

Outcomes after Endoscopic Mucosal Resection for T1a Esophageal Adenocarcinoma with Suggested Algorithm for Management

Christina Tofani, Kunjal Gandhi, Joseph Yoo, Megan Murphy, Danielle Fortuna, Jonathan Fenkel, Ali Siddiqui, Juan Palazzo, Robert Coben, Sidney Cohen, David Katzka, Anthony Infantolino

Christina Tofani, Kunjal Gandhi, Jonathan Fenkel, Ali Siddiqui, Robert Coben, Sidney Cohen, Anthony Infantolino, Department of Gastroenterology & Hepatology, Thomas Jefferson University Hospital, Philadelphia, PA, the United States

Joseph Yoo, Megan Murphy, Department of Internal Medicine, Thomas Jefferson University Hospital, Philadelphia, PA, the United States

Danielle Fortuna, Juan Palazzo, Department of Pathology, Anatomy, & Cell Biology, Thomas Jefferson University Hospital, Philadelphia, PA, the United States

David Katzka, Department of Gastroenterology & Hepatology, Mayo Clinic, Rochester, MN, the United States

Conflict-of-interest statement: The author(s) declare(s) that there is no conflict of interest regarding the publication of this paper.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Christina Tofani, 132 S. 10th St., Main Building, Suite 480, Philadelphia, PA 19107, the United States

Email: Christina.tofani@gmail.com

Telephone: +1-609-238-3981

Fax: 1-215-955-6678

Received: January 3, 2017

Revised: March 8, 2017

Accepted: March 10, 2017

Published online: April 21, 2017

ABSTRACT

BACKGROUND: Esophageal adenocarcinoma (EAC) is a well-

known complication of Barrett's esophagus (BE). The ASGE, AGA, and ACG have established guidelines regarding the diagnosis, management and surveillance of patients diagnosed with BE. Endoscopic mucosal resection (EMR) is an acceptable therapeutic option for T1a EAC versus esophagectomy. However, no clear guidelines exist regarding the management and follow up of patients with early EAC after EMR. The purpose of this study is: (1) to better define the outcome of EMR for T1a EAC; (2) to analyze the characteristics of our BE patients that underwent EMR for EAC; (3) to evaluate repeat EMR for positive margins of EAC in initial resection specimens.

METHODS: A retrospective cohort study was conducted of patients at a tertiary care center with BE patients with early EAC who underwent EMR. The electronic medical record was reviewed to collect the following data: age, sex, age at diagnosis of BE and EAC, length of BE segment, pathology results, and imaging.

RESULTS: 31 patients with BE who underwent EMR for early EAC were assessed. 29 (93.55%) were male. The median age was 67 ± 9.7 years. The median ages at BE and EAC diagnoses were 63 ± 10.5 years and 63 ± 10.3 years, respectively. The length of BE segments ranged from < 1 cm to 14cm and 17 (54.84%) patients had short segment BE. 19 (61.29%) patients had EAC diagnosed on their first EGD at our institution. On pathology, 8 (25.81%) EMR specimens had margins positive for EAC. 7 (87.5%) of these patients underwent repeat EMR; 5 were successful and 1 required esophagectomy for persistently positive margins. 26 (83.86%) patients had PET/CT after EMR, 4 (15.38%) of which were positive. Overall, 2 (6.45%) patients had EAC recurrence, occurring at 70 and 71 months; both had successful repeat EMR. Mean length of follow up at our institution was 29.1 ± 21.9 months (range 2-87 months).

CONCLUSIONS: BE is a known risk factor for EAC. Our study suggests BE patients with early EAC who undergo EMR have a low rate of EAC recurrence. In our population, short segment BE also carried a risk for EAC and should not be de-emphasized. EMR specimens with margins positive for EAC can be successfully managed with repeat EMR.

Key words: Barrett's esophagus; Adenocarcinoma; Endoscopic mucosal resection

Tofani C, Gandhi K, Yoo J, Murphy M, Fortuna D, Fenkel J, Siddiqui A, Palazzo J, Coben R, Cohen S, Katzka D, Infantolino A. Outcomes after Endoscopic Mucosal Resection for T1a Esophageal Adenocarcinoma with Suggested Algorithm for Management. *Journal of Gastroenterology and Hepatology Research* 2017; **6(2)**: 2307-2311 Available from: URL: <http://www.ghrnet.org/index.php/joghr/article/view/1958>

INTRODUCTION

Barrett's esophagus (BE) is a metaplastic replacement of the squamous epithelial mucosa of the esophagus with columnar-lined epithelium—a process referred to as esophageal intestinal metaplasia^[1]. Macroscopically, BE appears as red velvety, salmon-colored mucosa overlying the distal esophagus and gastroesophageal junction. BE can develop dysplastic changes, both low and high grade, and esophageal adenocarcinoma (EAC). The risk of progression from BE to EAC has been estimated to be between 0.12-0.4% per year^[2,3,4,5]. The risk of EAC is higher in patients with dysplastic BE on their index endoscopy, compared with those found to have non-dysplastic BE^[5]. The incidence of EAC is on the rise, especially in the Western hemisphere^[6,7].

