

## Consensus Statements for Management of Barrett's Dysplasia and Early-Stage Esophageal Adenocarcinoma, Based on a Delphi Process

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**BACKGROUND & AIMS:** Esophageal adenocarcinoma (EA) is increasingly common among patients with Barrett's esophagus (BE). We aimed to provide consensus recommendations based on the medical literature that clinicians could use to manage patients with BE and low-grade dysplasia, high-grade dysplasia (HGD), or early-stage EA. **METHODS:** We performed an international, multidisciplinary, systematic, evidence-based review of different management strategies for patients with BE and dysplasia or early-stage EA. We used a Delphi process to develop consensus statements. The results of literature searches were screened using a unique, interactive, Web-based data-sifting platform; we used 11,904 papers to

inform the choice of statements selected. An a priori threshold of 80% agreement was used to establish consensus for each statement. **RESULTS:** Eighty-one of the 91 statements achieved consensus despite generally low quality of evidence, including 8 clinical statements: (1) specimens from endoscopic resection are better than biopsies for staging lesions, (2) it is important to carefully map the size of the dysplastic areas, (3) patients that receive ablative or surgical therapy require endoscopic follow-up, (4) high-resolution endoscopy is necessary for accurate diagnosis, (5) endoscopic therapy for HGD is preferred to surveillance, (6) endoscopic therapy for HGD is preferred

**Abbreviations used in this paper:** BAD CAT, Barrett's dysplasia and cancer task force; BE, Barrett's esophagus; EA, esophageal adenocarcinoma; EMR, endoscopic mucosal resection; HGD, high-grade dysplasia; LGD, low-grade dysplasia; RFA, radiofrequency ablation.

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0016-5085/\$36.00

<http://dx.doi.org/10.1053/j.gastro.2012.04.032>

to surgery, (7) the combination of endoscopic resection and radiofrequency ablation is the most effective therapy, and (8) after endoscopic removal of lesions from patients with HGD, all areas of BE should be ablated. **CONCLUSIONS:** We developed a data-sifting platform and used the Delphi process to create evidence-based consensus statements for the management of patients with BE and early-stage EA. This approach identified important clinical features of the diseases and areas for future studies.

*Keywords:* BADCAT; Esophageal Cancer; Treatment Strategy; Systematic Analysis.

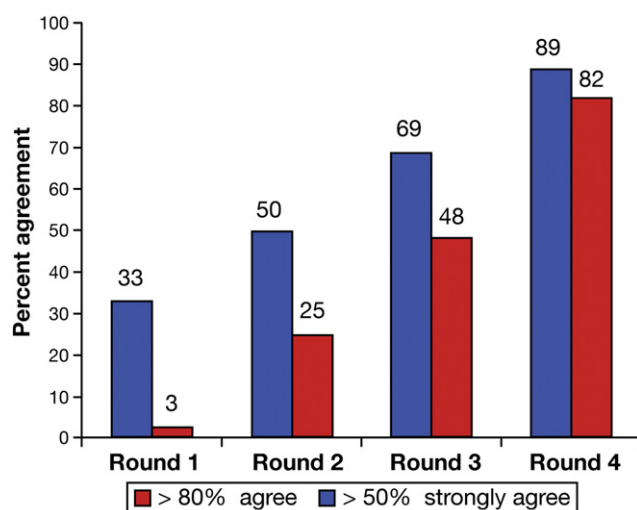
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Barrett's esophagus (BE) is defined as the replacement of distal esophageal squamous mucosa with metaplastic columnar epithelium.<sup>1</sup> It occurs in 4% of patients undergoing an upper gastrointestinal endoscopy, and in 9% of men over 50 years of age.<sup>2</sup> BE is more common in developed countries, affecting 2% of the population, because it is strongly associated with gastroesophageal reflux disease<sup>3,4</sup> and this disease incidence is increasing in developing countries.<sup>5</sup> The main concern with BE is the associated increased risk for esophageal adenocarcinoma (EA). EA is the fastest growing cause of cancer mortality,<sup>6</sup> and it is estimated that patients with BE have at least a 20-fold increased risk of developing EA.<sup>7-9</sup> Most guidelines<sup>10,11</sup> recommend surveillance endoscopy every 2 to 5 years in patients with BE to detect early, treatable neoplasia and early signs of high-grade dysplasia (HGD). If progression to low-grade dysplasia (LGD), HGD, or EA can be detected early in its course, cancer can either be prevented or treated at a curable stage.<sup>12,13</sup>

There is a lack of agreement concerning optimal management of dysplasia and early EA and, therefore, management practice patterns vary considerably among BE experts. The classification and recognition of dysplasia, both by endoscopy and histology, are variable among and within countries, and between some medical centers. There remains heterogeneity in the management of HGD/early EA throughout the world; the primary alternatives include managing HGD with surveillance alone, endoscopic therapy to remove HGD or early EA, or surgical resection of the BE (esophagectomy).<sup>14</sup> Innovations have taken place in the endoscopic management of EA.<sup>15</sup> In this rapidly changing field, a rational consensus approach to BE patients with LGD, HGD, and early EA is necessary to help inform the practicing clinician. Previously, several consensus papers have had some impact on clinical management<sup>1,10</sup> but



**Figure 1.** Proportion of statements achieving consensus with each round of voting. With each round voting improved with iterative changes to the question and supporting evidence.

have focused on BE in general; the focus of this guideline is LGD, HGD, and early EA.

