

## Endotherapy for superficial adenocarcinoma of the esophagus: an American experience

Shreyas Saligram, MD, MRCP,<sup>1</sup> Jennifer Chennat, MD,<sup>1</sup> Huankai Hu, MD,<sup>2</sup> Jon M. Davison, MD,<sup>2</sup> Kenneth E. Fasanella, MD,<sup>1</sup> Kevin McGrath, MD<sup>1</sup>

Pittsburgh, Pennsylvania, USA

**Background:** EMR and ablation are increasingly being used alone or in combination for treatment of Barrett's neoplasia. Given a very low rate of lymph node metastasis, endotherapy has become an accepted treatment option for T1a esophageal adenocarcinoma (EAC) with low-risk features.

**Objective:** To report our experience of endoscopic management of T1a EAC in a large, tertiary-care center.

**Design:** Retrospective review.

**Setting:** Tertiary-care referral center.

**Patients:** Patients treated endoscopically for low-risk T1a EAC at our center.

**Intervention:** EMR and endoscopic ablation.

**Main Outcome Measurements:** Death related to esophageal cancer, remission of adenocarcinoma, dysplasia, and intestinal metaplasia.

**Results:** A total of 54 patients underwent endotherapy for low-risk T1a EAC from 2006 to 2012. Mean ( $\pm$  SD) follow-up was 23 ( $\pm$  16) months, mean ( $\pm$  SD) size of resected adenocarcinoma was 7.1 ( $\pm$  4.3) mm, and mean ( $\pm$  SD) Barrett's esophagus length was 4.5 ( $\pm$  3.9) cm. Band-assisted, cap-assisted, and lift and cut EMR were performed in 85%, 11%, and 4% of patients, respectively; 81% underwent additional ablative therapy (radiofrequency ablation 95%, cryotherapy 9%, photodynamic therapy 2%). Complete remission from cancer was achieved in 96%, complete remission from dysplasia in 87%, and complete remission from intestinal metaplasia in 59%. The overall survival was 89%; there were no deaths related to esophageal cancer.

**Limitations:** Retrospective study.

**Conclusion:** Endotherapy for T1a EAC was safe and effective in our American cohort. Endotherapy should be considered primary therapy for appropriate patients with low-risk lesions. Complete Barrett's esophagus eradication after EMR is important to reduce the development of metachronous lesions. (Gastrointest Endosc 2013;77:872-6.)

The incidence of esophageal adenocarcinoma (EAC) has increased 6-fold in the last 3 decades.<sup>1,2</sup> It is the fastest rising cancer rate in the United States. Because it commonly presents as advanced disease, it has a poor prognosis, with a 5-year survival rate of 19% despite treatment.<sup>3</sup> Early detection and treatment are critical to

improving outcomes and survival. Preoperative chemoradiation is the favored approach for resectable stage II and/or III disease.<sup>4</sup> Esophagectomy alone has been the recommended treatment for T1N0 EAC; however, esophagectomy has significant morbidity (30%-40%) and mortality (0%-4%).<sup>5-9</sup>

*Abbreviations:* BE, Barrett's esophagus; EAC, esophageal adenocarcinoma; LNM, lymph node metastasis; PET, positron emission tomography.

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Current affiliations: Department of Medicine (1), Department of Pathology (2), University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA.

Reprint requests: Kevin McGrath, MD, UPMC Presbyterian, M2, C-Wing, 200 Lothrop Street, Pittsburgh, PA 15213.

If you would like to chat with an author of this article, you may contact Dr McGrath at [mcgrathkm@upmc.edu](mailto:mcgrathkm@upmc.edu).



