of dysphagia symptoms. A median of 5 (range: 1-11) sessions of weekly bougienage were performed for relief of dysphagia. Stricture developed in 7 patients with long-segment BE and 3 with short-segment BE. This difference was statistically not significant ($p>0.2$).

In one patient, deep tear of the esophageal wall occurred 4 weeks after EMR during the fourth session of bougienage which was performed incrementally with 33, 36 and 38 French Savary-Gilliard dilators. A limited resection of the distal esophagus and esophagogastric junction and reconstruction by interposition of isoperistaltic pedicled jejunal segment according to Merendino et al[(80)] was performed. The operation was suggested by the surgeon because CT-scan revealed free air in the mediastinum although patient was symptom free. Histological examination of the resected specimen showed no remnant of BE. No perforation was found. The postoperative course was uneventful.

The procedure time of each EMR session ranged from 30 to 60 minutes (median 30 minutes).

Re-grading of histologic diagnosis occurred in 5 of 14 patients (36%). There was a preoperative overgrading in 4 cases and an undergrading in one case. The difference of the pre-EMR diagnostic errors between long-segment BE (n=2) and short-segment BE (N=3) was statistically not significant ($p > 0.3$).

The aim of the trial, a complete resection (eradication) of the BE in one session, was achieved in 5 of 14 patients (36%), and almost achieved in another 6 cases. The total numbers of sessions needed did not reveal statistical significant differences between short-segement and long-segment BE ($p > 0.5$). For this statistical analysis, one patient who finally underwent surgery was excluded.

A summery of the data is shown in the **Table 9** containing informations about demography of patients, histopathology, numbers of EMR sessions, total number of specimens, and outcome/complications.

Table 9: List of all patients treated in present study with demographic, histopathologic, EMR and outcome data. LB = long-segment BE; SB = short-segment BE.

N.	Sex	Ages	Length [cm]	Segment LB/SB	Histology pre	Histology post	Treatment sessions (n)	Pieces (n)	Complications	Follow-up
1	M	64	5	LB	IMC	IMC	1	15	Stenosis	4x Bougienage
2	M	76	2	SB	IMC	IMC	1	3	Bleeding	1 clip
3	M	62	3	LB	IMC	IMC	4	17		
4	M	43	9	LB	HGD	HGD	1	18	Stenosis	4x Bougienage
										Operation
5	M	67	9	LB	IMC	IMC	4	49		Operation
6	M	72	10	LB	HGD	HGD	5	42	Stenosis	6x Bougienage
7	M	67	4	LB	IMC	IMC	1	4	Bleeding	3 clips
									Stenosis	3x Bougienage
8	M	49	3.5	LB	IMC	HGD	2	5	Bleeding	1 clip
									Stenosis	6x Bougienage
9	M	63	2	SB	IMC	IMC	1	6	Stenosis	6x Bougenage
10	M	57	4	LB	IMC	IMC	2	6	Stenosis	11x Bougienage
11	F	82	2	SB	IMC	HGD	2	14	Stenosis	1x Bougienage
12	F	77	2	SB	HGD	IMC	2	14	Bleeding	2 clips
13	M	56	2	SB	IMC	LGD	2	11	Stenosis	6x Bougienage
14	M	68	7	LB	IMC	BE	2	13	Stenosis	1x Bougienage

6. Discussion

It is well established that patients with BE have an increased risk of developing esophageal adenocarcinoma. The presence of dysplasia appears to predate the development of adenocarcinoma (metaplasia-dysplasia-adenocarcinoma sequence) in these patients. This is based on three observations: 1) a number of retrospective studies have shown that dysplasia was present in surgical specimens of 35-91% of patients with distal esophageal adenocarcinoma[81,82]; 2) approximately 50% of patients who had an esophageal resection for the diagnosis of HGD have been found to harbour small foci of adenocarcinoma on detailed

histologic examination of the resected specimens[83-85]; and 3) longitudinal studies in the same patients have shown the sequential progression of BE to LGD, HGD and adenocarcinoma.

