INTRODUCTION

During the last three decades, there has been a growing awareness that cancer of the upper gastrointestinal tract may develop in association with several underlying diseases. The literature has been difficult to evaluate in terms of formulating surveillance guidelines since most published studies are retrospective and deal with small numbers. This statement is an attempt to establish guidelines, keeping in mind cost considerations, with respect to the following conditions: achalasia, columnar epithelium-lined esophagus (Barrett’s esophagus), caustic ingestion, tylosis, gastric polyps, polyposis syndromes, pernicious anemia, and postgastrectomy surgery for benign disease. Well designed long-term, population-based prospective studies which more accurately define risk for malignancy are needed.

ACHALASIA

The risk of developing esophageal cancer in patients with achalasia appears to be higher than the general population. A single, population-based study from Sweden estimated this relative risk to be about 16-fold. However, the data are few and the true prevalence is unknown. The cancer risk in surgically treated patients may be less, but the data regarding this are also limited. These cancers rarely occur before fifteen years of symptomatic disease. The cancer risk in patients treated medically, as with calcium channel blockers or injection of botulinum toxin, is unknown.

RECOMMENDATION:

There are insufficient data to support routine endoscopic surveillance for these patients.

COLUMNAR EPITHELIUM-LINED ESOPHAGUS (BARRETT’S ESOPHAGUS)

There is a well recognized risk of developing adenocarcinoma in the esophagus of patients with Barrett’s esophagus with specialized intestinal metaplasia. Endoscopic screening studies suggest a cancer incidence ranging from 1 in 52 to 1 in 175 patient-years. More recent prospective case series suggest the cancer incidence is 1 in 208 patient-years. Effective medical or surgical antireflux therapy, while healing inflammation, ulceration and/or strictures, does not reverse the malignant potential of Barrett’s esophagus.

Cancer in Barrett’s esophagus may be microinvasive and multifocal. Extensive random sampling of the entire Barrett’s segment should be performed during surveillance endoscopy, and any macroscopic abnormalities should in particular be biopsied. There is some evidence that better tissue sampling may be achieved with a jumbo biopsy forceps; however, the best method for sampling the esophagus is not clear. One accepted method of tissue sampling involves four-quadrant biopsies with large particle forceps taken at 2 cm. intervals starting 1 cm. below the esophagogastric junction and extending 1 cm. above the squamocolumnar junction.

A histologic classification of invasive or intramucosal cancer, high-grade dysplasia (HGD), low-grade dysplasia/indefinite for dysplasia (LGD), and no dysplasia (ND) is useful and reproducible, with an 86% interobserver agreement among expert pathologists for the diagnosis of HGD. Collective reports have shown a high correlation between HGD and carcinoma (present in 32% of resected specimens). The significance of LGD is uncertain.

Most experts agree that surveillance endoscopy for patients with Barrett’s esophagus and no history of dysplasia should be performed every one to three years. Surveillance endoscopy is only appropriate for patients fit for therapy, should endoscopic/histologic findings dictate. The outcome of surveillance (i.e., impact on patient mortality due to esophageal cancer) is not established.

Changes in mucosal DNA content by flow cytometry may provide useful information in the surveillance of Barrett’s esophagus, but the technique is demanding, expensive and still under evaluation. There is no
role for endoscopic ultrasound in the surveillance of Barrett’s esophagus. Endoscopic mucosal ablation techniques are currently under investigation.

**RECOMMENDATIONS:**

1. The decision to perform surveillance endoscopy and biopsy for Barrett’s esophagus should be based on the risk versus potential benefit for individual patients. Surveillance endoscopy is appropriate for patients fit for therapy, should endoscopic/histologic findings dictate. In patients with established Barrett’s esophagus and no history of dysplasia in whom surveillance endoscopy and biopsy is performed, an interval range of one to three years is reasonable. The best method for sampling the esophagus is not clear; one acceptable method is described above. As active inflammation can impair the identification of dysplasia, surveillance should be performed while the patient’s reflux disease is well controlled, and not in the presence of ulceration or erosions.

