MANAGEMENT OF PATIENTS WITH EARLY ESOPHAGEAL CANCER, DYSPLASTIC AND NON-DYSPLASTIC BARRETT’S ESOPHAGUS

Effective Date: March, 2014

The recommendations contained in this guideline are a consensus of the Alberta Provincial Gastrointestinal Tumour Team synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.
BACKGROUND

Barrett’s esophagus is defined by the American Gastroenterological Association (AGA) as a condition in which the stratified squamous epithelium that normally lines the distal esophagus is replaced by metaplastic columnar epithelium that predisposes to cancer development. The prevalence of Barrett’s esophagus in patients who undergo an upper gastrointestinal endoscopy for any reason is 4 percent; this prevalence rises to 9 percent in males over the age of 50 years, and to as high as 12 to 15 percent in patients with gastroesophageal reflux disease (GERD). While up to 44 percent of the general population experiences GERD however, only approximately 10 percent of these individuals will go on to develop Barrett’s esophagus. Risk factors for Barrett’s esophagus have been established, and include: male gender, age greater than 50 years, white race, a history of chronic GERD greater than 10 years, a body mass index greater than 30, a family history of Barrett’s esophagus or esophageal cancer, the presence of a hiatal hernia, and a waist circumference greater than 35 inches for women or 40 inches for men. A history of heavy alcohol consumption and a history of smoking have also been identified as possible risk factors.

The risk of progression from Barrett’s esophagus to esophageal adenocarcinoma is difficult to predict accurately; predisposing risk factors include a length of Barrett’s esophagus > 6 cm, a hiatal hernia greater than 3 cm in length, and the presence of dysplasia. Most patients with Barrett’s esophagus and no or low-grade dysplasia will not progress to cancer. The incidence of esophageal cancer in patients with non-dysplastic Barrett’s esophagus is approximately 1 per 300 patients per year. In a recently published prospective cohort study of 713 patients with Barrett’s esophagus and no dysplasia or low-grade dysplasia, Sikkema and colleagues identified several risk factors significantly associated with progression to high-grade dysplasia or esophageal adenocarcinoma, including a duration of Barrett’s esophagus greater than 10 years (risk ratio (RR)=3.2; 95% confidence interval (CI) 1.3-7.8), the length of Barrett’s esophagus (RR=1.11 per cm increase in length; 95% CI 1.01-1.2), the presence of esophagitis (RR=3.5; 95% CI 1.3-9.5), and the presence of low-grade dysplasia (RR=9.7; 95% CI 4.4-21.5). Wani and colleagues followed 1204 patients with Barrett’s esophagus and no dysplasia for 5.52 years, and reported that 98.6 and 97.1 percent of patients had not developed cancer at 5 and 10 years, respectively. A length of Barrett’s esophagus >6cm was identified as a predictor of progression to adenocarcinoma. In contrast, high-grade dysplasia is frequently found in association with esophageal adenocarcinoma. In a systematic review and meta-analysis of 4 studies involving 236 patients with Barrett’s esophagus and high-grade dysplasia, Rastogi et al. reported a conversion rate of 6 percent per year to adenocarcinoma, while in a randomized trial examining radiofrequency ablation, Shaheen and colleagues reported a conversion rate of 19 percent per year in patients with Barrett’s esophagus and high-grade dysplasia.

The purpose of this guideline and accompanying clinical pathways is to describe the criteria for the use of endoscopic procedures for adult patients with Barrett’s esophagus in Alberta. For a detailed description of treatment modalities for esophageal cancer, please refer to the GI-009 Esophageal Cancer clinical practice guideline.

GUIDELINE QUESTIONS

- What are the recommended treatment options for patients with Barrett’s esophagus and early esophageal cancer?
In what clinical situations is endoscopic therapy the most appropriate treatment for patients with Barrett’s esophagus and early esophageal cancer?

DEVELOPMENT

This guideline was reviewed and endorsed by members of the Alberta Provincial Gastrointestinal Tumour Team. Members of the Alberta Provincial Gastrointestinal Tumour Team include medical oncologists, radiation oncologists, surgeons, hepatologists, gastroenterologists, interventional radiologists, nurses, pathologists, and pharmacists. Evidence was selected and reviewed by a working group comprised of gastroenterologists from the Provincial Tumour Team, and members of the Guideline Utilization Resource Unit. A detailed description of the methodology followed during the guideline development process can be found in the Guideline Utilization Resource Unit Handbook.

This guideline was originally developed in February, 2013. This guideline was revised in March, 2014.