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Barrett's esophagus (BE) increases the risk of adenocarcinoma 30 to 40 times, with a 0.1% to 0.5% risk per year.<sup>10-14</sup> Endoscopic surveillance of BE has led to early detection of dysplasia and superficial cancer.<sup>15,16</sup> Endoscopic ablation of high-grade dysplasia can decrease the rate of EAC.<sup>17,18</sup> In recent years, there has been a growing body of literature from European centers supporting excellent safety and patient outcomes for primary endotherapy for early Barrett's neoplasia. EMR for low-risk T1a (mucosal-based) EAC can be curative, and ablation of the remaining Barrett's epithelium decreases the risk of metachronous neoplasia.<sup>19,20</sup> To date, the literature reporting patient numbers and outcomes of primary endotherapy for the treatment of T1a EAC in America lags in comparison with the European experience.

Our BE treatment center has seen an increase in referrals for management of high-grade dysplasia and superficial cancer that parallels the increasing rate of EAC. We therefore sought to review our experience of primary endotherapy for low-risk, superficial adenocarcinoma of the esophagus.

## METHODS

A retrospective review was performed to identify patients with T1a EAC treated by our BE treatment center over a 6-year period (August 2006-December 2012). Medical records were reviewed to collect pertinent information to include demographics, endoscopic findings, pathology results, adverse events, and patient follow-up. Inclusion criteria were the presence of a low-risk T1a EAC (as defined in the following) and a minimum 3-month endoscopic follow-up. This study was approved by our hospital's Institutional Review Board.

All patients underwent diagnostic and/or staging EMR of visible nodular or polypoid lesions under monitored anesthesia care by using a lift and cut, cap-assisted (EMR kit; Olympus America, Inc, Center Valley, Pa), or band-assisted technique (Duette multi-band mucosectomy device; Cook Ireland, Limerick, Ireland). EUS was performed at the index examination if the patient had a known diagnosis of adenocarcinoma. Index EUS was performed at the discretion of the endoscopist if the referral diagnosis was high-grade dysplasia. All EMR specimens were pinned on cork for proper orientation and were evaluated by an expert GI pathologist. Low-risk histologic features were defined as well-to-moderate tumor differentiation and absence of angiolymphatic and submucosal invasion.

Patients underwent initial and annual CT scans or positron emission tomography CT (PET-CT) scans. For those with remnant BE, large-capacity biopsy specimens were taken every 1 cm through the BE field for mapping purposes during the index EMR or at the first endoscopic follow-up 6 to 12 weeks after EMR. Ablative therapy with porfimer sodium photodynamic therapy (Photofrin; Axcan Pharma, Mont-Saint-Hilaire, Quebec, Canada), liquid ni-

## Take-home Message

- The risk of lymph node metastasis in low-risk mucosal adenocarcinoma of the esophagus is minimal. Primary endotherapy for such lesions is appropriate, safe, and efficacious, and our study results parallel those of the larger European experience.
- Complete Barrett's esophagus eradication is recommended to decrease the risk of recurrent neoplasia.

trogen spray cryotherapy, or radiofrequency ablation was performed every 6 to 12 weeks at the discretion of the endoscopist, as previously reported.<sup>18,21,22</sup> Additionally, surveillance EUS was performed every 3 months for the first year, every 6 months for the second year, and yearly thereafter. Complete response, defined as all biopsies negative for cancer, dysplasia, and intestinal metaplasia, was assessed via 4-quadrant biopsy specimens taken every 1 cm through the original BE segment every 3 months for the first year, every 6 months for the second year, then yearly after BE eradication.

The primary outcome measure was death related to esophageal cancer. Secondary outcome measures included remission of adenocarcinoma, dysplasia, and intestinal metaplasia. All 3 subgroups of complete response were calculated by using an intention-to-treat analysis. Mean and standard deviation (SD) were used to summarize approximately normally distributed continuous variables, and median and range or interquartile range (IQR) were reported for variables with skewed distributions. Percentages were reported for categorical variables.

