Clinical Gastroenterology and Hepatology 2015;13:658–664

ALIMENTARY TRACT

Clinical and Histologic Determinants of Mortality for Patients With Barrett's Esophagus–Related T1 Esophageal Adenocarcinoma

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BACKGROUND & AIMS: **Superficial (T1) esophageal adenocarcinoma (EAC) commonly is treated by endoscopic resection, yet little is known about factors that predict outcomes of this approach. We assessed clinical and histologic variables associated with the overall survival times of patients with T1 EAC who received therapy.**

METHODS: **In a retrospective analysis, we collected data from patients who underwent endoscopic mucosal resection (EMR) for T1 EAC (194 patients with T1a and 75 patients with T1b) at the Mayo Clinic, from 1995 through 2011. EMR specimens were reviewed systematically for depth of invasion, presence of lymphovascular invasion, grade of differentiation, and status of resection margins. Kaplan–Meier curves and proportional hazards regression models were used in statistical analyses.**

RESULTS: **Demographic characteristics were similar between patients with T1a and T1b EAC. Overall survival at 5 years after EMR was 74.4% for patients with T1a (95% confidence interval [CI], 67.6%−81.8%) and 53.2% for patients with T1b EAC (95% CI, 40.3%–70.1%). Of surviving patients with T1a EAC, 94.1% remained free of cancer (95% CI, 89.8%–98.5%), and 94.7% of surviving patients with T1b EAC remained free of cancer (95% CI, 85.2%−100%). A multivariable model associated older age (per 10-year increment), evidence of lymphovascular invasion, and deep margin involvement with reduced overall survival in patients with T1 EAC.**

CONCLUSIONS: **Systematic assessment of EMR specimens can help predict mortality and potentially guide treatment options for patients with T1 EAC.**

Keywords: Tumor Progression; Endoscopic Therapy; Esophageal Cancer; Prognostic Factor.

Endoscopic therapy has gained acceptance as the treatment of choice for Barrett's esophagus (BE) with intramucosal esophageal adenocarcinoma (T1a EAC).[1] Overall survival in patients treated endoscopically is comparable with patients treated with esophagectomy with lower morbidity and mortality rates.[2–6] Endoscopic therapy involves a combination of endoscopic mucosal resection (EMR) of visible lesions followed by endoscopic ablation. EMR serves both diagnostic and therapeutic purposes because the EMR specimen(s) allow accurate evaluation of the depth of invasion and margin assessment, in addition to providing other histologic prognostic variables such as grade of differentiation and the presence or absence of lymphovascular invasion (LVI).[7]

Several surgical series have looked at the depth of invasion and its association with lymph node metastases (LNM). A recent meta-analysis showed that T1a EAC is associated with low rates of metastatic lymphadenopathy (<2%).[8] In contrast, rates are higher with submucosal invasion (20%–30%).[9–12] Other histologic factors that have been associated with a greater rate of LNM include the presence of LVI and poor grade of differentiation.[9,13]

Abbreviations used in this paper: **BE, Barrett's esophagus; CI, confidence interval; CT, computed tomography; EAC, esophageal adenocarcinoma; EGD, esophagogastroduodenoscopy; EMR, endoscopic mucosal resection; EUS, endoscopic ultrasound; HR, hazard ratio; IQR, interquartile range; LNM, lymph node metastasis; LP, lamina propria; LVI, lymphovascular invasion; MM, muscularis mucosae; OR, odds ratio; PET, positron emission tomography; SM, submucosa.**

1542-3565/$36.00
http://dx.doi.org/10.1016/j.cgh.2014.08.016

Few studies have looked at the influence of histologic characteristics and other clinical variables on overall survival of subjects treated endoscopically for T1 EAC.[14] Identification of prognostic determinants on long-term outcomes in subjects with T1 EAC may help with patient risk stratification and tailoring of treatment. For this purpose, we aimed to comprehensively assess the influence of clinical and histologic variables on overall survival in a large cohort of patients treated endoscopically at our institution's specialized BE Unit.

Methods

Study Population and Study Design

This was a retrospective cohort study using data from a prospectively maintained database of patients with T1 EAC who underwent EMR between 1995 and 2011 at our institution. Patients were referred for endoscopic treatment of T1 EAC or were enrolled in a multidisciplinary treatment program. Patients were treated with a combination of EMR followed by ablative techniques. Baseline clinical characteristics were obtained at the time of EAC diagnosis. Patients were followed up from diagnosis until the date of last clinical encounter or death.

