CLINICAL—ALIMENTARY TRACT

Long-term Efficacy and Safety of Endoscopic Resection for Patients With Mucosal Adenocarcinoma of the Esophagus

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This article has an accompanying continuing medical education activity on page e14. Learning Objective: Upon completion of this CME activity, successful learners will be able to discuss the effectiveness and safety of endoscopic resection of mucosal adenocarcinoma of the esophagus.

BACKGROUND & AIMS: Barrett's esophagus–associated high-grade dysplasia is commonly treated by endoscopy. However, most guidelines offer no recommendations for endoscopic treatment of mucosal adenocarcinoma of the esophagus (mAC). We investigated the efficacy and safety of endoscopic resection in a large series of patients with mAC. **METHODS:** We collected data from 1000 consecutive patients (mean age, 69.1 ± 10.7 years; 861 men) with mAC (481 with short-segment and 519 with long-segment Barrett's esophagus) who presented at a tertiary care center from October 1996 to September 2010. Patients with low-grade and high-grade dysplasia and submucosal or more advanced cancer were excluded. All patients underwent endoscopic resection of mACs. Patients found to have submucosal cancer at their first endoscopy examination were excluded from the analysis. **RESULTS:** After a mean follow-up period of 56.6 ± 33.4 months, 963 patients (96.3%) had achieved a complete response; surgery was necessary in 12 patients (3.7%) after endoscopic therapy failed. Metachronous lesions or recurrence of cancer developed during the follow-up period in 140 patients (14.5%) but endoscopic re-treatment was successful in 115, resulting in a long-term complete remission rate of 93.8%; 111 died of concomitant disease and 2 of Barrett's esophagus–associated cancer. The calculated 10-year survival rate of patients who underwent endoscopic resection of mACs was 75%. Major complications developed in 15 patients (1.5%) but could be managed conservatively. **CONCLUSIONS:** Endoscopic therapy is highly effective and safe for patients with mAC, with excellent long-term results. In an almost 5-year follow-up of 1000 patients treated with endoscopic resection, there was no mortality and less than 2% had major complications. Endoscopic therapy should become the standard of care for patients with mAC.

Keywords: Barrett's Esophagus; Esophageal Cancer; Endoscopic Mucosal Resection.

T he incidence of adenocarcinoma of the esophagus has been increasing rapidly in recent decades, and adenocarcinoma is now the cancer with the greatest relative increase in incidence over the past 20 years.[1] Patients with adenocarcinoma still have a poor prognosis because it is usually only diagnosed at advanced stages, even though surveillance programs for patients with Barrett's esophagus have been established in most countries. When it is diagnosed at an early stage, treatment is curative in almost all cases.[2–7]

During the past 15 years, endoscopic therapy has become an established and important component of the treatment algorithm for early neoplasias in patients with Barrett's esophagus. All of the international guidelines published by the various specialist societies recommend endoscopic therapy in the presence of high-grade dysplasia in Barrett's esophagus.[8–12] However, not all of the guidelines offer recommendations for the approach in patients with early adenocarcinoma (T1). The current guidelines of the specialist societies in the United States also do not take any position on the approach in patients with mucosal adenocarcinoma (mAC), although numerous published studies from various centers are available on endoscopic therapy for mucosal Barrett's carcinoma.[8,13] All of the series document excellent results with endoscopic therapy, but most of the publications only include small numbers of cases and have short follow-up periods. In addition, patients with high-grade dysplasia (HGD) and mucosal Barrett's carcinoma are combined in almost all of the publications, making it impossible to draw any clear conclusions thus far on the efficacy of endoscopic therapy in mucosal Barrett's carcinoma.

The present study was conducted to investigate the safety and efficacy of endoscopic therapy for mucosal Barrett's

carcinoma and to provide long-term follow-up data on the outcome of the treatment based on a large patient cohort.

Patients and Methods

During a 15-year period between October 1996 and December 2010, 2026 patients presented at our hospital with suspected intraepithelial neoplasia or early adenocarcinoma arising in Barrett's esophagus (Figure 1).

Data Collection

Data for the patients were prospectively documented on dedicated data sheets from October 1996 to October 2000. Starting in October 2000, the data were prospectively entered into a dedicated database (dBase) by a medical information specialist (J.H.) who was responsible for the administration of this database only. The medical information specialist checked

Figure 1. Flow diagram for the study patients. ET, endoscopic therapy; IN, intraepithelial neoplasia; LGIN, low-grade intra-epithelial neoplasia; HGIN, high-grade intraepithelial neoplasia; Tx, therapy; CR, complete remission; AC, adenocarcinoma.

on a regular basis that the follow-up for all of the patients was up to date, and referring physicians were contacted if the patients did not attend a scheduled follow-up examination.