SEARCH STRATEGY

A review of the literature was conducted by searching journal articles using the Medline (1946 to June Week 4, 2012), EMBASE (1980 to June Week 4, 2012), Cochrane Database of Systematic Reviews (2nd Quarter, 2012), and PubMed electronic databases. The following terms were searched in various combinations: Barrett Esophagus (MeSH heading), Esophageal Neoplasms (MeSH heading), Precancerous Conditions (MeSH heading), Esophagus (MeSH heading), Esophageal Diseases (MeSH heading), and dysplasia (keyword). The results were limited to practice guidelines, systematic reviews, meta-analyses, multicentre studies, randomized controlled trials, and clinical trials. Articles were excluded from the final review if they: had a non-English abstract, were not available through the library system, or were published before the year 2000. The references and bibliographies of articles identified through these searches were scanned for additional sources. A search for practice guidelines published since January 2000 was conducted by accessing the websites and/or print publications of the following organizations: Cancer Care Ontario, British Columbia Cancer Agency, the National Comprehensive Cancer Network (NCCN), the National Institute for Health and Clinical Excellence (NICE), the European Society for Medical Oncology (ESMO), the Scottish Intercollegiate Guidelines Network, the American Gastroenterological Association, the American College of Gastroenterology, and the Society of Thoracic Surgeons.

For the March, 2014 revisions, an update on endoscopic mucosal resection (EMR) was conducted.

TARGET POPULATION

The recommendations in this guideline apply to patients with a history of gastroesophageal reflux disease and either suspected or confirmed Barrett’s esophagus.

RECOMMENDATIONS AND DISCUSSION

Diagnosis

Diagnostic endoscopy should be performed using a white-light, high-resolution endoscope. On the initial endoscopy, columnar esophageal mucosa should be noted as “endoscopically suspected esophageal metaplasia (ESEM)”. The patient should be treated with a daily proton pump inhibitor (PPI), and a repeat endoscopy should be performed within 6-12 months. At this point, the Prague C & M Criteria should be
used to assess the presence and extent of suspected Barrett's esophagus. Targeted biopsies of every suspicious lesion, followed by 4-quadrant biopsies every 1cm throughout the entire Barrett's esophagus segment are recommended. Biopsies should be submitted in separate jars corresponding to the level from which it was taken. However, if visible mucosal irregularities such as flat or raised nodules that are suspicious for dysplasia or early carcinoma are visualized within the zone of Barrett's during endoscopic surveillance, the preferred method of sampling is an EMR. This allows for a larger sample, and therefore more precise assessment of depth of tumour invasion into the mucosa and submucosa.

The grade of dysplasia will determine the most appropriate surveillance interval and management strategy for patients with Barrett's esophagus. Dysplasia is defined microscopically based on cytological and structural changes to the intestinal epithelium severe enough to suggest neoplastic transformation; the distinction between low- and high-grade is based on the severity of these changes. We recommend that all Barrett's esophagus biopsies revealing any grade of dysplasia (indefinite, low or high grade) be reviewed and confirmed by 2 pathologists, one of whom should be an expert in interpreting esophageal histopathology.

- For patients with no dysplasia and a Barrett's esophagus segment <3cm, endoscopic surveillance is recommended every 5 years; for patients with no dysplasia and a Barrett's esophagus segment >3cm, endoscopic surveillance is recommended every 3 years, with 4-quadrant biopsies every 2cm.
- Patients with biopsies that are indefinite for dysplasia should have a repeat endoscopy every 3 to 6 months, with 4-quadrant biopsies every 1cm.
- For patients with low-grade dysplasia, endoscopic surveillance is recommended every 6 to 12 months, with the goal of detecting potential progression to high-grade dysplasia or esophageal adenocarcinoma early.
- Patients with high-grade dysplasia, early esophageal cancer, or invasive cancer should be referred to a tertiary centre for further evaluation.

Please refer to the GI-009 Esophageal Cancer clinical practice guideline for detailed staging information.

Treatment

Given the complexities in diagnosis and treatment of patients with dysplastic Barrett's esophagus or early esophageal cancer, as well as the risks associated with both over- and under-treatment of Barrett's esophagus, we recommend that these patients are best managed in a tertiary centre, with input from experienced gastroenterologists, surgeons, pathologists, and oncologists. The goal of treatment for Barrett's esophagus is to control the symptoms of GERD, heal the mucosal inflammation, manage any dysplasia, and prevent progression or improve survival for patients who progress to adenocarcinoma. Upon diagnosis of Barrett's esophagus, we recommend that all patients should be started on daily therapy with a proton pump inhibitor (PPI).