## RESULTS

A total of 67 patients were diagnosed with T1a EAC via EMR during the study period; 8 were excluded because of the presence of high-risk pathologic features (angiolymphatic invasion, poor tumor differentiation), and 5 were excluded because they had yet to meet the minimum 3-month follow-up period. The endotherapy cohort (Table 1) consisted of 54 patients (83% male) with a mean ( $\pm$  SD) age of 68 ( $\pm$  12.2) years. The mean ( $\pm$  SD) BE length was 4.5 ( $\pm$  3.9 cm); the mean ( $\pm$  SD) size of the resected adenocarcinoma was 7.1 ( $\pm$  4.3 mm). Eleven patients (20%) had multifocal cancer present; in these cases, the largest focus of cancer (mm) was used in the mean size calculation.

The EMR techniques (Table 2) included band-assisted resection in 46 (85%, median 1.5 resections, IQR 1-2), cap-assisted resection in 6 (11%, median 1.5 resections, IQR 1-3), and lift and cut resection in 2 patients (4%). Eighty-one percent of patients to date have undergone ablative therapy of remnant Barrett's epithelium. Radiofrequency ablation was performed in 95%, spray cryotherapy

**TABLE 1. Patient and tumor characteristics (n = 54)**

|                                   |                    |
|-----------------------------------|--------------------|
| Sex, % male                       | 83                 |
| Age, mean (SD), y                 | 68 (± 12.1)        |
| BE length, mean (SD) (range), cm  | 4.5 (± 3.9) (1-16) |
| Tumor size, mean (SD) (range), mm | 7.1 (± 4.3) (1-19) |

SD, Standard deviation; BE, Barrett's esophagus.

**TABLE 2. Treatment and ablation**

|                                                             |               |
|-------------------------------------------------------------|---------------|
| EMR technique (n = 54)                                      |               |
| Band-assisted (median no. resections, IQR), no.             | 46 (1.5, 1-2) |
| Cap-assisted (median no. resections, IQR), no.              | 6 (1.5, 1-3)  |
| Lift and cut, no.                                           | 2             |
| Ablation technique (n = 44)                                 |               |
| Radiofrequency ablation (median no. treatments, range), no. | 42 (2, 1-6)   |
| Cryotherapy (median no. treatments, range), no.             | 4 (4.5, 2-8)  |
| Photodynamic therapy (no. treatments), no.                  | 1 (1)         |
| Adverse event rate (%)                                      | 17            |

IQR, Interquartile range.

**TABLE 3. Remission rates and survival**

|                                  |                  |
|----------------------------------|------------------|
| Follow-up, mean (SD) (range), mo | 23 (± 16) (3-72) |
| CR-CA (%)                        | 96               |
| CR-D (%)                         | 87               |
| CR-IM (%)                        | 59               |
| Overall survival (%)             | 89               |
| Disease-free survival (%)        | 98               |

SD, Standard deviation; CR-CA, complete response for cancer; CR-D, complete response for dysplasia; CR-IM, complete response for intestinal metaplasia.

in 9%, and photodynamic therapy in 2%. The overall adverse event rate for endotherapy was 17% (9/54). There was one episode of acute bleeding requiring 23-hour admission for observation after EMR; no transfusion was necessary. Two patients were admitted with delayed bleeding (after 48 hours), for which 1 required endoscopic therapy. Six patients developed symptomatic strictures requiring dilation (median 2, range 1-5 dilations). There were no perforations as a result of EMR, ablation, or dilation.

The mean (± SD) follow-up duration was 23 (± 16 months) (Table 3). The remission of adenocarcinoma was 96% (52/54); 1 patient has persistent intramucosal carcinoma, and another patient developed a metachronous cancer 19 months after EMR. The former patient is undergoing spray cryotherapy for continued treatment. The latter patient underwent EMR, which revealed a superficial T1b lesion (1 neoplastic gland invading the superficial submucosa) with angiolymphatic invasion (tumor cells within one lymphatic channel). This patient underwent esophagectomy; there was no remaining cancer in the esophagus and all lymph nodes were negative for metastases.