Patient Workup and Staging Protocol

All of the patients underwent intensive initial staging with endoscopic ultrasonography, abdominal ultrasonography, and computed tomography of the chest and upper abdomen. High-resolution video endoscopy and chromoendoscopy (with methylene blue staining in the early period of the study, acetic acid staining [1.5%] starting in 2002, and later virtual chromoendoscopy) were performed using Fujinon EG-450HR, EG-450WR5, EG-530, and EG-590 instruments (Fujinon Europe, Inc, Willich, Germany). Targeted biopsies of all visible lesions and 4-quadrant biopsies every 1 to 2 cm over the entire Barrett's segment were performed. Assessment of the biopsy specimens taken during the diagnostic procedures was usually performed by at least 2 different pathologists. The histological criteria, classification, and assessment of the grade of differentiation corresponded to the World Health Organization classification.[14]

Treatment Protocol

The treatment strategy used for early Barrett's neoplasia at our center evolved during the study period. In the first 5 years, both endoscopic resection (ER) and ablative treatment methods (eg, photodynamic therapy, argon plasma coagulation [APC], or laser therapy) were used to treat neoplastic lesions. All patients who underwent tumor treatment with ablative techniques were excluded from the present study. Structured ablation of the residual Barrett's esophagus after successful eradication of the neoplastic lesions was not performed during the first phase of the study period.[3]

After 2001, all neoplastic lesions (HGD and adenocarcinoma) were treated exclusively with ER to allow precise histological diagnosis and staging. After all of the visible neoplastic lesions had been resected, stepwise ablative treatment of the remaining Barrett's mucosa was performed by means of APC. Endoscopic treatment was usually performed with the patients under sedation and analgesia (with midazolam and/or pethidine) or without premedication in individual cases.

Inclusion and Exclusion Criteria

The criterion for inclusion in the analysis was mucosal Barrett's carcinoma, diagnosed on biopsy or on the ER specimen, as the initial histology. Whenever the lesions were judged to be resectable by one of the experienced endoscopists, diagnostic ER was performed in all cases to allow histopathological staging, even when the macroscopic appearance had already suggested a submucosal Barrett's carcinoma.

The criteria for exclusion from the study were low-grade dysplasia, HGD, and submucosal or more advanced cancer (>T1) on staging or at the first diagnostic ER. Patients with incipient invasion of the submucosal layer (<500 μm) without further risk factors (lymph and blood vessel infiltration, poor differentiation grade, size >2 cm) were treated endoscopically. All other patients with submucosal cancer who were fit for surgery underwent esophagectomy.[15] Further exclusion criteria were lymph node or distant metastases found during the initial staging. If a final diagnosis of a submucosal lesion was made at
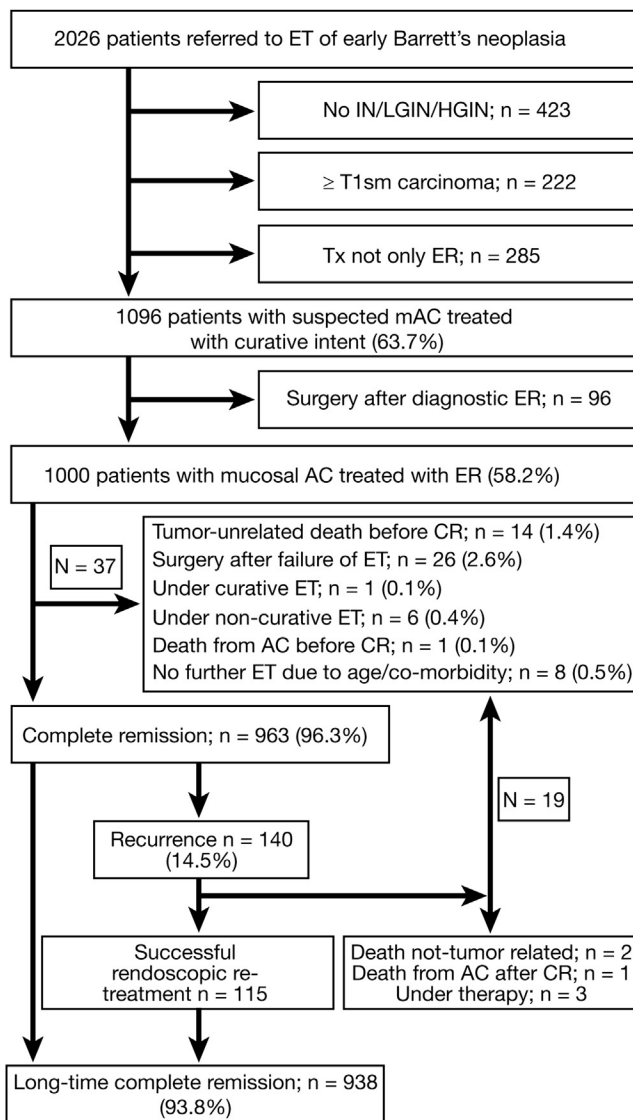
the first (diagnostic) ER (as described in the preceding text), the patient was excluded from analysis. Patients who underwent treatment of cancer by means of ablative techniques were also excluded. Whenever submucosal or more advanced cancer was diagnosed after the patient had entered the treatment protocol, endoscopic therapy was considered to have failed. Failure of endoscopic treatment was also noted when complete remission could not be achieved by endoscopic means and whenever there was progression to more advanced tumor stages ($\geq$T1sm).

