Do we still need EUS in the workup of patients with early esophageal neoplasia? A retrospective analysis of 131 cases CME

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Background: EUS is often used for locoregional staging of early esophageal neoplasia. However, its value compared with that of endoscopic examination and diagnostic endoscopic resection (ER) may be questioned because diagnostic ER allows histological assessment of submucosal invasion and other risk factors for lymph node metastasis, eg, poor differentiation/lymphovascular invasion.

Objective: To evaluate how often patients were excluded from endoscopic treatment of esophageal neoplasia based on EUS findings.

Design: Retrospective cohort study.

Setting: Tertiary care institution.

Patients: Patients with early esophageal neoplasia.

Interventions: EUS, diagnostic ER.

Main Outcome Measurements: Number of patients excluded from endoscopic treatment based on EUS results.

Results: A total of 131 patients were included (98 men, 33 women; age 66 ± 13 years). In 105 of 131 patients (80%), EUS findings were unremarkable. In 25 of 105 patients (24%), diagnostic ER showed submucosal invasion (n = 17), deep resection margins positive for cancer (n = 2, confirmed at surgery), or poor differentiation/lymphovascular invasion (n = 6). In 26 of 131 patients (20%), EUS findings raised the suspicion of submucosal invasion and/or lymph node metastasis. In the 14 of 26 patients (54%) with abnormal EUS findings, endoscopy results were unremarkable. Diagnostic ER showed submucosal invasion in 7 of 14 (50%) patients, whereas no lymph node metastasis risk factors were found in 7 of 14 patients (50%), who subsequently underwent curative endoscopic treatment. In 12 of 26 patients (46%) with abnormal EUS, endoscopy also raised doubts on whether curative endoscopic treatment could be achieved. After diagnostic ER, no risk factors for lymph node metastasis were found in 3 of 12 patients (25%).

Limitation: Retrospective study.

Conclusions: This study shows that EUS has virtually no clinical impact on the workup of early esophageal neoplasia and strengthens the role of diagnostic ER as a final diagnostic step. (Gastrointest Endosc 2011;73:662-8.)

Abbreviations: ER, endoscopic resection; EUS-FNA, EUS-guided FNA; HGIN, high-grade intraepithelial neoplasia; IQR, interquartile range.

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In the past 2 decades, endoscopic therapy has proved its role in the management of early neoplasia (ie, high-grade intraepithelial neoplasia [HGIN] or intramucosal cancer) of the esophagus and cardia. Endoscopic therapy offers a safe, effective, and significantly less-invasive alternative to surgical resection.[1-4] Only neoplasia limited to the mucosal layer, which is associated with a minimal risk of lymph node metastasis, is indicated for endoscopic management.[5-8] In the case of submucosal infiltration, the risk of lymphatic involvement increases significantly, and patients need to be referred for surgical resection.[7,8] The workup of patients who are considered for endoscopic treatment should therefore be aimed at identifying patients with neoplasia confined to the mucosa and thus with a low risk of lymphatic spread.[9,10]

In addition to endoscopic examination, EUS is often used to evaluate the infiltration depth of a lesion and the presence or absence of suspicious lymph nodes. Although EUS is the most accurate technique for locoregional staging of esophageal and cardia cancer, several studies have demonstrated that EUS is a suboptimal technique to distinguish mucosal from submucosal lesions and to assess for positive lymph nodes in the case of early neoplasia.[11-16]

Diagnostic endoscopic resection (ER) may be used as a final step in the workup for endoscopic treatment of early neoplasia. ER of a neoplastic lesion provides a relatively large tissue specimen that allows accurate histological staging of the infiltration depth as well as other prognostic factors such as tumor differentiation grade and lymphatic and vascular involvement (Fig. 1).[17]

In our center, ER is used in the workup of virtually all patients with early neoplasia of the upper GI tract, and because it provides more accurate information on infiltration depth than EUS, we questioned the value of EUS in this setting.

