Appendix 2 BAD CAT paper

Diagnosis of Barrett’s and high-grade dysplasia

**STATEMENT #21.** Intestinal metaplasia of the proximal stomach cannot be distinguished from intestinal metaplasia of the distal esophagus (Barrett’s esophagus), by histopathology.

<table>
<thead>
<tr>
<th>Percentage who agreed strongly</th>
<th>Percentage who agreed with reservation</th>
<th>Percentage who neither agreed nor disagreed</th>
<th>Percentage who disagreed</th>
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</tr>
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<tbody>
<tr>
<td>68</td>
<td>28</td>
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</table>

**Evidence:** Low

Pathologically, intestinal metaplasia (IM) is defined by the presence of cells normally located in small and/or large intestine situated in the stomach or esophagus. Goblet cells and Paneth cells are the two most common “intestinal” cells which develop in the esophagus or stomach as a result of chronic inflammation, such as H. pylori or autoimmune gastritis, and gastroesophageal reflux disease (GERD). In addition, metaplastic intestinal cells may show mixed or intermediate features, particularly in Barrett’s esophagus (BE). However, clinically, the term “intestinal metaplasia” is used most often to imply the presence of goblet cells. Intestinal metaplasia of the esophagus, secondary to GERD, is most often “incomplete”, showing a combination of mucinous columnar cells, and goblet cells, and, as mentioned above, cells with intermediate features. In contrast, IM of the stomach is most often a mixture of incomplete and complete intestinal epithelium. In addition, IM is often focal. Thus, differentiation of IM of the distal esophagus from IM of the proximal stomach (“cardia”) in a mucosal biopsy from the GEJ region is difficult, if not impossible, in most circumstances (Srivastava 2007). However, there are several morphologic features that if present in a biopsy from the GEJ region, can help define that biopsy as esophageal in origin (Odze 2005; Coad 2005). For instance, in one study by Srivastava et al, the presence of multilayered epithelium, deep mucosal hybrid glands, the finding of squamous epithelium overlying intestinalized glands, (“squamous islands”) and the finding of submucosal glands and/or ducts in a biopsy from the GEJ region were shown to be highly specific for mucosa of esophageal origin (Odze 2005). Unfortunately, one or more of these features are present in only a minority (up to 30%) of biopsies of the GEJ region, and, therefore, the sensitivity is low. Although their presence may help define a biopsy as esophageal, their absence in a biopsy from the GEJ region does not help distinguish esophageal from gastric mucosa. In summary, there are no reliable morphologic features useful to distinguish IM, and more specifically goblet cells, of the distal esophagus from the proximal stomach. In a minority of circumstances, there are histologic features diagnostic of esophageal origin, but the intestinal metaplasia that occurs in the distal esophagus and proximal stomach are histologically indistinguishable.


**STATEMENT #22.** Intestinal metaplasia of the proximal stomach cannot be distinguished from intestinal metaplasia of the distal esophagus (Barrett's esophagus), by histochemistry.

<table>
<thead>
<tr>
<th>Percentage who agreed strongly</th>
<th>Percentage who agreed with reservation</th>
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<tr>
<td>75</td>
<td>22</td>
<td>1</td>
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</tr>
</tbody>
</table>

**Evidence:** Low

Pathologically, intestinal metaplasia (IM) is defined by the presence of cells normally located in small and/or large intestine situated in the stomach or esophagus. Goblet cells and Paneth cells are the two most common "intestinal" cells which develop in the esophagus or stomach as a result of chronic inflammation, such as H. pylori or autoimmune gastritis, and gastroesophageal reflux disease (GERD). In addition, metaplastic intestinal cells may show mixed or intermediate features, particularly in Barrett's esophagus (BE). However, clinically, the term "intestinal metaplasia" is used most often to imply the presence of goblet cells. Some studies suggest that there are differences in mucin histochemical properties between IM of the distal esophagus and proximal stomach, such as increased high iron diamine positivity, and increased expression of MUC1 and MUC6 in the former compared to the latter (Glickman 2003). However, overall, these markers are not sensitive or specific enough to be used reliably in routine clinical practice. In general, goblet cells from both organs show positivity for acidic mucins, both sialomucins and sulfomucins. A variety of potential immunomarkers, such as CDX2, Hep, CD10, and DAS1 have been evaluated in IM of the distal esophagus and proximal stomach, but none of these markers have been shown to reliably differentiate goblet cells from these two organs (Das 1994; Glickman 2001; Glickman 2003; Glickman 2005). For instance, in a study by Philips et al, immunohistochemical expression of CDX2 was noted in 100% of biopsies from patients with BE, but in other studies, CDX2 has been noted in IM of the stomach as well (Phillips 2003). Similarly, DAS1, which is an antibody that recognizes colonic mucins, may react positively in both metaplastic columnar epithelium of the distal esophagus and proximal stomach (Das 1994; Glickman 2001). In 1999, Ormsby et al identified a distinctive type of cytokeratin (CK7/20) immunostaining pattern in BE consisting of diffuse strong CK7 staining of the
surface and gland epithelium, combined with weak superficial staining with CK20 (Ormsby 1999). In their study, a BE CK7/20 staining pattern was highly sensitive and specific for BE (IM of the esophagus) compared to gastric IM. However, several other investigators have not been able to confirm the findings by Ormsby et al, and instead have shown that a CK7/20 immunostaining profile in biopsies from the GEJ often show a BE pattern (DeMeester 2002; Odze 2002). Furthermore, there are variety of other factors that limit the utility of CK7/20 staining in GEJ biopsies, such as variation in staining depending on technical aspects of the staining procedure, observer variability in interpretation of a BE staining pattern, and variability of staining depending on the amount and types of samples utilized (biopsies versus resections). Furthermore, a major limitation of the CK7/20 immunostaining technique is that it requires an appropriate amount of mucosa with IM to be present in order for the staining reaction to be interpreted reliably (Glickman 2005). In summary, there are no reliable immunohistochemical features useful to distinguish IM, and more specifically, goblet cells, of the distal esophagus from the proximal stomach.


**STATEMENT #23.** In esophageal resection specimens, distinguishing intramucosal cancer from submucosal cancer is easier, compared to biopsies, although this has never been evaluated in a systematic study.
<table>
<thead>
<tr>
<th>Percentage who agreed strongly</th>
<th>Percentage who agreed with reservation</th>
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**Evidence:** Moderate

Other than surgical resection, alternatives for local endoscopic resection techniques include cap-assisted resection, rubber band ligation, ESD, en-bloc resection, and piecemeal resection. Piecemeal resections are usually difficult to stage accurately (Lauwers 2009). Unfortunately, few data are available on the level of agreement of mucosal vs. submucosal cancer, by pathologists. Recent evidence suggests that diagnoses rendered on biopsies are often upstaged in subsequent resection specimens. Reclassification of neoplastic lesions ranges between 26 - 37% (Mino-Kenudson 2005; Conio 2005). The accuracy of staging in resection specimens versus ultrasound has been evaluated as well. Via ultrasound, overstaging has been shown to occur in 12.5% of cases, and understaging in 16-20% of cases (Ell 2000; Nijhawan 2000; Scotiniotis 2001). Miniprobes show a higher accuracy in staging (Pech 2010), but still more than 30% of the cases are incorrectly staged compared to resection specimens. Regardless of the lack of studies comparing diagnoses in resection specimens versus biopsies, due to the ability of pathologists to evaluate the entire submucosa, including the orientation of the double muscularis mucosa in patients with Barrett’s esophagus, it is easier to accurately classify depth of invasion compared to biopsies, which often do not contain both layers of muscularis, and are not well oriented.


**STATEMENT #24.** There is some evidence that cancer preferentially occurs in the distal Barrett's segment, but this needs to be validated.

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<th>Percentage who agreed strongly</th>
<th>Percentage who agreed with reservation</th>
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<tr>
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**Evidence: Low**

There is some evidence that cancer preferentially occurs in the distal portion of the Barrett's segment. In a study of 213 patients with histologically proven adenocarcinoma of the esophagus, where 134 cases were early and 79 cases were locally advanced, the frequency of intestinal metaplasia, and the location of the tumour within the segment of intestinal metaplasia were documented. In 82.2% of cases, the tumour was located at the distal margin of the intestinal metaplasia in patients with early tumours, and also predominantly at the distal margin of the segment of intestinal metaplasia in 85% of the cases which had neoadjuvant therapy. The study concluded that almost all adenocarcinomas of the esophagus arose on a background of intestinal metaplasia, and that the most distal margin of Barrett's mucosa seemed to be the most likely location for the development of adenocarcinoma (Theisen 2006). In contrast, in a detailed mapping study of 10 resected specimens of Barrett's with high grade dysplasia or superficial adenocarcinomas arising in Barrett's esophagus, no preferential site for neoplastic transformation (into high grade dysplasia or adenocarcinoma) was noted, although dysplasia and adenocarcinoma always developed in ‘specialized mucosa’ (mucosa with goblet cells), and was often multifocal (Chatelain 2003). However this study involved far fewer cases than the Thiesen study. In conclusion, there is some evidence in the literature that cancer preferentially occurs in the distal, compared with the proximal portion of the Barrett's segment, but this needs further study.


**STATEMENT #25.** Barrett's neoplastic lesions show a predilection to occur in one quadrant (between 12 and 3 o'clock) of the right hemi-circumference of the esophagus

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<th>Percentage who agreed strongly</th>
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<tr>
<td>29</td>
<td>39</td>
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**Evidence:** Low

Pressure in the lower esophageal sphincter is higher on the left posterior compared to the right anterior portion of the esophagus (Stein 1991). This is postulated to be due to intrinsic muscle asymmetry, since the lower esophageal sphincter is not a muscular ring, and is thought to account for the asymmetrical circumferential distribution of esophagogastric junctional lesions, including Barrett's lesions (Kinoshita 2009). In Japanese patients, 99% of Barrett's esophagus is short segment type (3cm), and the majority of these are <1cm (ultra short segment Barrett's) in length (Kawano 2006). One study from Japan investigated the axial location of superficial Barrett's cancer and high grade dysplasia and found that 8 of 12 Barrett's neoplastic lesions were found on the right anterior wall of the oesophagus, and areas of non-circumferential Barrett's were found most frequently on the right side (Moriyama 2006). In a prospective study of 344 European patients with Barrett's esophagus referred for endoscopic therapy of high grade dysplasia or carcinoma, 48% of neoplastic lesions were found at the 12 o'clock or 3 o'clock position in the distal oesophagus (Pech 2007); given patients were endoscoped in the left lateral position (Japanese patients are usually endoscoped on their back) this corresponds to the right/anterior quadrant of the distal oesophagus. In conclusion, evidence is limited, but in several Japanese and European studies, the majority of Barrett's neoplastic lesions were preferentially located in one quadrant of the right hemi-circumference of the lower oesophageal wall suggesting particular attention should be paid to this area during endoscopic examination.


Note: clarification of position (between 12 and 3 o'clock) added after voting.

**STATEMENT #26.** Endoscopic resection ER specimens provide more reliable diagnostic information than biopsies.

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<th>Percentage who agreed strongly</th>
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**Evidence:** Low

Endoscopic mucosal resection (EMR or ER) for Barrett's dysplasia and early Barrett's adenocarcinomas is now more properly termed endoscopic resection (ER) as many endoscopic resections of the oesophagus often also include submucosal tissue. Reduplication of the muscularis mucosa is very common in these specimens. ER provides much larger pathology specimens than conventional endoscopic biopsies, typically these can be 10-30mm in size. Provided that the specimen is received intact (en bloc) and can be orientated so that the mucosa and submucosa can be identified, this allows the confirmation of the diagnosis of and grading of dysplasia (Mino-Kenudson 2007; Peters 2008) and also pathological staging of early cancers. ER provides better staging data than mucosal biopsy alone (Peters 2008). In another study of 251 EMR specimens and 269 biopsy specimens, examined using a detailed histological analysis, there was significantly greater interobserver agreement for the diagnosis of dysplasia in EMR specimens than in biopsy specimens (low grade dysplasia 0.33 vs. 0.22, P<0.001, high grade dysplasia, 0.43 vs. 0.35, P=0.18) (Wani 2010). ER specimens allow assessment of the vertical depth of tumour invasion, and the presence of lateral or deep margin involvement by carcinoma which cannot be assessed using standard mucosal biopsies (Lauwers 2009; Lewis 2008; Mino-Kenudson 2007; Peters 2008; Prasad 2007; Vieth 2005; Chennat 2009).


