Curative endoscopic resection of early esophageal adenocarcinomas (Barrett's cancer)

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Background: In view of the increasing incidence of adenocarcinoma in Barrett's esophagus and the mortality and high morbidity rates associated with surgical therapy for this condition, safe and effective but less invasive methods of treatment are needed.

Objective: To evaluate efficacy and safety of endoscopic resection in these patients.

Design: Single-center prospective study.

Setting: Teaching hospital, conducted between October 1996 and September 2003.

Patients: A total of 100 consecutive patients (mean age, 62.1 ± 10.9 years; range, 31–86 years) with low-risk adenocarcinoma of the esophagus (macroscopic types I, IIa, IIb, and IIc; lesion diameter up to 20 mm; mucosal lesion without invasion into lymph vessels and veins; and histologic grades G1 and G2) arising in Barrett's metaplasia.

Interventions: Endoscopic resection with the suck-and-cut technique.

Main Outcome Measurements: Complete local remission.

Results: A total of 144 resections (1.47 per patient) were performed without technical problems. No major complications and only 11 minor ones (bleedings without decrease of Hb >2 g/dL; treated with injection therapy) occurred. Complete local remission was achieved in 99 of the 100 patients after 1.9 months (range, 1–18 months) and a maximum of 3 resections. During a mean follow-up period of 36.7 months, recurrent or metachronous carcinomas were found in 11% of the patients, but successful repeat treatment with endoscopic resection was possible in all of these cases. The calculated 5-year survival rate was 98%. Two patients died of other causes.

Limitations: Nonblinded, nonrandomized study.

Conclusions: Endoscopic resection is associated with favorable outcomes for low-risk patients with early esophageal adenocarcinoma (Barrett's carcinoma). (Gastrointest Endosc 2007;65:3-10.)

Esophagectomy is regarded as the criterion standard for treatment in patients with early esophageal adenocarcinoma.[1] Because of the anatomical situation, the morbidity and the mortality associated with this procedure are usually high, even in specialized centers.[2-5] In addition, a considerable number of patients are inoperable, because they are too old or the rate of concomitant diseases involves too high a level of surgical risk, particularly in early

esophageal carcinoma; less invasive procedures are, therefore, desirable, although they need to provide curative treatment with the same degree of certainty. Promising initial reports and at least 1 paper provided long-term results with photodynamic therapy (PDT) in Barrett's neoplasia have been published previously.[6-8] Unlike PDT, endoscopic resection (ER) imitates the surgical situation: the tumor is excised electrosurgically, providing the pathologist with an opportunity to assess the specimen with regard to depth of invasion (T category), involvement of lymphatic vessels and veins, grade of differentiation (G status), and, above all, in relation to the question of radicality (R status). Promising initial reports with ER are

already published; however, long-term results have so far been lacking.[9,10] This prospective study for the first time presents long-term results for ER with curative intent in the treatment of early esophageal adenocarcinoma.

PATIENTS AND METHODS

During a 7-year period, between October 1996 and September 2003, 667 patients presented at the Wiesbaden Hospital with suspected intraepithelial neoplasia or early adenocarcinoma of the Barrett's type. All of the patients underwent intensive staging by using EUS and radiographic procedures. Videoendoscopy and chromoendoscopy with methylene blue staining of the entire Barrett's segment were also carried out. Biopsy specimens were taken from all macroscopically evident lesions and from unstained areas. In addition, we usually performed 4-quadrant biopsies every 1 to 2 cm over the entire Barrett's segment as well. Endoscopes used during the study were Fujinon EG-450HR instruments (Fujinon Europe, Inc, Willich, Germany) or, in the early phase of the study, Olympus 130 and 140 instruments (Olympus Optical Co [Europa], Hamburg, Germany). The macroscopic tumor type was assessed according to the Japanese classification for early stomach cancer, as follows: polypoid tumor (type I), flat and slightly elevated (IIa), flat and level (IIb), flat depressed (IIc), and ulcerated (III).[11] In addition to conventional EUS with a radial scanner to assess lymph-node status, miniprobe EUS with 20-MHz probes was also carried out in all patients with raised lesions, to assess the depth of infiltration.[12] Biopsy specimens were taken from all observed lesions, as well as 4-quadrant biopsies every 2 cm over the entire Barrett's segment. Assessment of biopsy specimens taken during the diagnostic procedures was carried out by at least 2 different pathologists. The histologic criteria, classification, and assessment of the grade of differentiation corresponded to the World Health Organization (WHO) classification.[13] In accordance with the WHO classification, the terms "low-grade intraepithelial neoplasia" (LGIN) or "high-grade intraepithelial neoplasia" (HGIN) were used instead of "low-grade dysplasia" or "high-grade dysplasia." In addition, a chest radiography, a CT of the chest and upper abdomen, and an US examination of the abdomen were carried out in all patients with proven adenocarcinoma.