Most studies have evaluated the accuracy of EUS for T and N staging. However, this does not allow assessment if EUS affects making appropriate decisions on whom to treat endoscopically. The aim of this retrospective study was therefore not to study the accuracy of EUS for T and N staging, but to evaluate how often the outcome of EUS changed the management approach of our patients with early esophageal neoplasia.

Take-home Message

- Along with endoscopic examination and diagnostic endoscopic resection (ER), EUS only has a limited value in the selection of patients for endoscopic treatment.
- The results of this study strengthen the role of diagnostic ER as a final diagnostic step because it allows accurate histological assessment of risk factors for lymph node metastasis.

METHODS

Patient selection and data collection

For this study, 2 reviewers independently performed a retrospective evaluation of all patients undergoing upper GI EUS between May 2001 and June 2007, at the Academic Medical Center, Amsterdam, the Netherlands. Only patients undergoing EUS for staging of early esophageal or cardia neoplasia who were considered for endoscopic treatment were included. Exclusion criteria were (1) all other indications than staging of neoplasia, (2) previous treatment of esophageal or cardia cancer, or (3) no confirmation of HGIN/intramucosal cancer in the ER specimen or surgical resection specimen.

For all included patients, relevant information was retrospectively retrieved from endoscopy, radiology, histology, and surgery reports and recorded on standardized case report forms.

Endoscopic workup

Endoscopic workup was performed by endoscopists with experience in the field of early esophageal neoplasia, using high-quality endoscopes (Olympus GIF-H180, GIFQ240Z, GIFQ260Z, or GIF-H260Z; Olympus Endoscopy, Tokyo, Japan), often supplemented with advanced imaging techniques such as chromoendoscopy, autofluorescence endoscopy, and/or narrow-band imaging. The type of lesion was reported, distinguishing squamous cell lesions, Barrett's lesions, and cardia neoplasia. The lesion size and type according to the Paris classification were recorded: type 0-Ip, polypoid; 0-Is, sessile; type 0-IIa, elevated; type 0-IIb, flat; type 0-IIc, depressed; and type 0-III, excavated.[18,19] In addition, it was reported whether a lesion appeared to be suspicious for deep submucosal infiltration and whether it seemed to be accessible with ER, based on criteria such as lesion size, type, location, and movement of the lesion with peristalsis.

For EUS examination, a standard radial EUS endoscope (GIF-UM130, GIF-UM160, XGF-UE140-AL5, GF-UE160-AL5; Olympus Europe, Hamburg, Germany), a high-frequency EUS 20-MHz catheter probe (UM-3-R; Olympus Europe), or both were used. If a lesion could be visualized with EUS, the infiltration depth was recorded as being mucosal, submucosal, doubtful, or not assessable. Furthermore, the presence of suspicious lymph nodes was assessed, and in the case of EUS-guided FNA (EUS-FNA), the number of punctured nodes and cytological results were recorded.

For each of these examinations, whether the results changed the management strategy by excluding patients from further workup for endoscopic treatment was recorded, ie, excluding patients from diagnostic ER and directly referring the patient for surgery.