2. The appropriate response to the discovery of dysplasia during surveillance endoscopy must be individualized. Multiple factors, including the subjectivity of histologic diagnosis and difficulty in distinguishing inflammatory change from dysplasia must be considered. In difficult cases, consultation between more than one experienced pathologist may be desirable. Some general guidelines include:
   a. When invasive or intramucosal cancer is diagnosed and confirmed, the patient should be referred for esophagectomy after complete staging.
   b. Management of HGD is controversial. Some centers perform esophagectomy for HGD, citing the high correlation between HGD and cancer. Other centers recommend operations only for cancer, and follow the patient with HGD with more frequent surveillance. Management must be individualized. For example, a relatively lower threshold for surgical intervention might be appropriate for the young, healthy patient with HGD in a long Barrett’s segment. More frequent surveillance might be chosen for HGD in a short segment of Barrett’s in a patient at higher operative risk, with surgery if intramucosal carcinoma is subsequently detected.
   c. If the degree of dysplasia is indeterminate due to possible inflammatory change, complete surveillance biopsies should be performed after approximately 4-8 weeks of aggressive antireflux therapy, as with a proton pump inhibitor.
   d. Management of the patient with LGD on surveillance biopsy is also controversial. Most experts agree that more frequent surveillance endoscopy, at least in the short term, is warranted. One possible management scheme would be to perform surveillance endoscopy with multiple biopsies at 6 and 12 months after the discovery of LGD. If no further evidence of dysplasia is described, the patient may return to the standard surveillance program.

**CAUSTIC INGESTION**

The risk for development of esophageal cancer in patients with a history of caustic ingestion has been estimated to be 1,000 times greater than the general population.61-63 The cumulative findings of four series has characterized the findings associated with lye-related esophageal cancer: mean age at onset 47 years; interval from caustic ingestion to development of cancer ranges from 14 to 47 years (mean 40 years), and the majority of cancers occur in the mid esophagus.61-63,66 Malignancy appears to develop after a shorter interval if the corrosive injury occurs later in life. The periesophageal fibrosis caused by the corrosive injury decreases esophageal compliance and cancer therefore usually presents at an earlier stage. The resectability rate and a 5-year survival for lye-associated esophageal carcinoma are 85% and 33%, respectively.66

**RECOMMENDATIONS:**

1. Begin endoscopic surveillance 15-20 years after caustic ingestion.

2. The periodicity and method of endoscopic surveillance requires study. Generally, endoscopic examination should not be conducted more frequently than every one to three years. The threshold to evaluate swallowing problems with endoscopy should be low.

**TYLOSIS**

Tylosis is an uncommon genetic disorder characterized by hyperkeratosis of the palms and soles.67 It is transmitted in an autosomal dominant pattern and associated with a predisposition for development of esophageal cancer.68 The prevalence of esophageal cancer in patients with tylosis has been
reported to be over 90% by 65 years of age. Death from esophageal cancer has been reported in tylosis patients as young as 30 years. A prospective endoscopic surveillance program has been initiated for a large family cohort in England.

**RECOMMENDATIONS:**

1. Start endoscopic surveillance at 30 years of age.

2. The periodicity and method of endoscopic surveillance requires study. Generally, endoscopic examination should not be conducted more frequently than every one to three years.

**GASTRIC POLyps**

Gastric polyps are rarely symptomatic. They are frequently an incidental finding on upper gastrointestinal (UGI) barium studies or upper endoscopy. The majority of gastric polyps (70-90%) are hyperplastic or fundic gland polyps. Only adenomatous polyps carry a risk for malignancy; this risk is size dependent. Polyph histology cannot be reliably distinguished by endoscopic appearance. Since polyps may be a combination of hyperplastic and adenomatous tissue, endoscopic biopsies of large gastric polyps may misidentify polyp histology. Endoscopic biopsies may miss areas of focal cancer in adenomatous polyps.

Some studies have suggested an increased risk of gastric cancer in the gastric mucosa distinct from the gastric polyp. This association, if true, appears greater with adenomatous gastric polyps, and increases with age. Therefore, it would appear prudent during the endoscopic evaluation of gastric polyps to also carefully examine the remaining gastric mucosa and biopsy any surface abnormalities.

The recurrence rate of adenomatous polyps may be as high as 16%.

**RECOMMENDATIONS:**

1. Polypoid defects of any size detected radiologically should be evaluated endoscopically, with biopsy and/or removal of the lesions.

2. Polyps causing symptoms, such as obstruction and bleeding, should be removed, preferably endoscopically.

3. Polyps greater than 2 cm in size should be endoscopically excised whenever feasible. If endoscopic polypectomy is not possible, the polyp should be biopsied. If adenomatous tissue is detected, referral for surgical excision should be considered. If no adenomatous tissue is detected, management must be individualized. If it is felt that there is a reasonable chance that endoscopic biopsy could have overlooked adenomatous change in a mixed polyp (as might be seen, for example, in a pedunculated polyp where sampling from all areas is difficult), referral for surgical excision is reasonable.