Patients were excluded if the staging examinations showed evidence or raised a suspicion of a more advanced tumor stage ($>$T1), lymph-node involvement, or metastasis (n = 109). Patients with LGIN (n = 65), HGIN (n = 64), and those with cancer who did not meet the low-risk criteria were also excluded (n = 229) (Fig. 1). The low-risk criteria for Barrett's cancer were based on the definition used by the Japanese Society for Endoscopy for low risk in early gastric cancer.[11] Additional criteria were absence of invasion of lymph vessels and veins. These

Capsule Summary

What is already known on this topic

- Esophagectomy, the criterion standard for treatment of early esophageal adenocarcinoma, has high morbidity and mortality.
- ER of early esophageal adenocarcinoma is promising, but long-term results are lacking.

What this study adds to our knowledge

- In a single-center prospective study of 100 consecutive patients with early esophageal adenocarcinoma, 144 resections were performed without major complications and achieved a CLR in 99 patients after a mean of 1.9 months (range, 1-18 months) and a maximum of 3 resections.
- During a mean follow-up of 36.7 months, 11% of patients had recurrent or metachronous carcinomas, and they were all treated successfully with ER.

criteria were previously used in our preliminary report on ER for early Barrett's cancer (Table 1).[9,11] Patients who met the low-risk criteria but were recorded after the first 100 consecutive patients with low-risk tumors had been included (the last patient was enrolled in April 2002), were also not taken into account (poststudy period; n = 85). Finally, patients who had been referred because of a suspicion of carcinoma that was not confirmed during the staging examinations and/or was excluded after a second pathology assessment were also not included in the study (n = 15).

All patients who did not meet any of the above exclusion criteria were offered ER as a new, minimally invasive form of curative treatment. During one or more information discussions, all of the patients received written and oral information that indicated that esophageal resection is the current criterion standard and that endoscopic therapy is an experimental procedure that has to be carried out in research conditions.