## Methods

The specific population under consideration consisted of adults aged 18 years or older with a diagnosis of BE plus LGD, HGD, or early EA, the latter being defined as intramucosal EA (T1m) or superficial submucosal EA (T1sm1). We used a Delphi process to develop consensus statements for LGD/HGD/early EA. This approach combines the principles of evidence-based medicine supported by systematic literature reviews with the use of an iterative anonymous voting process. This software program permitted anonymous individual feedback and changes of views during the process, together with controlled feedback of evidence regulated by the coordinator (CB) and the consensus chair (JJ). The Delphi process<sup>16</sup> is now increasingly used in health care as a rigorous means of determining consensus in a defined clinical area<sup>1,17</sup> and is reliable.<sup>18</sup>

The principal steps in the process were: (1) selection of the consensus group; (2) development of draft statements by panels; (3) systematic literature reviews to identify evidence to support each statement (search key words, Appendix 1); (4) 4 rounds of repeated anonymous voting on iterations of the statements (with feedback at each round) until consensus was reached (Appendix 2) (Figure 1); and (5) grading of the strength and quality of the evidence and strength of the recommendations using accepted criteria<sup>19,20</sup> (Appendix 2). Details are listed in Appendix 3.<sup>21</sup>

## Results

The initial stage was development of statements followed by a comprehensive literature review. Eventually, 4 in-person meetings followed by 4 rounds of consensus voting resulted in consensus (80% of respondents strongly agree or agree with reservation) being achieved in 81 of 91 statements. The respondents were asked to choose 1 of the following for each statement; agree strongly (A+), agree with reservation (A), undecided (U), disagree (D) or

disagree strongly (D+). Although evidence-based explanations with key references were provided when relevant, it was the statement on which people voted. Consistent with principles of the Delphi process,<sup>19</sup> the level of agreement increased with each round of voting (Figure 1). This high level of consensus was also exemplified by a post hoc analysis, where if >50% of respondents strongly agreed with the statement, it was accepted as a measure of agreement (Figure 1). Overall, the proportion of participants voting for each statement increased with each round of voting.

We selected 20 statements that represent the following key clinically relevant areas: diagnosis, epidemiology, methods of surveillance, approaches to treatment, and prevention of HGD and early adenocarcinoma in patients with BE. A description of any concerns about the statement is provided from the online comments of the respondents. We focused on HGD and early EA, as this area has the most evidence. All the remaining statements are outlined in Appendix 2.

### Diagnosis of BE and HGD

**Histologically, there is poor inter-observer agreement among pathologists in distinguishing HGD from intra-mucosal adenocarcinoma.** *Agreement:* A+ 62%, A 33%, U 4%, D 1%, D+ 0%. *Evidence:* Moderate. The extent and severity of the dysplastic changes distinguishes HGD from LGD.<sup>22</sup> Expert pathologists have found distinguishing HGD from intramucosal EA remains problematic.<sup>23</sup> The widely accepted definition of intramucosal EA is a lesion in which neoplastic cells have penetrated the basement membrane and invaded the lamina propria, but have not yet penetrated through the muscularis mucosae. However, reliable histologic recognition of lamina propria invasion is difficult due to the absence of objective and validated criteria. Kappa statistics for distinguishing between HGD and intramucosal EA vary between 0.21 and 0.47, suggesting poor, or at best, fair agreement.<sup>23-25</sup>

**At least 2 experienced gastrointestinal pathologists should evaluate all Barrett's biopsies when a diagnosis of dysplasia is considered.** *Agreement:* A+ 79%, A 15%, U 4%, D 1%, D+ 1%. *Evidence:* Moderate. It has long been recognized that there is inter-observer variability between pathologists in differentiating HGD from intramucosal EA as described here. Five studies<sup>26-30</sup> have shown that the prediction of progression of esophageal dysplasia is improved if at least 2 expert pathologists agree on a diagnosis of dysplasia, and increases when more pathologists concur with the diagnosis.<sup>27,29,30</sup>

