Gastroenterology 2014;146:652–660

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.

The 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

Abbreviations used in this paper: **APC, argon plasma coagulation; ER, endoscopic resection; HGD, high-grade dysplasia; LSBE, long-segment Barrett's esophagus; mAC, mucosal adenocarcinoma of the esophagus; PPI, proton pump inhibitor; RFA, radiofrequency ablation.**

0016-5085/$36.00
http://dx.doi.org/10.1053/j.gastro.2013.11.006

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 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.

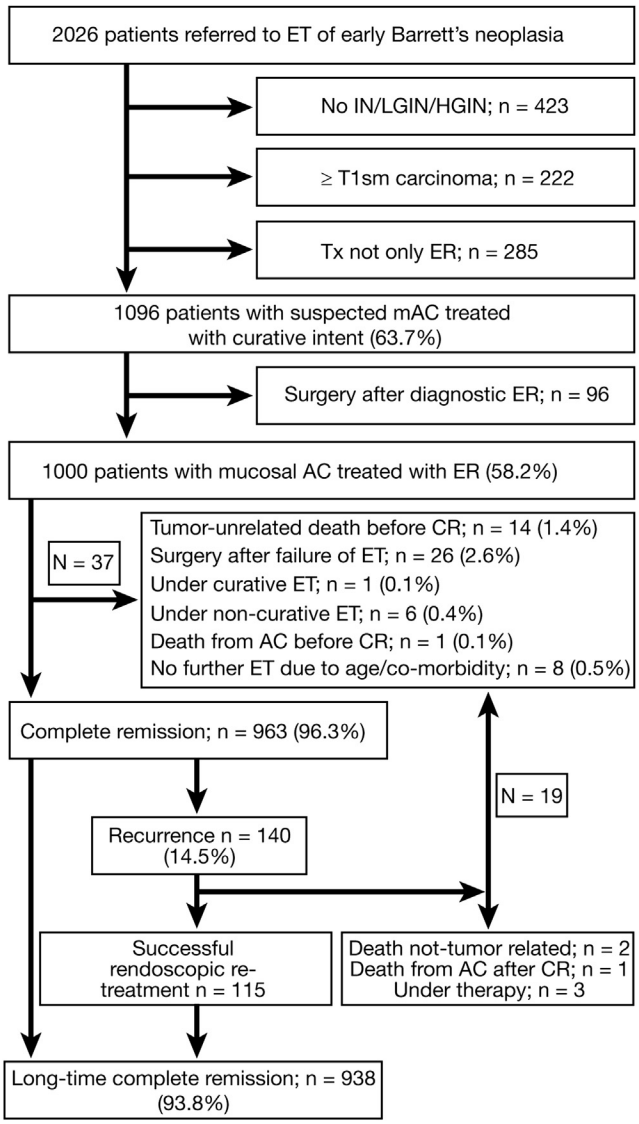

Figure 1. Flow diagram for the study patients. ET, endoscopic therapy; IN, intraepithelial neoplasia; LGIN, low-grade intraepithelial neoplasia; HGIN, high-grade intraepithelial neoplasia; Tx, therapy; CR, complete remission; AC, adenocarcinoma.

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