Data for the 100 patients who met the low-risk criteria and who were treated with ER are listed in Table 2. The initial results and the short-term follow-up of 35 patients of the study group were previously reported in our preliminary report on ER of early Barrett's cancer.[9] ER was carried out by using the "suck-and-cut" technique, either with a ligation device or with a cap system (Fig. 2A to D). In these techniques, the lesion being resected is sucked into a cylinder and then grasped with a polypectomy snare, resected with high-frequency diathermy current, and removed for histopathologic assessment. Further details of the techniques used have been published previously.[14,15] The 2 resection techniques have been shown to have equivalent efficacy in a randomized and controlled clinical trial.[16] Histomorphologic assessments of the resected specimens were carried out only by 2 investigators
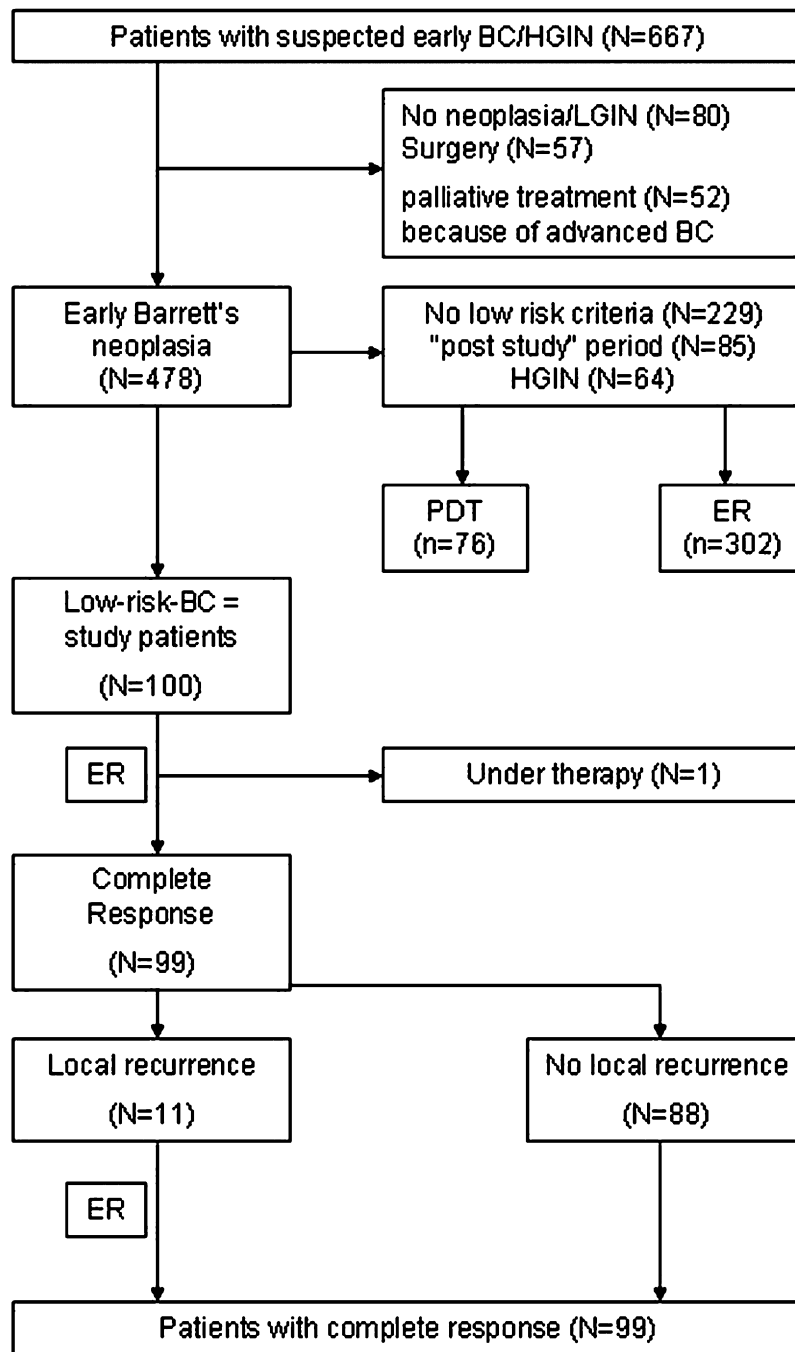
Figure 1. Flow diagram for study.

(M.V., M.S). The assessment included depth of invasion (mucosal level, 1-4), freedom from tumor on the lateral and basal resection margins of the specimen (R0/R1), the tumor's grade of differentiation, and involvement of the lymphatic vessels (L status) and veins (V status). HGIN is defined as not extending beyond the basement membrane. T1A (mucosal cancer) is defined as cancer that invades the lamina propria but not through the muscularis mucosa; T1B (submucosal cancer) is defined as cancer that extends through the muscularis mucosa into

the submucosa but does not invade the muscularis propria. Complete local remission (CLR) was defined as an R0 resection plus 1 normal endoscopic check-up examination. In R1 or Rx situations on the lateral margin of the resected specimen, 2 consecutive endoscopic check-up examinations without evidence of residual tumor were required to conclude that there was CLR. In R1 or Rx situations on the basis of the resected specimen, patients were defined as having treatment failure, and operable patients were scheduled for radical esophagectomy. By definition,

TABLE 1. Low-risk criteria*
Lesion diameter <20 mm; and macroscopically type I, IIa, IIb, or IIc lesions <10 mm; and
Well-differentiated or moderately differentiated adenocarcinoma (grading G1/G2); and
Lesions limited to the mucosa (m type) on the basis of staging procedures and proved by histology of the resected specimen
No invasion of lymph vessels or veins proved by histology of the resected specimen
*As defined in references 9 and 11.