Based on collected data, Falk[12] calculated that risk of progression from HGD to IMC after two years is 20-25% (***Table 10).*** The risk increases with the length of follow-up and also with the size of BE and the dysplastic area[43].

Table 10: Risk of developing adenocarcinoma in BE with HGD during 1-7 years surveillance[12]

Study	N	Developing cancer (%)	Follow-up interval (yr)
Reid	76	59%	5
Buttar	100	14% (focal high-grade dysplasia)	3
		56% (diffuse high-grade dysplasia)	3
Schnell	79	5%	1
		16%	7

The estimated incidence of adenocarcinoma in patients with BE is ranging from 0.2 to 2.0%[14, 15, 21, 86]The risk of malignant degeneration may be greater the longer the segment of BE[87] but even patients with short-segment BE are also at risk[88]. In this study, 3 of 5 patients with short-segment BE had IMC and two LGD.

Apart from the higher risk of having malignant changes, long-segment BE has been found to harbour multiple lesions. Heitmiller et al[45]reported that in 13 of 30 patients (= 43%) who underwent esophagectomy for HGD adenocarcinomas were found. The tumor stages in detail were: T1N0M0 in 8, T2N0M0 in 2, T3N0M0 in 2 cases

and T3N1M0 in 1 case. Intramucosal carcinoma was not separately mentioned.

Edwards et al[44] retrospectively studied resected specimens with BE and HGD. They found in 8 of 11 specimens infiltrating carcinomas with the following distribution: T1N0M0 in 4, T2N0M0 in 2, T2N2M0 and T3N1M0 in one case each. Collected data from the surgical literature revealed a cancer missing rate of 41% (***Table 11***).

Table 11: Frequency of missed carcinomas in BE with HGD. The data were collected from resected specimens[44]

Reference		No. of patients	No. with carcinoma in resected specimen
Lee	1985	2	1
Hamilton and Smith	1987	4	2
Reid et al	1988	3	0
Hameeteman et al	1989	2	2
Altorki et al	1991	8	3
Pera et al	1992	18	9
McArdle et al	1992	3	2
Rice et al	1993	16	6
Levine et al	1993	7	0
Cameron et al	1993	13	1
Peters et al	1994	9	5
Current series	1995	11	8
Total	1985-1995	96	39 (41%)

The present study revealed in 5 of a total of 14 patients (35.7%) underwent circumferential complete EMR multifocal malignant lesions. All 5 patients had long-segment BE (5-10 cm). This means 56% (5/9) of the patients presented with long-segment BE had multifocal lesions. In one of these patients with a 9 cm long Barrett's segment who underwent

four sessions of MBL-EMR, HGD and/or IMC were found in 24 of a total of 49 EMR specimens. This patient was finally referred to surgery as EMR could not be accomplished due to technical difficulties caused by mural thickening.

Another problem encountered in long-segment BE is that HGD and early carcinoma in BE often occur in the absence of endoscopic abnormalities. In a relatively high percentage of patients with BE, these early malignant changes were detected incidentally. In 28 patients with HGD without gross or microscopic evidence of carcinoma who underwent esophagectomy, unsuspected cancer was found in 10 of 28 (36%) of esophagectomy specimens. In 13 of these patients preoperative endoscopy revealed only BE. Four-quadrant jumbo biopsies at 2-cm intervals missed cancer in 33% of the patients [46]. In this study, pre-EMR diagnosis only detected a single malignant lesion in the 4 patients in whom multifocal malignant lesions were found in the specimens after circumferential complete EMR.

Local recurrence has been a major drawback of localized EMR. Long-segment BE is especially prone to have a high recurrence rate after localized EMR, although histological examination has shown complete removal of the malignant lesion in the EMR specimen. The recurrence rate rises with the length of the follow-up[37, 75]. In the largest single center series of EMR for HGD and early adenocarcinoma in BE, recurrence rate has been as high as 33% during a mean follow-up of 34±10 months. The high recurrence rate may be explained by the existence of multifocal malignant and premalignant lesions in BE which

have been overlooked in the initial diagnosis prior to EMR or by metachronous development of new dysplastic tissue.