**STATEMENT #27.** There is no internationally accepted standard method of reporting dysplasia in the oesophagus.

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<th>Percentage who agreed strongly</th>
<th>Percentage who agreed with reservation</th>
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<tr>
<td>55</td>
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**Evidence:** not applicable

There are no studies that have addressed the optimal method of reporting dysplasia in Barrett’s. In fact, there are few published guidelines on this matter by major governing bodies in gastroenterology. One publication from the American College of Gastroenterology (ACG) (Wang 2008) states that the grade and extent (focal or diffuse), should be included in all pathology reports, since the treatment is dependent on these features, although the criteria for focal versus diffuse are not specifically mentioned. Unfortunately, the approach to reporting dysplasia is variable in different parts of the world and is mainly related to expert opinion. The most recent recommendations by the WHO state that dysplasia should be graded as either low or high grade as per the Reid Classification, since most clinicians are aware of this system (Reid 1988), but also recognize that in some parts of the world the revised Vienna Classification for gastrointestinal...
mucosal dysplasia is preferred and acceptable, as long as the pathologists and clinicians are in agreement, and understand equally the meaning of the grading system as it relates to the published literature (Schlemper 2000).


**STATEMENT #28.** There is a widely accepted standard biopsy protocol for the diagnosis and follow up of dysplasia in Barrett’s esophagus.

<table>
<thead>
<tr>
<th>Percentage who agreed strongly</th>
<th>Percentage who agreed with reservation</th>
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</table>

**Evidence:** Low

A four quadrant biopsy protocol (the 'Seattle' protocol) consisting of 4 jumbo forceps biopsies from every 1 cm of columnar mucosa was proposed for surveillance of patients with Barrett’s oesophagus in 1993 (Levine 1993), and remains the standard of practice in many countries (Wang 2008; Koop 2005) despite only partial scientific validation. There is also evidence that the Seattle biopsy protocol allows for more accurate pathologic differentiation of HGD from early adenocarcinoma (Levine 1993). Support for this approach stems primarily from a study by Peters showing that 21% of patients in a surveillance program without low grade dysplasia (LGD) prior to a diagnosis of high grade dysplasia (HGD) or carcinoma had an insufficient number of biopsies obtained at endoscopy suggesting that sampling error was a factor (Peters 2008). Not all authorities have found similar results. For instance, a study by Falk (Falk 1999) showed that a jumbo biopsy protocol may miss unsuspected cancer in patients with Barrett’s oesophagus and HGD. Kariv 2009 reported that biopsy sampling according to the Seattle protocol did not predict the presence of cancer at esophagectomy more reliably compared to a less intensive biopsy protocol. A study by Abela 2008 showed that there was a 13 fold difference in detection of prevalent dysplasia between patients who underwent four quadrant biopsies every 2 cm (median biopsy number 16) compared to those who had non-systematic biopsies (median biopsy number 4) lending support to the use of a structured biopsy protocol. In contrast, systematic biopsies from every 2 cm of Barrett's oesophagus is the method of surveillance currently recommended by the British Society of Gastroenterology.
Preliminary results suggest that use of advanced imaging techniques, such as narrow-band imaging and confocal laser endomicroscopy may help detect early neoplasia. However, the data is mainly from single centre trials, with highly selected groups of patients, and, thus, needs further study.

In conclusion, there is reasonable evidence to continue to support the use of a structured biopsy protocol (such as the Seattle protocol) for the detection and follow up of dysplasia in Barrett's oesophagus.


**STATEMENT #29.** Since there is no internationally accepted method of processing esophageal endoscopic resection specimens, a generally accepted minimal standard should be developed.

<table>
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<tr>
<th>Percentage who agreed strongly</th>
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**Evidence:** Low

Endoscopic mucosal, and submucosal, resection (ER) is also termed "endoscopic mucosal resection" (EMR) by some authorities. This endoscopic technique involves removal of a
portion of the mucosa, and a variable amount of submucosa, by endoscopy. Most ER are performed for neoplastic lesions, such as dysplasia, intramucosal adenocarcinoma, or even early submucosal carcinoma (Scudiere 2009). Endoscopic resection is performed for diagnostic, and, in some cases, therapeutic purposes as well. Unfortunately, there is no universally accepted method for handling ER specimens in pathology laboratories. Furthermore, the ER technique may vary depending on the nature and anatomic location of the lesion, and also on operator and patient preferences. ER specimens provide improvements in pathologic diagnosis and tumor staging (Lauwers 2009). Regarding the latter, since ER specimens typically include a substantial amount of submucosal tissue, evaluation of depth of invasion of adenocarcinomas is easier due to an enhanced ability of pathologists to recognize both the inner (metaplastic) and the outer (original) muscularis mucosa. Most pathologists recognize that ER specimens should be photographed and well-oriented prior to fixation in order to provide optimal endoscopic/pathologic correlation (Vieth 2005). The specimens are typically submitted to the pathology department, in total, and then fixed for at least 24 hours in 10% aqueous formaldehyde. ER specimens should be maintained in a flat position so that the edges of the specimen do not curl and become distorted, which makes visualization of the margins difficult. For optimal evaluation, ER specimens are typically placed gently onto a cork board, without tension, for fixation and subsequent tissue processing. Small specimens may be laid flat and submitted on tissue paper, or wedged gently between sponges in a tissue cassette. For subsequent tissue processing, the ER specimen is either unpinned or removed from the tissue cassette or tissue paper, the deep and circumferential margins are evaluated carefully and marked with a colored dye or gelatin. The number, and size, of all portions of the tissue received in the pathology laboratory should be documented (in mm). As indicated above, all specimens should be photographed and described for the presence or absence of gross lesions, such as ulceration, nodules, mucosal irregularities, or polyps. In some cases, a dissecting microscope may help identify lesions that are difficult to visualize macroscopically. Tissue blocks may be cut at 1-2 mm intervals, and then embedded, on edge, in a tissue cassette for proper orientation. It is highly recommended that the entire specimen be processed for pathologic evaluation. Most pathologists examine at least three Hematoxylin and Eosin stained levels of each tissue block. Microscopically, pathologists should evaluate the tissue for the presence and degree of dysplasia, the presence or absence of adenocarcinoma, including its degree of differentiation and depth of invasion, and the presence or absence of potentially significant prognostic factors, such as lymphovascular invasion, perineural invasion, and tumor budding. The margins should be assessed carefully for the presence or absence of neoplastic tissue, particularly at the deep margin of the specimen. Careful attention should be paid to evaluating the location of invasive tumor in relationship to both the inner (metaplastic) and the outer (original) muscularis mucosa. Several staging systems have been published with regard to level of invasion within the lamina propria and submucosa (Vieth 2005), but none have been universally accepted at this point in time.


**STATEMENT #30.** For optimal detection of Goblet Cells, the neo squamo-columnar junction at the proximal end of the Barrett's segment should be targeted for biopsies.

<table>
<thead>
<tr>
<th>Percentage who agreed strongly</th>
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**Evidence:** Low

Mapping studies have shown that Barrett's esophagus is composed of a mosaic of different epithelial types, such as goblet cells, non-goblet columnar cells, intermediate cells and parietal cells. (Chandrasoma 2001; Paull 1976). With respect to the distribution of epithelial types in columnar lined esophagus, there is evidence that goblet cells show the highest density in the more proximal parts of the Barrett's segment; in a study of 32 patients, detailed mapping showed a distinct zonation of distribution of different epithelial types in the esophagus, with the density of goblet cells highest in the most proximal segments, (32/32 patients had goblet cells in biopsies from the proximal esophagus, compared to 22/32 patients with goblet cells in biopsies from the distal portion of the Barrett's segment). The density of goblet cells was also shown to be highest in the proximal esophagus (Chandrasoma 2001). In another study, a cephalo-caudal gradient of intestinal metaplasia (goblet cells) was demonstrated in patients with Barrett's esophagus, particularly evident in relationship to advancing age (Harrison 2007). In conclusion, there are some data to show that the chance of detecting (goblet cells) is maximized by obtaining biopsies from near the neo - squamo-columnar junction, at the most proximal end of the Barrett's segment.


STATEMENT #31. For reliable detection of Goblet Cells within a Barrett's segment, a minimum of 8 biopsies is recommended.

Evidence: Low

<table>
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<tr>
<th>Percentage who agreed strongly</th>
<th>Percentage who agreed with reservation</th>
<th>Percentage who neither agreed nor disagreed</th>
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In a study by Harrison et al (Harrison 2007) of 1646 biopsies from 125 patients with long segment Barrett's esophagus, the optimum number of biopsies needed to demonstrate goblet cells in 67.9% of endoscopies was 8, but in contrast, if only 4 were obtained, only 34.7% of endoscopies yielded a positive result for identification of goblet cells. The yield of positive endoscopies did not increase significantly unless 16 or more biopsies were obtained. The study also demonstrated a cephalocaudal gradient of goblet cells, especially with increasing patient age. Thus there are some data to show that the chances of detecting goblet cells is maximized by taking a minimum of 8 biopsies throughout the Barrett's segment. In addition, however, a number of studies have also evaluated the potential for methylene blue to enhance detection of goblet cells. In a small study of 10 patients in which endoscopic ultrasound was coupled with methylene blue staining and biopsy for detection of goblet cells and dysplasia, esophageal cases with goblet cells stained significantly more often than gastric mucosa; the sensitivity and specificity for detecting goblet cell containing mucosa was 68% and 85% respectively (Gangarosa 2000). In another study of 51 patients with visible columnar lined esophagus, methylene blue stained areas were specifically targeted. The sensitivity was 98% and the specificity was 61% for detection of goblet cell containing mucosa. The detection of goblet cells increased in patients with visible columnar lined esophagus compared to those without visible columnar lined mucosa (Keisslich 2001). Nevertheless, several studies are uninformative and therefore this technique has not gained wide acceptance for use in enhancing detection of goblet cell containing mucosa in patients with suspected Barrett's esophagus.


**STATEMENT #32.** The Prague C&M criteria are the best available tools for grading the endoscopic extent of Barrett's esophagus.

**Evidence:** not applicable

<table>
<thead>
<tr>
<th>Percentage who agreed strongly</th>
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<th>Percentage who neither agreed nor disagreed</th>
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The Prague C&M criteria: The diagnosis of Barrett's esophagus (BE) initially relies on recognition of a columnar-lined distal esophagus (CLE). The Prague C&M classification is based on validated explicit, consensus-driven criteria for the endoscopic diagnosis and grading of BE. The International Working Group for Classification of Oesophagitis (IWGCO) agreed on criteria and developed materials for their formal evaluation using video-endoscopic recordings gathered in a standardized manner in 29 patients. The criteria included assessment of the circumferential (C) and maximum (M) extent of the endoscopically visualized BE segment as well as endoscopic landmarks such as the diaphragmatic hiatus and the upper end of the gastric folds. The later was considered to represent the endoscopic mark for the gastro-esophageal junction and thus the lower end of the Barrett's segment. Video recordings were scored according to these criteria by a separate international panel of 29 endoscopists. The overall reliability coefficients (RC) for the assessment of the C & M extent of the endoscopic BE segment above the gastroesophageal junction were 0.95 and 0.94, respectively. The rates of exact agreement (for C & M values) for pairwise comparisons of individual patient values were 53% and 38%, respectively, whereas the values for agreement within a 2-cm interval were 97% and 95%, respectively. The overall RC for endoscopic recognition of BE >/= 1 cm was 0.72, whereas for BE <1 cm, it was 0.22. The RCs for recognizing the location of the gastroesophageal junction and the diaphragmatic hiatus were 0.88 and 0.85, respectively (Sharma 2006). These findings have been reproduced in different patient populations (Chang 2009; Lee 2010).


**STATEMENT #33.** The upper end of the gastric folds is the best available endoscopic landmark for the gastroesophageal junction.

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<thead>
<tr>
<th>Percentage who agreed strongly</th>
<th>Percentage who agreed with reservation</th>
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**Evidence:** Moderate

Should the pallisade zone or upper end gastric folds be used as the endoscopic landmark for the gastroesophageal junction? The endoscopic landmark of gastroesophageal (GEJ) for diagnosis BE differs between Japan and Western countries (Sharma 2006). Japanese endoscopists use the lower end of the palisade vessels (LEPV) to localize GEJ. In the West, endoscopists use the proximal gastric folds. Studies, however, have shown that LEPV cannot reliably detect BE. Ogiya et al. investigated 42 esophagi resected for squamous cell carcinoma of the esophagus. The position of the LEPV, squamocolumnar junction, the prevalence of columnar lined esophagus (CLE) and intestinal metaplasia were investigated both pre- and postoperatively. Preoperative endoscopy revealed CLE based on the Japanese criteria in half of all patients. In the resected specimens the distal limit of LEPV was lower than the squamocolumnar junction in 95.2%. Most of the CLE areas were very short and their average maximum length was only about 5 mm. In addition, no intestinal metaplasia was observed in any of the CLE cases (Ogiya 2006). Amano et al. compared the degree of diagnostic variation in results achieved by Japanese endoscopists when using the palisade vessels as a landmark of the distal esophagus and when using the gastric folds. Eighty-four endoscopists classified 30 BE patients by viewing endoscopic photographs. The Japanese criteria resulted in an overall kappa value of 0.14 and endoscopic experience had no impact on the level of concordance. After an explanation of the C&M Criteria there was a statistically significant improvement in the diagnostic concordance (Amano 2006).