TABLE 2. Data for 100 patients with low-risk esophageal adenocarcinoma	
Patients, n	100
Male/female	89/11
Mean and standard deviation age, y	62.1 ± 10.9
Short-segment Barrett's esophagus	69
Long-segment Barrett's esophagus	31
Macroscopic type	
Polypoid (type I)	17
Flat (II)	
Elevated, type IIa	37
Flat, type IIb	38
Depressed, type IIc	11
Elevated + depressed, type IIa + c	2
Differentiation	
Well differentiated (G1)	76
Moderately differentiated (G2)	24
Poorly differentiated (G3)	0
Undifferentiated (G4)	0

treatment was also considered to have failed if CLR was not achieved after 5 consecutive ERs. If CLR was achieved, ablation of the nonneoplastic part of the Barrett's epithelium was not generally performed in all patients, but individual decision making was allowed. Forty-nine patients underwent thermal ablation with argon plasma coagulation for short-segment Barrett's esophagus, or PDT with aminolevulinic acid (ALA) for long-segment Barrett's esophagus.

Endoscopic treatment was usually carried out with the patients under sedation and analgesia (with midazolam and/or pethidine) or in individual cases without premedication. After treatment, all of the patients received omeprazole or pantoprazole intravenously to begin with for 2 days and then 2 × 40 mg orally for at least 10 days, after that the proton pump inhibitor (PPI) dose was reduced to 40 mg per day. Long-term PPI treatment was carried out in accordance with the results of a 24-hour pH-metry. If the patient had a normal pH profile on 40 mg omeprazole or pantoprazole daily, this dose was maintained. When pH-metry revealed a pathologic pH profile, the PPI dose was increased to 40 mg twice daily and a pH-metry was repeated under that dose. The PPI dose was increased until the patient revealed a normal pH profile. On the day of treatment, the patients were only allowed to ingest liquids. On the following day, a check-up endoscopy examination was carried out. If the wound conditions were appropriate, the patient was allowed to resume a normal diet and was discharged 1 day after ER.

All of the patients were included in a strict follow-up program monitored in collaboration with the referring external gastroenterologists or hospitals. 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. Follow-up EGDs alternated between the referring physician and our unit. Referring physicians used 4-quadrant-biopsies and biopsies of visual lesions for follow-up examinations. Annual check-ups are planned thereafter. The check-ups 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. In addition, every second check-up included an EUS examination to assess the lymph-node status, as well as CT and abdominal US. Because of the close follow-up schedule, which was organized in collaboration with the referring physician, up to now in this setting, we fortunately had no drop outs. If the first or any other check-up showed residual neoplastic tissue or metachronous lesions, local endoscopic therapy was repeated after the patient had been provided with appropriate information. Metachronous lesions were defined as HIGN or early cancer detected during the follow-up after the patient had achieved CLR. The term "metachronous lesion" included local neoplastic recurrences or remnants at the margin of the prior resection zone, synchronous lesions not detected during the initial staging, and new lesions that developed during the follow-up in previously non-neoplastic residual Barrett's tissue.

Statistics and ethical considerations

Statistical analyses of the patients' data and clinical parameters are given as means (standard deviation) or as medians and ranges. Kaplan-Meier estimates of the survival curves were calculated for time to death with SPSS 10.0 (SPSS Inc, Chicago, Ill).[17] P values <.05 were considered to be significant (log-rank test). Patients who did not complete maximal follow-up or who were lost for

follow-up had their data treated as censored (Fig. 3). We also provided a table to the Kaplan-Meier plot, which illustrates the cumulative number of patients at risk.

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

The study was approved by the Ethics Commission of the Medical Council of the State of Hesse, and it was carried out in accordance with good clinical practice criteria.