For these reasons, several authors have recommended ablative treatments, such as APC or PDT. APC as the most commonly practiced method for BE with or without LGD has been shown to be ineffective in ablating BE. Greater length of BE is the major factor associated with a high relapse rate. Buried glands were observed in up to 69% of the cases[50].

PDT using photofrin as the most aggressive ablative treatment has been used for treating BE with HGD and T1 cancer. On the intention-to-treat basis, complete ablation was achieved in 53.8% of cases with HGD and in only 33.3% of cases with cancer. Persistent BE was observed in 11.1% and 22.3%, respectively.

The major drawback of PDT and other thermal ablative treatments is the lack of histologic confirmation.

Our group was the first to show that the problems of incomplete treatment associated with multifocal lesions and high relapse rate might be minimized by performing circumferential complete EMR. In our first 12 patients treated by the single snare resection technique, no residual tumor tissue or metachronous recurrence during a follow-up of 9 months was observed[78].

The present study is a continuation of this treatment concept, but focusing on technical improvement.

The band and snare technique seems to be safe and more effective than the cap technique[89] compared the two techniques for early esophageal

cancer in 72 patients. Hundred EMR were performed to resect mucosal SCC and adenocarcinoma of the distal esophagus, 50 with each technique in a randomized trial. The cap technique was carried out with submucosal saline injection, and the band technique using the euroligator (mandel + rupp medizintechnik gmbh, Erkrath, Germany). No significant differences were found in size of the resected specimens and size of ulcer measured 24 hours after EMR. Only one minor bleeding occurred in each group. No perforation or other complications were observed. Interestingly, the cap technique with submucosal saline injection was associated with a higher technical failure rate as compared to the band technique without submucosal injection (12% vs. 2%, $p < 0.01$).

Our long-term experience had proved that simple snare EMR technique in the esophagus does not require prior submucosal injection. Neither technical advantage nor prevention of perforation can be achieved by submucosal injection. In this preliminary experience with the modified MBL device, no involvement of the proper muscle layer was observed histologically in the resected specimens. No perforation was also documented.

The safety-profile of the circumferential EMR using the MBL device in the present study is however tainted by an absolutely high rate of strictures during the early postoperative week associated with clinical symptoms of dysphagia. This problem has not been described after local EMR[89] or seems to be of minor importance and infrequent (less than 3%) when local EMR is combined with PDT[37].

Stricture formation seems to be also a major problem in PDT when used as a monotherapy. Overholt et al[77] reported a stricture rate of 30%, and Falk et al[12] 36% after PDT with porfimer-sodium.

The only data about esophageal stricture formation following radical circumferential EMR was from our group[78] with a stricture rate of 16.7% (2 in 12 cases).
In this present study, stricture occurred in 10 of 14 patients (71%), in whom circumferential EMR was performed regardless the length of BE and the total number of EMR sessions required for complete removal of BE. Symptoms of dysphagia began 5-10 (median: 7) days after the initial circumferential EMR. Bougienage was performed to dilate the stricture using Savary-Gilliard dilators. Since the esophageal wall within the first two weeks after EMR is still fragile, bougienage has to be performed with extreme caution. In one patient with a 5 cm long BE who underwent a circumferential EMR using a total of 18 rubber bands in one session, deep tear of esophageal wall occurred during the fourth bougienage although dilation was done incrementally and only up to 38 French.

Due to the very high stricture rate, EMR at the present time should not be performed circumferentially in a single session. Complete endoscopic removal of long-segment BE can be achieved by doing sequential EMR accomplished in several sessions at 3-4 weeks interval. Systematic longitudinal piece-meal resections of about 75% of the circumference up to a maximal length of 4 cm of BE per session seems to be the most appropriate approach to accomplish complete EMR. For this extent of

EMR, a six-shooter MBL is sufficient. Further experiences are warranted to confirm this hypothesis.

