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Risk factors for serious adverse events associated with multiband mucosectomy in Barrett's esophagus: an international multicenter analysis of 3827 endoscopic resection procedures

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ABSTRACT

Background and Aims: Multiband mucosectomy (MBM) is a widely used technique for the treatment of Barrett's esophagus (BE). However, large multicenter studies enabling a generalizable estimation of the risk of serious adverse events, such as perforation and postprocedural bleeding, are lacking. The aim of this study was to estimate the rate of, and risk factors for, serious adverse events associated with MBM.

Methods: In this retrospective analysis consecutive patients who underwent MBM for treatment of BE in 14 tertiary referral centers in Europe, the United States, Canada, and Australia were included. Primary outcomes were perforation and postprocedural bleeding rate. Potential risk factors were identified by logistic regression.

Results: Between 2001 and 2016, a total of 3,827 MBM procedures were performed in 2,447 patients (84% male, mean age 66 years, median BE length C2M4). Perforation occurred in 17 procedures (0.4%; 95% CI, 0.3–0.7), of which 15 could be treated endoscopically or conservatively. Female gender was an independent risk factor for perforation (OR, 2.77; 95% CI, 1.02–7.57; $p=0.05$). Postprocedural bleeding occurred after 35 procedures (0.9%; 95% CI, 0.6–1.3). The number of resections (OR, 1.15; 95% CI, 1.06–1.25; $p<0.001$) was significantly associated with postprocedural bleeding.

Conclusion: The results of this study show that MBM for BE is safe with a low risk of serious adverse events. In addition, the vast majority of adverse events could be managed endoscopically or conservatively. The number of resections was an independent risk factor for postprocedural bleeding.

Keywords: endoscopic resection; multiband mucosectomy; Barrett's esophagus; perforation; bleeding

INTRODUCTION

Endoscopic resection (ER) is considered the cornerstone of endoscopic treatment and accurate staging for early neoplasia arising in Barrett's esophagus (BE). Multiband mucosectomy (MBM) is the preferred ER technique for piecemeal resection in BE. In MBM, a modified variceal band ligator is used. The mucosa is suctioned into a cap without the need for prior submucosal lifting. By the release of a rubber band, a pseudopolyp is created that can subsequently be resected with a snare

that can be used for en-bloc resection of small lesions or multiple piecemeal resections for larger lesions. Initially only the Duette device (Cook, Bloomington, Ind, USA) was available for MBM in BE. Recently, a new MBM device became commercially available. However, most clinical experience in ER using the MBM technique has been with the Duette device.

A limited number of studies have evaluated the safety of the Duette device [1-6]. Serious adverse events, such as an esophageal perforation or postprocedural bleeding, are uncommon in current literature. Only one esophageal perforation has been reported [1], accounting for a perforation rate of 0% to 2.4% [1-6]. Postprocedural bleeding is reported in 0% to 2% of the procedures [2-7].

However, a major limitation of these studies is their limited sample size, which ranges from 10 to 170 patients. Large studies enabling an accurate estimation of the serious adverse event risk of MBM are lacking and there have been no studies focusing on the risk factors for serious adverse events related to MBM for BE. Therefore, the aim of this study was to evaluate the rate of serious adverse events associated with MBM, using the Duette device, in a large cohort of BE patients treated in a multi-national group of institutions. In addition, we aimed to find potential clinical and endoscopic risk factors for these serious adverse events.

PATIENTS & METHODS

Study design and patient selection

This study was a retrospective analysis of data collected from 14 tertiary referral centers for the treatment of upper gastrointestinal neoplasia in 7 countries (Australia, Belgium, Canada, the Netherlands, Switzerland, United Kingdom, United States). Consecutive patients who underwent MBM using the Duette device for ER in BE from November 2001 to December 2016 were included in the analysis.

In the Netherlands, the study was exempted from official institutional review board (IRB) approval by the IRB of the Amsterdam University Medical Centers, location Academic Medical Center. IRB approval was not required in the United Kingdom and Switzerland because this project was a retrospective analysis of routine clinical care. In all other participating centers, IRB approval was obtained.