The complete response for dysplasia is 87% (47/54). Patients with persistent dysplasia are still undergoing ablation. The complete response for intestinal metaplasia is 59%. The overall survival is 89%; there were no deaths related to EAC. Additionally, no patient has developed lymph node metastasis (LNM) by EUS surveillance and/or PET-CT.

## DISCUSSION

Endoscopic therapy is currently an accepted treatment option for low-risk T1a adenocarcinomas of the esophagus. The absence of angiolymphatic invasion, submucosal invasion, and poor differentiation define a low-risk lesion. Extensive experience from Germany with mature data support endotherapy in this regard. None of 231 patients with T1a EAC developed LNM or died of esophageal cancer. The median follow-up in this study was 61 months, and the overall survival was no different when compared with the average German population when matched for age and sex.<sup>20</sup> It became apparent that ablation of the remaining Barrett's epithelium was necessary to decrease the rate of metachronous lesions. Pech et al<sup>20</sup> reported a metachronous neoplasia rate of 21% without uniform ablation of the remaining BE segment. Granted, the majority of metachronous lesions were managed endoscopically. More recent data support EMR followed by radiofrequency ablation for complete BE eradication, as opposed to stepwise radical endoscopic resection, which has a very high stricture rate (37%-88%).<sup>23-28</sup>

The obvious concern regarding endotherapy for a T1a lesion is the metastatic risk. As mentioned earlier, no patient in the large German experience (231 patients) developed LNM. In the 8 largest single-center surgical series of superficial esophageal cancer, 8 of 317 patients (2.5%) with T1a cancer had LNM on surgical pathology, as opposed to a LNM rate of 12% to 37% for T1b lesions.<sup>5-7,29-33</sup> The largest single-center series reported 1 of 75 T1a patients (1.3%) with LNM; this patient had a 2.2-cm lesion with angiolymphatic invasion and poor differentiation.<sup>33</sup>

This would not be a lesion considered appropriate for definitive endotherapy. Of the 7 other patients in these surgical series with LNM, there are no further pathologic characteristics reported, thus it is unknown whether they also had high-risk lesions. If we accept a 2.5% metastatic risk, this is not significantly different from the surgical mortality rate.<sup>5-9</sup> However, we believe that surgical series may over estimate the true metastatic risk for a pathologically confirmed T1a EAC, particularly if high-risk lesions are included. The risk of nodal metastasis is acceptably small for endoscopically resectable lesions in the context of the available therapeutic options, given the endoscopic experience reported to date.

Endotherapy for T1a EAC requires dedicated and experienced therapeutic endoscopists and expert pathologists. At our institution, we have developed a synoptic report for superficial cancer in EMR specimens, to include tumor size, grade, deep and/or lateral margin assessment, and the presence of angiolymphatic invasion to ensure identification of high-risk cancers. We also meet with our pathologists weekly to review our EMR specimens, which we feel is an important aspect to guide appropriate decision making in regard to patient care. Vigilant endoscopic surveillance is also paramount, to assess for recurrence or development of a metachronous lesion after EMR and ablation. Although we use surveillance EUS and annual PET-CT scans, we question the utility of these. In our experience, we have yet to detect a LNM during surveillance, similar to the German experience. Additionally, a previous surgical study concluded that PET-CT scanning was not indicated in staging superficial esophageal cancer, because it had a 0% sensitivity and positive predictive value for N1 status.<sup>34</sup>

Multifocal T1a EAC requires meticulous endoscopic follow-up. This can be a risk factor for recurrence.<sup>20</sup> However, the magnitude of this risk is unknown in the era of complete BE eradication after EMR. In the case of multiple mucosal resections, it is also very difficult to tell whether the lesion is truly multifocal when piecemeal resection is performed. We consider multifocal EAC a higher risk situation but not a contraindication to endotherapy. In these cases, we recommend extra vigilance in BE eradication and endoscopic follow-up. The presence of a multifocal lesion does make it more difficult to assess the overall size of the adenocarcinoma. In our study, we opted to use the largest adenocarcinoma focus as measured on histology to define the size of the lesion, likely underestimating the true size. Nevertheless, the size of the lesion was not used as a contraindication to endotherapy in our cohort. Greater tumor size has been reported to be a risk factor for lymph node metastases in some studies.<sup>33</sup>