3. Amano Y, Ishimura N, et al. Which landmark results in a more consistent diagnosis of Barrett’s esophagus, the gastric folds or the palisade vessels? Gastrointest Endosc 2006; 206-211

**Methods of surveillance for patients with BE and with HGD**
STATEMENT #34. Endoscopic work-up of BE patients with HGD/ca will generally identify the area with the most advanced neoplasia.

<table>
<thead>
<tr>
<th>Percentage who agreed strongly</th>
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</table>

**Evidence:** High

Studies on the endoscopic detection of early neoplasia show that most patients (approximately 80%) referred for endoscopically inconspicuous HGD/ca will have visible abnormalities detected during high-resolution endoscopy when performed by an endoscopist with expertise in the detection and treatment of early Barrett's neoplasia (Kara 2006; Curvers 2008; Curvers 2010). If these lesions are subsequently resected, the chance that the residual BE will harbour neoplasia that is worse than what has been resected is small: studies on stepwise complete endoscopic resection of BE < 5 cm containing HGD/ca show that after the most suspicious area has been resected during the first session, subsequent ER sessions do not show lesions that would change the management from an endoscopic to a surgical approach (e.g. submucosal invasion, poorly differentiated cancers, lymph-vascular invasion) (Pouw 2008). In conclusion: Endoscopic work-up of BE patients with HGD/ca will generally allow detection of the area with the most relevant neoplasia. This can be targeted for focal EMR after which histological evaluation of the resection specimens may guide further management decisions. The chance that the remaining BE will harbour a lesion that is more advanced than the one that has been resected is small.


**STATEMENT #35.** Endoscopic work-up of BE patients with HGD/ca will generally identify the most significant area of neoplasia but can allow only approximate demarcation of other areas of neoplasia occurring in the entire remaining Barrett's segment.

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<th>Percentage who agreed strongly</th>
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<th>Percentage who neither agreed nor disagreed</th>
<th>Percentage who disagreed</th>
<th>Percentage who disagreed strongly</th>
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<tr>
<td>45</td>
<td>45</td>
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**Evidence:** High

Studies on the endoscopic detection of early neoplasia show that most patients (approximately 80%) referred for endoscopically inconspicuous HGD/ca will have visible abnormalities detected during high-resolution endoscopy when performed by an endoscopist with expertise in the detection and treatment of early Barrett's neoplasia (Kara 2006; Curvers 2008; Curvers 2010). If these lesions are subsequently resected, the chance that the residual BE will harbour neoplasia that is worse than what has been resected is small. Studies on stepwise complete endoscopic resection of BE < 5 cm containing HGD/ca show that after the most suspicious area has been resected during the first session, subsequent ER sessions do not show lesions that would change the management from an endoscopic to a surgical approach (e.g. submucosal invasion, poorly differentiated cancers, lymph-vascular invasion) (Pouw 2010). However, imaging studies have also shown that in patients who undergo endoscopic imaging for the work-up of early BE neoplasia, a significant number of patients (approximately 20%) are still diagnosed with HGD by random biopsies only, despite the use of high-resolution endoscopy and high-tech imaging tools such as autofluorescence endoscopy and narrow band imaging (Kara 2006; Curvers 2008; Curvers 2010). In addition, studies on the use of ER for focal removal of lesions have shown that lesions that were resected en-bloc - under the presumption that the neoplasia was small and localized - have shown positive lateral resection margins for HGD/ca in 80% of cases (Peters 2008). Studies have also shown that in BE patients with HGD/ca, the neoplasia is often multifocal which means that even a radical en-bloc resection of a visible lesion is no guarantee for neoplasia elsewhere in the BE. Studies of focal ER followed by RFA for BE with HGD/ca have shown that >80% of patients will have HGD or LGD detected in the remaining BE after removal of visible lesions (Pouw 2010).

In conclusion: Endoscopic work-up of BE patients with HGD/ca will generally allow detection of the area with the most relevant (advanced) neoplasia. This can be targeted for focal EMR after which histological evaluation of the resection specimens may guide further management decisions. The chance that the remaining BE will harbour a lesion that is more advanced than the one that has been resected is small. Endoscopic work-up of BE patients with HGD/ca, however, does not allow the demarcation of the exact extent of neoplasia throughout the whole Barrett's segment. Work-up therefore still requires
random biopsies (especially in absence of visible abnormalities) and attempts should be made to eradicate the whole BE in these patients to reduce the risk of recurrence during follow-up.


STATEMENT #36. There is no proof that the Paris classification provides meaningful prognostic information when applied to Barrett's esophagus. A standardised, agreed system of descriptive criteria is required for the classification of mucosal irregularities in patients with Barrett's esophagus.

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<th>Percentage who agreed strongly</th>
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<tr>
<td>52</td>
<td>33</td>
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</table>

Evidence: moderate

There are no endoscopically reported standards for mucosal irregularities in Barrett's esophagus. There have been proposals that have generally been adaptations of classification systems from squamous esophagus and gastric neoplasia. The primary
purpose of a classification system is to have an impact on clinical outcomes and at this time this has not been demonstrated. There have been two different systems proposed. The first is the classification of the mucosal pit patterns that are generally found in columnar mucosa. There is evidence to suggest that certain pit patterns, in particularly cerebriform and ridged seem to have increased sensitivity for intestinal metaplasia in columnar mucosa. But this evidence comes from specialized centers in limited numbers of patients. It is unclear what the intraobserver and interobserver reproducibility of these mucosal pattern classifications would be if extended to other centers and in particular, non-expert endoscopists. Thus the translation of this mucosal classification system to clinical practice has not occurred despite their initial proposal over 5 years ago. The second classification system for superficial neoplasms was proposed even earlier and separated early cancers of the esophagus by their appearance in terms of being polypoid or non-polypoid with the primary clinical significance being that excavated or depressed lesions being more difficult to treat with mucosal resection techniques. However, evidence of worsened clinical outcomes has not been established and their use has not gained universal acceptance. It is also unclear if specific distinctions such as between flat lesions and raised lesions have any relevance in terms of tumor biology.


**STATEMENT #37.** High resolution white light endoscopy can detect mucosal cancer and sub-mucosal invasive dysplastic changes in majority of cases.

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<th>Percentage who agreed strongly</th>
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<tr>
<td>41</td>
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</table>

**Evidence:** Moderate
Recent advances in endoscope technological have made high resolution endoscopes available with charged coupled devices (CCD) containing up to one million pixels, compared with the 300,000 pixels of standard endoscopes (Mannath 2010). Recent studies suggest that high resolution endoscopy may have higher sensitivity for the detection of early neoplasia in Barrett's oesophagus than do standard video endoscopy systems (Kara 2005, Curvers 2010). Up to 80% of patients referred for work up of high grade dysplasia or early Barrett's oesophagus cancer without visible abnormalities will have at least one visible abnormality detected in their Barrett's oesophagus upon endoscopic inspection by expert endoscopists (Curvers 2008, Kara 2005). Although early Barrett's oesophagus neoplasia generally presents as subtle flat lesions that may be difficult to detect, most state of the art endoscopes do show these abnormalities to the experienced eye (Pech 2007, Thomas 2009). In a prospective, comparative, blinded trial high resolution endoscopy and high resolution EUS were equally accurate (80%) in detecting submucosal invasive cancer (May 2004).


**STATEMENT #38.** Currently there is no high quality evidence supporting the practice of tagging (tattooing) and measuring high grade dysplastic Barrett's mucosa.
Currently there is no high quality evidence supporting the practice of tagging (tattooing) and measuring high grade dysplastic Barrett's mucosa. Areas of dysplastic tissue are typically measured in cms from the incisors and nodular areas removed by endoscopic mucosal resection for histopathological analysis. Moreover, tattooing of high grade dysplasia detected on random biopsies would not be possible. While the practice of tattooing in the oesophagus has been shown to be feasible and safe (Shaffer 1998) further studies in this field are required before the routine tagging of dysplastic BM is advocated.


**STATEMENT #39.** There is no agreed standard uniform surveillance interval at which biopsies should be taken to ensure HGD has not progressed or regressed.

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<th>Percentage who agreed strongly</th>
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<tr>
<td>60</td>
<td>28</td>
<td>5</td>
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</table>

**Evidence:** High

Introduction Determining an optimal interval to study evolution of HGD requires detailed and accurate knowledge of the natural history, or evolution during medical therapy, of HGD. Only limited data addressing this issue are available in the literature. Moreover, the reported cancer risk in HGD seems to be highly variable between different series. Finally, most of the available literature is based on a definition of Barrett's which used a 3 cm cut-off. Because of the wide variations in the prevalence of adenocarcinoma of the esophagus among the race/ethnic groups, a standardized uniform surveillance interval is difficult to establish. Guidelines should be focused to the most high risk group (e.g. Male Caucasian), and mention should be made of this. National guidelines should reflect the local prevalence and surveillance programmes should be stratified to take account of underlying risk and presence, or absence, of dysplasia.

Literature summary
Initial reports  In a study from Nottingham, 56 Barrett’s patients were followed up with endoscopy every 6 months. Of 3 adenocarcinomas that occurred, two were preceded by HGD (Robertson 1988). In a cohort follow-up study in 50 patients with Barrett’s esophagus from The Netherlands, 5 out of 8 HGD patients had developed adenocarcinoma on repeat endoscopies within one year (Hameeteman 1989). In a cohort of 176 patients from Burlington, Mass., 5 adenocarcinomas were detected, 3 within the first 2 years, and preceded by HGD (Williamson 1991). In a report from the Cleveland Clinic, 136 patients were followed in an endoscopic surveillance program for a mean of 4.2 years. Only 2 adenocarcinomas developed in 570 patient-years of follow-up (O’Connor 1999). More recent follow-up series  In a study from Seattle, a cohort of 327 Barrett’s patients, including 76 with HGD at baseline, were followed prospectively. After 3 and 5 years follow-up, the incidence of adenocarcinoma was 55 and 59% respectively (Reid 2000). In 27 incident HGD patients, a 5-yr cumulative incidence of cancer of 31% was found (Reid 2000). The median interval between endoscopies in HGD was 4.6 months (compared to 15.7 in LGD). In a 1099 patient VA cohort from Illinois, 75 had HGD with development of adenocarcinoma in 12 (16%) (Schnell 2001). The protocol involved 4 endoscopies during the first year, at 3-months interval, to be decreased to 6-monthly after 2 consecutive negative endoscopies for the second year, and to annual thereafter. Another 4 patients diagnosed with HGD at initial endoscopy were found to have adenocarcinoma during the first year intense follow-up protocol. In a study from the Mayo clinic, 100 patients with HGD were prospectively followed up with repeat endoscopy at 3-month intervals. The authors defined focal HGD as HGD limited to 5 or fewer crypts and associated tubuloalveolar acini in 1 biopsy specimen of the entire set of endoscopic surveillance biopsies. After 1 year of follow-up, 7% of patients with focal HGD had developed adenocarcinoma compared with 38% of patients with diffuse HGD. On multivariate analysis, patients with diffuse HGD had more than 3.5 times the risk of esophageal cancer as those with focal HGD (Buttar 2001). These observations suggest a lower risk of cancer development in focal HGD as compared to diffuse HGD, but subsequent studies failed to confirm these findings. In a series from Kansas, patients with LGD were progressively followed up (Weston 2001). Multifocal HGD was considered and endpoint of follow-up, but in case of progression to HGD which was ‘unifocal’, new endoscopy with biopsies was performed after 4-8 weeks and then every 3-6 months until regression. During follow-up, 15 patients developed focal HGD of which 4 (27%) progressed to adenocarcinoma after a mean duration of 4 years (Weston 2001). In a large multi-center cohort of 618 Barrett’s patients followed for a total of 2546 patient-years with a mean follow-up of 4.12 years, 12 cancers developed and only 7 of these had previously detected HGD (Sharma 2006). In a multi-center, sham-controlled study of radiofrequency ablation in Barrett’s esophagus with dysplasia, 21 patients with high-grade dysplasia underwent sham treatment and were followed up for 12 months with endoscopy and biopsies at 3-months intervals. Progression to cancer occurred in 19% of the patients, while disappearance of HGD was seen in 19% (Shaheen 2009). Conclusions
1) Incidence rates of adenocarcinoma in HGD over time show major differences in the series published in the literature.
2) It has been proposed to differentiate follow-up between unifocal or multifocal HGD, but convincing evidence to justify such approach is lacking.
3) Most large series advocate intense follow-up during the first year (every 3 months; in some cases already a more rapid initial follow-up after 4 to 8 weeks). In case of ‘regression’
(no HGD on 2 consecutive endoscopies), less intense follow-up is advocated (every 6 months the first following year; annually thereafter).

