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A survey of expert follow-up practices after successful endoscopic eradication therapy for Barrett's esophagus with high-grade dysplasia and intramucosal adenocarcinoma

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Abstract

Background—Despite the increasing number of patients undergoing endoscopic therapy for Barrett's esophagus (BE) with high-grade dysplasia (HGD) or intramucosal cancer (IMC), there are few data to guide clinical decision making and research initiatives in the area of posttreatment follow-up.

Objectives—We aimed to define expert practice patterns regarding follow-up after endoscopic treatment of BE with HGD and IMC.

Design—Electronic survey.

Subjects—Forty-eight endoscopists in the United States with expertise in BE endotherapy based on high-impact publications and national reputation.

Intervention—A 21-item Web-based survey inquiring about post-BE endotherapy follow-up practices.

Results—Of 48 expert endoscopists, 42 completed the survey. After successful treatment of BE with HGD or IMC, all experts perform surveillance upper endoscopy, most commonly at 3-month intervals in the first posttreatment year, every 6 months during the second year, and annually thereafter. None of the experts perform surveillance EUS after treatment of HGD, and only 19% perform EUS after treatment of IMC. After cancer eradication, only 36% of experts refer patients for CT, and 24% refer patients for positron emission tomography. Thirty-eight percent of experts refer patients for a surgical opinion when IMC extends into the muscularis mucosa; 100% refer when IMC extends into submucosa.

Limitations—Not a consensus document; only U.S. experts included.

Conclusions—This study reports the follow-up practices of expert endoscopists after successful endotherapy for BE with HGD and IMC. Additional research is necessary to establish optimal surveillance intervals, the role of follow-up EUS, CT, and positron emission tomography, as well as the surgical implications of low-risk IMC extending into the muscularis mucosa.

The enthusiasm and progress surrounding endoscopic eradication therapy for neoplastic Barrett's esophagus (BE) have exploded in the past decade. Patients worldwide with high-

grade dysplasia (HGD) and intramucosal cancer (IMC) complicating BE are now commonly managed with endoscopic therapies, based on a growing literature that suggests favorable oncologic outcomes with minimal morbidity compared with surgical resection.¹⁻⁵

Accordingly, evidence-based guidelines and a consensus statement were recently published to guide clinical decision making in important areas such as pathologic evaluation of BE, progression to cancer, pretreatment surveillance strategies, as well as the role of and approach to endoscopic therapy.⁶⁻⁸ There are, however, very few data pertaining to the important and potentially costly aspect of the follow-up of patients who have undergone successful endoscopic treatment. Because recurrence of HGD or cancer after complete endoscopic eradication may occur in 15% to 30% of cases and the majority of recurrent lesions can be successfully re-treated endoscopically,^{3,9,10} follow-up of BE endotherapy patients is of significant potential importance. Given the rapidly growing number of patients undergoing endotherapy for BE with HGD and IMC, an improved understanding of optimal clinical practices and salient research questions in the area of posttreatment follow-up will be essential to delivering high-quality, value-based care to this patient population.

Because there is a current paucity of data to inform clinical decision making and research initiatives surrounding posttreatment surveillance and follow-up, we surveyed national experts in the field of BE endotherapy to better define their posttreatment practice patterns. We aimed to provide an expert-based clinical framework on which the endoscopy community may elect to model its practice while awaiting a more robust evidence base, as well as to identify important and timely research questions pertaining to this aspect of care.

METHODS

Survey development

The survey instrument was developed through a process of structured discussions within the advanced endoscopy group at the University of Michigan in parallel with a comprehensive review of the medical literature to identify studies potentially relevant to our questions of interest. The initial survey instrument was designed by 2 investigators (A.O.B., B.J.E.) and subsequently iteratively pilot tested by the remainder of the authors to establish face and content validity and to improve factors affecting test-retest reliability, such as the clarity and order of questions, length of the instrument, and ease of administration.