Endoscopic resection procedure

All endoscopic resection procedures were performed using the Duette system (Cook Medical, Bloomington, Ind, USA) (figure 1). Procedures were performed according to the standard operating

procedure at each center. Depending on the local policy of the hospital, the intended treatment zone was delineated by placement of coagulation markers. The mucosa was sucked into the cap followed by the release of a rubber band. The created pseudopolyp was subsequently resected with the snare using electrocautery. Although prior submucosal injection is not mandatory when using MBM, submucosal lifting could be used based on the discretion of the endoscopist or local policy.

Histological evaluation

Per local standard operating procedure, ER specimens were directly fixed in formalin, pinned down or placed in a tissue-cassette. The macroscopic measurement of the diameter of the specimen was documented. ER specimens were evaluated by an experienced pathologist.

Outcomes

Primary outcomes

1. Perforation rate and associated risk factors.
2. Postprocedural bleeding rate and associated risk factors.

Secondary outcomes

1. Stenosis rate and associated risk factors.
2. Size of the ER specimens.

Definitions of the outcome parameters can be found in Supplementary Table 1.

Data collection

Data were collected in a dedicated database. The majority of centers had prospectively collected data on MBM procedures as part of standard clinical practice or as part of a national registry. Other centers retrospectively retrieved data from medical charts, endoscopy reports, and pathology reports.

Statistical analysis

Primary analysis.

Perforation and postprocedural bleeding rate and associated risk factors were evaluated in a per-procedure analysis. A logistic regression model was used to identify endoscopic and clinical variables

associated with the occurrence of a perforation or postprocedural bleeding. These variables were selected based on a combination of a priori clinical judgment and an empirical investigation of missing data frequency. For each variable, univariable association with perforation or postprocedural bleeding was calculated and presented as an odds ratio (OR) with 95% CI. Multivariable logistic regression was used to assess adjusted associations between the variables and perforation or postprocedural bleeding. All variables with a p-value ≤ 0.2 in the univariable analysis were included in the multivariable analysis. A P value < 0.05 was considered statistically significant.

Missing data were assumed to be missing at random. Multiple imputation with 5 iteration, using multivariate imputation by chained equations (MICE package) in R was performed to handle missing data in variables with $< 15\%$ missing [8/10]. Prespecified potential risk factors, outcome variables, and variables that would potentially help predict missing values were used for imputation. Variables with $> 15\%$ missing values were not imputed, and the observed data was reported for these variables. Supplementary Table 2 shows the variables included in the imputation procedure and percentage of missing data per variable.

Secondary analysis.

Stenosis rate, calculated as proportion with 95% CI, was assessed on a patient-based analysis. Risk factors for stenosis were assessed using multivariable regression analysis.

For descriptive statistics, mean (standard deviation [SD]) was used in case of normal distribution of variables, and median (interquartile range [IQR]) for variables with skewed distribution. Categorical variables were presented as frequencies with percentages.

Data analysis was performed using SPSS statistical software package (version 24; SPSS Inc, Chicago, Ill, USA).

RESULTS

Patients and endoscopic procedures

A total of 2,447 patients treated with MBM between November 7, 2001 and December 31, 2016 were included. Baseline characteristics are presented in table 1. The mean age of patients was 66 years (± 11), 2,044 (84%) were male. Median BE length was C 2 (IQR 0–5) M 4 (IQR 2 – 7). In these 2,447 patients, 3,827 MBM procedures were performed for the following indications: focal lesion suspicious for dysplasia (n=2,510), diffuse high-grade dysplasia (n=239), as part of a radical ER

protocol (n=967), escape treatment after endoscopic ablation (n=111).

In 3,035 procedures, an endoscopically visible abnormality was recorded: the lesion was protruded in 435, flat in 2,590, and depressed in 1 case. Lesions had a median estimated diameter of 15 mm (IQR 10 – 30) and comprised median 30% (IQR 20 – 50) of the circumference. A median of 3 (IQR 2-5) resections were performed per procedure, with a total of 14,590 resections in this study. Worst pathology was cancer in 1,608, HGD in 1,171, LGD in 619, and no-dysplasia in 429 procedures.