Early detection of EAC can lead to appropriate management and improved outcomes. In the past, EAC, even in its early stages, was treated with esophagectomy with or without chemotherapy and radiation. More recently, endoscopic mucosal resection (EMR) of stage T1a EAC tumors has become the recommended treatment over esophagectomy^[8]. The current literature, although limited, shows favorable outcomes after EMR of early EAC with low complication rates^[9-13]. However, the surveillance and management of BE patients following endoscopic resection of early EAC is not standardized in many of the current guidelines.

The aim of our study is (1) to better define the outcomes of T1a EAC after EMR; (2) to analyze the characteristics of BE patients that underwent EMR for early EAC at a single tertiary care medical center; (3) to evaluate the outcomes of repeat EMR for positive margins of EAC in initial resection specimens.

PATIENTS AND METHODS

Approval was obtained from the Institutional Review Board at Thomas Jefferson University Hospital. This study is a retrospective medical record review. We included 31 consecutive patients with BE and T1a EAC that underwent EMR at Thomas Jefferson University Hospital between January 2009 and October 2015. All EMRs were performed by an endoscopist experienced in EMR (AI, RC, AS). All EMR specimens were reviewed by an expert pathologist (JP) for T1a adenocarcinoma. Only those with T1a adenocarcinoma were included in this study. Pathology was also evaluated for positive margins, degree of differentiation, and lymphovascular invasion. The following data were obtained from the electronic medical record: age, sex, race, age at diagnosis of BE, age at diagnosis of EAC, endoscopy results, pathology results, and PET/CT results.

RESULTS

Thirty one consecutive patients with T1a EAC in the setting of BE were analyzed. All patients underwent cap-assisted en-bloc EMR of an esophageal nodule containing early EAC. The median age of all patients was 67 ± 9.7 years old, with an age range of 44-87

years. Twenty nine (93.6%) patients were male and all patients were Caucasian. The median ages at diagnosis of BE and EAC were 63 ± 10.5 years and 63 ± 10.3 years, respectively. The length of BE segment ranged from < 1 cm to 14 cm on index endoscopy at our institution. Seventeen (54.84%) patients were classified as short segment BE. Nineteen (61.29%) patients had EAC diagnosis on their index endoscopy at our institution. In those patients not diagnosed with EAC on their index endoscopy, EAC was diagnosed at a mean 17.5 months (range 6-96 months, median 12 months) after the index endoscopy at our institution. (Table 1) On pathology review of EMR specimens, 17 were moderately differentiated, 11 were well differentiated, and 3 did not have specified differentiation. No specimens were classified as poor differentiation. Eight (25.81%) had margins positive for EAC. Three had deep margin positivity, 2 had lateral margin positivity, and 3 had both deep and lateral margin positivity. Seven (22.58%) had margins positive for HGD. Six had deep margin positivity and 1 had both deep and lateral margin positivity. No patients had lymphovascular invasion. (Table 2) Radiofrequency ablation (RFA) was performed on all patients that underwent EMR. The need for repeat EMR was determined by raised or nodular mucosa at the EMR site at surveillance endoscopy. Seven (87.5%) patients with margins positive for EAC underwent repeat EMR. Six patients had successful tumor eradication with repeat EMR. One patient had persistently positive margins with EAC and eventual progression to stage T1b EAC. This patient was referred for esophagectomy. Twenty six (83.86%) patients had PET/CT after EMR; 4 (15.38%) of which were positive. The mean time from EMR to first PET/CT was 6.31 weeks (range 1-64 weeks). Nine (31.62%) of the 26 patient had more than one PET/CT. The mean time from index PET/CT to surveillance PET/CT was 17.11 months (range 7-48 months). Two patients with positive PET/CT had negative margins on initial EMR and no evidence of residual EAC on surveillance

Table 1 Baseline Characteristics of patients

Sex	29 (93.6%) male; 2 (6.4%) female
Race	100% white
Median age	67 ± 9.7 years old
Age range	44-87 years
Median age at diagnosis of BE	63 ± 10.5 years
Median age at diagnosis of EAC	63 ± 10.3 years
BE segment length	< 1 cm to 14 cm
Short segment BE (≤ 3 cm)	17-54.84%
EAC diagnosis on index endoscopy	19-61.29%

Table 2 Characteristics of EMR specimens

Differentiation	
Well	11 (35.48%)
Moderate	17 (54.89%)
Poor	0
Unspecified	3 (9.63%)
Margins positive for EAC	8 (25.81%)
Deep	3
Lateral	2
Deep + Lateral	3
Margins positive for HGD	7 (22.58%)
Deep	6
Lateral	0
Deep + Lateral	1
Lymphovascular invasion	0

endoscopy. One patient with positive PET/CT had negative margins on initial EMR but had repeat EMR for persistent nodularity at the EMR site on surveillance endoscopy performed 3 months after the first EMR. One patient with positive PET/CT had margins positive for EAC on initial EMR. This patient underwent successful repeat EMR. There were no distant metastases in any patients that underwent PET/CT.