### Risk of Progression to Esophageal Adenocarcinoma

**Non-goblet columnar metaplasia of the esophagus can progress to cancer, but the magnitude of risk is unknown.** *Agreement:* A+ 59%, A 33%, U 6%, D 2%, D+ 0%. *Evidence:* Low. The US definition of BE requires that intestinal metaplasia is present in the salmon-colored esophageal columnar-lined mucosa of the tubular esophagus. There is, however, evidence that non-goblet columnar

metaplasia of the distal esophagus shows biological features of intestinal differentiation, and possesses molecular abnormalities consistent with a risk of malignancy of neoplasia precursor lesions.<sup>31-34</sup> Two retrospective studies<sup>35,36</sup> evaluated the risk of neoplasia in patients with columnar metaplasia of the esophagus either with or without goblet cells. There were 991 patients with intestinal metaplasia and 631 without intestinal metaplasia. The incidence of cancer progression from BE was similar in the 2 patient groups (4.5% vs 3.6% in one study<sup>35</sup> and 3.1% vs 3.2% in the other<sup>36</sup>). Non-goblet cell columnar metaplasia has malignant potential, although the relative risk is unclear.

**Extent of dysplasia can correlate with progression to cancer in BE.** *Agreement:* A+ 52%, A 44%, U 4%, D+ 0%, D 0%. *Evidence:* Very low. The majority of participants agreed with this statement and 3 articles have evaluated whether the extent of dysplasia is a risk factor for EA in BE.<sup>37-39</sup> Two studies<sup>37,38</sup> (total of 177 patients) concluded that the extent of dysplasia was correlated with the risk of progression.<sup>37,38</sup> However, one retrospective study<sup>39</sup> of 42 patients from a pathology database with BE and HGD who underwent esophagectomy failed to show a significant association between extent of dysplasia and the risk of malignancy. Each of the 3 studies used different criteria and definitions for dysplasia.

**Ulcers in BE that fail to heal with proton pump inhibitor therapy are a very suspicious finding and should be monitored closely for development of carcinoma.** *Agreement:* A+ 66%, A 24%, U 10%, D 0%, D+ 0%. *Evidence:* Very low. Unfortunately, there are no good case series on ulcerating lesions in BE that do not heal with proton pump inhibitor therapy,<sup>40</sup> although experts would suggest that BE-related ulcers are associated with malignancy.

**Visible lumps or nodules consisting of HGD suggest a more advanced lesion with invasion might be present.** *Agreement:* A+ 73%, A 26%, U 1%, D 0%, D+ 0%. *Evidence:* Low. Endoscopic mucosal resection (EMR/ER) of visible lumps with HGD on endoscopic biopsy results in upgrading the final diagnosis to cancer in 40% of cases.<sup>41,42</sup> In a series of esophagectomies performed for presumed HGD identified by endoscopic biopsies, coexisting EA was found in 7 of 9 patients (78%) with a visible lesion and 7 of 22 patients (32%) without a visible lesion ( $P = .02$ ).<sup>43</sup>

**Risk of progression from HGD to EA is approximately 10% per year (range 6%–19%).** *Agreement:* A+ 45%, A 40%, U 5%, D 6%, D+ 4%. *Evidence:* Low. This statement achieved consensus based on a systematic review,<sup>44</sup> which identified 4 studies<sup>45-48</sup> involving 236 BE patients with HGD that suggested a conversion rate of 6% per year, contrasting with a large randomized controlled trial demonstrating conversion from HGD to EA of 19% in 1 year.<sup>49</sup> This risk estimate assumes that no endoscopic or surgical intervention takes place and that there are no macroscopically visible lesions. The issue of concomitant EA in patients who are diagnosed with BE and HGD is another consideration. In the absence of visible lesions in BE, the

prevalence of EA in patients who underwent esophagectomy was 3%.<sup>50,51</sup>

### **Methods of Surveillance for Patients With BE and With HGD**

**For evaluation of patients with BE, the use of high-resolution endoscopes and targeted biopsies of every suspicious lesion followed by 4-quadrant biopsies every 1–2 cm are recommended.** *Agreement:* A+ 60%, A 38%, U 1%, D 0%, D+ 1%. *Evidence:* Very low. A high-resolution endoscope (>850,000 pixels) should be used to evaluate patients with BE. Standard-resolution endoscopes are not recommended, although there is scant scientific evidence for this recommendation. Evidence that greater resolution improves diagnosis is only available and supports narrow band imaging,<sup>52</sup> but for chromoendoscopy there was no superiority to chromoendoscopy over standard endoscopy, although acetic acid spraying can improve visualization of lesions.<sup>53,54</sup> Even with high-resolution endoscopes, 4-quadrant biopsies are still necessary after careful evaluation of the BE segment to exclude synchronous neoplastic lesions. They should be performed with 4 biopsies at 1–2-cm intervals throughout the entire BE segment. There are no data demonstrating superiority of 1-cm intervals compared with 2-cm intervals.<sup>55,56</sup>