Data for the 1000 patients included are listed in Table 1. The results of endoscopic treatment and follow-up data for 238 of the patients in the study group have been reported previously.[3]

ER Procedure

ER was performed with the ligation device or the cap. Details of the 2 techniques and the histopathological evaluation procedure have been reported elsewhere.[3,16–18] In cases in which the basal margin of the resected specimen was not free of tumor (R1 situation) or when the pathologist was not able to state tumor freedom due to artifacts (Rx situation), patients were defined as having treatment failure, and operable patients were scheduled for radical esophagectomy.

All biopsy and resection specimens were reviewed by at least 2 expert pathologists. Diagnostic criteria for the differentiation between low-grade dysplasia, HGD, and adenocarcinoma remained consistent over the whole study period.

Ablation Therapy for Residual Nondysplastic Barrett's Mucosa

Ablative treatment was performed with APC using a forward-spraying APC probe (Erbe VIO APC 300; Erbe Elektromedizin, Tübingen, Germany; power, 50 W; effect, 2; argon flow, 1.5–2.0 L/min). Circumferential ablation in one session was avoided to reduce the stricture rate. Since 2009, radiofrequency ablation (RFA; Halo 360 and Halo 90; BARRx Medical, Sunnyvale, CA) has been used in 19 patients. All of these patients were treated in the protocol for the Euro-II Study, matching the 2-step protocol (ER followed by ablation) that we have followed since 2002. Photodynamic therapy was not used as a treatment method in this series.

All patients were treated with 40 mg omeprazole or an equivalent dose of another proton pump inhibitor (PPI) before the endoscopic workup. After treatment, all of the patients were treated with a PPI intravenously for 2 days and then 40 mg orally 3 times a day for at least 3 weeks, after which the dosage of PPI was reduced to 40 mg/day.

End Points

The primary end points were assessed at the end of the treatment phase and at the time of the last follow-up. Primary end points were as follows:

1. Complete remission of all high-grade intraepithelial neoplasia and cancer, defined as an R0 resection plus one normal endoscopic checkup examination. In R1 or Rx situations (Rx meaning that evaluation of the margin was not possible due to coagulation artifacts) on the lateral margin of the resected specimen, 2 consecutive endoscopic checkup examinations without evidence of residual tumor were required to conclude that there was a complete response.

2. Tumor-associated death, defined as death caused by metastatic esophageal adenocarcinoma or metastatic adenocarcinoma from an unknown primary.

Secondary end points were as follows:

1. Recurrence of high-grade intraepithelial neoplasia and adenocarcinoma.

2. The long-term complete remission rate, defined as a status of complete remission at time of writing, independently of previous recurrences.

3. Number of treatment failures.

4. Complications during the treatment phase and follow-up. Major complications were defined as perforation and bleeding, with a decrease in the hemoglobin level of $\geq$2 g/dL. Minor complications consisted of symptomatic esophageal strictures requiring dilation or bougienage.

Follow-up Program

All of the patients were included in a strict follow-up program monitored in collaboration with the referring external gastroenterologists. Follow-up examinations were planned 1, 2, 3, 6, 9, and 12 months after treatment and then at 6-month intervals up to the end of a 5-year period after treatment. Every other follow-up endoscopy was performed at our institution (at 6, 12, 24, 36, 48, and 60 months and every 2 years thereafter). Follow-up endoscopies in between were performed by the referring gastroenterologist. Annual checkups were planned thereafter. However, patients were not considered lost to follow-up if they stopped attending follow-up endoscopies after 5 years. The checkups included endoscopy with high-resolution endoscopes and biopsies of any suspicious lesions as well as 4-quadrant biopsies and/or chromoendoscopy of residual Barrett's mucosa. During the first 8 years of the study phase, every second checkup included an endosonographic

Table 1. Characteristics of the Patients and Tumors

Patients (N)	1000
Male/female	861/139
Mean age $\pm$ SD (y)	69.1 $\pm$ 10.75
Short-segment Barrett's esophagus	481
LSBE	519
Differentiation	
Well differentiated (G1)	691
Moderately differentiated (G2)	255
Poorly differentiated (G3)	54
Local tumor stage after first ER session	
T1m1	493
T1m2	240
T1m3	124
T1m4	143

T1m1, intraepithelial adenocarcinoma; T1m2, adenocarcinoma invading the tunica propria; T1m3, adenocarcinoma invading the first layer of the muscularis mucosae; T1m4, adenocarcinoma invading the second layer of the muscularis mucosae.

examination to assess the lymph node status as well as computed tomography and abdominal ultrasonography. However, with growing experience and the knowledge that metastatic disease is virtually never found in mucosal Barrett's carcinoma, we later stopped performing endoscopic ultrasonography, abdominal ultrasonography, or computed tomography during follow-up visits for patients with HGD and mAC.