Prevention of stricture formation must be the most important aim of any EMR technique attempting for complete removal of BE. Following proposals have been discussed: 1) Combination of different techniques (multimodal therapy) as it has been practiced by[37] with local EMR plus PDT or APC. 2) Use of stricture-preventing medication following EMR. Radu[90]reported on significant reduction of stricture and perforation rates by administrating Mitomycin C in an animal study.

Finally, procedure-related morbidity, long-term survival rate and quality of life of patients after complete EMR need to be compared with those of limited distal esophageal resection or radical esophagectomy. The risk of regional lymph node metastasis in BE with HGD or IMC is negligible[91] However, continuous PPI administration and regular endoscopic surveillance are mandatory for patients treated with EMR to prevent recurrent GERD, and to detect newly formed BE and eventually early malignant changes as well. Long-term follow-up of larger number of patients treated with complete EMR are therefore needed for a final and firm conclusion.

The different technologies to treat HGD and intramucosal carcinoma in BE have their specific advantages, drawbacks and risk profiles as shown in ***Figure 13***. Some of the drawbacks and risks are inherent to the treatment procedures and cannot be significantly reduced by changing e.g. the performance or protocol. Others are reducible to a certain extent like the post-procedural stricture. In this context the technique of MBL-

CEMR described in this present study seems to have some potential for the future.

Figure 13: Comparison of different treatment modalities for HGD and IMC in BE.

Treatment modality	Drawback/Risk	Frequency	Significance
Conservative/Surveillance	Uncertainty of diagnosis	+ +	++
	Progression to carcinoma	+	+ +
Surgery	Mortality	+	+ + +
	Post-op morbidity	+ +	+ +
	Unnecessary resection	(+)	+ +
PDT	Incomplete eradication	+ +	+ +
	Stricture	+ +	+ +
	Lack of histology	+ ++	+++
Electrocoagulation/	Incomplete eradication	+ +	+ +
Argon plasma coagulation/	Lack of histology	+ ++	+ + +
Laser- coagulation	stricture	(+)	+ +
Localized EMR	Incomplete eradication	+ +	+ +
	Recurrence/Residual lesion	+ +	+ +
	Stricture	+	+ +
CEMR	Incomplete eradication	(+)	++
	Recurrence/Residual lesion	(+)	++
	Stricture	+ +	++

7. Summary

Various techniques are available for endoscopic mucosal resection (EMR) in the upper and lower gastrointestinal tract. For early cancers of the esophagus, “suck and cut” technique using a transparent cap or variceal band ligator is the most commonly practiced method. To facilitate multiple or circumferential EMR, a modified multiband variceal ligator (MBL) is introduced which allows sequential banding and snare resection without the need to withdraw the endoscope. To enable band delivery with a snare inserted in the therapeutic endoscope, the threading channel of the cranking device is enlarged from 2 mm to 3.2 mm. The six shooter MBL was used.

The aim of this study is to evaluate the feasibility and short-term results of CEMR using this new device.

14 consecutive patients with BE containing HGD and/or IMC referred during the first 10 months of 2004 to the Department of Interdisciplinary Endoscopy, University Hospital Hamburg-Eppendorf were treated with this new technique. There were 12 men and 2 women with a median age of 64 years (range 43-82yrs). 9 patients had long-segment BE (≥ 3 cm) and 5 short-Segment BE (< 3 cm). In the initial biopsy prior to EMR, IMC was found in 11 and HGD in 3 cases, respectively. No multifocal lesions were diagnosed. In 5 of 14 patients, complete circumferential EMR was accomplished in one session using 3-18 bands (median: 6). Six patients required a total of 2 sessions, one patient 4 sessions, and one patient 5 sessions until the entire BE was removed. One patient having multifocal HGD and/or IMC in 24 of a total of 49 specimens was finally

recommended to surgery because of technical difficulties caused by mural thickening after 4 sessions. The median number of EMR sessions was 2 (range 1-5). The procedure time of each EMR session ranged from 30 to 60 minutes (median 30 minutes).

The mean size of EMR specimens measured prior to formalin fixation was 14.2 ± 4.1 mm (range 7-22 mm).