4) The available literature is limited because studies mainly focused on ‘long-segment’ Barrett's and did not take into account improved and advanced imaging techniques that are currently available.


**STATEMENT #40.** There is no evidence to determine the number of biopsies necessary to ensure HGD has not progressed or regressed.

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<th>Percentage who agreed strongly</th>
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Evidence: Very low

There is no evidence to determine the agreed number of biopsies to ensure there has not been progression (Levine et al, 1993, Falk et al, 1999, Hoffman et al, 2006, Peters et al, 2008, and Abela et al, 2008). There is evidence that indicates that a minimum of 8 biopsies is necessary to map most Barrett's and this should be considered the minimum standard for Barrett's greater than C2M2 (Abela et al, 2008). In the absence of specialist endoscopic techniques (i.e. NBI, AF, etc, which may increase the yield of dysplasia), where there is a suspicion of a higher risk of dysplasia or cancer it is recommended that 4 biopsies per 2cm segment would be the minimum recommended biopsy protocol, with a minimum of 8 biopsies (Sharma et al, 2006).


Risk of progression to esophageal adenocarcinoma

STATEMENT #41. The incidence of high grade dysplasia/cancer in Barrett's esophagus increases with age.
Evidence: Moderate

Several studies have shown that the peak age of incidence of esophageal adenocarcinoma is in the 7th decade and beyond. In a Dutch study of 42,207 patients with Barrett’s esophagus age was a significant predictor of the development of esophageal adenocarcinoma (Hazard Ratio 12; 95% CI 8.0 to 18) (de Jonge P 2010). Another study conducted between 1994 and 1998 found that the risk of dysplasia in Barrett’s esophagus increased with age with an estimated increase in risk of 3.3% per year of age (Gopal 2003). In a study from the Cleveland Clinic, The odds of those 50 yr or older being a prevalent case of high-grade dysplasia or cancer was five times the odds of those younger than 50 years (Guardino 2006). Data from the SEER study also show an increase in the incidence of adenocarcinoma in both men and women in the USA with increasing age (Morris 2008).


STATEMENT #42. Males have approximately twice the rate of developing high-grade dysplasia or esophageal cancer compared to women and the rate at which esophageal adenocarcinoma is increasing in Western populations is twice as high in men as it is in women.

### Evidence: High

In a study of 9526 US patients with adenocarcinoma of the esophagus (Morris 2008), the incidence of esophageal adenocarcinoma was 1.01 per 100,000 person-years (95%
confident interval (CI) = 0.90 to 1.13) in 1975-1979 in white men and rose to 5.69 per 100,000 person-years (95% CI = 5.47 to 5.91) in 2000-2004. In women the incidence was 0.17 (95% CI = 0.13 to 0.21) in 1975-79 and rose to 0.74 per 100,000 person-years (95% CI = 0.67 to 0.81) in 2000-2004. In a Dutch study of patients with Barrett's esophagus, male sex was a significant risk factor for the development of high grade dysplasia or cancer (Hazard Ratio: 2.01, 1.68 to 2.6) (de Jonge 2010). In a registry study of patients with Barrett’s esophagus from the Cleveland Clinic, men had twice the prevalence of high grade dysplasia or cancer compared to women (Falk G 2005). Similar data were reported in another US cohort (Anandasabapathy 2007).


STATEMENT #43. Non-Hispanic whites with Barrett’s esophagus are at higher risk for the development of high grade dysplasia/ cancer compared to other racial/ethnic groups with Barrett’s esophagus.

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<th>Percentage who agreed strongly</th>
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<td>15</td>
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</table>

Evidence Moderate/High

In a study of 4205 patients with Barrett's esophagus in Northern California, the annual incidence in 2006 was highest among non-Hispanic whites (39/100,000 race-specific member-years, 95% confidence interval (95% CI) 35 to 43), with lower rates among
Hispanics (22/100,000, 95% CI 16 to 29), Asians (16/100,000, 95% CI 11 to 22), and blacks (6/100,000, 95% CI 2 to 12) (Corley 2009). Data from the SEER 1992-2005 database suggest that the incidence of esophageal adenocarcinoma is highest for non Hispanic white males (incidence=5 per 100,000; 95%CI 4.9-5.1 per 100,000) and lower for Hispanic white males (2.8 per 100,000; 95%CI 2.6-3.1 per 100,000) (Cook 2009). In Black American males, the incidence was 1 per 100,000 (95%CI 0.8-1.2 per 100,000) and in Asian Americans was 0.8 per 100,000 (95% CI=0.7-1 per 100,000). Native Americans who are grouped together with native Alaskans had an intermediate incidence between Black Americans and white Americans (incidence 2.6 per 100,000; 95%CI1.7-3.8 per 100,000) (Cook 2009).


**STATEMENT #44.** It is uncertain if aspirin or NSAIDs prevent the development of HGD/cancer.

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<th>Percentage who agreed strongly</th>
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<td>67</td>
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<td>5</td>
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</table>

**Evidence:** Low

Observational studies have suggested that use of aspirin or NSAIDs can decrease the risk of esophageal adenocarcinoma (Farrow et al, 1998, Abnet et al, 2009, . In a study of 116 cases of esophageal adenocarcinoma cases and 696 matched controls most of whom were taking
proton pump inhibitors, NSAID/aspirin prescriptions were associated with a trend towards a reduced risk of esophageal adenocarcinoma (adjusted incidence density ratio, 0.64; 95% confidence interval, 0.42-0.97) (Nguyen 2010). In an Australian population-based study use of aspirin and NSAIDs was associated with a two-thirds reduction in risk of developing esophageal adenocarcinoma (Pandeya 2010). Contrary data were reported in a large UK cohort of Barrett's esophagus (Gatenby et al, 2008). There was no significant difference in the rates of developing high grade dysplasia or cancer in patients taking aspirin or not taking aspirin (Gatenby 2009). Similar data were reported in other cohort studies (Abnet 2009, Sadeghi 2008). A meta-analysis performed by the same authors suggested a potential benefit for aspirin use (Odds ratio: 0.64 (0.52-0.79). There is considerable potential for bias and confounding with all of these studies.


**STATEMENT #45.** It is uncertain if proton pump inhibitors prevent the development of HGD/cancer.

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<th>Percentage who agreed strongly</th>
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<td>6</td>
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</table>

**Evidence:** low
Observational studies suggest that proton pump inhibitors may reduce the risk of high grade dysplasia or cancer (Nguyen, 2009). In a study of US veterans, the use of proton pump inhibitors after a diagnosis of Barrett’s esophagus was independently associated with reduced risk of dysplasia, hazard ratio: 0.25 (95% CI 0.13-0.47), p < 0.0001 (El Serag 2004). In an Australian study of patients in a private practice setting, patients who delayed using a PPI for 2 years or more after diagnosis with Barrett’s esophagus had 5.6 times (95% CI, 2.0-15.7) the risk of developing low-grade dysplasia at any given time as those who used a PPI in the first year. Similar results were found for the risk of developing high-grade dysplasia or adenocarcinoma (hazard ratio, 20.9; 95% CI, 2.8-158) (Hillman 2004). A recent population-based study showed no benefit for acid suppressants in preventing esophageal adenocarcinoma in Barrett’s esophagus (Pandeya 2010). There are a number of limitations with the available studies including potential confounders, selection biases and the lack of randomization.


**STATEMENT #46.** A family history of esophageal adenocarcinoma is a risk factor for the development of esophageal adenocarcinoma.

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<th>Percentage who agreed strongly</th>
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<tr>
<td>35</td>
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**Evidence:** low
In a small case-control study, of 58 patients with Barrett's esophagus or adenocarcinoma, a family history of Barrett's esophagus or adenocarcinoma was independently associated with the presence of Barrett's esophagus, esophageal adenocarcinoma, or esophagogastric junctional adenocarcinoma (odds ratio 12.23, 95% confidence interval 3.34-44.76) after adjusting for age, sex, and the presence of obesity 10 or more years prior to study enrolment (Chak 2002). A family history of Barrett's esophagus or adenocarcinoma is found in 7% of patients presenting with Barrett's esophagus or adenocarcinoma (Chak 2006). The available data are weak and the studies are small with a substantial risk for bias.


**STATEMENT #47.** Obesity is an independent risk factor for the development of esophageal adenocarcinoma.

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<thead>
<tr>
<th>Percentage who agreed strongly</th>
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<td>58</td>
<td>37</td>
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</table>

**Evidence:** moderate

Several case control studies have suggested that obesity is a risk factor for esophageal adenocarcinoma. The strongest data come from a large prospective study that evaluated cancer risk in a large cohort of European subjects. 346,554 men and women participating in the European Prospective Investigation into Cancer and Nutrition were evaluated (Steffen 2009). BMI, waist circumference, and waist-to-hip ratio (WHR) were positively associated with the risk of esophageal adenocarcinoma; relative risk (RR), 2.60; 95% (95% CI: 1.23-5.51); RR, 3.07 (95% CI, 1.35-6.98) and RR, 2.12 (95% CI, 0.98-4.57). Similar results have been reported in case control studies (Chak 2009; Whiteman 2008; Corley 2008; Lagergren 1999).


**STATEMENT #48.** While a number of risk factors have been identified in populations, there is no reliable method of predicting if high grade dysplasia or cancer will develop in a given patient.

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<th>Percentage who agreed strongly</th>
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<td>80</td>
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</table>

**Evidence:** Low

The previous statements identify risk factors that have been determined in populations of patients with adenocarcinoma or high grade dysplasia. The rate of development of adenocarcinoma remains low. A recent study estimated that 4% of the Barrett's esophagus population develop high grade dysplasia or cancer and that the primary risk factors were increasing age, male sex and the presence of low grade dysplasia at baseline. Unfortunately, none of these individual risk factors helps the clinician in making a determination of whether a patient is likely to develop high grade dysplasia or adenocarcinoma. Epidemiologic factors that predict the progression of Barrett's esophagus to HGD/ cancer in the individual patient are not available.


**STATEMENT #49.** The evidence to determine what is the natural history of LGD including the risk of progression or regression is poor.

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<th>Percentage who agreed strongly</th>
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<tbody>
<tr>
<td>61</td>
<td>31</td>
<td>3</td>
<td>4</td>
<td>1</td>
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</table>

**Evidence:** Low

There is huge variation in the natural history of low grade dysplasia. Any good data rely heavily on very good and standardised pathology and ensuring that there is adequate sampling to ensure 'regression'. Recent data however indicates that if LGD is verified by at least 2 other pathologists it has a highly predictive value as 14% progress per year to adenocarcinoma.


**STATEMENT #50.** The distinction between the natural history of uni and multifocal dysplasia is not adequately known.

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<th>Percentage who agreed strongly</th>
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<th>Percentage who disagreed</th>
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<td>30</td>
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<td>9</td>
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</table>

**Evidence:** Low

The natural history of HGD is highly variable (16-60%/year) with multifocal quoted in the higher end of the range.
STATEMENT #51. In a community-based setting, estimates of the incidence of regression and progression of high grade dysplasia are variable.

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<th>Percentage who agreed strongly</th>
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<tbody>
<tr>
<td>63</td>
<td>28</td>
<td>8</td>
<td>3</td>
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</table>

Evidence: Moderate/Low

Meaningful rates of regression and progression for high grade dysplasia require three pieces of knowledge that are difficult to obtain from the current literature: accurate definitions of high grade dysplasia, sensitive detection programs in large numbers of patients that approximate the general population, and sustained follow-up. Current knowledge of these rates has been curtailed through difficulties with consistent definitions (due to inter-observer variation), (Weston 1999) the selected settings of reported populations (primarily in referral or veterans populations), and the relatively small numbers of persons with high grade dysplasia followed for long periods of time (which decreases the precision of the estimates). In the context of these limitations, reported progression rates include estimates as disparate as 59% over five years (in a referral population) (Weston 1999) and, in a veterans population, 16% during a mean 7.3 year period (after a one year intensive search to exclude prevalent cancers) (Reid 2000). The concept of "regression" is complicated by the observation that intensive biopsy programs may, in fact, "ablate" detected dysplastic areas through their endoscopic removal. Regression rates for unifocal high grade dysplasia of 47% have been reported over 24-73 months of follow-up, although with wide confidence intervals (Sharma 2004).


STATEMENT #52. The majority of cancers appear to be diagnosed within the first 1-2 years after HGD diagnosis.

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<th>Percentage who agreed strongly</th>
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<tr>
<td>50</td>
<td>45</td>
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Evidence: moderate

Estimates of the time frame for progression from high grade dysplasia to cancer are even more imprecise than the calculation of progression and regression rates (Weston 1999; Weston 2000; Reid 2000). These estimates vary, in part, because of differences in surveillance techniques and reporting of potentially prevalent cancers. Among patients with a new diagnosis of high grade dysplasia, the majority of cancers appear to be diagnosed within the first 1-2 years after dysplasia diagnosis. (Reid 2001; Montgomery 2001; Schnell 2001).