Primary outcomes

Perforation – Perforation occurred in 17 out of 3,827 procedures accounting for a perforation rate of 0.4% (95% CI, 0.3 – 0.7) (Table 2). Six patients had a history of prior esophageal treatment: 1 patient underwent esophageal surgery for placement of an Angelchik antireflux prosthesis, 4 patients had prior ER, and 1 patient underwent photodynamic therapy once and ER twice.

All perforations were diagnosed based on a transmural defect seen during the MBM procedure. The vast majority of patients (14/17) could be treated endoscopically with clips (n=11) or a combination of clips and a stent (n=3) (figure 1 and 2). In one patient, clipping was not successful due to poor tissue grasping. This patient was therefore treated conservatively with antibiotics. The endoscopically and conservatively treated patients were admitted for a median of 4 days (IQR 1 – 5), and all cases were considered to be mild (n=7) or moderate (n=8) adverse events.

Two patients were referred for surgery; both were graded as severe adverse events. In the first patient, ER was performed because of a local recurrence after a large ER. During the procedure, a perforation occurred within the previous ER site. Because there was clear evidence of residual neoplasia, the decision was made to perform an emergency esophagectomy as local control of the disease was not achieved. In the second patient, a perforation was observed immediately after the first resection. Because of the combination of residual neoplasia and periesophageal scarring after prior surgery for placement of an Angelchik prosthesis, endoscopic treatment was not considered and the patient underwent an esophagectomy.

There was no procedure-related mortality, and all patients fully recovered.

Risk factors for perforation are presented in Table 3. In the univariable analysis, female gender (OR, 3.19; 95% CI, 1.17 – 8.65; p=0.02) and age (OR, 1.05; 95% CI, 1.00 – 1.10; p=0.04) were significantly associated with the occurrence of a perforation. In the multivariable analysis, only female gender remained statistically significant (OR, 2.77; 95% CI, 1.02 – 7.57; p=0.05).

Postprocedural bleeding Postprocedural bleeding was diagnosed in 35 out of 3,827 MBM procedures (0.9%; 95% CI, 0.6 – 1.3). Of these 35 patients, 46% (16/35) used anticoagulant medication (platelet aggregation inhibitors n=11, vitamin K antagonist n=2, heparin n= 2, factor Xa inhibitors n=1).

In 16 patients, bleeding occurred within 48 hours after ER, in 17 patients $\geq$ 48 hours. Patients were hospitalized for a median of 2 days (IQR 1 – 3). Repeat endoscopy was performed in 26 out of 35 patients, and bleeding was successfully treated using clips (n=9), coagulation therapy (n=9), or adrenalin injection (n=2). In 6 patients, no active bleeding was observed during re-endoscopy. Eleven patients received a median of 1 blood unit (IQR 1 – 3). Seven patients were hospitalized solely for observation, without the need for intervention or transfusion. All patients fully recovered.

Table 4 shows risk factors for postprocedural bleeding. In the univariable analysis the number of resections during the procedure (OR, 1.15; 95% CI, 1.07 – 1.25; $p < 0.001$) and use of anticoagulant medication (OR, 1.94; 95% CI, 1.00 – 3.79; $p = 0.05$) were associated with postprocedural bleeding. Multivariable regression analysis showed that number of resections (OR, 1.15; 95% CI, 1.06 – 1.25; $p < 0.001$) was the only significant independent risk factor for postprocedural bleeding.

Secondary outcomes

Stenosis Stenosis requiring endoscopic treatment was observed in 231 out of 2447 patients accounting for a stenosis rate of 9.4 % (95% CI, 8.3 – 10.7). The number of resections per procedure was significantly higher in the stenosis group (median 5, IQR 3 – 8) compared with the nonstenosis group (median 3, IQR 2 – 5), $p < 0.001$.

In the multivariable regression analysis a significant association was found between stenosis and number of resections per procedure (OR, 1.19; 95% CI, 1.14 – 1.24; $p < 0.001$), when ER was performed as part of a radical ER protocol (OR, 2.26; 95% CI, 1.60 – 3.19; $P < 0.001$) and when there was stenosis present at baseline (OR, 2.02; 1.18 – 3.45; $P = 0.01$) (Supplementary Table 3).