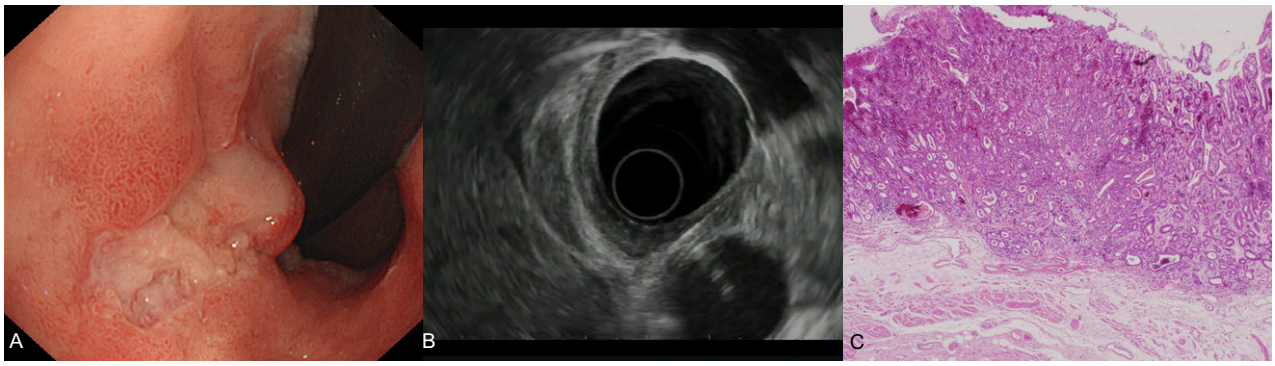

Figure 1. Images obtained during the workup of an early Barrett's cancer. **A**, Retroflexed view on a type 0-IIa-IIc lesion in the distal part of a Barrett's esophagus. The lesion was suspicious for submucosal invasion, but appeared accessible for diagnostic ER. **B**, During EUS examination, the lesion appeared to be infiltrating the submucosa (Tsm). **C**, The lesion was removed by diagnostic ER, and histological evaluation of the resected specimen showed a moderately differentiated adenocarcinoma limited to the muscularis mucosae (Tm3), without lymphovascular invasion.

ER

ER was performed as the final diagnostic step in the workup for endoscopic treatment in all patients with endoscopically visible abnormalities, no matter how subtle. During detailed endoscopic examination, the target lesion was delineated and marked with coagulation markings. ER was performed with the ER cap technique after submucosal lifting, using either an 18-mm flexible oblique cap (D206-5; Olympus GmbH, Hamburg, Germany) if there was a suspicion on submucosal infiltration or a 16.1-mm hard oblique cap (MAJ-297/296; Olympus GmbH) if the lesion appeared to be mucosal. Starting in November 2004, ER was also performed using the multiband mucosectomy technique (Duette; Cook Endoscopy, Limerick, Ireland), without previous submucosal lifting, for lesions that were not suspicious for submucosal infiltration. After complete endoscopic removal of the marked target area, all resection specimens were retrieved, paraffin embedded, and fixed in formalin for histological evaluation.

Histological evaluation of ER specimens

ER specimens were sectioned into 2-mm slices, embedded in paraffin, and at a minimum of 4 levels, 200-μm thick slices were cut, mounted on glass slides, and routinely stained with hematoxylin and eosin. All slides were evaluated by a junior pathologist supervised by an experienced GI pathologist (F.J.W.t.K., M.V.). The presence of neoplasia and cancer was evaluated according to World Health Organization classification,[20] as well as tumor infiltration depth, differentiation grade, presence of lymphovascular infiltration, and the radicality of the resection at the deep resection margin.

Patient management

The optimal treatment strategy for each patient was based on the outcome of the diagnostic ER procedure. If a diagnostic ER showed risk factors for lymphatic spread, ie, submucosal invasion (or T1m3 cancer for patients with squamous cell dysplasia), poorly differentiated cancer, lymphovascular infiltration, or tumor involvement at the deep resection margin, patients were considered for surgery. Patients in whom a diagnostic ER was not feasible because of poor lifting or the inability to suction the lesion into the ER cap, both possible signs of submucosal growth, were also considered for surgery. Patients who were not surgical candidates because of age or comorbidity or who refused surgery were referred for chemoradiotherapy or were further managed endoscopically on a relative indication. The majority of patients with Barrett's neoplasia and no contraindications to endoscopic management after diagnostic ER underwent additional treatment to eradicate all Barrett's mucosa using one of the following: photodynamic therapy,[21] stepwise radical ER,[22,23] or radiofrequency ablation.[24]

After endoscopic treatment, all patients entered endoscopic follow-up. EUS during follow-up was not routinely performed if patients had no risk factors for lymph node metastasis (mucosal cancer, well/moderately differentiated cancer, no lymphovascular infiltration, and radical resection of neoplasia). Patients with risk factors for lymph node metastasis who were treated endoscopically on a relative indication all underwent EUS in addition to endoscopic examination with biopsies during follow-up.