### **Treatment of HGD and Early EA**

**Endoscopic treatment should be preferred over endoscopic surveillance for management of most BE patients with HGD/T1m Barrett's esophagus.** *Agreement:* A+ 78%, A 19%, U 4%, D 0%, D+ 0%. *Evidence:* Moderate. There was strong agreement with this statement among the group. It is difficult to exclude EA complicating HGD based on biopsies only. Endoscopic surveillance can lead to underdiagnosis of cancer at baseline, especially when HGD is located in the area of BE that is endoscopically unremarkable.<sup>23,42</sup> Endoscopic therapy (initially EMR for visible lesions) aimed at removing all BE mucosa should treat all areas of HGD and early EA that might have been missed by surveillance alone. Two randomized sham-controlled studies<sup>46,49</sup> of ablation therapy (after initial EMR where appropriate) vs endoscopic surveillance have shown a significantly higher progression rate to cancer in the surveillance arm. Endoscopic treatment can cause complete remission of neoplasia in 80%–100% of cases and complete removal of BE with intestinal metaplasia in >75% of cases.<sup>40,49,57–60</sup> Severe complications (such as bleeding, perforation, or stricture) are uncommon.<sup>40,49,57–60</sup>

**For patients with HGD in an endoscopically visible abnormality, endoscopic resection is essential for proper diagnosis and staging.** *Agreement:* A+ 79%, A 16%, U 3%, D 1%, D+ 1%. *Evidence:* Moderate. EMR can lead to a significant change in diagnosis compared with a previous biopsy diagnosis.<sup>42,61–63</sup> EMR provides a larger tissue specimen that is generally better orientated, allowing easier interpretation by pathologists.<sup>62</sup> In addition, when an area of HGD is endoscopically visible, it is more likely to harbor EA.<sup>42,63,64</sup> If EA is found in the EMR specimen, the risk of

local lymph node metastasis has been shown to correlate with the depth of invasion,<sup>65,66</sup> allowing better selection of therapy.<sup>67,68</sup>

**Endoscopic treatment should be preferred over surgical treatment for management of most patients with HGD in BE.** *Agreement:* A+ 64%, A 29%, U 3%, D 2%, D+ 2%. *Evidence:* Low. There was strong consensus for this approach. HGD in BE is rarely associated with lymph node involvement, provided that deeper invasion has been ruled out by EMR (as described in statement 10).<sup>57,58,69,70</sup> Two case series<sup>40,57,58</sup> reported that survival after EMR was high, similar to that expected in a surgical cohort. One cohort study<sup>71</sup> reported that the disease-specific survival rate after endoscopic treatment was not different from surgical therapy. The case series reported a lower morbidity than might be expected in surgical patients.<sup>40,57,58</sup> Endoscopic treatment is associated with a higher rate of HGD recurrence,<sup>40,57,58,71</sup> although this can usually be treated endoscopically.<sup>40,57,58,72</sup> Finally, on the rare occasion that endoscopic treatment fails, surgical resection is still possible and generally curative.<sup>40,57,58</sup>

**Widespread EMR can cause strictures (especially when more than two thirds of the circumference is removed).** *Agreement:* A+ 74%, A 21%, U 4%, D 1%, D+ 0%. *Evidence:* Low. The intention of EMR/ER) should be to remove all visible dysplasia. It should ideally be restricted to less than two thirds of the esophageal circumference in order to reduce the risk of strictures, but all visible lesions should be resected. Strictures resulting from EMR respond well to dilation.<sup>73–75</sup>

**Endoscopic treatment of HGD/T1m should only be performed in tertiary referral care centers after proper training of the endoscopists and pathologists involved.** *Agreement:* A+ 57.5%, A 34%, U 2.5%, D 6%, D+ 0%. *Evidence:* Very low. There are no studies that have shown that centers with expertise, or those that have high case volumes, provide better quality care for BE patients with HGD/early EA. The consensus group voted positively for this statement because in other areas of gastroenterology, expertise and case volumes are associated with better outcomes.<sup>76,77</sup> Adequate management of these patients encompasses a wide range of experience, equipment, and a certain case volume (which we arbitrarily defined as >10 cases per year).<sup>78–82</sup>

**After EMR has removed visible lesions with HGD/T1m, the remaining BE segment should be eradicated regardless of whether or not it includes the presence or absence of dysplasia.** *Agreement:* A+ 54%, A 30%, U 13%, D 3%, D+ 0%. *Evidence:* Very low. Statement 10 recommended EMR for visible abnormalities with HGD. If EMR is the only modality that is used and the remaining BE mucosa is left untreated, case series have reported recurrence of neoplasia. Rates vary from 11% to 30% (mean follow-up of 3 years).<sup>57,83</sup> Ablation of the remaining BE is associated with a lower recurrence rate.<sup>40,49,59,60,84,85</sup>

**Radiofrequency ablation is currently the best available ablation technique for treatment of flat HGD and for eradication of residual BE mucosa after focal EMR.** *Agreement:* A+ 59%, A 25%, U 11%, D 1%, D+ 4%.