**STATEMENT #53.** It is not known if there are differences between prevalent (sporadic) and incident (surveillance detected) HGD cases in terms of age and time from first endoscopy.

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<th>Percentage who agreed strongly</th>
<th>Percentage who agreed with reservation</th>
<th>Percentage who neither agreed nor disagreed</th>
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<th>Percentage who disagreed strongly</th>
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<tbody>
<tr>
<td>59</td>
<td>31</td>
<td>6</td>
<td>0</td>
<td>4</td>
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</table>

**Evidence:** Low

Much uncertainty surrounds high-grade dysplasia and its natural progression. It is seen as the final step before neoplastic invasion, but even its histological diagnosis remains controversial. Accurate diagnosis is thought to require more than one pathologist’s opinion, and also relies on accurate biopsy sampling. Four-quadrant biopsy surveillance may detect 13-fold greater numbers of patients with dysplasia than non-systematic biopsy protocols (Abela 2008). Yet even systematic biopsies can fail to detect high-grade dysplasia (HGD) and foci of invasive carcinoma can be missed given that only a small fraction of the total Barrett’s oesophagus surface area is sampled (Cameron 1997). One study that retrospectively evaluated cases of high-grade dysplasia found that those with no prior low-grade dysplasia detected on an earlier endoscopies had insufficient biopsies taken, suggesting again that it had simply been missed (Peters 2008). It is important to highlight this because when comparing ‘sporadic’ and ‘incident’ cases, it is possible that some ‘incident’ cases simply had insufficient sampling at the first endoscopy and pre-existing dysplasia was missed. The frequency of detecting HGD at initial ‘sporadic’ diagnosis of Barrett’s oesophagus is less than 3 % (Weston 1997). A large cohort study of Barrett’s patients found that half of patients who developed HGD or early cancer had no dysplasia detected on their first two endoscopies (Sharma 2006). Indeed, in the UK National Barrett’s Oesophagus registry, 95 % of the cases of HGD were incident cases (detected during a surveillance program) (Ramus 2009). The rarity of ‘sporadic’ cases limits our ability to compare data on age, length-time bias, extent of dysplasia or stage. Several retrospective studies suggest a survival advantage if adenocarcinoma is detected by endoscopic
surveillance, but few evaluated high grade dysplasia. One such study compared 54 cases of 'sporadic' adenocarcinoma with 16 cases of 'incident' surveillance cases (van Sandick 1998). Lymph node involvement was more common in 'sporadic' cases than 'incident' cases. The groups were not significantly different with respect to age. However, only 1 of the sporadic cases and 4 of the incident cases were of HGD. Comparing age or any other characteristics between such small sample sizes is meaningless. Another study (Schnell TG 2001) detected 34 prevalent cases and 45 incident cases of HGD. The data concerning Barrett's length and age of patient were not given but it is stated that 'there were no significant differences between prevalent and incident cases'. The time from HGD detection to development of adenocarcinoma for prevalent cases (n=6) was from 3 months to 120 months. The range for incident cases (n=10) was from 2 months to 115 months. In summary, studies on of patients with high-grade dysplasia detection have small numbers of patients and minimal data comparing age, intervals from Barrett's diagnosis, and extent of dysplasia are sparse. Therefore we conclude that it is not known if there are any significant differences in these characteristics between prevalent and incident cases.


**STATEMENT #54.** Multifocal HGD has proven to have a worse prognosis than unifocal HGD.

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<th>Percentage who agreed strongly</th>
<th>Percentage who agreed with reservation</th>
<th>Percentage who neither agreed nor disagreed</th>
<th>Percentage who disagreed</th>
<th>Percentage who disagreed strongly</th>
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</table>

Evidence: Low

The concept that multifocal HGD carries a worse prognosis than unifocal HGD was proposed by the Mayo group reporting on a retrospective series of 100 patients with HGD. The cumulative incidence of esophageal adenocarcinoma at 3 years was 56% for patients with multifocal disease and 14% for patients with only focal dysplasia (Buttar 2001). Subsequently, 5-year follow-up data from a large prospective study of almost 500 patients undergoing either EMR or PDT for Barrett’s or Barrett’s cancer analyzed risk factors for recurrence. Among the risk factors most frequently associated with recurrence were long-segment Barrett’s oesophagus and multifocal neoplasia, although this could be either HGD or cancer (Peck 2008). Contradictory evidence for the statement comes from a prospectively analyzed series of 42 patients with Barrett’s oesophagus and high grade dysplasia who underwent oesophagectomy (Dar 2003). Twenty four of 42 patients (57%) had unsuspected cancer at the time of esophagectomy. Using Cleveland Clinic criteria, ten of 21 (48%) patients with focal high grade dysplasia had carcinoma compared with 14 of 21 patients (67%) with diffuse high grade dysplasia (p=0.35). Using the Mayo Clinic definition (Buttar 2001), adenocarcinoma was found in five of seven (72%) patients with focal high grade dysplasia compared with 19 of 35 (54%) with diffuse high grade dysplasia (p=0.68). These findings led the authors to argue against the premise that the extent of HGD was predictive of cancer.


STATEMENT #55. The timescale of progression from intra-mucosal cancer to advanced adenocarcinoma in Barrett’s is unknown.

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<tr>
<th>Percentage who agreed strongly</th>
<th>Percentage who agreed with reservation</th>
<th>Percentage who neither agreed nor disagreed</th>
<th>Percentage who disagreed</th>
<th>Percentage who disagreed strongly</th>
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<tbody>
<tr>
<td>84</td>
<td>14</td>
<td>1</td>
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</table>
Evidence: none available

There are no trials published that focus on the natural history of early stage EAC. Studies that report stage-dependent mortality from EAC concern patients who had some type of therapeutic intervention for early stage cancers (Larghi 2007; Brant 2009; Oh 2006; Scotiniotis 2001). There are no data available that document accurately the natural history of early stage EAC separate from patients with HGD (Waxman 2006; Chennat 2009; Sikkema 2009).


2. Oelschlager BK. Intramucosal esophageal cancer and high-grade dysplasia: which treatment frames the debate? J Gastrointest Surg 2009; 1169-71


5. Waxman I. EUS and EMR/ESD: is EUS in patients with Barrett's esophagus with high-grade dysplasia or intramucosal adenocarcinoma necessary prior to endoscopic mucosal resection? Endoscopy 2006; S2-4


STATEMENT #56. There are no proven clinically relevant biomarkers for scoring cancer risk.

<table>
<thead>
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<th>Percentage who agreed strongly</th>
<th>Percentage who agreed with reservation</th>
<th>Percentage who neither agreed nor disagreed</th>
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<tbody>
<tr>
<td>83</td>
<td>10</td>
<td>3</td>
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</table>

Evidence: Low
Several biomarkers are currently under investigation, but have not been sufficiently investigated prospectively. Nuclear DNA abnormalities (aneuploidy and tetraploidy), loss of heterozygosity of specific genes such as P16 and P53 are the most applied for this purpose. Methylation of the genes HPP1, p16, and RUNX3 have been shown to predict future neoplastic progression in BE. A panel consisting of methylation levels of the genes HPP1, p16, RUNX3, AKAP12, NELL1, CDH13, SST, and TAC1 has been shown to predict future neoplastic progression in BE. LOH on chromosomes 9 and 17 are also predictive. High expression levels of microRNAs 106b, 25, 93, and possibly others show some promise in this context. Nevertheless they are not available for clinical practice. Moreover, validation of biomarkers should be implemented.


STATEMENT #57. There are no currently known heritable factors that identify patients who have an increased risk of progression from Barrett's esophagus to esophageal adenocarcinoma.

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<tr>
<th>Percentage who agreed strongly</th>
<th>Percentage who agreed with reservation</th>
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<tr>
<td>78</td>
<td>19</td>
<td>1</td>
<td>3</td>
<td>0</td>
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</table>

Evidence: Low

There is evidence to suggest an inherited risk for a subset of patients developing BE and EAC, as demonstrated by familial clustering (Chak 2002; Chak 2006). However, there are relatively few studies investigating genetic susceptibility to these disease states, the majority of which are epidemiological case-control in design and take a candidate gene
approach, examining a handful of genetic variations at a time (Reid 2010). Most importantly, no study specifically addresses the risk of progression from BE to EAC, hence the culpable genes that may contribute to progression have yet to be identified (di Pietro 2009). Comprehensive genome wide association studies (GWAS), such as IPOD (Eagle consortium) (di Pietro 2009; Jankowski 2010) and BEAGESS (Beacon consortium) are underway. The study design of GWAS takes an unbiased approach, examining allele frequencies of hundreds of thousands of single nucleotide polymorphisms (SNPs) across the human genome in several thousand cases compared to healthy controls. The results of these studies will be vital in identifying genes, or regions of the genome, underlying the inherited risk of BE progression.


**Treatment of HGD and early EA**

**STATEMENT #58.** Cost effectiveness data on different strategies for the management of HGD are, currently, insufficient to determine the optimal treatment strategy for HGD.

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<th>Percentage who agreed strongly</th>
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<td>58</td>
<td>29</td>
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</table>

**Evidence:** Not applicable

Is it known what therapy for HGD is most cost-effective? Currently there are a number of different therapeutic approaches to high-grade dysplasia. These include continued surveillance, endoscopic ablation alone with RFA, PDT or cryotherapy, diagnostic EMR alone, circumferential EMR or EMR combined with ablative therapy. All of these approaches have advantages and disadvantages, although long-term follow up information is available only for PDT. Short term follow up is available comparing RFA to continued surveillance and 5 year follow up is available comparing PDT to continued surveillance. While we know there is considerable upfront cost to surgery, the costs of continued endoscopic surveillance after ablation therapy as well as the appropriate interval for surveillance remains unknown. These costs can be substantial depending on both the age of the patient and the follow up intervals and techniques. Multiple modeling studies have examined this question. However, these studies are hampered by inadequate information to address the true costs of each
therapy. As such, despite data supporting endoscopic therapies as the most cost-effective strategy to treat HGD, these modeling studies should be interpreted with caution.


**STATEMENT #59.** The lack of long term follow up data for patients having endoscopic eradication of HGD means that the most appropriate measurable outcomes of cancer prevention and/or mortality for comparative assessment of treatments is not yet available.

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<th>Percentage who agreed strongly</th>
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<td>56</td>
<td>31</td>
<td>5</td>
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</table>

**Evidence:** Moderate

Measurable patient outcomes for documenting total HGD eradication include absence of HGD on follow up, prevention of development of EAC, long term survival and the cost of treatment. Currently endoscopic eradication of HGD by radiofrequency ablation (Shaheen 2009) or EMR + radiofrequency (Pech 2008) gives good short term results: 90.5% eradication at 12 months (Shaheen 2009) and 96.6% at 63 months (Pech 2008) determined by follow up systematic biopsies. If eradication is complete it should result in the prevention of EAC and improved long term survival. A decision analysis model (Inadomi 2009) suggests that endoscopic treatment could be cost-effective but depends upon the long-term effectiveness of ablation and whether surveillance endoscopy can be discontinued after successful ablation. Further long term post ablation data is required to clarify these points and to determine outcomes in terms of cancer prevention and survival.


STATEMENT #60. For patients with HGD without endoscopically visible abnormalities, ‘blind’ EMR is not likely to have a significant impact on the diagnosis and staging.

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<th>Percentage who agreed strongly</th>
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<td>60</td>
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Evidence: High

Is the "better" histological assessment as provided by EMR essential for staging of HGD? The answer to this question is "Yes", but only when the area of HGD is known and can be targeted for the following reasons: Studies in patients referred for endoscopically inconspicuous HGD/early cancer show that the majority of patients with HGD will have visible abnormalities when investigated with high-resolution endoscopy by an experienced endoscopist (Kara 2005; Curvers 2008). EMR of endoscopically visible lesions with a biopsy diagnosis of HGD leads to upstaging to invasive cancer in up to 20% of cases (Peters 2008; Vieth 2004). There are some other considerations: In cases where no visible abnormalities are seen during high-resolution endoscopy by an experienced endoscopist, the value of a ‘blind’ EMR is unknown. We have assumed that for HGD patients in whom tri-monthly endoscopic surveillance is preferred, the risk and clinical consequences of missing an invasive cancer likely to be small. For HGD patients in whom endoscopic ablation therapy is preferred the chance of under-treating an invasive cancer that should have been treated surgically is remote (Shaheen 2009).

In conclusion: While targeted EMR allows for a better histological assessment of a lesion of interest than biopsies, for patients with HGD without endoscopically visible abnormalities, (after inspection with high-resolution endoscopy by an endoscopist with experience in the endoscopic detection of early neoplasia), (random) EMR is not likely to have a significant impact on the clinical outcome of the patient.