Outcome parameters

The following were the outcome parameters: the frequency with which patients were excluded from endoscopic treatment based solely on the outcome of EUS and the frequency with which EUS detected a recurrence of neoplasia during follow-up.

Statistical analysis

Statistical analysis was performed with SPSS 12.0.1 Software for Windows (SPSS Inc, Chicago, Ill). For descriptive statistics, the mean (± standard deviation) was used in cases of a normal distribution of variables, and the median (interquartile range [IQR]) was used for variables with a

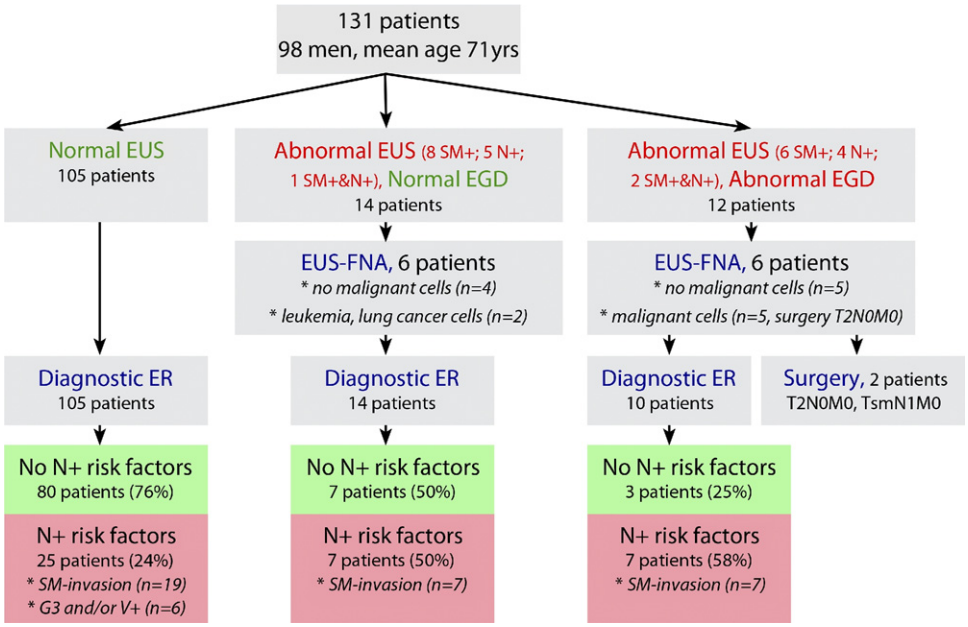

Figure 2. Chart illustrating patient flow after endoscopic and EUS examination. SM+, submucosal infiltration; N+, lymph node metastasis; G3, poor differentiation; V+, vascular infiltration.

skewed distribution. Where appropriate, the Student *t* test and the Mann-Whitney *U* test were used.

RESULTS

Patients

Between May 2001 and July 2007, a total of 1027 patients underwent esophageal EUS. We found 131 patients eligible for this study (98 men, 33 women; mean age 66 ± 12.6 years). Early neoplasia of the cardia was diagnosed in 7 patients; neoplasia arose in Barrett's esophagus in 114 patients, and 10 patients had early esophageal squamous cell neoplasia.

Endoscopy and EUS findings in the workup

Normal EUS. All 131 patients underwent an endoscopic workup and EUS. In 105 of 131 (80%) patients, EUS did not show any suspicion on deep submucosal invasion or suspicious lymph nodes. All 105 patients underwent ER of their endoscopically visible lesion, and in 25 of the 105 patients (24%) the ER specimens showed submucosal invasion (n = 17), poor differentiation and/or lymphovascular invasion (n = 6), or deep resection margins positive for cancer (n = 2; subsequent surgery revealed T1sm1N0 and T3N0) (Fig. 2).