*Evidence: Low.* Statement 14 recommended endoscopic ablation of BE after EMR for visible lesions. The question remains, what is the most appropriate endoscopic technique? The alternatives that have been most frequently studied include photodynamic therapy, radiofrequency ablation (RFA), and/or stepwise EMR of all BE. A systematic review<sup>86</sup> of photodynamic therapy for HGD of BE mucosa esophagus suggests that this approach reduces the risk of progression to cancer compared with surveillance alone.<sup>46,87</sup> However, complications remain a problem with this technique,<sup>46</sup> and HGD dysplasia persists in 33%–50% of patients.<sup>87,88</sup> Other therapeutic modalities include cryotherapy and argon plasma coagulation. Cryotherapy has not been evaluated in randomized controlled trials and argon plasma coagulations has only been reported in small randomized controlled trials, although there are anecdotal high-success rates.<sup>89</sup> One systematic review<sup>90</sup> suggests that success rates with RFA are superior, with approximately 90% of patients having no HGD after therapy and this seems to be maintained.<sup>49,59,91–93</sup>

**In patients with superficial submucosal cancer in BE and low-risk characteristics (invasion <500  $\mu\text{m}$ ; G1–G2 cancers, no lymph–vascular invasion), endoscopic treatment is a valid alternative to esophagectomy.** *Agreement:* A+ 41%, A 35%, U 8%, D 11%, D+ 5%. *Evidence: Very low.* This statement failed to achieve consensus. The paradigm comes from studies from Japan on early gastric cancer, which have shown that well to moderately differentiated cancers that invade into the submucosa <500  $\mu\text{m}$  and have no lymphovascular invasion, have virtually no risk of lymph node metastases.<sup>94</sup> Furthermore, in a prospective series of 21 BE patients meeting these low-risk criteria,<sup>95</sup> no lymph node metastases were found in any of the patients after a median follow-up period of 62 months. The implications of lymph node spread are so important that more data are needed before this statement can be supported.

**Successful surgery/intervention for early cancer can be determined by long-term (5 years or longer) survival.** *Agreement:* A+ 73%, A 23%, U 3%, D 1%, D+ 0%. *Evidence: Very low.* The group reached consensus that successful surgery is determined by 5-year survival. However, most patients with HGD should receive EMR and/or RFA because it is safer and carries a similar efficacy rate,<sup>96</sup> although more studies are needed (see statements 11, 14, and 15). Surgery is still considered the treatment of choice for early EA that has extended into the submucosa.<sup>97,98</sup> Case series suggest that the 5-year survival rates range from 80% to 90%.<sup>99,100</sup>

**Reported operative mortality rate for esophagectomy for HGD and T1m generally ranges from 0% to 4%, with a mean overall operative mortality of 2%.** *Agreement:* A+ 65%, A 30%, U 3%, D 1%, D+ 1%. *Evidence: Very low.* Operative mortality for patients undergoing esophagectomy for HGD or early EA is difficult to generalize because data are primarily from self-selected high-volume centers and analysis is retrospective. We identified 10 case series<sup>71,98,101–108</sup> evaluating a total of 567 HGD

**Table 1.** Operative Mortality for Surgical Series in Patients With HGD or Early EA With BE

First author	Year	HGD	T1m	Operative mortality
Tseng <sup>101</sup>	2003	60	0	1
Reed <sup>102</sup>	2005	49	0	1
Chang <sup>103</sup>	2006	9	16	0
Rice <sup>104</sup>	2006	111	0	0
Moraca <sup>105</sup>	2006	23	1	0
Peyre <sup>106</sup>	2007	24	85	7
Williams <sup>107</sup>	2007	38	0	0
Prasad <sup>98</sup>	2007	70	0	1
Mirnezami <sup>108</sup>	2009	23	0	0
Prasad <sup>71</sup>	2009	0	46	1
		407	160	11/567 (1.9%)

Mean operative mortality is 2%.

or early EA patients (Table 1). Operative mortality rate for esophagectomy for HGD and early EA ranges from 0% to 4%, with an overall operative 30-day mortality rate of approximately 2%.<sup>101</sup>