RESULTS

The acute and the long-term results after ER are shown in Table 3. CLR was achieved in a total of 99 of the 100 patients. The treatment was classified as having failed in 1 patient. This 42-year-old man had a long-segment Barrett's esophagus, with a total length of 6 cm. During the initial staging, only 1 circumscribed lesion, with a diameter of less than 2 cm, was noted. Moderately differentiated adenocarcinoma (G2) was confirmed in the lesion by histology. After ER, the grade of differentiation was confirmed, and the tumor was only found to be invading as far as the newly developed muscularis mucosae, without invasion of the lymphatic vessels or veins. The tumor was removed with a healthy margin at the base, but the lateral margin was not tumor-free. A further ER, therefore, was carried out. However, CLR was not achieved over a 12-month period. Because the patient declined to undergo radical esophagectomy, a further 5 ERs were carried out over a length of more than 4 cm. The histologic assessment still corresponded to that of the first ER. The patient became tumor-free after the seventh ER, showing only LGIN in 2 consecutive check-up examinations.
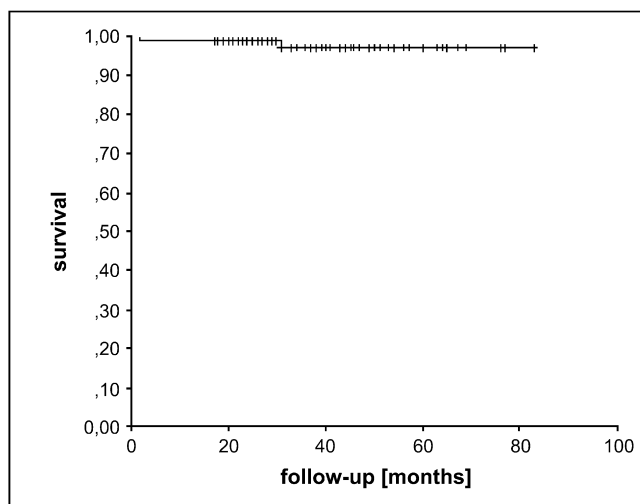
No severe complications, such as perforation, bleeding with a decrease in Hb >2 g/dL, or bleeding that required transfusion, occurred in any of the patients during the acute phase, and none of the patients died. Only minor complications occurred (hemorrhage after ER; n = 11), which were treated successfully in all cases by injecting saline solution–diluted epinephrine (1:100,000; 5–50 mL). There was no need for coagulation or clipping to achieve hemostasis in this series.

The median follow-up period at the time of writing was 33 months (range, 2-83 months; mean, 36.7 ± 15.45 months). No complications, such as ER-induced strictures, were observed during the follow-up period. During follow-up, 11 metachronous lesions were detected in 11 patients (local recurrence n = 6; different localization in Barrett's segment n = 5). All of these lesions successfully underwent repeat endoscopic treatment, and all of the affected patients achieved CLR again. The results of histologic examination showed that the metachronous lesions were
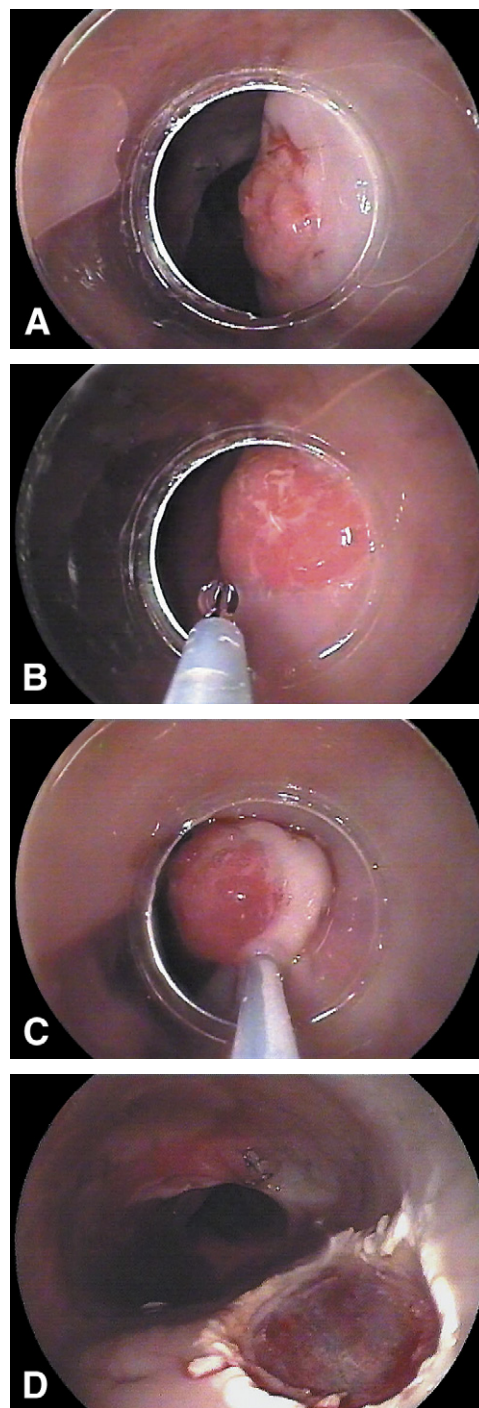
Figure 2. (A-D), ER with the suck-and-cut technique in a case of low-risk adenocarcinoma of the esophagus.