Endoscopic Evaluation

All patients underwent esophagogastroduodenoscopy (EGD) with a detailed examination of the Barrett's mucosa and standardized surveillance consisting of 4-quadrant biopsy specimens every 1 to 2 cm every 3 months. Mucosal irregularities were targeted with the Duette multiband mucosectomy (Cook Ireland, Limerick, Ireland), EMR cap (EMR-001; Olympus America, Inc, Center Valley, PA), variceal ligation with snare (Bard Interventional Products, Billerica, MA), or snare-alone techniques.[15] Endoscopic characteristics of the lesions including number, size, and appearance were reported. Endoscopic ultrasound (EUS) was used to assess the extent of disease (using standard TNM criteria). Fine-needle aspiration of suspicious lymph nodes was performed when clinically indicated. Computerized tomography (CT) scans of the chest, abdomen, and pelvis, and/or positron emission tomography (PET) scans were used to exclude distant metastasis (performed since 2003).

Histopathologic Assessment

The initial diagnosis of T1 EAC in this patient cohort was established by 2 experienced gastrointestinal pathologists following a published protocol.[15] T1a EAC was defined as tumor showing invasion into the lamina propria (LP) or muscularis mucosae (MM). T1b EAC was defined as tumor invading the submucosa (SM). EMR histology was reviewed systematically to assess the following: (1) tumor grade (well, moderate, or poorly differentiated), (2) depth of invasion (LP, MM, or SM), (3) presence or absence of LVI, and (4) status of deep and lateral margins (positive or negative for carcinoma). Tumor grade was based on standard histologic features, including the percentage of gland formation, growth pattern, and degree of cytologic and nuclear atypia (Figure 1).

LP invasion was defined as penetration of the basement membrane by neoplastic cells, which included isolated malignant cells within the LP as well as larger proliferations of glands showing architectural complexity that exceeded that of high-grade dysplasia. MM invasion was defined as the presence of infiltrative glands within the smooth muscle fibers of a single MM, the space between duplicated layers of the MM, or the outer layer of the MM. The majority of EMR specimens do not extend to the level of the MP. Mistaking a duplicated layer of MM for MP is a known pitfall of EMR evaluation given the variable depth of endoscopic mucosal resection.[16] To minimize the chances of overestimating invasion into the space between duplicated MM as true submucosal invasion, we classified a tumor as showing SM invasion when the following occurred: (1) it extended beyond a duplicated layer of MM, (2) it involved a tissue plane containing submucosal glands, or (3) it was adjacent to

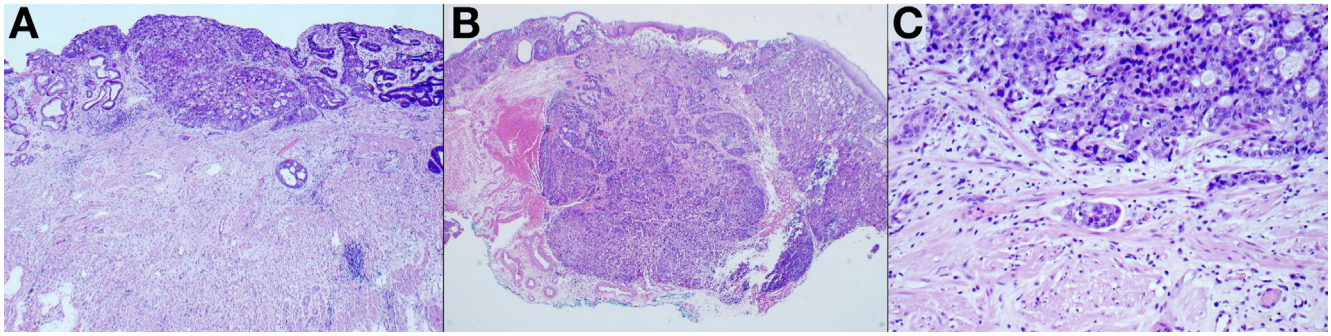

Figure 1. Histopathologic assessment of endoscopic mucosal resections. (*A*) T1a esophageal adenocarcinoma was defined as tumor showing invasion into the lamina propria or muscularis mucosa. (*B*) T1b esophageal adenocarcinoma was defined as tumor that invades through the muscularis mucosa into the submucosa. (*C*) Lymphovascular invasion was defined as the presence of clusters of malignant cells within an endothelial-lined vascular channel.