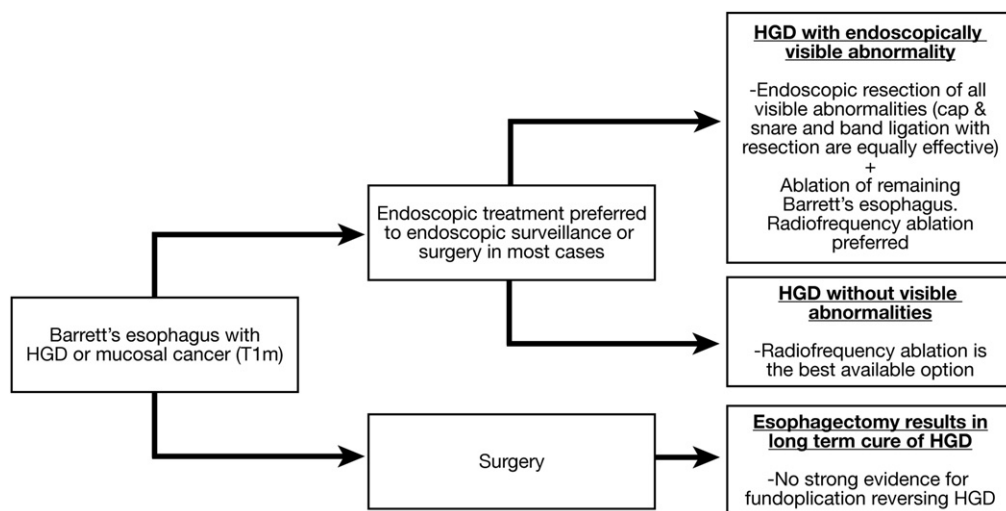
**Operative mortality is improved if surgery is undertaken in specialist surgical centers.** *Agreement:* A+ 90%, A 8%, U 2%, D 0%, D+ 0%. *Evidence: Moderate.* In contrast to the evidence for endoscopic therapy (statement 13), there are good observational data to support the performance of esophageal surgery in specialist centers for treatment of EA. Results for individual surgeons improve with experience<sup>109</sup> and patient outcomes have consistently been shown to be better in high-volume centers.<sup>110–113</sup>

**After eradication of HGD by endoscopic therapy or surgery, endoscopic follow-up is required.** *Agreement:* A+ 72.5%, A 20%, U 5%, D 0%, D+ 2.5%. *Evidence: Very low.* There are 2<sup>114,115</sup> surgical follow-up series involving 57 BE patients that support this statement. Both studies report that new BE occur after curative subtotal esophagectomy with gastric conduit reconstruction for either EA, squamous cell carcinoma, or HGD.<sup>114,115</sup> Development of BE occurs in half of patients studied<sup>114,115</sup> and can recur from 6 months or less after surgery<sup>114</sup> to 10 years after surgery.<sup>115,115</sup> The risk of developing dysplasia or malignancy in the “neoesophageal” epithelium is unknown, but goblet cells are detected with increasing frequency as follow-up continues.<sup>115</sup> Based on available evidence, a suggested strategy for post-esophagectomy surveillance is to perform screening endoscopy at 2, 5, and 10 years after surgery. If the risk of dysplasia is assumed to be similar to patients with de novo BE, it is reasonable to recommend every 2-year surveillance endoscopies once BE has been detected.<sup>116</sup> The surveillance interval for patients that have BE ablated with RFA is unclear, but a 5-year follow-up study evaluated patients every 2.5 years without any recurrence of dysplasia and a low recurrence of BE.<sup>91</sup>

## Discussion

We focused on statements concerning HGD and EA as evidence relating to LGD is particularly weak. The management of HGD and EA of the esophagus is heterogeneous and the clinician’s perception of the available

**Figure 2.** Management of HGD and/or mucosal cancer (stage T1m) in BE. This consensus has allowed the development of a care pathway for HGD and early adenocarcinoma.



evidence is one major determinant of this variation in practice. The relatively poor quality of data relating to dysplasia in BE is emphasized by 46 statements having a very low or low level and 38 having moderate or high levels of evidence. However, in many cases, it is unlikely that large, well-designed randomized trials will ever be done and in this information vacuum there is a need for an authoritative consensus on areas where there is good agreement. Our multidisciplinary international group has developed consensus to help the practicing clinician with the diagnosis and management of HGD and early EA in BE. We focused on patient populations with high-risk disease rather than including those statements about LGD, a condition for which there are even less objective data in the literature.

The literature search technique used for this consensus process was unique in a number of ways. It was much more inclusive than more focused searches, and permitted inclusion of additional articles during the consensus process that might have been missed during initial searches. Before including articles for citation, the articles were

reviewed by panel members and a panel chair and were ultimately reviewed and graded by a single senior author, resulting in consistency in assessment of the evidence. This mechanism resulted in the largest number of articles ever captured in a literature review for gastrointestinal diseases. We found that the overall quality of evidence related to the statements was low.

