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Survival in esophageal high-grade dysplasia/adenocarcinoma post endoscopic resection

Bashar J. Qumseya, Abraham M. Panossian, Cynthia Rizk, David J. Cangemi, Christianne Wolfsen, Massimo Raimondo, Timothy A. Woodward, Michael B. Wallace, Herbert C. Wolfsen*

Division of Gastroenterology and Hepatology, Mayo Clinic, Jacksonville, FL, United States

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ABSTRACT

Background: Endoscopic resection followed by ablative therapy is frequently used to treat esophageal high-grade dysplasia or early esophageal adenocarcinoma.
Aims: To study outcomes in patients with high-grade dysplasia compared to those with esophageal adenocarcinoma after endoscopic resection.
Methods: Retrospective, observational, descriptive, single-centre study from a prospective database. We extracted data from 116 endoscopic resections. Survival was plotted using Kaplan–Meier curves multivariable Cox-proportional hazard assess for possible predictors of survival post-endoscopic resection was performed.
Results: 116 patients (64 esophageal adenocarcinoma, 52 high-grade dysplasia) underwent endoscopic resection from May 2003 to June 2010. Mean age was 71 ± 11 years for high-grade dysplasia and 72 ± 10 years for esophageal adenocarcinoma. Median follow-up was 17 months. Eighty-five patients had negative margins on endoscopic resection. Five-year survivals for high-grade dysplasia and esophageal adenocarcinoma were 86% (range 68–100%) and 78% (59–96%), respectively. Survival was not significantly different between groups (p = 0.20). Overall mortality rate was 10.6% (9/85). At multivariable Cox regression increased Barrett's oesophagus length was associated with worse survival (HR 1.18 [1.06–1.33], $p = 0.0039$). Survival was not affected by the pathology before resection: HR 2.4 [95%CI, 0.70–8.4], $p = 0.16$.
Conclusions: Survival in patients with high-grade dysplasia of the oesophagus is similar to those with esophageal adenocarcinoma. Longer Barrett's oesophagus segments are associated with decreased survival.

1. Introduction

The incidence of esophageal adenocarcinoma (EAC) is on the rise [1,2]. Barrett's oesophagus is one of the major risk factors for the development of esophageal cancer [3], which is thought to evolve through a sequence of low-grade dysplasia (LGD) that progresses to high-grade dysplasia (HGD) and eventually progresses to adenocarcinoma [4]. Studies have suggested that there is improved survival in BE patients who undergo surveillance [5–8], which is both recommended by the major gastrointestinal associations [9–11] and is a common practice among US endoscopists [12]. HGD is more common than EAC; yet, outcomes in patients with HGD have not been compared head-to-head with patients with EAC. Studies have shown that 3–50% of patients with HGD may have a concurrent undetected neoplasia [13]. Until recently, the main treatment for patients with HGD or early esophageal adenocarcinoma was esophagectomy [14–16]. This treatment is not ideal given its risks and associated complications [17–19]. Endoscopic treatment has gained increased acceptance. Endoscopic resection (ER), also called endoscopic mucosal resection (EMR), involves the resection of dysplastic or neoplastic esophageal lesions using a diathermy snare. ER can be used for both staging and for curative intent [20]. Several studies have reviewed the utility of ER, with or without ablation therapy, for treatment of EAC and HGD in patients with BE [21–24]. Ablative therapies include photodynamic therapy (PDT), radiofrequency ablation (RFA), cryotherapy, and argon plasma coagulation (APC) [25–27].

This study aims to analyze the outcomes and survival in a cohort of patients with esophageal HGD who underwent endoscopic management compared to those with EAC who also had endoscopic

* Corresponding author at: Division of Gastroenterology and Hepatology, Mayo Clinic, 4500 San Pablo Road, Jacksonville, FL 32224, United States.
Tel.: +1 9049536319.
E-mail address: wolfsen.herbert@mayo.edu (H.C. Wolfsen).

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management. We hypothesize that outcomes, including long-term survival in patients with HGD, are similar to those of patients with EAC.

2. Patients and methods

2.1. Data collection

We conducted a retrospective, observational, descriptive study using a prospective ER database. This study was approved by the Mayo Clinic Institutional Review Board. The database contains information about 195 esophageal ERs that were performed in 175 patients at a tertiary referral centre from May 2003 to June 2010. These patients were referred to our centre with a diagnosis of HGD or EAC based on outside assessment. We included patients who were confirmed to have HGD or EAC on the ER specimen. Patients who did not have HGD or EAC on the ER specimen were excluded. We used our institution's electronic medical records to extract the following data on each patient: age at the time of ER, sex, use of aspirin or nonsteroidal anti-inflammatory drugs, previous diagnosis of BE, maximum BE segment length, histology and disease TNM staging based on endoscopic ultrasound and computed tomographic (CT) scan results, use of ablative therapies before and after ER (including photodynamic therapy (PDT), radiofrequency ablation (RFA), argon plasma coagulation (APC), and cryoablation), need for esophagectomy, survival, and follow-up times. The primary outcome of this study was survival at the end of the follow-up period. Details of survival and cause of death were obtained from the database or from medical records. Most of the patients had long-term follow-up at our institution. Otherwise, the patient status was obtained from the referring physician.