Abnormal EUS. In 26 of 131 patients (20%), abnormalities were found during EUS examination: suspected submucosal invasion (n = 14), suspicious lymph nodes (n = 9), or both (n = 3). To investigate the relative contribution of EUS over the preceding endoscopic examination, cases were separated into 2 groups: abnormal EUS and unremarkable endoscopy and abnormal EUS and abnormal endoscopy.

In 14 patients with abnormal EUS findings, endoscopic examination was unremarkable and did not raise any doubts about whether curative endoscopic treatment could be achieved. The abnormalities found on EUS in these 14 patients consisted of suspected submucosal invasion (n = 8), suspicious lymph nodes (n = 5), or both (n = 1). In the 6 patients with suspicious lymph nodes, EUS-FNA was performed and did not show malignant cells in 4 patients. In 2 patients, atypical cells were found, originating from undiagnosed small cell lung cancer and known chronic lymphatic leukemia.

Diagnostic ER confirmed submucosal invasion in 7 of 14 patients (50%). However, in 7 of 14 patients (50%) with abnormal EUS findings, no submucosal invasion or other risk factors for lymph node metastasis were found on diagnostic ER (Fig. 2). These 7 patients were successfully treated endoscopically without any signs of recurrent neoplasia after a median follow-up of 42 (IQR 26-72) months.

In the other 12 patients with abnormal EUS findings (suspected submucosal invasion [n = 6], suspicious lymph nodes [n = 4], both [n = 2]), findings on endoscopic examination were also abnormal and had already raised doubts on whether the patients could be treated endoscopically, either because the lesion was not accessible or was too widespread for ER or because it appeared to be invading the submucosa. These doubts were confirmed in 8 of 12 patients (67%) by diagnostic ER that showed submucosal invasion (n = 4), poorly differentiated cancer/lymphovascular invasion (n = 2), a nonlifting sign in an

87-year-old patient who was subsequently treated with radiotherapy, and surgery in 1 patient (TsmN1M0). In the 6 patients with suspicious lymph nodes, EUS-FNA was performed and did not show malignant cells in 5 patients. In 1 of these patients with negative EUS-FNA findings, subsequent surgery showed tumor localization in 4 of 16 resected lymph nodes (TsmN1M0, see earlier). In 1 of 12 patients (8%) in whom endoscopic treatment was considered doubtful given severe pre-existing stenosis, EUS-FNA showed malignant cells. The patient was referred for esophagectomy (T2N0M0); however, none of the 16 resected lymph nodes showed metastasis.

Three of the 12 patients (25%) with abnormal findings on both EUS and endoscopy did not have risk factors for lymph node metastasis in the diagnostic ER specimens and were further treated endoscopically with no signs of recurrence of neoplasia after a median follow-up of 30 months (Fig. 2).

EUS during follow-up

A total of 53 patients underwent EUS in addition to endoscopic examination during follow-up. The median follow-up time from the removal of the neoplasia until the last endoscopy or the last EUS examination was 39 months (IQR 22-56) and 25 months (IQR 14-47), respectively. A median of 8 endoscopies (IQR 6-10 endoscopies) and 2 EUS examinations (IQR 1-3) were performed during follow-up in these 53 patients.

Neoplasia recurred in 10 of 53 patients (19%), all in patients with an initial diagnosis of Barrett's neoplasia. There were recurrences in areas of residual Barrett's mucosa in 8 patients, in a recurrent island of Barrett's mucosa after eradication of all Barrett's mucosa by photodynamic therapy in 1 patient, and at the cardia after radical endoscopic resection of all Barrett's mucosa in 1 patient. All 10 intraesophageal recurrences were detected primarily during endoscopic examination. EUS findings were abnormal in 3 of 10 patients. The first patient had T1/2N1Mx on EUS; a repeat ER showed poorly differentiated cancer, and the patient was referred for surgery (T1N1M0). The second patient had T2N1Mx on EUS; biopsy samples showed poorly differentiated cancer, and the patient was referred for surgery (T3N1M0). The third patient had TxN1Mx on EUS; a repeat ER showed HGIN, and EUS-FNA showed no malignant cells.