In 219 out of 231 patients, median 2 (IQR 1 – 4) dilations were required. The remaining patients underwent incision therapy (n=2) or stent placement (n=10).

Size of ER specimens. Mean maximum and minimum diameter of ER specimens was 14 mm (± 5) and 10 mm (± 5), respectively.

DISCUSSION

MBM is the most commonly used technique for ER in Barrett's esophagus, with the vast majority of these procedures performed using the Duette device. A reliable estimation of potentially serious adverse events of MBM such as perforation or postprocedural bleeding is lacking because the incidence of these adverse events is low and only small studies describing safety of MBM are available [2-7]. Robust safety data of MBM in Barrett's esophagus are, however, of great importance because the Duette device is part of the toolbox of most interventional endoscopists. Our international multicenter cohort study is the largest study to date providing an accurate assessment of the perforation and postprocedural bleeding risk after MBM and associated risk factors. The results of this study show that MBM is safe with a low risk of serious adverse events, with perforation occurring in 0.4% and postprocedural bleeding after 0.9% of procedures. There was no mortality related to MBM.

Esophageal perforation is the most-feared adverse event of ER because it may require surgical intervention and may result in serious morbidity and mortality. However, the vast majority of perforations (15/17) in our study was graded as a mild or moderate adverse event and could be treated endoscopically or conservatively. All 17 patients with a perforation fully recovered without related mortality.

It has been shown that early diagnosis and treatment of an esophageal perforation are essential for a favorable outcome [11–13]. Perforations caused by ER are generally recognized immediately during endoscopy, before mediastinal contamination has occurred, and the defect can be treated immediately as was the case for all perforation cases in our study. The fact that all procedures were performed by experienced interventional endoscopists, may have also played a role in the favorable outcome of these patients.

In 2015 a new MBM device (the Captivator EMR device, Boston Scientific, Marlborough, Mass, USA) became available for ER. The recently published results of the first large prospective cohort study evaluating efficacy and safety of the Captivator device showed that a perforation occurred in 0.9% (95% CI, 0.65 – 3.48) and postprocedural bleeding in 1.5% (95% CI, 0.31 – 2.62) of the resections [14]. All patients with a perforation could be treated endoscopically and recovered quickly. Data from the study by Pouw et al and data from our study suggest that perforations occurring during MBM are generally amenable for endoscopic closure and may not always be the severe adverse event that most endoscopists fear.

Overall, we can conclude that MBM (regardless of the device) is associated with a low perforation rate of <1.0%. When comparing the results of Duette MBM with Captivator MBM, it is however

striking that although the absolute difference is not that large; Duette MBM is associated with half the perforation rate compared with Captivator MBM. This difference may be explained by several factors. The sample size of the current study is more than 10 times larger than the Captivator study, which may lead to a more accurate estimation of the true perforation risk. On the other hand, the study on Captivator MBM was a prospective study and given the retrospective design of the current study, selection bias cannot be ruled out which may have led to an underestimation of the perforation risk of the Duette device. Furthermore, inclusion criteria for both studies differed when looking at indication for ER, hampering head-to-head comparison of both techniques. It may also be possible that the difference in perforation rates found in these 2 studies reflects a true difference in perforation risk, and this can best be answered by the results of a properly conducted randomized controlled trial powered on safety outcomes. However, given the very low event rate and the good clinical outcome in patients with a perforation, one may question whether such a trial requiring a large sample size, would be relevant.

In a recent retrospective study, ER with the Duette device was compared to the Captivator device in 39 BE patients [15]. There was no difference in safety outcomes. However, the authors did find a difference in the size of the ER specimens obtained with both devices: the Captivator specimens were significantly larger. One may hypothesize that larger resections may also lead to deeper resections which carries a higher risk of perforation. However, other studies did not find a difference in size of ER specimens obtained with the Duette and Captivator device [15,16]. A recent randomized study comparing the size of paired Duette and Captivator specimens in pre-esophagectomy patients showed that there was no significant difference in size [16]. In addition, when comparing the results of the current study to the results of the prospective study on the Captivator device [15], the mean maximum size of the specimens is comparable (14 versus 15 mm, respectively).