HGIN or mucosal cancer; submucosal infiltration was never observed by histology. At the time of writing, 98 of the 100 patients (98%) were alive. One patient with CREST syndrome (calcinosis, Raynaud phenomenon, esophageal motility disorders, sclerodactyly, and telangiectasia) died of pneumonia after 2 months, and the second patient died of a carcinoma in the oral cavity after 31 months.

Figure 3. Life-table analysis of estimated survival in 100 patients treated with ER. Number of patients at risk: patients who did not complete follow-up without event at that specific time point.

FU [months]	12	24	36	48	60	72
Number of pts at risk	99	80	43	21	11	3

Life-table analysis shows the estimated probability for survival over time for the patients. In the life-table analysis, the 1-, 2-, 3-, and 5-year survival rates were calculated as 99%, 99%, 98%, and 98%, respectively. (Fig. 3).

In 41 patients, pH-metry resulted in adequate acid suppression (mean pH value, 5.9 ± 0.4) under 40 mg omeprazole/pantoprazole and, in 59 patients, in inadequate suppression (mean pH value, 4.5 ± 1.0; average measurement period with pH value <4, $29\% \pm 17\%$). Of those patients with inadequate acid suppression at first pH-metry, 30 patients required 60 mg PPI, 27 required 80 mg PPI and 2 required 120 mg PPI. A lack of pH control at first pH-metry did not correlate significantly with a recurrence of neoplasia ($P > .05$).

DISCUSSION

The incidence of esophageal adenocarcinoma (Barrett's carcinoma) has increased dramatically during the last 20 years.[18-20] The development of carcinoma is causally linked to GERD, probably via the premalignant stages of what is known as Barrett's metaplasia, LGIN, and finally HGIN.[21,22]

When the acute results of ER for early adenocarcinoma of the Barrett's type are compared with those for the current criterion standard, radical esophageal resection, endoscopic therapy appears to be clearly superior to surgery with regard to morbidity and mortality. Even in experienced centers, esophageal resection for early neoplasia is associated with a mortality rate of at least 2% or

TABLE 3. Acute and long-term results in 100 patients with low-risk adenocarcinoma of the esophagus after endoscopic resection

Endoscopic resections (ERs) (n)	144
ERs per patient [mean ± SD (range)]	1.47 ± 0.89 (1-5)
Patients with	
1 resection (n)	70
2 resections (n)	20
3 resections (n)	6
4 resections (n)	1
5 resections (n)	3
R0/R1–Rx resection (%)	
R0 (basal margin)	100
R1 (basal margin)	0
R0 (lateral margin)	33
R1 (lateral margin)	34
Rx (lateral margin)	33
Major complications/ER (major bleeding, perforation, stricture)	0
Minor complications/ER	11/144
Minor bleeding (%)	8
Complete local remission (CLR)/patients	99/100 (99%)
Time [months] until CLR [mean ± SD]	1.9 ± 2.1
Range	1–18
Follow-up (months)	
Range	2–83
Mean ± SD	36.7 ± 15.4
Median	33
Metachronous lesions	11/100 (11%)
CLR after repeat endoscopic therapy	11/11 (100%)

R0 (basal margin), Basal margin of resected specimen histologically tumor free; *R1 (basal margin)*, basal margin of resected specimen histologically not tumor free; *R0 (lateral margin)*, lateral margin of resected specimen histologically tumor free; *R1 (lateral margin)*, lateral margin of resected specimen histologically not tumor free; *Rx (lateral margin)*, lateral margin could not be evaluated because of coagulation artefacts.

more and a morbidity rate of at least 40%.[2-5] In patients over the age of 70 years, the mortality rate associated with esophagectomy increases to more than 10%,[23] and, in hospitals with a low frequency of esophageal resections, it can amount to up to 20%, even in the hands of experienced surgeons.[24,25] By contrast, no deaths were recorded in the group of patients investigated in the present study. Severe complications, such as perforation, hemorrhage

that required transfusion, or strictures, were also not observed.