In 7 of 10 patients with a recurrence detected during endoscopy, EUS findings were normal, and a repeat ER confirmed HGIN (n = 3) or T1m2 cancer (n = 4).

In 4 patients with no signs of recurrence on endoscopy, EUS-FNA was performed to sample suspicious lymph nodes, which did not show malignant cells in any of the cases.

No recurrence of neoplasia was detected solely by EUS or missed during endoscopic examination.

DISCUSSION

EUS is still routinely used in the workup for endoscopic therapy in most centers, despite disappointing sensitivity and specificity for infiltration depth and lymph node metastasis demonstrated by several studies.[11-16] We therefore sought to evaluate from clinical and practical points of view how often the outcome of EUS, after endoscopic examination, changed patient management and excluded patients from diagnostic ER during the workup for possible endoscopic management.

Although EUS is an accurate technique for staging esophageal and cardia cancer, a number of studies have demonstrated that the resolution of standard EUS is not sufficient to distinguish mucosal from submucosal invading lesions in the case of early neoplasia.[11-15] Even when using high-frequency EUS miniprobes, the discrimination between mucosal and submucosal lesions is only 80% accurate.[14,16] In particular in Barrett's esophagus, the heterogeneous tissue architecture with crypts and villi, the mucosal inflammation, and often doubled muscularis mucosae impede accurate EUS assessment. Furthermore, EUS evaluation of neoplastic lesions located in the distal esophagus and cardia may be complicated because of the anatomical conditions at the esophagogastric junction.[11,16]

The diagnostic accuracy of EUS for N staging in esophageal cancer ranges between 68% and 86%.[11-15] EUS-FNA of suspicious lymph nodes has been shown to increase the specificity of EUS N staging and can increase the accuracy of EUS N staging by as much as 90% in advanced esophageal carcinomas.[25] In our study, 12 patients underwent EUS-FNA, which showed malignant cells in 3 patients: 1 patient had a known chronic lymphatic leukemia, another patient had undiagnosed small cell lung cancer, and the third patient with malignant cells on EUS-FNA underwent surgery, which showed T2N0M0 cancer. This false-positive finding was probably caused by contamination of the EUS-FNA needle by puncturing through the neoplastic lesion. Although this should always be avoided, it may be difficult to avoid puncturing through neoplastic mucosa, especially in the case of suspicious lymph nodes within the peritumoral region. In these cases, it may be advisable to remove the neoplasia first by endoscopic resection to then be able to sample the lymph node without contamination by the tumor.[26] In addition, another patient who was referred for surgery to resect a lesion that was too widespread for endoscopic treatment and who had a negative EUS-FNA did have 4 of 16 positive lymph nodes in the esophagectomy specimen.

In this study, 105 patients had normal EUS findings without signs of submucosal growth or lymph node metastasis. After diagnostic ER, however, 17 patients did have submucosal invasion, 2 patients had deep resection margins positive for cancer with T1sm1 and T3 cancer at subsequent surgery, and 6 patients had poorly differenti-

ated cancer and/or lymphovascular invasion. Thus, based on the diagnostic ER, 25 of the 105 patients (24%) with normal EUS findings had risk factors for lymph node metastasis that would have been missed without histological correlation of the diagnostic ER. Normal EUS findings should thus not be considered sufficient to perform endoscopic ablation therapy (eg, photodynamic therapy, radiofrequency ablation) without diagnostic ER of all visible abnormalities first for accurate staging of the disease.