Two (6.45%) patients had recurrence of EAC (Table 3) after complete resection of EAC. On their index endoscopies, both patients had long segment BE (11cm and 15cm) and one patient was diagnosed with EAC at that time. The other patient was diagnosed on repeat endoscopy 2 weeks later. The mucosal recurrences occurred at 70 and 71 months after initial EMR for the original EAC tumor. Both recurrences were found as nodules on surveillance endoscopies. The two patients were 61 and 63 years old at the time of their original EAC diagnosis and were 67 and 69 years old, respectively, at the time of their EAC recurrence. The original EAC was classified as moderately differentiated in both patients. One patient had EMR margins positive for HGD while the other had negative margins on initial EMR. Both patients had two negative PET/CTs after initial EMR. Both patients underwent successful EMR of their recurrent tumor and at the present time have no evidence of disease. One patient had tumor recurrence at the location of the original tumor (34cm) while the other patient had recurrence at a different location (32cm) from the original tumor (28 cm). Of all patients that underwent EMR of early EAC, 7 (22.58%) were evaluated by a medical oncologist. Only 1 of the 4 patients with a positive PET/CT was evaluated by a medical oncologist. The mean length of follow up at our institution was 29.1 ± 21.9 months (range 2-87 months) (Figure 1).

DISCUSSION

EMR of esophageal nodules found in a bed of Barrett's mucosa is recommended by all Barrett's guidelines as a result of the high prevalence of dysplasia and adenocarcinoma. However, the management and follow up of BE patients after EMR of T1a EAC have not been well-established. In this study we demonstrated that with a rigid follow up method using endoscopy 6-8 weeks after EMR, then every 3 months for the first year, every 6 months for the second year and annually thereafter with biopsies following the Seattle Protocol^[10] and RFA of remaining Barrett's mucosa, 27 of 29 patients remained cancer free after EMR. Furthermore, of the two patients who developed EAC after initial successfully performed EMR, both recurred at stages where EMR could lead to cure. Unfortunately, there were no clear factors that predicted recurrence in these two patients.

The cost-effectiveness of endoscopic surveillance of BE, both non-dysplastic and dysplastic, has been frequently questioned^[11,12]. Pohl, et al, recently questioned the surveillance of short segment and ultra-short segment BE given the low likelihood of EAC in non-long segment BE. In this study of 1017 BE patients with early EAC, 56% had long segment, 24% had short segment, and 26% had ultrashort segment^[13]. However, short segment BE still carries a significant risk for developing HGD and EAC^[14,15]. Our study also suggests that short segment BE carries a risk for EAC. In fact, in our study more patients had short segment (54.84%) than long segment (45.16%) BE. Our suggestion is to not neglect surveying patients with short segment BE for EAC, as they can also develop early EAC in their BE segment, regardless of length.

Huntington, et al. suggested that early EAC could be successfully managed with EMR alone. Sixteen percent of EMR specimens in

Table 3 Characteristics of patients with recurrent esophageal adenocarcinoma

	Patient 1	Patient 2
Sex	Male	Male
Race	Caucasian	Caucasian
Age at BE diagnosis (years)	63	61
Length of BE (cm)	11	15
Age at EAC diagnosis	63	61
Time from BE to EAC (months)	0.5	0
EAC differentiation	Moderate	Moderate
EMR specimen margins	Positive for HGD (lateral)	Positive for HGD (lateral)
Lymphovascular invasion	No	No
Time from EMR to first PET-CT (weeks)	16	64
First PET-CT result	Negative	Negative
Time from 1st PET-CT to 2nd PET-CT (months)	11	13
Second PET-CT result	Negative	Negative
Age at EAC recurrence (years)	69	67
Time between EMR and EAC recurrence(months)	70	71
Original EAC location	34cm	28cm
Recurrent EAC location	34cm	32cm
Oncology evaluation	No	No