Although these welcome results document a clear superiority of endoscopic therapy over surgical treatment during the acute phase, it is the long-term course that will be decisive in establishing endoscopic therapy as the primary treatment procedure. A mean follow-up period of more than 3 years allows reliable assessment of the long-term survival. This shows that the calculated 5-year survival is 98%. It seems very unlikely that surgical treatment could achieve better survival than that in the patients in our study, but, certainly, conclusive evidence of the superiority of local endoscopic therapy could only be provided by a randomized prospective study that compared endoscopic therapy with radical esophagectomy, as the current criterion standard. While this would, in principle, be desirable, it would be difficult to justify such a study in view of the clear results presented here and because of the high number of patients necessary for inclusion in this study to show noninferiority of endoscopic therapy with respect to mortality.

The reason for the extremely favorable 5-year survival rate after endoscopic therapy lies in the fact that mucosal adenocarcinomas in the esophagus almost never show lymph-node metastases at the time of diagnosis. In the largest series of surgically treated mucosal adenocarcinomas of the esophagus so far published (n = 41), lymph-node metastases were not observed in a single node from among 350 resected.[4] In a small series with only 15 patients with mucosal cancer, only 1 of more than 300 lymph nodes showed metastasis.[26] These surgical data and the results of the present study provide the basis for the conclusion that such patients should undergo endoscopic treatment instead of surgery. The situation is completely different in patients with submucosal invasion, in whom lymph-node metastases can be expected in 15% to 25%,[3,4,26] so that esophagectomy is the treatment of choice in such cases.

In the group of patients with early Barrett's carcinoma presented here, the rate of metachronous neoplastic lesions was 11%. It was possible to carry out repeat endoscopic therapy and to achieve a renewed CLR in all cases. Nevertheless, the risk of metachronous lesions underlines the need for a rigorous follow-up program, in which precise inspection of the luminal surface by using a high-resolution endoscope and additional chromoendoscopy undoubtedly represent the most important examinations.

This prospective observational study only included patients with Barrett's cancer who met the low-risk criteria (Table 1). It remains to be seen whether the results of endoscopic therapy will be similarly good in patients with, for example, larger tumors or multifocal cancer limited to the mucosa, good or moderate differentiation, and no lymphatic or venous infiltration. In any case, a longer interval until CLR is achieved can be expected.[9] HGIN was also not included in this study, because the diagnostic and therapeutic strategy in these cases is still controversial, and a more expectant approach is regarded as adequate by many groups, in contrast to confirmed cases of Barrett's cancer.[2,27]

With regard to the various endoscopic techniques available, there is no question that ER is the method of choice if the malignant lesion can be detected precisely by endoscopy. The suck-and-cut technique allows the removal of mucosal lesions with a diameter of 10 to 30 mm, and complete histopathologic processing to assess tumor-free margins on the sides and at the base, depth of tumor invasion, grade of differentiation, and involvement of lymphatic vessels and veins. PDT and thermal ablation methods do not provide these options, owing to the nature of the techniques. In addition, PDT with porphyrins as photosensitizers is associated with major complications (mainly strictures) in up to 30% of the patients.[8] Thermal procedures and/or PDT with ALA as the photosensitizer might, however, be appropriate as low-risk methods of removing minimal residual lesions and reducing the rate of metachronous lesions by providing as complete as possible an ablation of nonneoplastic or not yet neoplastic residual Barrett's mucosa. This hypothesis is currently being investigated in an ongoing study.

In summary, the results of the present prospective study in 100 consecutive patients with low-risk early esophageal adenocarcinoma show that endoscopic therapy appears to be superior to surgery with regard to morbidity and mortality, and at least equivalent to it with regard to the long-term survival. In addition, it provides a further decisive advantage by maintaining the patients' quality of life, which is substantially impaired after esophageal resection for a prolonged period at least and often for the rest of the patient's life. We concluded that patients with low-risk early esophageal adenocarcinoma should primarily undergo endoscopic therapy and that esophageal resection should become a reserve procedure. However, as in the case of open esophageal surgery, this conclusion presupposes the availability of sufficient experience (in terms of the frequency of procedures conducted) in the diagnosis and endoscopic treatment of early upper-GI tract cancers.

DISCLOSURE

We, the authors, have nothing to disclose.

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