Our rate of remission of adenocarcinoma (96%) is similar to that of other studies.<sup>19,20,35</sup> Our one patient who developed a metachronous lesion had a multifocal T1a lesion, with multifocal dysplasia throughout a 7-cm BE segment. Acid reflux control was inadequate despite high-

dose acid suppression regimens and even a repeat Nissen fundoplication. The patient persisted with small BE islands and erosive esophagitis despite ablative therapy. We believe the inability to accomplish complete BE eradication because of inadequate reflux control was the risk factor for the patient's metachronous lesion. Our other patient who persists with focal intramucosal adenocarcinoma has a recalcitrant esophageal stricture that prevents ideal endotherapy. This patient has been deemed a high-risk surgical candidate because of his previous esophageal perforation and recently diagnosed recurrent head and neck cancer.

Our complete response for dysplasia of 87% is reflective in the fact that several patients with dysplasia are still undergoing active ablation. With continued therapy, the complete response for dysplasia is likely to increase. Our complete response for intestinal metaplasia of 59% is not significantly different from other single-center experiences.<sup>25</sup> As mentioned earlier, many patients are still undergoing ablation, which will translate to a higher complete response for intestinal metaplasia with continued follow-up. Our primary endpoint in this study was not complete intestinal metaplasia ablation, and 3 patients at extremes of age or comorbidity did not undergo ablation after EMR. However, these patients were included in the intention-to-treat analysis, reflecting real-life practice as opposed to protocol.

This is a large, American, single-institution experience of endotherapy for T1a EAC. Our experience, backed by existing literature, shows that endotherapy is safe and effective for low-risk mucosal EAC. The adverse event rate of endotherapy (0%-17%) is far lower than the 20% to 40% morbidity rate of esophagectomy.<sup>5-9,36</sup> The true LNM rate for low-risk T1a EAC is likely to be less than the surgical mortality of esophagectomy in an experienced center. The largest American experience of endotherapy for T1a EAC (132 patients) reported excellent results with longer follow-up (43 months), with no difference in overall survival as compared with a surgical cohort. However, remission of dysplasia and intestinal metaplasia was not reported. Photodynamic therapy was used in this study in combination with EMR. There was a 12% recurrent cancer rate in the endotherapy group; one case was managed by repeat endotherapy. The authors of this study concluded that endotherapy was a reasonable alternative to esophagectomy, and overall survival was similar.<sup>35</sup> Diligent endoscopic follow-up is important, because recurrent EAC is endoscopically treatable. These findings were reinforced by two recent studies comparing endotherapy to surgical resection for T1a EAC. There was no difference in overall survival; disease-free follow-up was lower in the endotherapy group (91% vs 100%, not significant), which is not unexpected, and recurrences still can be managed endoscopically. The major difference was the morbidity rate of 0% for endotherapy versus 32% to 39% for the esophagectomy cohorts.<sup>8,9</sup>



There are several limitations to our study. First, this is a retrospective study from a single, tertiary-care center. Second, our mean follow-up is only 23 months; however, this short time frame is because of the increasing rate of referrals for early Barrett's neoplasia in our center. Third, a standardized endoscopic classification system to describe the resected lesions was lacking in this study.

Given the existing literature, which parallels our experience, endotherapy for low-risk T1a EAC is safe and effective and should be considered the treatment of choice. Decisions regarding higher risk situations (multifocality, difficult anatomy) require individualized management. Complete BE eradication after EMR is important to reduce recurrences; we favor EMR followed by radiofrequency ablation, given the safety, efficacy, and lower risk profile of this hybrid approach. Endotherapy for low-risk T1a EAC requires dedicated endoscopic follow-up. The role of surveillance EUS and imaging remains to be defined.

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