The consensus process resulted in a high level of consensus for most statements, which suggests that many results are appropriate for clinical application at this time. The relationship of highly relevant clinically applicable consensus findings regarding EMR is appreciable. First, EMR provides better staging for visible lesions than do biopsies alone. Second, careful mapping of the size of the dysplastic areas by EMR is important to assess the prognosis and risk of progression. Third, EMR combined with RFA is the most proven ablative therapy for visible HGD and for ablation of BE in patients with HGD (Figure 2). HGD should be managed by RFA with or without EMR, and surgery can be considered for early EA.

**Table 2.** Areas Ready to Be Applied to Clinical Management

**Pathology**

- 1. At least 2 experienced gastrointestinal pathologists should evaluate all Barrett's biopsies when a diagnosis of dysplasia is considered.

**Endoscopy**

- 1. The Prague C&M<sup>a</sup> Criteria is the best available tool for grading the endoscopic extent of BE.
- 2. Visible lumps in nodules consisting of HGD suggest a more advanced lesion with invasion might be present.

**Populations at risk**

- 1. Men have approximately twice the rate of developing HGD or esophageal cancer compared with women, and the rate at which EA is increasing in Western populations is twice as high in men as it is in women.
- 2. Non-Hispanic white patients with BE are at higher risk for development of HGD/cancer compared with other racial/ethnic groups with BE.
- 3. Obesity is an independent risk factor for development of EA.

**Therapy**

- 1. Endoscopic treatment should be preferred over endoscopic surveillance for management of most patients with HGD/T1m BE.
- 2. RFA is currently the best available ablation technique for treatment of flat HGD and for eradication of residual BE after focal EMR.
- 3. The operative mortality is improved if surgery is undertaken in specialist surgical centers.

NOTE. Several areas that can be applied to clinical practice now include use of Prague Criteria, recognition of subtle masses and use of ER to stage lesions.

<sup>a</sup>C, circumferential length, M, maximal length.

In defining early cancer, we chose T1sm1 as being the extent of early cancer, as beyond this point metastases increases from ~1% to >10% for T1sm2. Including T1sm1 could be controversial, but if low-risk sm1 (differentiation grades 1 and 2, without lymphovascular invasion and with a negative deep resection margin) tumors are selected, they might be more amenable to successful endoscopic therapy. We recognize that evidence from larger series is still required to conclude that sm1 are to be considered amenable to endoscopic therapy. Using a multidisciplinary approach, surgical treatment should still be considered for early cancer (as opposed to HGD) for all patients fit for surgery.

The consensus process also identified several areas where urgent research is needed (Appendix 2), including evaluation of genetic markers to determine cancer risk.<sup>117,118</sup> Determining the true risk of progression from dysplasia to EA has implications in term of the cost effectiveness of surveillance strategies and impacts on the provision of effective treatments. There are no randomized controlled trials, but large epidemiology studies<sup>119–121</sup> and one meta-analysis<sup>122</sup> have reinforced the low conversion rate to cancer for nondysplastic Barrett's<sup>123,124</sup> and short Barrett's.<sup>120,121</sup>

There are a number of potential shortcomings of this study. First, some geographical areas were under-represented. We did not use meta-analysis techniques in a more rigorous approach to evaluating the literature, as we believed that the relevant literature was relatively scant in quality (even though 11,000 articles were assessed) and diverse in approaches and reporting styles, both of which would have severely limited the applicability of these techniques to our process. Finally, a template was not used to standardize comments for statements, which might have resulted in some unevenness in the presentation of clinical view points.

This work represents the most far-reaching, inclusive, and informative consensus process on evaluation and management of BE with HGD/early cancer published to date. Most of the findings are clinically relevant and the high degree of consensus achieved for most of the questions indicates that many of the statements are appropriate for immediate use in guiding clinical activity. In addition, areas in which consensus was not achieved are identified, helping to guide areas in which future clinical research is likely to be productive (Table 2).

## Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at [www.gastrojournal.org](http://www.gastrojournal.org), and at <http://dx.doi.org/10.1053/j.gastro.2012.04.032>.

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Received December 22, 2011. Accepted April 6, 2012.

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#### Acknowledgments

We thank Marion Lawlor of University Hospitals of Leicester, National Health Service Trust for administrative support and accounts. In addition, others provided essential core support, including Jan Lillieyman (administration). We would also like to thank the various funders for their contributions, which enabled this process to occur completely independently of pharmaceutical support. Literature searches were designed by LUCID Health, University of Leeds, UK (Pat Spoor and Ros Dunleavy). Peer review comments were offered by Hanna Lewin (National Institute for Health and Clinical Excellence), Sara Clarke (National Health Service evidence—gastroenterology and liver diseases), Karin Dearness (Cochrane UGPD group), and Iris Gordon (Cochrane Collaboration Eyes and Vision Group).

