Endoscopic eradication of Barrett's oesophagus with early neoplasia
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Do we still need endoscopic ultrasound (EUS) in the work-up of patients with early oesophageal neoplasia? A retrospective analysis of 131 cases

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INTRODUCTION

The last two decades, endoscopic therapy has proven its role in the management of early neoplasia (i.e. high-grade intraepithelial neoplasia (HGIN) or intramucosal cancer (IMC)) of the oesophagus and cardia. Endoscopic therapy offers a safe, effective and significantly less invasive alternative to surgical resection. Only neoplasia limited to the mucosal layer, which is associated with a minimal risk for lymph node metastasis, is indicated for endoscopic management.5,6 In the case of submucosal infiltration the risk of lymphatic involvement increases significantly and patients need to be referred for surgical resection. The work-up 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 for lymphatic spread. Next to endoscopic inspection, endoscopic ultrasonography (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 oesophageal 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. Diagnostic endoscopic resection (ER) may be used as a final step in the work-up for endoscopic treatment of early neoplasia. ER of a neoplastic lesion provides a relatively large tissue specimen, which allows for accurate histological staging of the infiltration depth, as well as other prognostic factors such as tumour differentiation grade and lymphatic and vascular involvement (Fig. 1). In our center, ER is used in the work-up of virtually all patients with early neoplasia of the upper GI tract and since 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 assessing if EUS rightfully impacts on making appropriate decisions on who to treat endoscopically and who not. 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 oesophageal neoplasia.

Figure 1. Images obtained during work-up of an early Barrett’s cancer.
A: Type 0-IIa-IIc lesion, suspicious for submucosal invasion, but accessible for diagnostic ER. B: During EUS the lesion appeared to be infiltrating the submucosa. C: The lesion was removed by ER and histological evaluation showed a moderately differentiated adenocarcinoma, limited to the muscularis mucosae, without lymph-vascular invasion.
METHODS

Patient selection and data collection
For this study two reviewers independently performed a retrospective evaluation of all patients undergoing upper gastrointestinal EUS between May 2001 and June 2007, at the Academic Medical Center, Amsterdam, the Netherlands. Only patients undergoing EUS for staging of early oesophageal or cardia neoplasia who were considered for endoscopic treatment were included. Exclusion criteria were: (1) all other indications than staging of neoplasia; (2) prior treatment of oesophageal or cardia cancer; (3) no confirmation of HGIN/IMC 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 work-up
Endoscopic work-up was performed by endoscopists with experience in the field of early oesophageal neoplasia, using high-quality endoscopes (Olympus GIF-H180, GIF240Z, GIF260Z, or GIF-H260Z, Olympus Endoscopy, Tokyo, Japan), often supplemented with advanced imaging techniques such as chroendoendoscopy, 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 typification according to the Paris classification were recorded: type 0-Ip being polypoid, 0-Ia sessile, type 0-IIa elevated, type 0-IIb flat, type 0-IIc depressed, and type 0-III excavated. In addition, it was reported if a lesion appeared to be suspicious for deep submucosal infiltration, and if it seemed to be accessible for ER, based on criteria such as lesion size, type, location, and movement of the lesion with peristalsis.

For the EUS examination a standard radial EUS-scanner (GIF-UM130, GIF-UM140, XGF-UE140-AL5, GF-UE160-AL5, Olympus Europe), a high-frequency EUS 20-MHz catheter probe (UM-3-R; Olympus), 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-FNA, the number of punctured nodes and cytological results were recorded. For each of the above mentioned examinations, it was recorded if its results changed the management strategy by excluding patients from further work-up for endoscopic treatment, i.e. excluding patients from diagnostic ER and directly referring the patient for surgery.

Endoscopic resection
ER was performed as the final diagnostic step in the work-up for endoscopic treatment in all patients with endoscopically visible abnormalities, no matter how subtle. During detailed endoscopic inspection, 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 (ID206-5, 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, Hamburg, Germany) if the lesion appeared to be mucosal. From November 2004, ER was also performed using the multi-band mucosectomy (MBM) technique (Duette®, Cook endoscopy, Limerick, Ireland), without prior 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, pinned down on paraffin and fixed in formalin for histological evaluation.