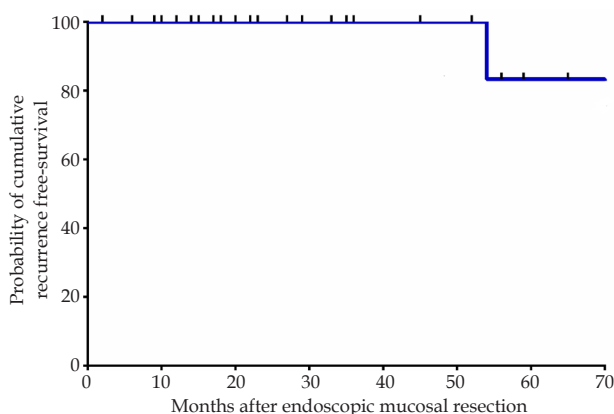


Figure 1 Cancer-free survival in patients after EMR of T1a esophageal adenocarcinoma

their study had radial margins positive for EAC. All of which were successfully managed with repeat EMR or RFA during subsequent endoscopies^[16]. In our study, 25.8% EMR specimens had margins positive for EAC and 5 (16.13%) had margins positive for HGD. Our study describes favorable outcomes after repeat EMR or RFA in patients with positive margins on initial EMR. Repeat endoscopy must be performed in all patients with positive margins to evaluate for residual nodularity at the EMR site that may require further endoscopic therapy.

EMR has become the preferred method over surgical esophagectomy to treat early EAC. However, as always, these patients require a multidisciplinary approach with management tailored to the individual^[17,18]. Outcomes of EMR of early EAC have been positive, with very low rates of recurrence^[8]. Patients in our study had a recurrence rate of 6.45%, with recurrences occurring > 5 years after the original EAC diagnosis and EMR.

Our study is not without limitations. Our study is limited by its small sample size which, although only observational, could underpower some subset analyses. Our patient population was only of one racial background which inhibited subanalyzing the effect

10. Levine DS, Haggitt RC, Blount PL, Rabinovitch PS, Rusch VW, Reid BJ. An endoscopic biopsy protocol can differentiate high-grade dysplasia from early adenocarcinoma in Barrett's esophagus. *Gastroenterology* 1993; **105**: 40-50. [PMID: 8514061]
11. Garside R, Pitt M, Somerville M, Stein K, Price A, Gilbert N. Surveillance of Barrett's oesophagus: exploring the uncertainty through systematic review, expert workshop and economic modelling. *Health Technol Assess*. 2006 Mar; **10(8)**: 1-142, iii-iv. [PMID: 16545207]
12. Somerville M, Garside R, Pitt M, Stein K. Surveillance of Barrett's oesophagus: is it worthwhile? *Eur J Cancer*. 2008 Mar; **44(4)**: 588-589. [PMID: 18272361]; [DOI: 10.1016/j.ejca.2008.01.015]
13. Pohl H, Pech O, Arash H, Stolte M, Manner H, May A, Kraywinkel K, Sonnenberg A, Ell C. Length of Barrett's oesophagus and cancer risk: implications from a large sample of patients with early oesophageal adenocarcinoma. *Gut*. 2016 Feb; **65(2)**: 196-201. [PMID: 26113177]; [DOI: 10.1136/gutjnl-2015-309220]
14. Kariyawasam V, Bourke M, Hourigan L, Lim G, Moss A, Williams SJ, Fanning SB, Chung AM, Byth K. Circumferential location predicts the risk of high-grade dysplasia and early adenocarcinoma in short-segment Barrett's esophagus. *Gastrointest Endosc*. 2012 May; **75(5)**: 938-944. [PMID: 22381529]; [DOI: 10.1016/j.gie.2011.12.025]
15. Crane S, Locke G, Romero Y, Zinsmeister AR, Talley NJ. Adenocarcinoma of the esophagogastric junction may arise from short-segment Barrett's esophagus. *Am J Gastroenterol*. 2008 Feb; **103(2)**: 493-494. [PMID: 18289221]; [DOI: 10.1111/j.1572-0241.2007.01646_14.x]
16. Huntington J, Walker J, Meara M, Hazey JW, Melvin WS, Perry KA. Endoscopic mucosal resection for staging and treatment of early esophageal carcinoma: a single institution experience. *Surg Endosc*. 2015 Aug; **29(8)**: 2121-2125. [PMID: 25472745]; [DOI: 10.1007/s00464-014-3962-3]
17. Nealis T, Washington K, Keswani R. Endoscopic therapy of esophageal premalignancy and early malignancy. *J Natl Compr Canc Netw*. 2011 Aug 1; **(8)**: 890-899. [PMID: 21900219]
18. Schmidt H, Mohiuddin K, Bodnar A, El Lakis M, Kaplan S, Irani S, Gan I, Ross A, Low DE. Multidisciplinary treatment of T1a adenocarcinoma in Barrett's esophagus: contemporary comparison of endoscopic and surgical treatment in physiologically fit patients. *Surg Endosc*. 2015 Nov 5. [PMID: 26541725]; [DOI: 10.1007/s00464-015-4621-z]

Peer reviewer: Weibiao Cao