For postprocedural bleeding, we identified a strong association with the extent of the resection. For every extra resection during the procedure, the odds of a postprocedural bleeding increased with 1.07. The use of anticoagulant medication did not appear to be an independent risk factor for postprocedural bleeding in the multivariable analysis. However, it must be noted that we did not have reliable information on whether the anticoagulant medication was stopped before or continued during the MBM procedure. We believe that this information is of great importance in evaluating the relation between anticoagulant medication and the risk of bleeding. We did collect this information; however, because of substantial missing data for this variable we were not able to include this information in the analysis.

The only significant independent risk factor for perforation found in our study was female gender. To

our knowledge, no prior studies have evaluated risk factors for an esophageal perforation after ER for the treatment of BE. However, several studies have been published that focused on risk factors for perforation after ER or endoscopic submucosal dissection (ESD) elsewhere in the gastro-intestinal tract [17-26]. In none of these studies an increased risk of perforation among females was observed. Given the combination of the lack of theoretical basis for the increased risk of an esophageal perforation among females and the barely significant association with a wide confidence interval that was found, one may question the clinical relevance of this finding.

Two remarks must be made regarding the risk factors for perforation. First, despite the large multicenter study cohort, the event rate for perforations was very low. Therefore, this study may be underpowered to find statistically significant risk factors for perforation. Second, after studying all perforation cases, in more than a third of the patients we observed factors that may have played a role in the development of a perforation (see remarks column in Table 2). For example, 2 patients had an underlying disease (achalasia and scleroderma) that may have influenced the esophageal tissue making it more susceptible for injury. In 4 patients, the presence of fibrosis may have played a role: in the first patient a perforation occurred at the site of an old perforation after prior ER-cap treatment; in the second patient, the perforation occurred during resection of recurrent neoplasia at the prior ER site; in the third patient, prior surgical placement of an Angelchik prosthesis may have led to fibrosis; and in the last patient, a fibrotic lesion likely due to prior scarring was observed. We believe that the presence of fibrosis may have played a role in some of the perforation cases. This is supported by multiple studies that have identified the presence of fibrosis as an independent risk factor for perforation after ESD for gastric or colorectal lesions [17,19,21,25]. Therefore, we advise to be careful in performing recurrent-ER when the intended ER zone is fibrotic as a result of prior endoscopic treatment or due to an underlying inflammatory disease.

Based on existing literature, we know that the risk of stenosis is influenced by the extensiveness of the resection [25, 26]. Prior studies have shown that patients treated with ER as part of a radical endoscopic resection protocol have a high risk of stenosis formation [29, 30]. The results from our study are in line with these findings. The number of resections per procedure appeared to be significantly associated with the occurrence of stenosis. In addition, we identified ER as part of a radical endoscopic resection protocol as an independent risk factor for stenosis.

The third independent risk factor we found was the presence of a stenosis at baseline. We believe that the abovementioned risk factors for stenosis formation are not specific to MBM treatment but apply to all ER techniques.

The current study represents the largest cohort of BE patients treated with MBM to date, enabling a robust estimate for risk of serious adverse events and potential risk factors. This study has a

multicenter cohort design and included patients from Europe, Northern America, and Australia. The ER procedures were not performed according to a strict study protocol but according to local clinical guidelines. In addition, we included patients treated with MBM for BE regardless of the indication. We therefore believe that the results are a representation of current clinical practice in tertiary referral centers.

However, there are several limitations that must be acknowledged. First, the study has a retrospective design. There was no uniform search strategy to identify all patients from each center. Although in more than half of the patients the data were prospectively collected, this study still carries a risk of selection bias and information bias. In addition, some variables were not classified in a uniform manner. For example, not all lesions were classified according to the Paris classification system. Including lesion type in the regression analysis may have influenced the reliability of the results, and therefore we decided to leave this variable out of the risk analysis. Although we encountered the challenge of missing data, we were able to include all cases in the multivariable model by using multiple imputation. We examined the imputed data and compared the distribution of the observed data to the imputed data and found no relevant differences.