Histology of the EMR specimens confirmed IMC in 8 and HGD in 4 cases, LGD in 1. In one patient, no dysplasia in BE could be detected. In 5 patients with long-segment BE, multifocal lesions were found (56% of patients with long-segment BE).

Minor bleeding occurred in 4 patients which were controlled in all at the end of the EMR procedure. In one patient with liver cirrhosis who first underwent TIPS, additional bleeding from a submucosal collateral vein was controlled by immediate obliteration using a total of 2 cc of cyanoacrylate/Lipiodol mixture. Hemorrhages occurred equally in 2 patients with short-segment and 2 with long-segment BE.

Esophageal strictures occurred in 10 patients (71%), all following the first circumferential EMR after a median of 7 days (range: 5-10). A median of 5 (range: 1-11) sessions of weekly bougienage were performed for relief of dysphagia. Stricture developed in 7 patients with long-segment BE and 3 with short-segment BE. This difference was statistically not significant.

In one patient, deep tear of the esophageal wall occurred during the fourth session of bougienage. A limited distal resection of the esophagus was performed. Histological examination of the resected specimen showed no remnant of BE. The postoperative course was uneventful.

The novel technique of MBL-EMR described here is a safe and effective method which facilitates and simplifies circumferential removal of BE containing HGD and/or IMC. However, the method is associated with a very high stricture rate if circumferential EMR is performed in one single session. Complete removal of BE should therefore be achieved by repeated partial EMR. Long-term follow-up is needed to observe for late recurrence and determining the clinical impact of this method in comparison to surgery, especially to the limited distal esophageal resection.

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2001 Third class of national award for the scientific research, Xiamen,China

RESEARCH INTEREST AND CLINICAL SKILLS

I attended the Fujian Medical University in 1985, following five years studying, I received my Bachelor degree in 1990 and then started my career as a physician in Xiamen Zhongshan Hospital. Firstly, I finished three years internship and then received five years specialist training as a gastroenterologist. During this period, I learned almost all the diagnostic techniques and medical therapy as a physician. As a gastroenterologist, I

received the training of endoscopic diagnosis and therapy. I am experienced in general endoscopic diagnosis and therapy. In 2003, I became deputy director of the Dept. of gastroenterology at the Zhongshan Hospital. As a Gastroenterologist, my research interest is to investigate new ideas and to master new skills and techniques and to explore the novel approaches for diagnosis and treatment.

EMPLOYMENT HISTORY

01.2003-present, Deputy director of the Dept. of gastroenterology Xiamen Zhongshan Hospital, Xiamen University.
01, 1997-12, 2002 Consultant, Xiamen Zhongshan Hospital, Xiamen University.
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PUBLICATIONS

1. Zhong Y. 2003. Relationship Between Periampullary Diverticula And Biliary Calculi. Fujian Medical Journal.
2. Zhong Y. 2002. The application of EUS in diagnosis and treatment of upper gastroenterology. Fujian Medical Journal. 24 (6); 171-174
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Appreciation

I would like to thank Prof. Dr. Nib Soehendra for giving me the opportunity of writing this thesis in his Department and for his supports.

Prof. Dr. Manfred Rehner deserves my heartiest thanks for his valuable advices and great help in accomplishing my thesis.

Priv.-Doz. Dr. Stefan Seewald, Dr. Salem Omar, Dr. Stefan Groth and Dr. Uwe Seitz also deserve my sincere thanks for their supports.

Declaration of Authenticity

Ich versichere ausdruecklich, dass ich die Arbeit selbstaendig und ohne fremde Hilfe verfasst, andere als die von mir angegebenen Quellen und Hilfsmittel nicht benutzt und die aus den benutzten Werken woertlich oder inhaltlich entnommenen Stellen einzeln nach Ausgabe (Auflage und Jahr des Erscheinens), Band und Seite des benutzten Werkes kenntlich gemacht habe. Ferner versichere ich, dass ich die Dissertation bisher nicht einem Fachvertreter an einer anderen Hochschule zur Ueberpruefung vorgelegt oder mich anderweitig um Zulassung zur Promotion beworben habe.

Yan Zhong