Study questionnaire

The Web-based survey included multiple-choice and table-based questions designed to assess individual practice patterns pertaining to surveillance and follow-up after eradication therapy for HGD or IMC in BE. The complete 21-item instrument, which also included questions pertaining to respondent practice volume and a few nonsurveillance issues (such as pretreatment EUS patterns), is included in Appendix A (available online at www.giejournal.org). For this survey, low-risk IMC was defined as (1) uninvolved deep histologic margins, (2) no angiolymphatic invasion, and (3) the absence of poorly differentiated histology.^{8,11}

Study sample

A purposeful sample of interventional gastroenterologists with established expertise in endotherapy of BE was generated after a comprehensive computer-assisted literature search with the OVID interface to MEDLINE. A search of human studies from January 1, 1995 to April 1, 2012 was performed by using the MeSH and keyword terms “(exp Barrett esophagus AND (dysplasia (keyword) OR exp adenocarcinoma)) AND (endoscopic mucosal resection (keyword) OR radiofrequency ablation (keyword) OR cryoablation (keyword)).

The corresponding authors of all potentially relevant articles (including review articles and editorial pieces) were noted; those U.S. authors with multiple and/or influential publications made up the list of experts from which the final study sample was selected after discussions among the authors to identify those endoscopists with a national presence in the field of BE endotherapy. To maximize the validity of the results, our a priori plan was to conduct the survey only if we could identify 40 or more U.S. experts, although we intended to include as many endoscopists as possible who met our expertise criteria.

Survey administration and interpretation

An electronic message including a link to the Web-based version of the survey (Qualtrics Systems, Hong Kong) was e-mailed to all potential subjects in February 2012. Participants were contacted multiple times by 1 or more of the authors during the study period to encourage completion of the survey and maximize the response rate. The survey was closed after 75 days. Consent to participate in this study was inferred from completion of this voluntary and anonymous survey, which was approved by the University of Michigan Institutional Review Board. Descriptive statistics were used to interpret and report survey results. For surveillance questions, when a respondent initially indicated a surveillance interval but subsequently registered no response, it was assumed that annual surveillance is discontinued. For example, if an expert responded that he or she perform surveillance every 3 months for the first year, every 6 months for the second year, annually in years 3 and 4, but then registered no subsequent interval, he or she was assumed to have stopped annual surveillance after year 4. This assumption was relevant only to a minority of respondents.

RESULTS

Of the 48 invited experts, 42 completed the survey (87.5% response rate). All respondents confirmed that after treatment of focal HGD or focal adenocarcinoma (by either EMR or ablation), they routinely perform eradication therapy of all remaining nondysplastic BE, consistent with published consensus.⁸

EUS before endoscopic eradication therapy

EUS is performed before endoscopic eradication therapy by 95% of respondents in patients with BE and IMC. In patients with BE complicated by HGD, 55% of respondents report performing EUS before providing endoscopic eradication therapy.

Surveillance EGD after eradication of HGD

Surveillance EGD is performed after eradication of HGD by 100% of respondents. During the first posttreatment year, 74% of respondents perform EGD every 3 months, whereas 24% perform EGD every 6 months; only 1 respondent (2.4%) reported performing surveillance EGD a full year after eradication therapy. During the second posttreatment year, 64% of respondents perform surveillance EGD every 6 months and 31% at the end of year 2. During this year, 1 expert (2.4%) continued 3-month intervals and 1 expert (2.4%) discontinued surveillance. During year 3, 76% of respondents perform a single annual EGD, and 6 respondents (14%) continue 6-month intervals, whereas 3 experts (7%) discontinue surveillance. Beyond 3 years, the majority of experts perform annual surveillance, although as many as 30% of experts will have discontinued annual surveillance or surveillance altogether by year 6 (Fig. 1). The most commonly indicated surveillance pattern of EGD every 3 months during the first posttreatment year is consistent with the follow-up protocol used in the landmark AIM dysplasia trial (Ablation of Intestinal Metaplasia Containing Dysplasia trial).^{4,9} Approximately 40% of survey participants were AIM dysplasia investigators, potentially explaining this association.

Histologic sampling practices during surveillance EGD after eradication of HGD

During surveillance EGD of completely eradicated HGD, approximately 90% of respondents perform routine biopsies of the neosquamous epithelium and 93% of experts perform routine biopsies of the normal-appearing Z-line.

Surveillance EUS after eradication of HGD

None of the respondents perform surveillance EUS after eradication of HGD.