In conclusion, the results of this large international multicenter cohort study show that MBM for the treatment of BE is safe with a low perforation and postprocedural bleeding rate and no procedure related mortality. In addition, the vast majority of adverse events can be managed endoscopically or conservatively.

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TABLES

Table 1. Baseline characteristics

Patients, (n)	2,447
Male, n (%)	2,044 (84)
Mean age, years (SD)	66 (11)
Median BE length at first Duette procedure, cm (IQR)*	C 2 (0-5) M 4 (2-7)
Procedures, (n)	3,827
Indication for ER, n (%)	
Focal lesion suspicious for dysplasia	2,510 (66)
As part of a radical endoscopic resection protocol	967 (25)
Diffuse high-grade dysplasia	239 (6)
Escape treatment after prior ablation	111 (3)
Prior surgical treatment esophagus, n (%)	115 (3)
- Fundoplication	87
- Esophagectomy	28
Prior endoscopic treatment esophagus, n (%)	1,845 (48)
- Endoscopic resection	1,654
- Radiofrequency ablation	167
- Argon plasma coagulation	6
- Photodynamic therapy	18
Use of anticoagulant medication at time of Duette procedure, n (%)	1,163 (30)

- Platelet aggregation inhibitors	976
- Vitamin K antagonist	148
- Heparin	12
- Factor Xa inhibitor	27
Stenosis before ER, n (%)	304 (8)
Main macroscopic appearance lesion, n (%)	
Protruded lesion	435 (11)
Flat lesion	2,599 (68)
Excavated lesion	1 (0.03)
No visible lesion	792 (21)
Median estimated diameter lesion, mm (IQR)*	15 (10-30)
Median estimated circumferential extent lesion, % (IQR)*	30 (20-50)
Total number of resections	14,590
Median number of resections per procedure, n (IQR)	3 (2-5)
Mean maximum diameter of ER specimen, mm (SD)	14 (5)
Mean minimum diameter of ER specimen, mm (SD)	10 (5)
Worst histopathological diagnosis ER specimen, n (%)	
No dysplasia	429 (11)
Low-grade dysplasia	619 (16)
High-grade dysplasia	1171 (31)
Cancer	1608 (42)

Table 2. Overview of perforation cases.

No.	Gender	Age	Prior surgical Tx	Prior endoscopic Tx	Indication for ER	No. of resections	Remarks regarding patient/procedure	Treatment	No. of days admission	Severity
1	Female	28	No	No	Lesion suspicious for dysplasia	6	PEG tube placement and severe mental retardation in the past history. Fibrotic lesion, difficulty sucking lesion into cap.	Clips	1	Mild
2	Female	84	No	No	Lesion suspicious for dysplasia	5	Esophagus dilated and looks twisted	Clips	4	Moderate
3	Male	66	No	Yes, ER	Lesion suspicious for dysplasia	10		Clips + stent	4	Moderate
4	Female	73	No	No	Lesion suspicious for dysplasia	2		Clips	3	Mild
5	Male	73	No	Yes, ER	As part of a radical ER protocol	1		Clips	2	Mild
6	Female	66	No	No	Lesion suspicious for dysplasia	2		Clips	0	Mild
7	Female	73	No	No	Lesion suspicious for dysplasia	4		Clips	1	Mild
8	Male	82	No	No	Lesion suspicious for dysplasia	4		Clips	4	Moderate
9	Male	77	No	Yes, ER	As part of a radical ER protocol	3		Clips + stent	1	Mild
10	Male	86	No	Yes, 2x ER and PDT	Lesion suspicious for dysplasia	6	Perforation at the place of prior perforation after ER-cap resection	Clips + stent	5	Moderate
11	Male	65	Yes, vagotomy and placement of an Angelchick prosthesis	No	Lesion suspicious for dysplasia	1	Angelchik procedure in the past medical history	Esophagectomy	21	Severe
12	Male	74	No	No	Lesion suspicious for dysplasia	11		Clips	5	Moderate
13	Female	65	No	No	Lesion suspicious for dysplasia	2		Clips	1	Mild
14	Male	81	No	Yes, ER	Lesion suspicious for dysplasia	6	Resection of recurrent lesion at prior ER site	Esophagectomy	20	Severe
15	Male	67	No	No	Lesion suspicious for dysplasia	3		Clipping not fully successful due to poor tissue grasping+ admitted to surgical ward	7	Moderate
16	Male	82*	No	No	Lesion suspicious for dysplasia	1	Achalasia	Clips	6	Moderate
17	Male	72*	No	No	Lesion suspicious for dysplasia	3	Scleroderma	Clips	5	Moderate

*Based on imputation

Table 3. Clinical and endoscopic risk factors for a perforation.