If any checkup showed residual neoplastic tissue or metachronous neoplastic lesions, ER was repeated. Metachronous lesions were defined as HGD or early cancer detected during the follow-up after the patient had achieved a complete response.[3]

Statistics

All authors had access to study data and have reviewed and approved the final manuscript. For the final analysis, patients who were lost to follow-up or subsequent treatment were censored. At the end of the follow-up phase, patients who were lost to follow-up but in whom the last follow-up had shown no tumor recurrence, and patients in complete remission who discontinued follow-up, were censored. The status of the patient at the last follow-up endoscopy was documented at the time of exit from the study. In patients who were referred for esophageal resection for various reasons, patients with progression of cancer ($\geq$T1sm) who were unfit for surgery, and patients who never achieved complete remission from HGD/early cancer, treatment was also considered to have failed.

Statistical analyses of the patients' data and clinical parameters are given as means $\pm$ SD for normally distributed variables. Medians with interquartile ranges were used for variables with a skewed distribution. Kaplan–Meier estimates of the survival curves were calculated for time to recurrence.

Ethical Considerations

All of the patients provided written consent to undergo local therapy after receiving extensive information. All patients were informed about the option of surgery, and if patients were interested in receiving a second opinion, a surgeon was regularly asked to discuss all of the issues with them once again.

The study was approved by the Ethics Commission of the Medical Council of the State of Hesse (no. 48/99) and was performed in accordance with Good Clinical Practice criteria.

Results

In total, 1096 consecutive patients with mucosal Barrett's carcinoma underwent ER. Ninety-six patients were excluded because the first diagnostic ER showed cancer invading the submucosa. The remaining 1000 patients were included in the analysis (mean age, 69.1 $\pm$ 10.7 years; 861 men). A total of 481 patients had short-segment Barrett's esophagus, and 519 had long-segment Barrett's esophagus (LSBE).

A total of 2687 ERs were performed (a median of 1 per patient; interquartile range, 1–3) (Table 2). The ligation device was used in 911 patients and the cap in 89 patients. En bloc resection was performed in 508 patients and piecemeal resection in the remaining 492 patients. A total of 552 patients had lesions $\leq$2 cm in diameter, and the remaining patients had larger lesions. The mean follow-up period was 56.6 $\pm$ 33.4 months. Twenty-two patients

Table 2. Acute and Long-term Results

ERs (n)	2687
ERs per patient; median (interquartile range)	1 (1–3)
Major complications, n (%)	15 (1.5%)
Major bleeding	14
Perforation	1
Complete local remission, n (%)	963/1000 (96.3)
Time until complete local remission (mo), median (interquartile range)	1 (1–3)
Follow-up (mo), mean $\pm$ SD	56.6 $\pm$ 33.4
Metachronous lesions, n (%)	140/963 (14.5)
Long-term complete local remission after repeat ER, n (%)	938/1000 (93.8)

were considered lost to follow-up after a mean follow-up period of 25.6 $\pm$ 22.9 months. In 10 of these 22 patients, follow-up was discontinued because of advanced age or severe comorbidities.

Primary End Points

1. Complete remission. Complete remission of neoplasia was achieved in 96.3% (963/1000) of the patients. Thirty-seven patients did not achieve complete remission; 1 patient is still receiving treatment, 14 patients died during the treatment phase of causes unrelated to tumor, 12 patients underwent esophageal resection because complete remission could not be achieved with endoscopic treatment, and 4 patients continued with noncurative endoscopic treatment due to advanced age and comorbidities. In addition, endoscopic treatment was discontinued in 5 patients because of significant comorbidities (1 with severe pulmonary disease, 2 with a second cancer, and 2 with advanced cirrhosis) and 1 patient died of metastatic adenocarcinoma. In patients who never achieved complete remission or were referred for surgery, treatment was considered to have failed at the first primary end point. The only factor negatively associated with complete remission was the presence of LSBE ($P <$ .0001).