Furthermore, 14 patients in whom ER was possible after endoscopic examination had signs of submucosal invasion or lymph node metastasis on EUS. Diagnostic ER confirmed submucosal invasion in 7 patients. In the other 7 patients, however, there was no evidence of submucosal invasion or other risk factors for lymph node metastasis in the ER specimens. Thus, abnormal EUS findings alone are not enough to refer a patient for surgery without a diagnostic ER first because half of the patients may still be eligible for curative endoscopic treatment.

Last, there was a group of 12 patients in whom endoscopic examination raised doubts on the feasibility of ER, in addition to an abnormal finding on EUS. As already described, EUS-FNA in 1 patient resulted in a false-positive diagnosis of tumor spread, and another patient undergoing surgery did have lymph node metastases in the resection specimen that were missed during EUS-FNA. The other 10 patients underwent diagnostic ER, after which 3 patients still had an indication for curative endoscopic treatment. Thus, even if findings on both endoscopic examination and EUS are abnormal, it is recommended not to directly proceed to surgery but to perform a diagnostic ER first, provided that the lesion is accessible for a safe ER. In this respect, it is also noteworthy to mention that none of the diagnostic ER procedures in this study resulted in a severe complication.

The results of this study strengthen our opinion that the optimal workup for endoscopic treatment of early esophageal and cardia neoplasia should consist of detailed endoscopic examination to evaluate the macroscopic appearance of a lesion and to evaluate whether a lesion is accessible for ER. If the endoscopic appearance of a lesion does not raise suspicion on deep submucosal infiltration, the lesion may be removed by ER. The resected specimen then allows for accurate histological evaluation of infiltration depth and other prognostic factors. Patients with mucosal lesions can be managed by further endoscopic treatment or follow-up, whereas a diagnosis of submucosal infiltration, poorly or undifferentiated cancer, lymphovascular invasion, or tumor involvement at the deep resection margin warrants surgical treatment. We think that this approach allows the optimal selection of patients for endoscopic management, omitting the additional step of EUS, which often does not result in a clear-cut differentiation between mucosal and submucosal lesions, lacks assessment of other prognostic factors, and has a poor positive predictive value for the presence of lymph node metastasis.

Follow-up with EUS along with endoscopic examination was performed in 53 patients. Neoplasia recurred in 10 of these 53 patients, detected primarily during endoscopic examination. None of the recurrences was solely detected by EUS. This suggests that after successful endoscopic treatment, endoscopic examination is the most important modality to detect intraesophageal recurrence that can then undergo biopsy or be removed by ER for histological confirmation. Although we cannot conclude this from our results, it may suffice to reserve EUS for those patients with a higher risk of lymph node metastasis based on biopsy or ER specimen histology, instead of performing routine follow-up EUS after endoscopic therapy.

This study has several limitations that need to be discussed. First, this was a retrospective study, and therefore there may have been selection bias in patient inclusion. However, by having 2 independent researchers screening all patients undergoing any type of EUS within the predetermined time frame to identify patients undergoing EUS for the workup of early esophageal or cardia neoplasia, we tried to minimize selection bias. Second, endoscopic assessment and EUS were often not performed as independent investigations, and we cannot therefore exclude the possibility that the outcomes of endoscopy and EUS influenced each other. However, because we did not attempt to compare the diagnostic accuracy of endoscopic examination with that of EUS, but aimed to evaluate the clinical value of EUS along with endoscopic examination, this back-to-back use of endoscopy and EUS, as routinely practiced in most centers, may not be very relevant for the outcomes of this study. Furthermore, the numbers in some of the subgroups were relatively small and conclusions based on these small groups should therefore be considered carefully. Last, all endoscopic, EUS, and ER procedures were performed by endoscopists with extensive experience in this field, and extrapolation of the results to centers with less experience in the management of early neoplasia should be performed with caution.

In conclusion, in this retrospective study of 131 patients with early esophageal and cardia neoplasia, we found that the additional value of EUS during the workup including ER and follow-up was very limited. In none of the patients did EUS alone change the treatment policy. In addition, the results of this study strengthen the role of diagnostic ER as a final step in the workup for endoscopic treatment.

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