2.2. Standard protocol

First, patients were evaluated by an experienced gastroenterologist (H.W.) using a standard protocol, and including a review of medical history and CT scan of chest, abdomen, and pelvis. This was followed by esophagogastroduodenoscopy (EGD) to detect suspicious lesions, such as raised nodules and discrete, depressed, or flat lesions that are associated with abnormal mucosal or vascular features of neoplasia. In the absence of visible lesions, advanced imaging techniques (narrow band imaging and/or confocal laser endomicrosopy) were used in some patients as part of other investigative studies to better delineate the abnormal mucosal or vascular features of dysplasia. At a separate encounter, patients underwent endosonography and staging of possible cancers. If indicated lymph nodes that were suspicious for the presence of neoplasia were removed by fine needle aspiration. If there was no evidence of locally advanced disease, ER was used to remove suspicious areas at the same encounter. Patients were considered for surgery if they had a confirmed diagnosis of EAC with positive ER margins or features suggestive of a risk of nodal metastases, including poor differentiation, perineural or lymphovascular invasion, and submucosal invasion. For patients with a piecemeal resection who also had carcinoma at the edge of one of the resected pieces. Surgical triage was individualized on the basis of endoscopic assessment of whether a radical resection (R0) had been achieved since the true lateral margins could not be assessed. Triage was also based on the patient preference. For patients who did not undergo surgery, surveillance was performed at 2–3-month intervals following the Seattle protocol, with ablative therapy and biopsy or ER of any remaining Barrett metaplasia. Following complete eradication of Barrett metaplasia, patients were followed by endoscopy with surveillance biopsy of neosquamous epithelium at yearly intervals. All pathology reviewed was performed by an experienced GI pathologist who reviewed and reported results for all patients in our Barrett's programme.

2.3. Endoscopic resection

Methods of ER have been described in detail elsewhere [28]. Briefly, the majority of ER procedures were performed using the multiband mucosectomy method with or without saline injection lift to remove the most suspicious lesions (DT-6-5F; Cook Medical, Bloomington, IN). The Wallace "rosette pattern" of 4–6 additional resections was then performed to completely remove the tissue around the index resection margin including up to 75% of the lumen circumference. Index lesions greater than 3 cm in diameter were removed using the cap technique with Olympus accessories (K-008; Olympus America Inc, Centre Valley, PA).

2.4. Endoscopic ablation therapy

Prior to ablation therapy, patients were prescribed high daily doses of a proton pump inhibitor medication before the morning and evening meals; this was done to aggressively control acid reflux and optimize the results of ablation therapy. Patients returned for treatment every 3–6 months until all esophageal glandular mucosa had been successfully ablated and replaced with neosquamous epithelium. Surveillance endoscopy was performed every 6–12 months thereafter to detect and treat any recurrent or residual Barrett mucosa using additional ER or ablation. Our methods of ablative modalities have been previously described. These include the use of porfimer sodium PDT [29,30], RFA [31], APC [28], and cryotherapy [28,32–35]. Details of each of these techniques are not described here because of space limitations. The choice of which ablative modality to use was individualized based on best evidence at the time, patient comorbidities, and patient preference. In general, PDT seems to have been performed between 2003 and 2008, with RFA largely replacing it in recent years.

2.5. Statistical analysis

We used SAS software, version 9.2 (SAS Institute Inc, Cary, NC) for statistical analysis. For continuous variables, we used the Shapiro–Wilk test to assess normality. For normal variables, we reported means (standard deviations). For skewed data, we reported medians with interquartile ranges or ranges. For discrete data, we reported proportions. We used the Student t-test to assess the differences between means for normal data and we used the Wilcoxon rank sum test for continuous skewed data. We used the Fisher exact or χ^2 test to assess the differences between proportions in different categories. Survival was plotted using Kaplan–Meier curves and reported as proportion with 95% confidence intervals (CIs). The log-rank χ^2 test was used to assess the difference in survival between groups. A p value of less than .05 indicated statistical significance. We fit univariable Cox-proportional hazard models for all candidate predictors of survival. We included age and gender in the multivariable model into all other predictors that reached significance in a univariable analysis with $p < 0.3$. We tested for co-linearity and confounding. Effect modification between variables were also tested. Using the final multivariable model, we reported the effect of predictors on survival as hazard ratios (HR) with 95% confidence intervals and p-values. We tested the proportional hazards assumption by calculating Martingale residuals for the variables included in the final model. This study was reviewed and approved by the Mayo Clinic Institutional Review Board.