2. Tumor-related death. There were 2 tumor-related deaths due to metastatic adenocarcinoma during follow-up (2 of 1000 patients; 0.2%) and 111 non–tumor-related deaths. The overall survival at 5 years was 91.5%. One patient never achieved complete remission and died of metastatic Barrett's carcinoma. Another patient who did not follow the recommendations for regular follow-up endoscopies had a recurrence of Barrett's carcinoma, which was detected at an advanced stage.
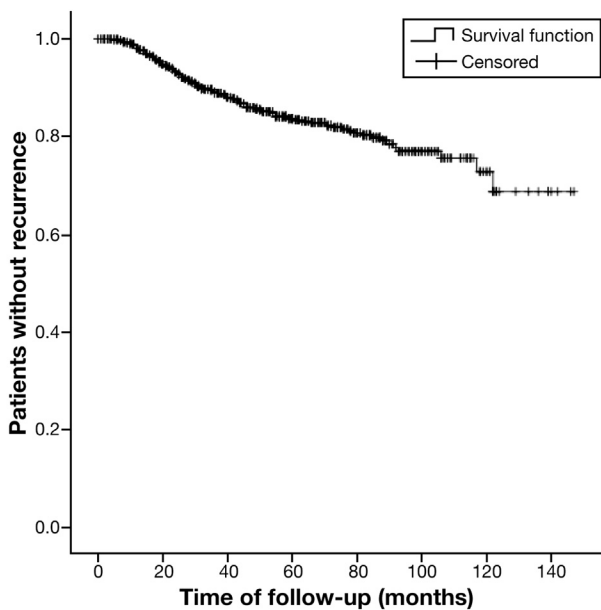
Secondary End Points

1. Recurrence of neoplasia. Recurrence of neoplasia (HGD or adenocarcinoma) was detected in 14.5% of the patients (140/963) after a median of 26.5 months (interquartile range, 17.25–44.75) (Figure 2). Disease-free survival at 5 years was 87.1%. Repeat endoscopic treatment was successful in 82.1% (115/140). Of the other 25 patients in whom complete remission could not be achieved

after detection of metachronous neoplasia, 2 patients are still receiving treatment and 2 died during the repeat treatment phase of causes unrelated to tumor. Endoscopic therapy was considered to have failed in 21 of the patients with recurrent neoplasia; 1 patient died of metastatic adenocarcinoma (already counting as treatment failure at a primary end point), and 1 patient declined repeat treatment at our center due to the long distance from his home. He was subsequently lost to follow-up. Fourteen patients were referred for surgery, and 6 continued with noncurative endoscopic treatment. Patients with LSBE had a significantly higher risk for recurrence than patients with SSBE (Figure 3).
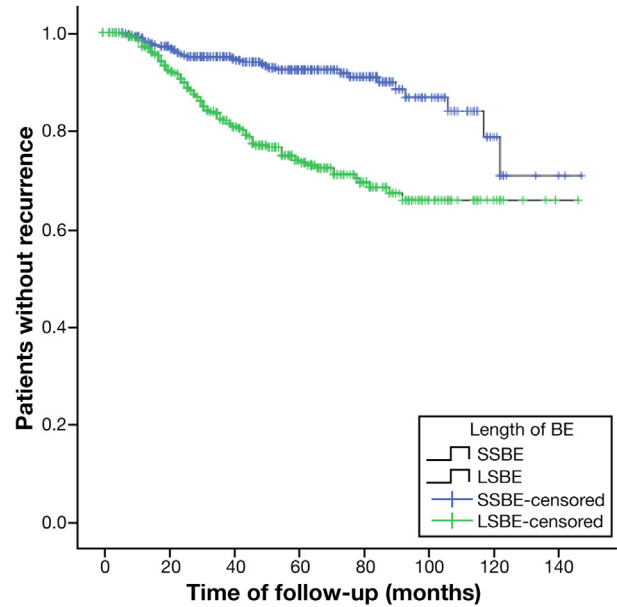
2. Long-term complete remission rate. At the time of writing, 93.8% of the patients were free of neoplasia after a mean follow-up period of 56.6 ± 33.4 months. After recurrence, repeat endoscopic treatment was successful in 115 of 140 patients. Estimated survival after 12.25 years was 75%.

3. Failure of endoscopic therapy. Overall, 42 of the 1000 patients would have required esophageal resection. Twenty-six patients were referred for surgery, 14 patients were inoperable due to advanced age and comorbidities, and 2 patients died of metastatic adenocarcinoma. The reasons for failure of endoscopic therapy were poor healing after endoscopic treatment (n = 12) despite high-dose PPI treatment combined with cholestyramine therapy, a second unrelated cancer found during the treatment phase or follow-up (n = 2), or inability to perform ER due to scarring (n = 6). Scarring occurred after previous ER because the neoplastic lesion was not removed in one session (Table 3). Poor healing was defined as a failure of

Figure 3. Kaplan–Meier plot for recurrence after complete local remission in patients with short-segment Barrett's esophagus (SSBE; *blue line*) in comparison with LSBE (*green line*) ($P < .001$).

squamous re-epithelialization of the ER wound. Barrett's carcinoma was incorrectly assessed initially in 22 patients, and it was only during the endoscopic treatment phase that it became evident that endoscopic therapy would not be successful. Patients with LSBE and poorly differentiated mACs had a significantly higher risk for failure of endoscopic treatment (both $P < .0001$).