**STATEMENT #61.** The most appropriate staging test for ulcerated HGD is unknown.

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<th>Percentage who agreed strongly</th>
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<td>56</td>
<td>34</td>
<td>4</td>
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</table>

**Evidence:** Low

It is not known what staging tests should be done in ulcerated HGD/lesion. These lesions could be regarded as Paris Classification 0-IIc for excavated lesions or 0-III for truly ulcerated lesions. Although it has been shown that ulcerated lesions cannot be easily treated with EMR as there is an increased risk of complications and complete removal is difficult, it is unclear if EMR might be valuable as a staging study since complete removal is not essential for depth staging. EUS may be suboptimal due to the overlying inflammation and also the air that is often trapped within the ulceration causing loss of an acoustical window for visualization of the lesion. These risks are hypothetical and there is no good evidence that has characterized the degree of attenuation ulceration produces.


**STATEMENT #62.** Acetic acid assisted chromoendoscopy improves the identification and characterization of visible and invisible dysplasia in Barrett's oesophagus.
Evidence: Moderate

Acetic acid assisted chromoendoscopy has certainly shown a potential in diagnosing otherwise invisible dysplasia, but more research will be required before accepting this as standard practice. Outcome is dependent on the experience and expertise of the individual endoscopist. Acetic acid: 3 studies examined (64 patients 5 LGD, 1 HGD, 3 adeno carcinoma) (Fortun 2006), (57 patients 24 HGD/adeno carcinoma) (Pohl 2007), (190 procedures, 90 HGD / adenocarcinoma) (Longcroft-Wheaton 2010). The largest study consisted of 190 procedures with acetic acid identifying invisible dysplasia or cancer 2.2x more frequently than WLI with a sensitivity of 97% for the detection of dysplasia or cancer. Most studies which support acetic acid can detect intestinal metaplasia and dysplasia with a high sensitivity.


STATEMENT #63. There is insufficient evidence to support the routine use of methylene blue or indigo carmine in the detection of neoplasia in Barrett's oesophagus.

Evidence: Moderate
Indigo carmine: one cohort study involving 80 patients showed a high degree of accuracy in the identification of both Barrett’s metaplasia and dysplasia. However, there were only 24 dysplasia cases in the series (Sharma 2003). Methylene blue: Three studies identified but unfortunately, the number of patients with HGD or early cancers were very low in all of these studies. (48 patients 21 dysplasia) (Horwhat 2008), (43 patients, 19 dysplasia) (Canto 2001), (47 patients with Barrett’s, 48 oesophagectomy sections from 5 surgical specimens all with HGD) (Canto 2000). Methylene blue is very effective at identifying metaplasia but very limited evidence for the detection of dysplasia. Most studies are suggestive that HGD and cancer detection is improved, with a sensitivity of 80-100%. However, methylene blue is very difficult to use dye with great variability in results depending on the concentration, staining time washing time, interpretation of the staining etc. It has also been found to have DNA toxicity (Mansannat 2009). Methylene blue and Indigocarmine therefore cannot be recommended as per the current evidence.


STATEMENT #64. There is insufficient proof to recommend routine EUS for staging prior to ER for suspected early lesions.

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<th>Percentage who agreed strongly</th>
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<td>55</td>
<td>29</td>
<td>6</td>
<td>9</td>
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</table>

Evidence: Moderate

High frequency probe EUS has been found to be no better than high resolution endoscopy in local staging of early cancer (mucosal vs. submucosal invasion) but conventional EUS has a role in assessment of nodal staging and is certainly superior to CT scan in both T and N staging. However, it cannot reliably exclude submucosal invasion. The data is not enough to recommend routine use of EUS prior to EMR for HGD. It should be considered in staging of high risk nodules as the risk of invasive cancer remains high in nodules. A negative EUS is not very helpful but a positive EUS can change management.


**STATEMENT #65.** There are no evidence-based guidelines for photo documentation of BE, despite common clinical usage.

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<th>Percentage who agreed strongly</th>
<th>Percentage who agreed with reservation</th>
<th>Percentage who neither agreed nor disagreed</th>
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<tr>
<td>73</td>
<td>19</td>
<td>8</td>
<td>1</td>
<td>0</td>
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</table>

**Evidence:** Not applicable

There are no evidence-based guidelines for photo documentation of BE. It is recommended to obtain still images at the landmarks required for the C&M classification, at 1 cm intervals throughout the BE, the retroflexed position in the stomach and of all visible lesions within the BE. There is no need for video documentation if the aforementioned conditions are met.


STATEMENT #66. There are no evidence-based guidelines for video documentation of BE.

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<th>Percentage who agreed strongly</th>
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<td>75</td>
<td>18</td>
<td>8</td>
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</table>

**Evidence:** Not applicable

There are no evidence-based guidelines for the video documentation of BE. The following guidelines may be used as guidance: Obtain still images at the landmarks required for the C&M classification, at 1 cm intervals throughout the BE, the retroflexed position in the stomach and of all visible lesions within the BE. There is no need for video documentation if the aforementioned conditions are met.


STATEMENT #67. There is a paucity of evidence evaluating whether PPIs prevent the progression of LGD/HGD to esophageal adenocarcinoma.

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<th>Percentage who agreed strongly</th>
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<tbody>
<tr>
<td>66</td>
<td>28</td>
<td>3</td>
<td>4</td>
<td>0</td>
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**Evidence:** Low

PPIs by reducing acid exposure to Barrett’s oesophagus may theoretically increase or decrease the risk of progression to neoplasia. By reducing acid directly and bile acid reflux indirectly (due to decreased refluxate volume), PPIs will reduce mucosal damage and cell proliferation thereby increasing cell differentiation (Vaezi and Richter, 1999).

On the other hand the bile acid that does reflux to the oesophagus is more likely to be unconjugated with PPI therapy and therefore more harmful. PPI therapy also increases trypsin toxicity and intermittent oesophageal damage may be more harmful than continuous damage. Finally PPIs are associated with a slight rise in serum gastrin, which may increase
the risk of oesophageal adenocarcinoma. There are no robust data on whether PPIs reduce or increase the risk of neoplastic progression in LGD or HGD. Case series have suggested that low grade dysplasia regresses with PPI therapy (Wilkinson SP et al. 1999) but this is difficult to interpret without a control group. There is also a report (Cooper 2006) that Barrett's patients followed up for 13 years on a PPI exhibited less dysplasia and oesophageal adenocarcinoma than would be expected from other case series but such indirect comparisons are again difficult to interpret. Two observational studies (Hillman 2004; El-Serag 2004) suggest that PPI therapy is associated with a lower risk of Barrett's progression to dysplasia but these studies do not address the risk of adenocarcinoma once dysplasia develops.


STATEMENT #68. After ablation, there is no evidence that PPI therapy can prevent progression to cancer.

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<th>Percentage who agreed strongly</th>
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<tbody>
<tr>
<td>75</td>
<td>20</td>
<td>4</td>
<td>1</td>
<td>0</td>
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</table>

Evidence: Moderate

This is biologically plausible as there is strong epidemiological data including good cohort studies to suggest gastro-esophageal reflux and esophagitis are risk factors for Barrett's esophagus. There are however no randomized trial data or observational studies to support this statement. Most RCTs of ablation therapy have given all patients PPI therapy so there is no control group for comparison (Overholt 2007; May 2003; Gatenby 2009; Sampliner 2001; Schultz 2000; Ackroyd 2000).


**STATEMENT #69.** There is no evidence that NSAIDs or ASA can modulate the natural history of established HGD.

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<th>Percentage who agreed strongly</th>
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<th>Percentage who neither agreed nor disagreed</th>
<th>Percentage who disagreed</th>
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<tr>
<td>65</td>
<td>23</td>
<td>10</td>
<td>1</td>
<td>1</td>
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</table>

**Evidence:** Moderate

a) NSAIDs decrease the risk of esophageal cancer.
b) there is no evidence that NSAIDs can modulate the natural history of HGD.


**STATEMENT #70.** There is no evidence that HP eradication can modulate the natural history of LGD or HGD.

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<th>Percentage who agreed strongly</th>
<th>Percentage who agreed with reservation</th>
<th>Percentage who neither agreed nor disagreed</th>
<th>Percentage who disagreed</th>
<th>Percentage who disagreed strongly</th>
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<tbody>
<tr>
<td>75</td>
<td>21</td>
<td>3</td>
<td>1</td>
<td>0</td>
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</table>

**Evidence:** Low

Should we eradicate Helicobacter pylori in Barrett’s dysplasia? Several epidemiological studies have suggested that Hp may be protective against the development of gastro-esophageal reflux disease and its complications (Islam 2008; Wang 2009). However, such an association could be explained by confounding factors and interventional studies evaluating the effect of HP eradication have produced conflicting results concerning esophageal diseases in general. Hp infection can affect molecular alterations associated with genetic instability, CpG island methylation status, and biomarkers associated with carcinogenesis (Farinati 2004; MacNamara 2003; Moriichi 2009). In the gastric tissues, H. pylori infection leads to gastric mucosal inflammation. High-output nitric oxide production by inducible nitric oxide synthase (iNOS) mediated by H. pylori infection in macrophages is associated with immune activation and tissue injury in vitro (Wilson 1996) and NOS and COX-2 are induced in H. pylori-positive gastritis. This mechanism may modulate the inflammation and alterations in epithelial cell growth that occur in this disease. In patients with H. pylori infection, higher levels of iNOS and COX 2 were seen in areas of the stomach where...
bacterial colonization was most dense (Fu 1999). However, these data were derived from patients with gastritis, not BE. Although these data may be relevant to gastric carcinogenesis it is impossible to extrapolate to BE carcinogenesis. The results of mechanistic studies are difficult to interpret and there is no clear evidence of a protective or aggravating carcinogenetic effect of HP that may be relevant to the treatment of BE with or without dysplasia. Although, some studies have used surrogate markers to assess the effects of the eradication of Hp infection (Tanaka 2006; Toyoda 2006; Yu 2001), no controlled study had directly measured the cancer risk and clinical outcome in BE dysplasia after eradication of the bacterium compared to no intervention. In summary, there is no evidence-based literature supporting either eradication or preservation of HP in BE with or without dysplasia.


STATEMENT #71. Endoscopic treatment should be preferred over endoscopic surveillance for management of most patients with mucosal cancer (T1m) in BE.

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<th>Percentage who agreed strongly</th>
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<th>Percentage who neither agreed nor disagreed</th>
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<th>Percentage who disagreed strongly</th>
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<tbody>
<tr>
<td>84</td>
<td>15</td>
<td>1</td>
<td>0</td>
<td>0</td>
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</table>

Evidence: High

Endoscopic treatment should be preferred over endoscopic surveillance for management of most patients with mucosal cancer (T1m) in BE because of the following reasons: Biopsies do NOT allow to reliable staging of invasive cancer. Endoscopic surveillance of patients with a supposedly ‘early’ cancer may thus be associated with under diagnosis of more advanced cancer at baseline and/or to progression to a incurable cancer, especially when cancer is located in endoscopically visible lesions (Ormsby 2002; Peters 2008); For a small subgroup of selected patients with early cancer (e.g. significant co morbidity and estimated short survival) an expectant management may be justified yet for those cases continued endoscopic surveillance bears no relevance. Endoscopic treatment is associated with complete remission of neoplasia in 80-100% of cases and complete removal of intestinal metaplasia in >75% of cases. Severe complications are rare (Peters 2005; Ell 2007; Pech 2008; Shaheen 2009; Pouw 2010a; Pouw 2010b). For these reasons, most patients with mucosal cancer in BE should undergo endoscopic treatment instead of endoscopic surveillance.


STATEMENT #72. Endoscopic treatment should be preferred over surgical treatment for management of most patients with mucosal cancer (T1m) in BE.

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<th>Percentage who agreed strongly</th>
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<tbody>
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<td>58</td>
<td>28</td>
<td>5</td>
<td>8</td>
<td>3</td>
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</table>

Evidence: Moderate

Endoscopic treatment should be preferred over surgical treatment for management of most patients with mucosal cancer (T1m) in BE because of the following reasons 1) T1m in BE is associated with a low rate of lymph node metastases, provided that deeper invading lesions have been ruled out by adequate endoscopic inspection and EMR of all visible lesions (Vieth 2004; Westerterp 2005; Peters 2005; Ell 2007). 2) Cohort studies suggest that the long-term disease specific survival after endoscopic treatment is >95% and not significantly different from that after surgery (Peters 2005; Ell 2007; Pech 2008; Prasad 2009). 3) Surgical treatment is associated with a higher morbidity rate than endoscopic treatment yet the preservation of the esophagus after endoscopic treatment is associated with a higher rate of recurrences during follow-up (Peters 2005; Ell 2007; Pech 2008; Prasad 2009). 4) Recurrent lesions during follow-up can be effectively treated endoscopically. (Peters 2005; Ell 2007; Pech 2008; Badreddine 2010). 5) Recurrence rates after endoscopic treatment are significantly lower for cases where the residual Barrett’s segment is completely removed and effective techniques are available for this purpose. (Pech 2008; Badreddine 2010; Pouw 2010a; Pouw 2010b; Shaheen 2009). 6) In case endoscopic treatment fails; surgical resection is still possible and generally curative (Peters 2005; Ell 2007; Pech 2008). For these reasons, endoscopic treatment should be preferred over surgical treatment for management of most patients with mucosal cancer (T1m) in BE.