A total of 104 people were approached, of whom 95 took active part in the process, 92 completed their conflict of interest forms. Three contributors of the 95 active participants did not complete a declaration of conflicts of interest at any time and are not authors, 9 respondents took no part in the process or withdrew at an early stage (4 from Europe, 3 from the United States, 1 from Australia and 1 from Asia).

#### Conflicts of interest

These authors disclose the following: Janusz Jankowski is a paid consultant to AstraZeneca UK and Almirall and a grant holder from FALK. He is Chief Investigator for the AspECT and CHoPIN trials, which are supported by AstraZeneca. Cathy Bennett is the proprietor of Systematic Research Ltd and received a consultancy fee for her work on this consensus document. Paul Moayyedi is a consultant to AstraZeneca. Nimish Vakil is a consultant to AstraZeneca, Takeda, Ironwood, Restech, and Orexo. Robert Ganz is the primary inventor and the cofounder of BARRX Medical, holds equity in the company, and

serves as a paid consultant. Peter Kahrilas performs ad hoc consulting for AstraZeneca, Eisai, EndoGastric Solutions, and Ironwood, and serves on advisory boards for Torax and Reckitt Benckiser. Michio Hongo is a consultant to Abbott Japan, AstraZeneca Japan, AstellasPharma, Daiichi-Sankyo, Dainippon Sumitomo Pharma, Eisai, Kissei Pharmaceutical, Takeda Pharmaceutical, Scampo Pharma, and Zelia Pharmaceutical. Yvonne Romero is a consultant to AstraZeneca, Santarus, Takeda, Kala, Pfizer, and Aptalis. David Armstrong has received one or more of the following: educational and research grants, honoraria, consulting fees, and related travel expenses from Abbott Laboratories, AltanaPharma, AstraZeneca, Axcen, Eisai Limited, Gilead, Janssen Ortho Inc, Merck, NPS Pharmaceuticals, Nycomed, Olympus Canada Inc, Pentax Medical Inc, Pfizer, Proctor & Gamble, Schering-Plough, Shire Canada, Takeda Canada, Warner-Chilcott, and XenoPort Inc. Richard Sampliner received a BÂRRX research grant. Oliver Pech is a consultant to Hitachi Medical, Fujinon, Norgine, and AstraZeneca. Jaroslaw Regula is a consultant to Abbott, Astellas, AstraZeneca, Krka, MSD, Polpharma, Sandoz, and Warner-Chilcott. M. Brian Fennerty is a consultant for Aptalis, OncoScope, and Meridian Bioscience. Nicholas Talley has had grant support from Falk, Forest, Janssen, and Takeda, has been a consultant for ARYx, Astellas, AstraZeneca, Boehringer Ingelheim, Care Capital, ConCERT, Edusa, Falk, Focus Medical Communications, Forest, Ironwood, Janssen, Johnson & Johnson, Meritage, NicOx, Novartis, Prometheus, Salix, Sanofi-Adventis, Shire, Tranzyme, Theravance, XenoPort, and Zeria, and is a key opinion leader for Doyen Medical Inc. John de Caestecker is Chair of AspECT Trial Management Group, which is AstraZeneca supported. Jacques Bergman is a consultant for Boston Scientific and has research support from BÂRRX Medical, Olympus, and Cook.

Stephen Attwood is on the aspect trial management committee, which is AstraZeneca supported. JeanPaul Galmiche is a consultant and speaker for Given Imaging, Mauna Kea Technologies, Shire, Norgine, and Xenoport. His institution has received research grants from AstraZeneca, Janssen Cilag France, ADDEX, and Pentax. Laurence Lovat is on the Advisory Board of Ninepoint Medical and performed ad hoc consulting for Given Imaging and research support for Axcen Pharma, DUSA Pharmaceuticals, and BÂRRX. Peter Watson is a member of AspECT Trial Management Group, which is AstraZeneca sponsored. Kenneth Wang is a consultant to BÂRRX, Ironwood Pharma, CDX Diagnostics, Pinnacle Pharma, and CSA. David Johnston has received speaker's fees and support to attend educational meetings from AstraZeneca. Krish Ragunath received research support, educational grants and speaker honoraria from Olympus Keymed, Cook Medical and BÂRRX Medical. Stuart Gittens is managing director of ECD solutions web data handling company. The remaining authors disclose no conflicts.

#### *Funding*

Funding has been received from the International Society of Diseases of the Esophagus (\$3500), British Society of Gastroenterology (£2500), American College of Gastroenterology (\$2000), American Gastroenterological Association (\$2000), American Society for Gastrointestinal Endoscopy (\$2000), Association of Upper Gastrointestinal Surgeons (£1000), Fight Oesophageal Reflux Together (£1000), German Society of Endoscopy (€2000), Netherlands Association of Hepatogastroenterologists (€1100), and Oesophageal Cancer Fund of Ireland (€3000).