4. Complications during the treatment phase and follow-up. Major complications occurred in 15 of the 1000 patients (1.5%). The major complications consisted of bleeding, with a decrease in the hemoglobin level of ≥2 g/dL (n = 14), and perforation (n = 1). Minor complications were seen in 13 patients (stenosis requiring dilation). Three patients had more than one complication. All of the complications were managed endoscopically.

Figure 2. Kaplan–Meier plot for estimating freedom from tumor.

Table 3. Reasons for Failure of Endoscopic Treatment in 42 of the 1000 Patients Included in the Study

Reason for failure of endoscopic therapy	n	%
Poor healing after ER	12	28.6
Technical problems of ER due to previous endoscopic therapy	6	14.3
Wrong decision at initial assessment	22	52.4
No further endoscopic therapy due to second cancer	2	4.7
Total	42	100.0

Patients With Lymphatic Infiltration

Twelve patients with mucosal adenocarcinoma (1.2%) were found to have lymphatic infiltration (L1) in the resected specimen after ER. Eight patients were referred for surgery, and 4 patients were not operable or declined surgery. Only 2 of the 8 patients were found to have lymph node metastases in the resected specimen after esophageal resection. In the 4 patients who were treated conservatively, no lymph node metastases were detected during follow-up.

Patients With Poorly Differentiated mACs

Fifty-four patients with poorly differentiated mACs (5.4%). Patients with poorly differentiated mACs (G3) had a significantly higher risk of recurrence and failure of endoscopic treatment than those with well-differentiated or moderately differentiated mACs (G1, G2) ($P = .03$) (Figure 4).

Patients With Infiltration of the Muscularis Mucosae

A total of 267 patients had infiltration of the first layer (T1m3; n = 124) and second layer (T1m4; n = 143) of the muscularis mucosae. There were no differences regarding recurrence and failure of endoscopic therapy between patients with and without infiltration of the muscularis mucosae.

Discussion

The first larger case series on ER for early neoplasia in Barrett's esophagus was reported in 2000 by our group,

Time (months)	12	24	36	48	60	72	84	96	108	120
Patients at risk										
G1/2		764	634	522	412	297	189	125	71	73
G3/4		45	33	25	17	11	8	7	4	2

Figure 4. Kaplan–Meier plot for recurrence after complete local remission in patients with poorly differentiated mACs (*solid line*) compared with well-differentiated and moderately differentiated mACs (*dashed line*) ($P < .03$).

showing that endoscopic therapy is safe and effective.[16] However, the series was comparatively small and only had a short follow-up period. The data presented here on the largest series published to date on endoscopic therapy for mACs in 1000 patients confirm the safety of ER, with a treatment-related mortality rate of 0.2% and a major complication rate of 1.5%. However, all of the complications were managed endoscopically, with no need for surgery. In contrast, the morbidity and mortality rates associated with esophageal resection are significantly higher at 30% to 50% and 2% to 5%, respectively, in high-volume expert centers.[19–23]

Compared with our previously reported study,[3] the current series has several important novelties. First, the cohort of patients with mucosal cancer treated by ER is almost 5 times larger. Second, the cohort reported on in the current study is a purified cohort with mucosal cancer treated by ER only. All patients with HGD and submucosal cancer were excluded. In addition, contrary to our previous series, only patients who underwent ER as the only tumor treatment were included, and all patients who received photodynamic therapy or APC as a tumor treatment were excluded from the analysis. Moreover, our current series for the first time analyzes reasons for failure of endoscopic treatment and gives important insights into endoscopic treatment of patients with poorly differentiated mucosal adenocarcinoma or patients with lymph vessel infiltration.

The follow-up period in the present series was almost 5 years, showing that endoscopic treatment is also highly effective in the longer term. The long-term complete remission rate of 93.8% was excellent. Twenty-six patients in whom endoscopic therapy was not successful were referred for surgery. Endoscopic therapy was considered to have failed in these patients, but curative treatment is possible in almost all patients even if endoscopic therapy is not successful. Deaths due to metastatic Barrett's carcinoma only occurred in 2 of the 1000 patients in this series, representing a tumor-related mortality rate of 0.2%. This is well below the mortality rate associated with esophageal resection, which amounts to 1% to 5% with HGD and mAC even in highly specialized centers; this would correspond to 10 to 50 deaths in the present series.[19,22,23] These excellent results with endoscopic therapy can only be achieved in centers with extensive experience in the method; however, the same also applies to esophageal resection. Published reports have shown that the mortality rate with esophageal resection rises to more than 20% in nonexpert centers.[24,25] Another advantage of endoscopic therapy is the minimal invasiveness of the procedure, which is evident from the absence of mortality in the present series.