Variables	Procedures without a perforation (n=3,810)	Procedures with a perforation (n=17)	Univariable OR (95% CI)	P value	Multivariable OR (95% CI)	P value
Female gender, n (%)	557 (15)	6 (35)	3.19 (1.17-8.65)	0.02	2.77 (1.02-7.57)	0.05
Age, years (mean)	66 (11)	71 (13)	1.05 (1.00-1.10)	0.04	1.05 (0.99-1.10)	0.07
Prior surgical treatment esophagus	114 (3)	1 (6)	2.03 (0.27-15.41)	0.50		
Prior endoscopic treatment esophagus	1,840 (48)	5 (29)	0.45 (0.16-1.27)	0.13	0.59 (0.20-1.77)	0.35
Stenosis before ER	303 (8)	1 (6)	0.72 (0.10-5.47)	0.75		
Indication for ER, n (%):						
Focal lesion dysplasia	2,495 (66)	15 (88)	Reference	-	reference	
Diffuse high-grade dysplasia	239 (6)	0 (0)	*	0.99	*	*
As part of a radical ER protocol	965 (25)	2 (12)	0.35 (0.08-1.51)	0.16	0.51 (0.11-2.43)	0.40
Escape treatment	111 (3)	0 (0)	*	0.99	*	*
Number of resections, mean (SD)	4 (3)	4 (3)	1.04 (0.89-1.21)	0.65		

* No event in this category, therefore coefficient and corresponding 95% CI (zero to infinity) are not calculable.

CI: Confidence interval; ER: endoscopic resection; OR: Odds ratio.

Table 4. Clinical and endoscopic risk factors for post procedural bleeding.

Variables	Procedures without postprocedural bleeding (n=3792)	Procedures with post procedural bleeding (n=35)	Univariable OR (95% CI)	P value	Multivariable OR (95% CI)	P value
Female gender	557 (15)	6 (17)	1.20 (0.50-2.91)	0.68		
Age, mean (SD)	66 (11)	66 (12)	1.00 (0.97-1.03)	0.97		
Use of anticoagulant medication	1147 (30)	16 (46)	1.94 (1.00 – 3.79)	0.05	1.88 (0.96-3.68)	0.07
Prior surgical treatment esophagus	115 (3)	0 (0)	*	*		
Prior endoscopic treatment esophagus	1830 (48)	15 (43)	0.80 (0.41-1.58)	0.53		
Stenosis before ER	300 (8)	4 (11)	1.50 (0.53-4.28)	0.48		
Indication for ER:						
Focal lesion dysplasia	2487 (66)	23 (66)	reference			
Diffuse high-grade dysplasia	236 (6)	3 (8)	1.38 (0.41-4.61)	0.61		
As part of a radical ER protocol	959 (25)	8 (23)	0.90 (0.40-2.02)	0.80		
Escape treatment	110 (3)	1 (3)	0.98 (0.13-7.35)	0.99		
Number of resections, mean (SD)	4 (3)	6 (4)	1.15 (1.07-1.25)	<0.001	1.15 (1.06-1.25)	<0.001

* No event in this category, therefore coefficient and corresponding 95% CI (zero to infinity) are not calculable.

CI: Confidence interval; ER: endoscopic resection; OR: Odds ratio.

FIGURE LEGENDS

Figure 1. Duette device. The transparent plastic cap with 6 rubber bands is placed at the tip of the endoscope, and the stiff hexagonal snare is advanced through the working channel.

Figure 2. Endoscopic images of 4 perforations after MBM treated successfully with an over-the-scope clip (A and B) and regular clips (C-H).

Figure 3. Endoscopic images of two perforations after MBM treated successfully with clips and an esophageal stent.