Surveillance EGD after eradication of low-risk IMC involving the lamina propria (no deep margin involvement, no angiolymphatic invasion, and no poorly differentiated histology)

After complete endoscopic eradication of BE adenocarcinoma involving the lamina propria alone (assuming the absence of high-risk features), 100% of experts report performing surveillance EGD. During the first posttreatment year, 83% of respondents perform EGD every 3 months, whereas 17% perform EGD every 6 months. In the second year after treatment, 76% of participants perform surveillance EGD every 6 months, whereas 21% perform annual EGD, and 1 expert (2.4%) continued surveillance every 3 months. During the year 3, 74% of respondents perform a single annual EGD, 8 respondents (19%) continue 6-month intervals, 1 expert (2.4%) continued surveillance every 3 months, and 1 expert (2.4%) discontinued surveillance. Beyond 3 years, the majority of experts perform annual surveillance, although as many as 31% of experts will have discontinued annual surveillance or surveillance altogether by year 6 (Fig. 2).

Surveillance EUS after eradication of low-risk IMC involving the lamina propria (no deep margin involvement, no angiolymphatic invasion, and no poorly differentiated histology)

Eighty-one percent of participants do not perform surveillance EUS after endoscopic eradication of low-risk IMC. Of the 19% who do perform EUS, 2 experts perform it every 3 months during the first year, and 6 perform a single annual EUS during this first posttreatment year. During the second year, 2 experts perform EUS every 6 months, and 5 perform an annual EUS. During year 3, 6 of the respondents who perform surveillance EUS perform a single annual examination. By year 5, all but 2 experts will have discontinued surveillance, and only 1 endoscopist continues annual EUS after year 5 (Fig. 3).

CT and positron emission tomography after eradication of low-risk IMC

After complete EMR eradication of BE adenocarcinoma involving the lamina propria alone (assuming a negative deep margin, the absence of angiolymphatic invasion, and the absence of poorly differentiated histology), 36% of experts refer their patients for a CT scan of the chest, abdomen, and pelvis. Twenty-four percent of respondents refer such patients for a positron emission tomography (PET) scan.

Surgical and oncologic referral for completely resected, low-risk IMC that extends beyond the lamina propria

After complete EMR eradication of BE adenocarcinoma extending beyond the lamina propria into the muscularis mucosa (assuming a negative deep margin, the absence of angiolymphatic invasion, and the absence of poorly differentiated histology), 38% of experts refer their patients for consideration of surgical resection. In this situation, if esophagectomy is not an option, only 14% will refer their patients for consideration of chemotherapy and radiation therapy. When the adenocarcinoma is found to involve the submucosa, all participating experts refer their patients for consideration of surgical resection, and if an operation is not an option, 82% refer the patient for consideration of chemoradiation.

DISCUSSION

Through this survey we have better defined the posttreatment practice patterns of national experts in the field of BE endotherapy (1) to provide an expert-based clinical framework of posttherapy surveillance and follow-up on which endoscopists may choose to model their practices until evidence-based guidelines are available and (2) to identify important research questions that may affect clinical outcomes and health care costs in this area.

For patients who have undergone successful eradication therapy of BE with HGD or low-risk IMC, experts uniformly perform follow-up upper endoscopy. For cases of HGD, the majority of experts perform mucosal biopsies of the normal-appearing neosquamous epithelium and Z-line. Although this question was not specifically asked regarding patients with treated cancer, it may be reasonable to assume that experts would also perform biopsies of the normal-appearing neosquamous epithelium and Z-line in IMC patients. This practice appears justified by multiple studies demonstrating that recurrent HGD and IMC may be buried beneath normal neosquamous epithelium.¹²⁻¹⁴

Regarding the interval of surveillance endoscopy after treatment of HGD and low-risk IMC, the majority of experts perform EGD every 3 months during the first year. Almost all others perform EGD every 6 months during this year. Subsequently, the majority of experts perform endoscopy every 6 months in the second year and annually thereafter. Approximately 30%, however, will have discontinued annual surveillance or surveillance altogether after year 5. Long-term outcomes studies defining the chronologic and biological patterns of recurrence are necessary to determine whether the 3-month interval during year 1 is necessary and cost-effective, what the optimal surveillance interval is in subsequent years, and whether surveillance remains necessary beyond 3 to 5 years.

After successful treatment of BE with HGD, none of the experts perform surveillance EUS. This practice appears reasonable in light of a recent systematic review showing no incidence of lymph node metastasis in 524 patients undergoing esophagectomy for HGD.¹⁵ After successful eradication of low-risk IMC, only 19% of experts perform surveillance EUS. The majority of these experts perform this procedure annually. Multicenter registries from institutions and practitioners who perform surveillance EUS are necessary to determine whether the clinical yield of this practice justifies the associated opportunity and economic costs. Moreover, long-term outcomes studies are necessary to determine whether earlier detection of recurrences by EUS actually improves clinical outcomes or simply increases apparent survival through the phenomenon of lead-time bias.