The increased rate of metachronous lesions and recurrences after successful ER was the greatest problem with endoscopic therapy for many years. While the initial publications on endoscopic therapy in the early 2000s were still showing a rate of metachronous neoplasias of up to 35%, the recurrence rate has declined drastically in recent years.[3,16,26] In our study published in 2008, 349 patients who did not undergo ablative therapy for residual non-neoplastic Barrett's esophagus after successful ER had a significantly greater risk of developing neoplasia again
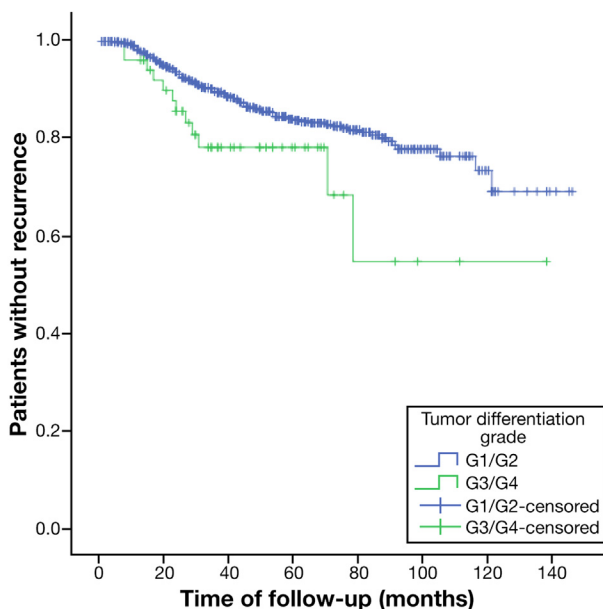
during the subsequent course.[3] We therefore performed a prospective randomized study in which patients who underwent successful ER for early Barrett's carcinoma were randomly assigned to an ablation arm with APC or an observational arm with no intervention. The results showed a highly significant increase in the rate of metachronous lesions in the observational arm (2.6% vs 38%).[27] We realized more than 10 years ago that ablation of the Barrett's mucosa after ER is able to reduce the recurrence rate. The logical consequence of this recognition was that the approach in this group of patients was altered such that all patients received staged APC treatment for residual Barrett's mucosa during the planned follow-up examinations.[28] The effectiveness of this was also clearly seen in the low rate of recurrence and metachronous neoplasia, which was 14.9% in the present series. However, because we performed ablative therapy for residual Barrett's esophagus in all patients presenting at our center for endoscopic follow-up in the meantime, it is no longer possible to analyze the efficacy of ablation on the basis of the data now available. Ablation with RFA seems to be superior to APC, especially in patients with LSBE. Because LSBE is a risk factor for both recurrence and treatment failure, the use of RFA might have even improved our results.[29–31]

The follow-up regimen in our study protocol was rather intense. Based on our experience, we now would suggest a less aggressive follow-up program with endoscopies at 3, 6, 12, 18, and 24 months and yearly thereafter until 5 years and then every 2 years afterward. In selected cases with short-segment Barrett's esophagus and a unifocal well-differentiated mAC, the recurrence rate seems to be lower and a less strict follow-up protocol might be adequate. Follow-up should not stop after 5 years because 12% of all recurrences were detected afterward.

The rate of treatment failure in the present study was 4.2%. The decisive reasons for the failure of treatment are of interest. One of the main reasons, in more than half of the patients, was initially incorrect assessment of the endoscopic treatability of a mAC. It only emerged during the course of treatment that complete remission would not be achievable with endoscopic therapy. Another major reason for treatment failure was poor healing after ER. In one-third of the patients in whom the treatment failed, poor healing of the resection wounds despite high-dose PPI therapy was the reason. In 6 patients, further ER was not possible because of scarring after previous endoscopic therapy. Therefore, complete removal of the whole neoplastic lesion in one session should be the goal to reduce the risk of treatment failure. Risk factors for treatment failure included poor tumor differentiation and LSBE. Patients with mAC in LSBE or with poorly differentiated mACs can be treated endoscopically, but due to the high rate of recurrence and treatment failure, a tighter schedule for follow-up examinations should be used. However, a poor grade of differentiation does not appear to be associated with an increased rate of lymph node metastasis. Other factors such as multifocal neoplasia, piecemeal resection, length of the treatment phase, and the method of Barrett's ablation might also influence the rate of recurrence and metachronous neoplasia.[3]