Histological evaluation of ER specimens
ER specimens were sectioned in 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 eosine. All slides were evaluated by a junior pathologist supervised by an experienced GI pathologist (FK and MV). Presence of neoplasia and cancer was evaluated according to WHO classification, as well as tumour infiltration depth, differentiation grade, presence of lymph-vascular 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, i.e. submucosal invasion (or T1m3 cancer for patients with squamous cell dysplasia), poorly differentiated cancer (G3), lymph-vascular infiltration or tumour involvement at the deep resection margin, patients were considered for surgery. Patients in whom a diagnostic ER was not feasible, due to 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 due to age, co-morbidity 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 for endoscopic management after diagnostic ER, underwent additional treatment to eradicate all Barrett’s mucosa using either photodynamic therapy, stepwise radical ER, or radiofrequency ablation. 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 lymph-vascular 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 inspection with biopsies during follow-up.

Outcome parameters
1. The frequency in which patients were excluded from endoscopic treatment based solely on the outcome of EUS.
2. The frequency with which EUS detected recurrence of neoplasia during follow-up.

Statistical analysis
Statistical analysis was performed with SPSS 12.0.1 Software for Windows. For descriptive statistics mean (±SD) was used in case of a normal distribution of variables, and median (interquartile range, IQR) was used for variables with a skewed distribution. Where appropriate, the student t test and the Mann-Whitney test were used.
RESULTS

Patients
Between May 2001 and July 2007 a total number of 1,027 patients underwent oesophageal EUS. We found 131 patients eligible for this study (98 men, mean age 66 ±12.6 years). Early neoplasia of the cardia was diagnosed in 7 patients; neoplasia arising in Barrett’s oesophagus in 114 patients and 10 patients had early oesophageal squamous cell neoplasia.

Endoscopy and EUS findings during work-up

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

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

In 14 patients with an abnormal EUS, endoscopic inspection was unremarkable and did not raise any doubts on the attainability of curative endoscopic treatment. The EUS abnormalities 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, which did not show malignant cells in 4 patients. In two patients atypical cells were found, originating from an undiagnosed small cell lung cancer and known chronic lymphatic leukemia. Diagnostic ER confirmed submucosal invasion in 7/14 (50%) patients. However, in 7/14 (50%) patients with an abnormal EUS, no submucosal invasion or other risk factors for lymph node metastasis were found upon 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] months.

In the other 12 patients with an abnormal EUS (suspected submucosal invasion (n=6), suspicious lymph nodes (n=4), both (n=2)), endoscopic inspection was also abnormal and had already raised doubts on attainability of endoscopic treatment, either because the lesion was not accessible or too widespread for ER, or because it appeared to be invading the submucosa. These doubts on attainability of endoscopic treatment were confirmed in 8/12 (67%) patients by EUS-FNA that showed submucosal invasion (n=4), poorly differentiated cancer/lymph-vascular invasion (n=2), non-lifting sign in an 87-yr old patient who was subsequently treated with radiotherapy, and by surgery in one patient (TsmN1M0). In the 6 patients with suspicious lymph nodes EUS-FNA was performed, which did not show malignant cells in 5 patients. In one of these patients with a negative EUS-FNA, subsequent surgery showed tumour localization in 4 of 16 resected lymph nodes (TsmN1M0, see above). In 1/12 (8%) patient in whom endoscopic treatment was considered doubtful given severe pre-existing stenosis, EUS-FNA showed malignant cells. The patient was referred for oesophagectomy (T2N0M0) yet none of the 16 resected lymph nodes showed metastasis. Three of the 12 patients (25%) with both an abnormal EUS and abnormal 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 inspection during follow-up. Median follow-up time from the removal of the neoplasia until the last endoscopy or the last EUS investigation was 39 (IQR 22-56) months and 25 (IQR 14-47) months, respectively. A median of 8 (IQR 6-10) endoscopies and 2 (IQR 1-3) EUS investigations were performed during follow-up in these 53 patients. Recurrence of neoplasia occurred in 10/53 patients (19%), all in patients with an initial diagnosis of Barrett’s neoplasia. Recurrences occurred 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 one patient, and at the cardia after radical endoscopic resection of all Barrett’s mucosa in one patient. All 10 intra-oesophageal recurrences were detected primarily during endoscopic inspection. EUS was abnormal in 3/10 patients: the first patient had T1/2N1Mx upon EUS, repeat ER showed poorly differentiated cancer and the patient was referred for surgery (T1N1M0); the second patient had T2N1Mx upon EUS, biopsies showed poorly differentiated cancer and the patient was referred for surgery (T3N1M0); the third patient had TxN1Mx upon EUS, repeat ER showed HGIN, EUS-FNA showed no malignant cells. In 7/10 patients with a recurrence detected during endoscopy, EUS was normal and repeat-ER confirmed HGIN (n=3) or T1m2 cancer (n=4). In 4 patients with no signs of recurrence upon 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 and missed during endoscopic inspection.