SUPPLEMENTARY TABLES

Supplementary Table 1. Definition outcome parameters.

Primary outcomes	
Perforation rate and associated risk factors.	Perforation was defined as a transmural defect of the esophageal wall diagnosed during or immediately after the endoscopy. When the endoscopic diagnosis was uncertain, the diagnosis had to be confirmed by free air or leakage on radiologic examination.
Postprocedural bleeding rate and associated risk factors.	Postprocedural bleeding was defined as bleeding (signs of hematemesis, melena or drop in hemoglobin level) that occurred after the MBM procedure and for which hospital admission or an intervention was required.
Secondary outcomes	
Stenosis rate and associated risk factors.	A stenosis was defined as symptomatic esophageal narrowing requiring an intervention (e.g. dilation, incision therapy or stent placement).
Size of the ER specimens.	Maximum and minimum diameter in mm.
Classification adverse events	Adverse events were graded as 'mild' (unplanned hospital admission, hospitalization <3 days, hemoglobin drop <3 g/dL, no transfusion), 'moderate' (4-10 days hospitalization, ≤4 units blood transfusion, need for endoscopic intervention, radiological intervention), 'severe' (hospitalization >10 days, intensive care unit admission, need for surgery, >4 units of blood transfusion) or 'fatal' (death attributable to procedure <30 days or longer with continuous hospitalization).

Supplementary Table 2. Variables included in the imputation set.

Variable	Missing values, n (%)
Center	0 (0%)
Gender (male,female)	1 (0.03%)
Age	305 (8.0%)
Type of prior endoscopic resection (none, ER, RFA, APC, PDT)	167 (4.4%)
Type of prior esophageal surgery (none, fundoplication, esophagectomy)	517 (13.5%)
Type of anticoagulant medication (none, platelet aggregation inhibitor, heparin, DOAC)	486 (12.7%)
Stenosis before resection (yes, no)	4 (0.1%)
Indication for ER (focal lesion suspicious for dysplasia, diffuse HGD, as part of a radical ER protocol, escape treatment)	116 (3.0%)
Lesion type (no visible lesion, flat type lesion, protruded lesion, excavated lesion)	417 (10.9%)
Number of resections	24 (0.6%)
Worst pathological result (no dysplasia, LGD, HGD, cancer)	325 (8.5%)
Perforation (yes, no)	0 (0%)
Postprocedural bleeding (yes, no)	0 (0%)

Variables	Univariable OR (95% CI)	P value	Multivariable OR (95% CI)	P value
Female gender, n (%)	0.68 (0.45 – 1.03)	0.07	0.74 (0.49 – 1.14)	0.18
Age, years (mean)	0.99 (0.98 – 1.01)	0.25	-	
Prior surgical treatment esophagus	1.72 (0.62 – 4.75)	0.30	-	
Prior endoscopic treatment esophagus	1.04 (0.75 – 1.45)	0.82	-	
Stenosis before ER	1.75 (10.05 – 2.91)	0.03	2.02 (1.18 – 3.45)	0.01
Indication for ER, n (%):				
Focal lesion dysplasia	Reference	-	reference	-
Diffuse high-grade dysplasia	1.29 (0.75 – 2.21)	0.36	1.55 (0.89 – 2.70)	0.12
As part of a radical ER protocol	3.04 (2.20 – 4.21)	<0.001	2.26 (1.60 – 3.19)	<0.001
Escape treatment	0.19 (0.03 – 1.41)	0.11	0.21 (0.03 – 1.59)	0.13
Number of resections, mean (SD)	1.21 (1.16 – 1.26)	<0.001	1.19 (1.14 – 1.24)	<0.001

Supplementary Table 3. Clinical and endoscopic risk factors for stenosis.

Abbreviations: APC: argon plasma coagulation; BE: Barrett's esophagus; CI: confidence interval; EC: early cancer; ER: endoscopic resection; IQR: interquartile range; HGD: high-grade dysplasia; LGD: low-grade dysplasia; MBM: multiband mucosectomy; OR: odds ratio; PDT: photodynamic therapy; RFA: radiofrequency ablation; SD: standard deviation.