Approximately 35% of experts refer patients for a CT scan after eradication of low-risk IMC, and 24% of experts refer such patients for a PET scan. Additional multicenter observational data are necessary to determine the yield of these approaches and whether these modalities should have a role in the surveillance or pretreatment evaluation of this patient population.

When IMC extends beyond the lamina propria into the muscularis mucosa, 38% of experts refer their patients for a surgical opinion; however, only 14% refer their patients for consideration of chemoradiation if surgery is deemed too risky. Several studies have shown an increased risk of lymph node metastasis of 5% or more in patients with involvement of the muscularis mucosa¹⁵; therefore, additional clinical studies and simulation models focusing on the risk-benefit ratio of esophagectomy and/or chemoradiation in this scenario are necessary. In the interim, practitioners should be clear about the elevated risk of lymph node metastasis associated with muscularis mucosa cancers so that patients can make an informed decision regarding surgery.

In patients with IMC extending into the submucosa, all experts refer for consideration of esophagectomy, and if this is not an option, more than 80% refer for chemoradiation. Submucosal involvement has been shown to portend a 15% to 20% risk of lymph node metastasis, thus justifying this practice.^{11,16,17}

These results should be interpreted in the context of several important limitations. First, although a survey of experts may provide clinically helpful information in the short and medium term, the results are not intended to be a substitute for primary research and subsequent evidence-based guidelines in this area. Second, this document is not intended to be a consensus statement because expert responses were independent and the discourse necessary to establish consensus did not occur. Along these lines, we did not use the Delphi process, which has recently been used to generate consensus statements regarding the management of BE dysplasia and early-stage adenocarcinoma.⁸ This process, however, is most effective when based on review of high-quality published literature, not available on the topic of postendotherapy surveillance and follow-up.

Further, our study sample was composed entirely of experts from the United States; experts from other geographic regions may have varying practice patterns that reflect regional experiences, resources, and values. Moreover, the process that we used to select experts was based primarily on the impact of scientific publications, which is only 1 aspect of expertise. The survey questions did not allow free text responses, perhaps failing to capture certain practice patterns not included in the multiple choice and table-based response choices. Last, when an expert initially indicated a surveillance interval but subsequently registered no response, it was assumed that surveillance is discontinued, potentially overestimating the surveillance termination rates. Despite these limitations, however, this study is the first to address this important aspect of BE endotherapy.

In summary, this survey revealed the following expert practice patterns regarding surveillance and follow-up of treated BE with HGD or low-risk IMC:

- a. All experts perform surveillance upper endoscopy after treatment of BE with HGD and IMC, most commonly every 3 months during the first posttreatment year, every 6 months during the second posttreatment year, and annually thereafter.
- b. During surveillance EGD, all experts perform biopsies of the normal-appearing Z-line and neosquamous epithelium.
- c. None of the experts perform surveillance EUS after successful treatment of HGD, and only 19% of experts perform EUS surveillance after treatment of IMC, most commonly at annual intervals.
- d. After eradication of BE with IMC, 36% of experts refer patients for a CT scan, and 24% refer patients for a PET scan.
- e. Approximately 40% of experts refer patients for a surgical opinion when the IMC extends into the muscularis mucosa; all refer patients for a surgical opinion when there is extension into the submucosa.

Additional research is necessary to establish optimal surveillance intervals, the role, if any, of EUS, CT, and PET scan, as well as the surgical implications of low-risk IMC extending into the muscularis mucosa.

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Abbreviations

BE	Barrett's esophagus
HGD	high-grade dysplasia
IMC	intramucosal cancer
PET	positron emission tomography

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Take-home Message

- This survey of expert follow-up practices after Barrett's esophagus endotherapy provides a framework on which the endoscopy community may model its practice while awaiting evidence-based guidelines and identifies important and timely research questions pertaining to this aspect of care.

Figure 1.
Surveillance EGD frequency after endoscopic treatment of high-grade dysplasia (HGD) in Barrett's esophagus.

Figure 2. Surveillance EGD frequency after endoscopic treatment of intramucosal cancer (IMC) in Barrett's esophagus.

Figure 3.
Surveillance EUS frequency after endoscopic treatment of intramucosal cancer (IMC) in Barrett's esophagus.