The present study has numerous limitations. First, referral bias cannot be excluded, because it is possible that only patients with early Barrett's carcinoma that were endoscopically well treatable may have been referred. However, of 2026 referred patients with suspected early Barrett's carcinoma, only 58% ultimately received curative endoscopic treatment; this argues against a referral bias and appears to show that the group of patients corresponds to the usual distribution of patients with early Barrett's neoplasia. The long study period is an advantage on the one hand but a disadvantage on the other. The treatment approach changed over the entire study period, moving away from multimodal therapy for early Barrett's carcinoma using a combination of ER, photodynamic therapy, APC, and laser toward a strict and purely resectional form of treatment in which all patients with HGD and mAC were only treated with ER. This change toward exclusive ER is justified by the recognition that histopathological diagnosis based on a resection specimen should represent the gold standard and that ablative therapy should never be performed on the basis of a diagnosis obtained using biopsy specimens.[32] Another weakness in the present study is that, during the initial phase, no ablation of residual Barrett's mucosa was performed after complete remission of the neoplasia.[3] Although this change in the treatment approach reflects the general development of endoscopic therapy for Barrett's neoplasia, it distorts the results of this study to the extent that the recurrence rate was relatively high in the initial years, so that the overall recurrence rate on average in the study is higher than would be expected today. The Prague C & M classification was not available for the majority of the patients included and has only been systematically documented since 2008.[33] In addition, we were not able to report on the macroscopic type of the lesions because the Paris classification was introduced in 2003. Because there was no reimbursement for RFA in Germany until 2013, almost all patients in this series underwent ablation of the nondysplastic Barrett's mucosa with APC. Another possible limitation is the interobserver variation of histological diagnosis. We excluded patients with HGD, but it is possible that some of our patients with T1m1 adenocarcinoma might have been diagnosed as HGD by other pathologists (Supplemantary Table 1; Supplementary Figure 1*A* and *B*). However, because we were not able to show a clinically relevant difference between mACs with different infiltration depths (T1m1–4), the clinical relevance of this possible limitation seems to be very low.

In summary, endoscopic therapy for mucosal Barrett's carcinoma is extremely effective and safe. Using a 2-stage treatment consisting of ER of all neoplastic lesions followed by ablation of the residual non-neoplastic Barrett's mucosa, a complete remission rate of 96% was achieved in 1000 patients, and this rate remained largely stable even over a long-term follow-up period of approximately 5 years. Endoscopic therapy for mucosal Barrett's carcinoma should therefore become the international gold standard for treatment. Due to its high rates of mortality and morbidity, esophageal resection should only be a reserve procedure in patients with mucosal adenocarcinoma and used if endoscopic therapy fails.

Supplementary Material

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Supplementary Material

Supplementary Table 1. Diagnostic Histopathological Criteria for Early Barrett's Neoplasia

Glands	Barrett Nonbranching	Low-grade dysplasia Villiform	HGD Slightly irregular	Cancer Branching, cribriform, irregular, solid
Expansion	Up/down	To surface	To surface	Lateral under surface
Epithelial differentiation	Up/down	To surface	Not to surface	Not to surface
Goblet cells	++	(+)	−/(+)	−
Surface epithelium	+++	−	−	−
Nuclear rows	1	2–3	2–5	Changing
Nuclear size	Small, basal	Palisading	Enlarged	Vesicular
Chromatin	Few	+	++	++/+++
Nucleoli	None	None	Few small	Several prominent
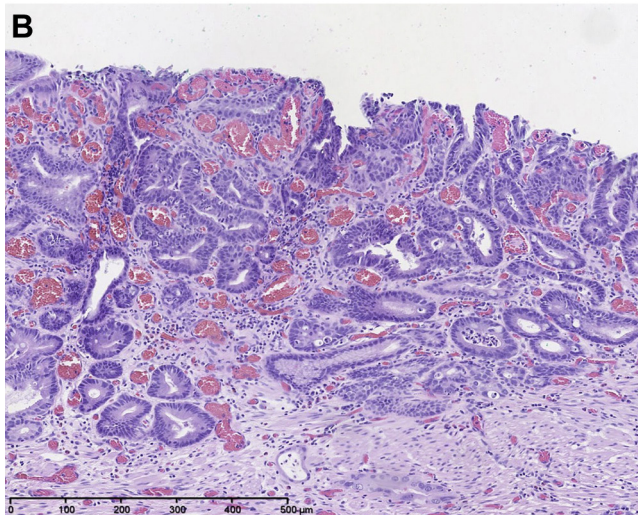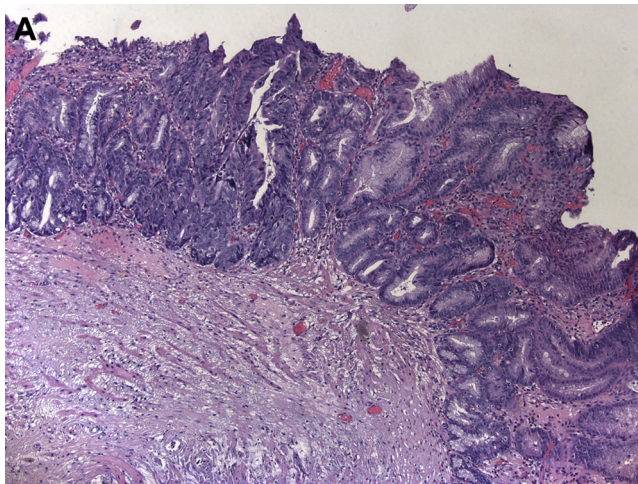
Supplementary Figure 1. (*A*) Histological image of HGD in Barrett's mucosa. (*B*) Histological image of mAC (pT1m2).