4. Polyps less than 2 cm in size may be initially biopsied or excised. If representative biopsies are obtained and the polyp non-adenomatous, no further intervention is necessary. If biopsies reveal adenomatous change, endoscopic excision should be considered whenever feasible.

5. When multiple gastric polyps are encountered, the largest polyps should be biopsied or excised, and representative sample biopsies taken from some others. Further management should be based on histologic results.

6. Surveillance endoscopy one year after removing adenomatous gastric polyps is reasonable to assess recurrence at prior excision site, new or previously missed polyps and/or supervening early carcinoma in gastric mucosa apart from the site of coincident polyps. If this examination is negative, repeat surveillance endoscopy should be repeated no more frequently than three to five year intervals.

7. No surveillance endoscopy is necessary after removal of non-adenomatous gastric polyps.

**FAMILIAL ADENOMATOUS POLYPOSIS/GARDNER’S SYNDROME**

Duodenal and gastric polyps may occur in 33 - 100% of patients with familial adenomatous polyposis (FAP). Up to 90% of patients with FAP may have distal duodenal or jejunal adenomas discovered at push enteroscopy. Gastric polyps in FAP patients are most often fundic gland polyps, which have no malignant potential. Gastric adenomas may be detected. Duodenal polyps are typically adenomatous, and occur primarily in the ampulla or periampullary region. Upper gastrointestinal polyps may appear synchronous or metachronous to the identification of colonic polyps. Adenomatous change of the papilla may not be apparent without biopsy. While the risk of malignancy from adenomatous colon polyps is well established, the natural history of UGI adenomas is less understood; however, adenocarcinoma developing from UGI adenomas, particularly in the periampullary region, is well-recognized, and is the most common...
cause of death in FAP patients once colorectal cancer is excluded. Although its efficacy is yet to be established, a surveillance program is advisable.

RECOMMENDATIONS:
1. Patients with FAP should undergo upper endoscopy with both end-viewing and side-viewing instruments. The optimal timing of initial upper endoscopy is unknown, but could be performed around the time the patient is considered for colectomy, or early in the third decade of life. Multiple biopsies should be obtained from the papilla even if the endoscopic appearance is normal. Pancreatitis has been reported following biopsies of the papilla. If no adenomas are detected, another exam should be performed in three to five years, as adenomatous change may occur later in the course of the disease.

2. For patients with periampullary adenomas, surveillance endoscopy and biopsy should be performed at one to three year intervals. Duodenal adenomas may be biopsied or sampled at the time of initial discovery, or if they appear to have enlarged or otherwise changed on subsequent exams. Biopsies of gastric polyps are not needed, as the risk for adenomatous, or malignant, transformation is low.

3. Surgical consultation should be obtained for those patients with ampullary carcinoma. Management of high-grade dysplasia in the periampullary region (surgery/ablative therapy vs. more frequent surveillance) is controversial, and must be individualized. Most experts would follow the patient with low-grade dysplasia with more frequent surveillance. One possible management scheme would be to perform surveillance endoscopy with biopsies at 6 and 12 months after the discovery of low-grade dysplasia. If no further evidence of dysplasia is described, the patient may return to the standard surveillance program.

4. The exact role of ERCP and push enteroscopy for patients with FAP is unclear.

PERNICIOUS ANEMIA

Whether pernicious anemia alone, or pernicious anemia associated with atrophic gastritis, is precursor to gastric cancer is unknown. Several large studies addressing the risk of gastric cancer in patients with pernicious anemia and the possible role of surveillance endoscopy have been somewhat contradictory in their conclusions.

RECOMMENDATION:
A single endoscopy is indicated to identify prevalent lesions (carcinoid tumors, gastric cancer), but there are insufficient data to support subsequent endoscopic surveillance for these patients.

POSTGASTRIC SURGERY

Cancer occurring in patients previously operated on for benign gastric or duodenal ulcer disease has been recognized for several decades in autopsy and retrospective studies. In some series, the frequency ranges from 2% to 8.7%. Other series have demonstrated no increased risk. Endoscopic surveillance studies have detected gastric cancer in 4% to 6% of these patients, and the dysplasia to carcinoma sequence has been described. However, a large population based study suggests that surgery for benign peptic ulcer disease does not increase the risk of gastric cancer.

RECOMMENDATION:
There are insufficient data to support routine endoscopic surveillance for these patients.

REFERENCES
13. Reid BJ, Weinstein WM, Lewin KD, et al. Endoscopic biopsy can detect high-grade dysplasia or early carcinoma in