STATEMENT #73. Endoscopic treatment of HGD/T1m in BE requires endoscopic resection (ER) of all visible abnormalities.

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<th>Percentage who agreed strongly</th>
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<th>Percentage who neither agreed nor disagreed</th>
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<td>80</td>
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</table>

Evidence: High

The risk of local lymph node metastases is strongly dependent on the depth of invasion of early lesions (Vieth 2004; Westerterp 2005). EMR of early lesions allows for more reliable staging of the depth of invasion than EUS or endoscopic inspection (May 2004; Pech 2006). EMR is also more reliable than biopsies for diagnosing features such as tumor differentiation and lymphatic invasion that are relevant for further management decisions (Peters 2008).
selected patients with HGD/T1m focal EMR achieves complete remission for neoplasia in over 95% of patients and has a low rate of serious complications (<3%) (Ell 2007; Peters 2007; Pech 2008)


**STATEMENT #74.** Cap & snare technique with submucosal injection as well as band ligation technique without submucosal injection are equally effective EMR techniques.

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<th>Percentage who agreed strongly</th>
<th>Percentage who agreed with reservation</th>
<th>Percentage who neither agreed nor disagreed</th>
<th>Percentage who disagreed</th>
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<td>54</td>
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**Evidence:** Moderate

For EMR, cap & snare technique with submucosal injection as well as band ligation technique without submucosal injection have been found to be equally effective. The choice should depend on the expertise of the endoscopist and the type of lesion. Techniques: The
common EMR techniques are cap and snare, band ligation and Strip biopsy. However, the strip biopsy technique is only reported in the context of stomach lesions or squamous dysplasias with no literature on its role in the setting of Barrett's dysplasia. Studies into esophageal EMR are all small. They are all case series apart from one RCT comparing band ligator with cap and snare technique. Both cap and snare and band ligation techniques appear to have similar success rates in the order 85-98% (May 2002; Lopes 2007; Giovannini 2004; Conio 2005; Soehendra 2006; Nijhawan2000; Pacifico 2003; Seewald 2003). The optimal number of sessions required to completely eradicate dysplasia is unclear although it is demonstrated in most series that residual or recurrent dysplasia can be treated successfully by further EMR. There is one study which compares suck and ligate technique to cap and snare (May 2003). This is a RCT involving 100 procedures in 72 patients allocated to either suck-and-ligate device without prior submucosal injection or to the cap technique with prior submucosal injection of a dilute saline solution of epinephrine. This study did not show any difference in the size of resection specimen or complication rates concluding that both techniques were similar in efficacy and safety. Some endoscopists believe that submucosal injection provides an extra safety cushion and reduces the risk of perforation and is specially suited for nodular lesions which carry a high risk of invasive cancers as the presence of non-lifting sign will stop the endoscopist from resecting a potentially deep invasive cancer with its associated risks. However, this cannot be recommended purely from the evidence reviewed, and further efficacy and safety studies are needed in this area. The optimum lifting solution for esophageal EMR has not been established in the literature examined, therefore we cannot draw any conclusions regarding this. The type of solutions used for esophageal EMR is not that important as the procedure is quick and achievable with elevations achieved by saline. Minor bleeding appears to be the main complication encountered in most of the studies however, so an argument could be made for a mix containing adrenaline.


**STATEMENT #75.** Submucosal injection for lifting should be recommended for cap and snare based EMR technique but not for band ligation based technique.

<table>
<thead>
<tr>
<th>Percentage who agreed strongly</th>
<th>Percentage who agreed with reservation</th>
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<tr>
<td>46</td>
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</table>

**Evidence:** Moderate

Lifting is not recommended for band ligation and is only used with cap and snare. Oesophageal EMR is a quick procedure as compared to ESD so a simple saline solution with or without adrenaline / indigocarmine would be advisable. However, if large lesions are resected then injection with colloids might help. Further research is required in this area. Techniques: The common EMR techniques are cap and snare, band ligation and Strip biopsy. However, the strip biopsy technique is only reported in the context of stomach lesions or squamous dysplasias with no literature on its role in the setting of Barrett’s dysplasia. Studies into esophageal EMR are all small. They are all case series apart from one RCT comparing band ligator with cap and snare technique. Both cap and snare and band ligation techniques appear to have similar success rates in the order 85-98%. (May 2002; Lopes 2007; Giovannini 2004; Conio 2005; Soehendra 2006; Nijhawan 2000; Pacifico 2003; Seewald 2003). The optimal number of sessions required to completely eradicate dysplasia is unclear although it is demonstrated in most series that residual or recurrent dysplasia can be treated successfully by further EMR. There is one study which compares suck and ligate technique to cap and snare (May 2003). This is a RCT involving 100 procedures in 72 patients allocated to either suck-and-ligate device without prior submucosal injection or to the cap technique with prior submucosal injection of a dilute saline solution of epinephrine. This study did not show any difference in the size of resection specimen or complication rates concluding that both techniques were similar in efficacy and safety. Some endoscopists believe that submucosal injection provides an extra safety cushion and reduces the risk of
perforation and is specially suited for nodular lesions which carry a high risk of invasive cancers as the presence of non-lifting sign will stop the endoscopist from resecting a potentially deep invasive cancer with its associated risks. However, this cannot be recommended purely from the evidence reviewed, and further efficacy and safety studies are needed in this area. The optimum lifting solution for esophageal EMR has not been established in the literature examined, therefore we cannot draw any conclusions regarding this. The type of solutions used for esophageal EMR is not that important as the procedure is quick and achievable with elevations achieved by saline. Minor bleeding appears to be the main complication encountered in most of the studies however, so an argument could be made for a mix containing adrenaline.


**STATEMENT #76.** Esophageal strictures post EMR may complicate RFA therapy.
The intention of EMR should be to remove all visible dysplasia and it should ideally be restricted to < 2/3 rd of the esophageal circumference to reduce the risk of strictures. If HALO ablation is planned after EMR then a more conservative EMR strategy is recommended to reduce the risks of post HALO stricturing and perforation, but still all visible lesions should be resected. EMR resection invariably resects the mucosa along-with a substantial depth of submucosa. The resection length has been variable reported between 1 to 5 cm. Complete Circumferential EMR has been reported and is associated with stricture formation but responds well to dilatation (Giovannini 2004; Lopes 2007; Seewald 2003). The concept of complete Barrett’s ablation by circumferential EMR has been superseded by HALO ablation in recent time.


2. Giovannini M, Bories E, et al. Circumferential endoscopic mucosal resection in Barrett’s esophagus with high-grade intraepithelial neoplasia or mucosal cancer, preliminary results in 21 patients. Endoscopy 2004; 782-787


STATEMENT #77. After endoscopic treatment for HGD/early cancer, endoscopic follow up is required.

<table>
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<tr>
<th>Percentage who agreed strongly</th>
<th>Percentage who agreed with reservation</th>
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Evidence: High

Follow-up after endoscopic treatment: Most series on endoscopic treatment of neoplasia have used tri-monthly intervals for the first year, 6-monthly for the second year, and annual surveillance thereafter (May 2002; Peters 2005; Ell 2007). This is based on the initial studies from the Wiesbaden group in which monotherapy with focal EMR was the dominant treatment strategy (May 2002). Follow-up studies from Wiesbaden and
Amsterdam have shown a recurrence rate of 30% during a mean follow-up of 3 years (May 2002; Peters 2005). In these studies most of the recurrences occurred within 12 months after treatment suggesting that an intense follow-up regimen during the first year is indeed justified. Risk of recurrence is associated with residual Barrett's esophagus, patient age, and smoking history, and occurred a mean of 17 months after treatment from a Mayo series (Prasad 2009; Badreddine 2009). These data of mostly combinational therapy does suggest that there are patients at risk for longer periods of time. Ranges for recurrence of early cancers extend to 7 years after treatment so prolonged observation is required (Pech 2008). Protocols to follow patients include careful 4 quadrant biopsies of the normal appearing mucosa encompassing the prior area of Barrett's mucosa with particular attention to any residual columnar mucosa and the gastric cardia. Studies in which the complete Barrett's segment is removed (either by EMR or ablation) have shown a much lower recurrences rates (Pouw 2009; Pouw 2008; Pouw 2010). This makes it likely that the follow-up regimen can be less strict for those cases where complete removal of the Barrett's segment is achieved. Most recent prospective studies of EMR and RFA advice follow-up after 3 months, 6 and 12 months and annual follow-up thereafter in cases where endoscopic and histological complete remission has been documented (Pouw 2008; Pouw 2009). Suggested follow-up: In case of residual Barrett's mucosa without dysplasia after endoscopic treatment: tri-monthly intervals for the first year, 6-monthly for the second year, and annual surveillance thereafter. In case of documented endoscopic and histological eradication of neoplasia and IM: 3 months, 6 and 12 months and annual follow-up thereafter. Individualized follow-up for higher risk individuals.

STATEMENT #78. In case of residual BE after endoscopic treatment, endoscopic follow-up may be performed with tri-monthly intervals for the first year, 6-monthly intervals for the second year and annual surveillance thereafter.

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<th>Percentage who agreed strongly</th>
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**Evidence: Low**

Follow-up after endoscopic treatment: Most series on endoscopic treatment of neoplasia have used tri-monthly intervals for the first year, 6-monthly for the second year, and annual surveillance thereafter (May 2002; Peters 2005; Ell 2007). This is based on the initial studies from the Wiesbaden group in which monotherapy with focal EMR was the dominant treatment strategy (May 2002). Follow-up studies from Wiesbaden and Amsterdam have shown a recurrence rate of 30% during a mean follow-up of 3 years (May 2002; Peters 2005). In these studies most of the recurrences occurred within 12 months after treatment suggesting that an intense follow-up regimen during the first year is indeed justified. Risk of recurrence is associated with residual Barrett’s esophagus, patient age, and smoking history and occurred a mean of 17 months after treatment from a Mayo series (Prasad 2009; Badreddine 2009). These data of mostly combinational therapy does suggest that there are patients at risk for longer periods of time. Ranges for recurrence of early cancers extend to 7 years after treatment so prolonged observation is required (Pech 2008). Protocols to follow patients include careful 4 quadrant biopsies of the normal appearing mucosa encompassing the prior area of Barrett's mucosa with particular attention to any residual columnar mucosa. Studies in which the complete Barrett's segment is removed (either by EMR or ablation) have shown a much lower recurrences rates (Pouw 2009, Pouw 2008, Pouw 2010). This makes it likely that the follow-up regimen can be less strict for those cases where complete removal of the Barrett's segment is achieved. Most recent prospective studies of EMR and RFA advice follow-up after 3 months, 6 and 12 months and annual follow-up thereafter in cases where endoscopic and histological complete remission has been documented (Pouw 2008; Pouw 2009). Suggested follow-up: In case of residual Barrett's mucosa without dysplasia after
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**STATEMENT #79.** The incidence of adverse events attributable to endotherapy is known.

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<th>Percentage who agreed strongly</th>
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**Evidence:** High

The risk of bleeding with endoscopic mucosal resection in the esophagus is approximately 3-10% in Barrett's esophagus and does appear to be related to the number of mucosal resection performed. Circumferential mucosal resection for complete resection of a
Barrett's esophagus is associated with a 50% stricture rate in a prospective cohort study. The issue of strictures is approximately 6% with RFA, especially when used circumferentially in a prospective randomized study.


3. Clarification: added after voting: Perforation is a possible complication and does occur. Although some series did not have any perforations related to EMR, other studies, such as Peters FP Eur J Gastroenterol Hepatol.2007, found a risk of about 1%.

**STATEMENT #80. Fundoplication surgery does not reliably result in regression of BE.**

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<tr>
<th>Percentage who agreed strongly</th>
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</table>

**Evidence:** Moderate

Complete Barrett regression is reported in up to one-third of patients after fundoplication surgery, whereas small numbers of patients experience progression of the Barrett length. Whether Barrett mucosa regresses as a result of the antireflux effects of fundoplication is an important question that has bearing on the potential referral of large numbers of patients for possible antireflux surgery. To date, the bulk of data related to this question come from studies that lack important design elements including mandated long-term follow-up, use of a standard biopsy protocol, and/or a technique for ensuring that the site from which the extent of Barrett esophagus was originally measured is identified for subsequent postoperative measurements. The literature published from 2000 through 2009 regarding the effects of fundoplication on Barrett esophagus consists primarily of retrospective observational studies, one prospective observational study, one open-label randomized trial, and one meta-analysis. Complete Barrett regression is reported in up to one-third of patients, whereas small numbers of patients experienced progression of the Barrett length.