DISCUSSION
EUS is still routinely used during work-up for endoscopic therapy in most centers, despite disappointing sensitivity and specificity for infiltration depth and lymph node metastasis demonstrated by several studies.11-14 We therefore sought to evaluate from a clinical and practical point of view how often the outcome of EUS, after endoscopic inspection, changed patient management and excluded patients from diagnostic ER during work-up for possible endoscopic management. Although EUS is an accurate technique for staging of oesophageal 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.13-15 Even when using high-frequency EUS mini-probes, the discrimination between mucosal and submucosal lesions is only 80% accurate.14,16 Especially in Barrett’s oesophagus 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 oesophagus and cardia may be complicated due to the anatomical conditions at the oesophago gastric junction.11,14 The diagnostic accuracy of EUS for N-staging in oesophageal cancer ranges between 68% and 86%.11-13 EUS-guided fine-needle aspiration (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 up to 90% in advanced oesophageal carcinomas.17 In our study 12 patients underwent EUS-FNA, which showed malignant cells in 3 patients: one patient had a known chronic lymphatic leukemia, another patient had an undiagnosed small cell lung cancer. The third patient with malignant cells upon 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 peri-tumoural region. In these cases, it may be recommendable to remove the neoplasia first by endoscopic resection, to be able to sample the lymph node without contamination by the tumour.18 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 4/16 positive lymph nodes in the oesophagectomy specimen. In this study, 105 patients had a normal EUS 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 differentiated cancer and/or lymph-vascular invasion. Thus, based on the diagnostic ER, 25 of the 105 patients with a normal EUS (24%) had risk factors for lymph node metastasis that would have been missed without histological correlation of the diagnostic ER. Normal EUS should thus not be considered enough to engage in endoscopic ablation therapy (e.g. photodynamic therapy [PDT], radiofrequency ablation [RFA]) without diagnostic ER of all visible abnormalities first for accurate staging of the disease. Furthermore, 14 patients without doubts on attainability of ER upon endoscopic inspection, had signs of submucosal invasion or lymph node metastasis upon EUS. Diagnostic ER confirmed submucosal invasion in 7 patients. The other 7 patients, however, did not have submucosal invasion or other risk factors for lymph nodes metastasis in the ER specimens. Thus, only abnormal EUS is not enough to refer a patient for surgery without a diagnostic ER first, since half of the patients may still be eligible for curative endoscopic treatment. Lastly there was a group of 12 patients in whom endoscopic inspection raised doubts on the feasibility of ER, in addition to an abnormal EUS. As already described above, EUS-FNA in one patient resulted in a false positive diagnosis of tumour 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 both endoscopic inspection and EUS are abnormal, it is recommendable 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 work-up for endoscopic treatment of early oesophageal and cardia neoplasia should consist of detailed endoscopic inspection to evaluate the macroscopic appearance of a lesion and to evaluate if 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,
lymph-vascular invasion or irradical resection at the deep resection margin, warrants surgical treatment. We think that this approach allows for 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 which has a poor positive predictive value for the presence of lymph node metastasis.

Follow-up with EUS next to endoscopic inspection was performed in 53 patients. Recurrence of neoplasia occurred in 10 of these 53 patients, all detected primarily during endoscopic inspection. None of the recurrences was solely detected by EUS. This suggests that after successful endoscopic treatment, endoscopic inspection is the most important modality to detect intra-oesophageal recurrences that can then be biopsied or 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 for 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 patient inclusion may have suffered from selection bias. However, by having two independent researchers screening all patients undergoing any type of EUS within the pre-determined time frame to identify patients undergoing EUS for work-up of early oesophageal or cardia neoplasia, we tried to minimize selection bias. Secondly, endoscopic assessment and EUS were often not performed as independent investigations and we can therefore not exclude the possibility that the outcomes of endoscopy and EUS have influenced each other. However, since we did not attempt to compare the diagnostic accuracy of endoscopic inspection versus EUS, but aimed to evaluate the clinical value of EUS next to endoscopic inspection, 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. Lastly, all endoscopies, EUS and ER procedures were performed by endoscopists with extensive experience in this field and intermediate results of a new treatment approach. Eur J Gastroenterol Hepatol 2002; 14: 1085-1091.


REFERENCES