**STATEMENT #81.** There is no strong evidence regarding the effects of fundoplication on reversion of HGD in Barrett's.

<table>
<thead>
<tr>
<th>Percentage who agreed strongly</th>
<th>Percentage who agreed with reservation</th>
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<td>11</td>
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</table>

**Evidence:** Moderate

Whether Barrett high grade dysplasia regresses as a result of the antireflux effects of fundoplication is an important question that has bearing on the potential referral of patients at substantially increased risk for cancer for possible antireflux surgery. To date, regression of HGD has not been adequately studied or reported.

**STATEMENT #82.** The indications for fundoplication with BE should be similar to those for patients without BE in uncomplicated reflux disease.
<table>
<thead>
<tr>
<th>Percentage who agreed strongly</th>
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</table>

**Evidence:** Low


**STATEMENT #**83. Oesophagectomy, regardless of the approach, results in long term cure of HGD.

<table>
<thead>
<tr>
<th>Percentage who agreed strongly</th>
<th>Percentage who agreed with reservation</th>
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<td>70</td>
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</table>

**Evidence:** Moderate

There is good evidence that successful surgery using any recognized procedure results in long term cure of high grade dysplasia in selected patients. There is insufficient evidence to support the use of one technique above the others. Esophagectomy provides the opportunity to resect the whole metaplastic segment including any previously unrecognized foci of invasive adenocarcinoma or synchronous high grade dysplasia. Attempts have been made to tailor a less radical, less morbid surgical procedure for these patients with early lesions who do not require extensive lymphadenectomy. These are not associated with a detrimental effect on long term survival. The majority of surgical data come from retrospective observational studies, often comparing outcomes with outdated historical controls. Data directly comparing the various techniques or from series restricted to HGD are extremely limited. Modern specialist centers consistently report overall surgical mortality rates of less than 5% (Griffin 2002; Lerut 2009). A series including left thoraco abdominal esophagectomy (60%), transhiatal esophagectomy (20%) and Ivor Lewis esophagectomy (20%) reported no operative mortality and major complications in only 11%
of patients (Moraca 2006). At a mean follow up of 5 years, quality of life outcomes were comparable with age and sex matched controls. A further series of patients with HGD and T1 esophageal cancer undergoing open surgery by either the transhiatal or transthoracic routes reports operative mortality of 2.5% and 5 year survival of 77%. This series included patients with tumor involved lymph nodes for whom survival is significantly impaired compared to patients with HGD (Rice 2001). The vagal sparing technique aims to reduce the post operative dumping and diarrhea associated with esophagectomy. A study of patients with HGD or intramucosal cancer found that the 49 patients who underwent vagal sparing oesophagectomy had shorter hospital stays and less major complications than 39 patients who underwent transhiatal procedures and 21 who underwent en-bloc resections (Peyre 2007). Post-operative dumping syndrome and diarrhea were decreased in the vagal sparing group and there was no detrimental effect on long term outcomes. The vagal-sparing procedure does not involve a lymphadenectomy and meticulous pre-operative staging is required to exclude the presence of submucosal invasive disease where the risk of lymph node involvement would make this procedure inadequate. Transhiatal esophagectomy avoids the need for thoracotomy. Concerns about the adequacy of lymphadenectomy with this procedure do not apply in the context of HGD. In a randomised controlled trial the transhiatal procedure was associated with less peri-operative morbidity than a transthoracic procedure, there was no significant difference in peri-operative mortality (2% vs. 4%, p=0.45) (Hulscher 2002). Long term follow up showed no difference in overall survival (Omlo 2007). This trial included patients with operable disease of all stages. There is no randomised trial involving HGD patients only. The largest reported single centre experience of transhiatal esophagectomy includes 143 HGD patients included in a total cohort of 2007 patients. Overall in-hospital mortality in this series is 3% with 50% of recent patients discharged within 1 week of surgery (Orringer 2007). A further option for HGD arising within a short (<3cm) segment of Barrett’s is a Merendino limited resection with jejunal interposition. In a series of 24 patients this was associated with no operative mortality, significantly less peri-operative morbidity than standard esophagectomy and a normal quality of life at one year (Stein 2000). The term minimally invasive esophagectomy (MIE) incorporates a very heterogeneous group of procedures. There are no randomised controlled trials comparing minimally invasive esophagectomy with open surgery. A series of 222 patients undergoing MIO including 47 with HGD has shown that this procedure is safe with a 30 day mortality of 1.4%. Median hospital stay was shorter than that usually seen in open surgery at only 7 days but the procedure remains associated with major complications including a leak rate of 11.7% (Luketich 2003) A UK series has attempted to compare consecutive series of open Ivor Lewis and minimally invasive procedures. This group found that overall morbidity and mortality were similar for both groups but there were less pulmonary complications in the minimally invasive group (8% vs. 23%) (Parameswaran 2009).


**STATEMENT #84.** All patients with high grade dysplasia should be managed in a specialist centre to exclude more advanced disease.

<table>
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<th>Percentage who agreed strongly</th>
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**Evidence:** Low

Biopsy detected high grade dysplasia can reflect a tip of the iceberg situation. It is well recognized that a significant proportion of patients diagnosed with high grade dysplasia on mucosal biopsies actually have more advanced disease. Several surgical series have...
described rates of undiagnosed invasive adenocarcinoma in patients undergoing surgery for high grade dysplasia of between 30 and 50% (Falk 1999; Heitmiller 1996; Reed 2005). More recent literature has suggested that the risk of this may be lower than previously suggested (Wang 2009) but this remains a potential problem. A meta-analysis reporting rates of adenocarcinoma in patients undergoing surgery for high grade dysplasia reports that the rate of previously unrecognized submucosal invasion is 12.7% (Konda 2008) This still represents a significant proportion of patients who could potentially be undertreated on the basis of biopsy diagnosis alone. It is important to recognize that endoscopic evaluation is highly operator dependent. Whilst the evidence in this area is limited it seems likely that specialist centers dealing with large numbers of patients with dysplasia arising in Barrett’s oesophagus are likely to stage patients more accurately than centers dealing with small numbers of patients. In addition the routine use of endoscopic ultrasound can help to improve staging accuracy and again this is operator dependent and likely to be more sensitive in expert hands.


**STATEMENT #85** Successful surgery for HGD/early cancer may be determined by pathological outcomes (resection margins)

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<th>Percentage who agreed strongly</th>
<th>Percentage who agreed with reservation</th>
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<td>37</td>
<td>4</td>
<td>3</td>
<td>3</td>
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</table>

**Evidence:** Low

Surgical resection for Barrett’s must include complete resection of the Barrett’s segment (longitudinal margins). Radial margin involvement does not occur in early cancer since the muscularis propria is excised. Lymphadenectomy should be performed because of the
possibility of lymph node involvement in previously unrecognized submucosal tumors (Pennarthur 2009; Portale 2006; Stein 2007).


**STATEMENT #86.** Successful surgery for HGD/early cancer may be determined by surgical outcomes (perioperative survival).

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<th>Percentage who agreed strongly</th>
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</table>

**Evidence:** Low

Surgical resection is associated with significant short term morbidity (6-37%). (Williams 2007; Sujendran S 2005; Reid 2007). Perioperative mortality however is low with levels similar to non-surgical therapies. (Williams 2007)


**STATEMENT #87.** Successful surgery for HGD/early cancer may be determined by long term pathological and surgical outcomes (recurrence).

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<th>Percentage who agreed strongly</th>
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<td>62</td>
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**Evidence:** Low

Tumor recurrence after resection of early cancer is rare (1%). There are no reports of long term tumor recurrence in patients who have had complete surgical resection of HGD alone and all cause mortality is equivalent to non-surgical treatments (Prasad 2007; Green 2008).


**STATEMENT #88.** Successful surgery for HGD/early cancer (oesophagectomy) may be determined by the impact on measures of quality of life.

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<th>Percentage who agreed strongly</th>
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<td>56</td>
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**Evidence:** Low

Patients having esophagectomy report worse functional, symptom, and global QL scores than before surgery. Oesophagectomy has a negative impact on QL; the adverse effects lessen in patients who survive for 2 or more years.


**STATEMENT #89.** Nissen fundoplication does not protect against neoplastic progression in patients with high grade dysplasia.
Evidence: Low/Moderate

Complete barrier to all refluxate is possible with Nissen Fundoplication and it may be thought that this will be beneficial to reduce neoplastic progression. However there is no evidence to indicate that progression to high grade dysplasia is reduced.


STATEMENT #90. When consenting to treatment, a patient with Barrett's dysplasia should be provided with up to date reliable information relating to treatment options (including surveillance or no active treatment), treatment complications, best and worst case outcomes. Specifically, information about risks (morbidity and mortality, QoL and psychological consequences) health benefits, short term and long term survival of any therapeutic option should be given.
What information should be given to a patient in whom any form of intervention (surgery or endotherapy) has been deemed high risk? It can be argued that "No treatment" is still "treatment" and that the patient should be provided with reliable information on the risks and benefits, incorporating (as necessary) considerations of the patient's general health and ability / willingness / readiness to evaluate the information. In the high risk situation, counseling should include discussion of the merits and risks of the 'watch-and-wait' intensive surveillance option.


STATEMENT #91. There is insufficient evidence to support different information being given to patients with unifocal compared to multifocal HGD.

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<th>Percentage who agreed strongly</th>
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</table>

Evidence: Low

3 studies have addressed the issue of whether unifocal or multifocal HGD influences the likelihood of unsuspected cancer either developing or being found at subsequent oesophagectomy (Srivastava 2007; Dar 2003; Buttar 2001). Two (Buttar 2001; Dar 2003) were retrospective cohort studies and used the same definition of focal (5 or less crypts showing HGD) or multifocal (more than 5 crypts showing HGD). In the Mayo clinic study, patients were followed up but not all had oesophagectomy (Buttar 2001). This study found a 3.7 fold increased risk of cancer in patients with multifocal HGD compared to unifocal at 1 and 3 years’ follow up. The second study (Dar 2003) found that 72% of the focal group had unsuspected cancer at oesophagectomy compared to 54% of those with multifocal HGD (p=0.68). When these authors re-defined multifocal HGD as dysplasia found at more than one level within the Barrett's segment (a definition most endoscopists would be more comfortable with), the figures were 48% for focal and 67% for multifocal HGD (p=0.35). The numbers of patients in this study were relatively small (n=42) compared to the Mayo clinic study (n=99). In the final study, 77 patients with low grade dysplasia (LGD) or HGD were followed up; 44 eventually developed cancer. Extent of LGD but not extent of HGD was associated with risk of subsequent cancer (Srivastava 2007). There is therefore insufficient evidence to support providing patients with different information depending on the extent of high grade dysplasia.


**STATEMENT #92.** Patients should be told that HGD in the presence of a visible lesion, especially polypoid (Type I) or lesion containing a depressed element (Type IIc), has a higher risk of containing an unsuspected invasive cancer which more often involves submucosa (25% risk).

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</table>

**Evidence:** Moderate

Should information provided to patients with HGD after two endoscopies and detailed biopsies but not EMR differ depending on whether HGD is visible, nodular or ulcerated? A recently published meta-analysis of surgical series of patients undergoing oesophagectomy for HGD found that the pooled risk of an unsuspected cancer was higher among those with an endoscopically visible lesion (11%) compared to those with flat mucosa [3%] (Konda 2008). Two large series from Weisbaden (Pech 2007) and Amsterdam (Peters 2008) have compared histology of ER specimens (for both HGD and suspected mucosal [T1a] cancer) to endoscopic findings (classified according to the Paris system); both found that polypoid (Type I) lesions and depressed or mixed elevated/depressed lesions (Type IIc; Type IIa + IIc) were more likely to be associated with invasive cancer. The Amsterdam group showed that Type I and Type IIc morphology was significantly more likely to be associated with submucosal invasion [approximately 25% of each, compared to approximately 10% of the other types] (Peters 2008). T1b staging with submucosal invasion was more common among Type IIa + IIc (18%) and IIc lesions (25%) in the Weisbaden series (Pech 2007). Ulcerated or deeply excavated lesions (Type III) were not reported in the Amsterdam series (Peters 2008) and only represented 2% (6 cases) of the 380 lesions in the Wiesbaden series (Pech 2007), presumably because this type of lesion is rarely amenable to endotherapy. However, in the Weisbaden series all the Type III lesions were T1a lesions and endoscopically resectable. Other evidence exists that ulcerated HGD is very likely at oesophagectomy to harbor invasive cancer - 80% in one series though the denominator was only 10 patients (Montgomery 2002). By contrast flat HGD submitted to ER was frequently confirmed on subsequent histology (Pech 2007). Both ER studies (Pech 2007; Peters 2008) and other evidence (Mindy 2006; Chennat 2009) confirm that ER specimens frequently
result in a change in diagnosis and management due both to overstaging and understaging if relying on biopsies.