In general, routine endoscopic or surgical treatment for patients with Barrett's esophagus in which there is no dysplasia, is indefinite for dysplasia or has low-grade dysplasia is not recommended. However, if these patients have one or more additional risk factors, including: i) age younger than 30 years at the time of Barrett's diagnosis, ii) a family history of Barrett's esophagus or esophageal cancer, and iii) a segment of circumferential Barrett's esophagus greater than 6 cm, endoscopic ablative therapy can be considered. If these additional risk factors are not present, patients should continue to be monitored with endoscopic surveillance at the appropriate intervals and the appropriate number of biopsies. Patients with high-grade
dysplasia or early esophageal cancer should be referred to a tertiary centre, and an endoscopic ultrasound and/or enhanced computed tomography (CT) scan of the chest should be considered in order to rule out lymphadenopathy as these patients are at risk of lymph node metastasis, although this risk is not well-defined.\textsuperscript{23} If visible lesions, nodules, or mucosal irregularities are seen during endoscopic surveillance, the patient should first undergo EMR instead of a standard endoscopic biopsy. This provides a larger tissue sample with better orientation, therefore allowing for more accurate diagnosis, staging, and improved treatment planning.\textsuperscript{1,18} We recommend these samples are pinned flat before fixation and histologic sectioning should be in a “bread loaf” manner to allow for assessment of depth of invasion (see Appendix A). These samples should be handled by a lab and pathologists with expertise in esophageal dysplasia. Samples should be mapped and tagged corresponding as precisely as possible to the location in the esophagus from which it was resected. For patients without evidence of invasive adenocarcinoma, it is recommended that EMR be followed by non-surgical ablative therapy to the remaining Barrett’s esophagus, in order to achieve complete eradication of intestinal metaplasia.\textsuperscript{1,16,24} For patients with any evidence of submucosal invasion (T1b or deeper) or lymph node metastasis, esophagectomy is the most appropriate therapy, and the patient should be referred for surgical evaluation.\textsuperscript{1,16} Esophagectomy is associated with significant rates of post-operative and long-term complications, with lower morbidity and mortality rates being associated with higher-volume centres and more experienced surgeons.\textsuperscript{24-26} It is therefore recommended that patients be referred to a thoracic/upper gastrointestinal (GI) surgeon specializing in the treatment of foregut cancers at a high-volume centre.\textsuperscript{1,14,16} Any patient with poor prognostic factors should be discussed at a multidisciplinary Tumour Board, which should include a thoracic/upper GI surgeon.

Following diagnostic EMR, non-surgical ablation options for the treatment of Barrett’s esophagus with high-grade dysplasia, or select patients with no or low-grade dysplasia and additional risk factors are recommended for patients without remnant visible lesions or mucosal irregularities and include:

1. **Endoscopic mucosal resection.** EMR involves the use of an endoscope to diagnostically and therapeutically resect mucosal lesions. During a therapeutic EMR, lesions may be lifted using a saline solution or suction and then directly excised using a cap and/or snare accessory. Lateral and deep margins can be assessed with proper specimen handling. In the context of Barrett’s esophagus and early esophageal carcinoma, an EMR is performed to both accurately diagnose the depth of a visible esophageal lesion and as a potential curative procedure for Tis (high-grade dysplasia) and T1a (tumour invades lamina propria or muscularis mucosa) disease.

   The evidence suggests that EMR can be performed with curative intent in intramucosal carcinoma (T1a) under acceptable clinicopathological criteria. In a prospective case series of 349 patients, Pech \textit{et al.} found that complete response was achieved in 96.6\% of endoscopically-treated patients; the 5-year survival rate was 84\%.\textsuperscript{27} A similar study of 100 patients at a single centre found that complete local remission was achieved in 99\% of patients treated with EMR after 1.9 months; the 5-year survival rate was 98\%.\textsuperscript{28} In a recent systematic review of the safety and effectiveness of endoscopic approaches, study authors found that complete response following EMR ranged from 67-100\% and recurrence ranged from 0-28\%.\textsuperscript{29} Although the ‘gold standard’ approach to the management of early esophageal cancer has been esophagectomy, studies comparing EMR to surgery found no difference in survival and greater complications with surgery.\textsuperscript{30,31} Furthermore, intramucosal tumours are associated with minimal nodal metastases risk,\textsuperscript{23} and therefore, may be treatable endoscopically. Specifically, EMR as curative therapy is indicated for T1a patients if all of the following criteria are met:
   - The patient has been assessed by a multidisciplinary Tumour Board
   - The diagnostic specimen has been properly handled by an expert pathologist
- The procedure will be performed by an endoscopist who is expert in EMR at a tertiary centre.
- The patient does not present with any high risk features, which include:
  - Tumour size > 2cm
  - Poor differentiation
  - Lymphovascular invasion

Patients who do not meet the above criteria may need surgical assessment. Any patient referred to surgery should undergo a full nutritional assessment.

2. **Radiofrequency ablation.** Radiofrequency ablation (RFA) involves the application of direct thermal energy to the lining of the esophagus using an endoscopic platform. The equipment includes balloon-based and pad-based probes fixed to the tip of an endoscope to provide circumferential and focal radiofrequency ablation.‡ There is strong evidence to support the use of RFA for the eradication of flat, residual Barrett’s esophagus (following EMR) in patients with high-grade dysplasia,13,32,33 as well as for patients with no or low-grade dysplasia who have additional risk factors.34,35 In a landmark randomized placebo-controlled trial examining 127 patients with Barrett’s esophagus, RFA therapy was associated with significantly higher rates of complete disease eradication compared to the placebo group for patients with both high-grade dysplasia (81.0% versus 19.0%, p<0.001) and low-grade dysplasia (90.5% versus 22.7%, p<0.001).13 In a 5-year follow-up to the prospective multi-centre AIM-II trial of patients with Barrett’s esophagus and no dysplasia, Fleischer et al. reported a complete response-intestinal metaplasia (CR-IM) in 92 percent of patients (N=46/50) treated with RFA.35 Eight percent of patients developed focal non-dysplastic Barrett’s esophagus at 5 years, and a single session of RFA converted all these to CR-IM. There were no buried glands, dysplasia, strictures, or serious adverse events reported at 5 years. In a recent study addressing the efficacy of a stepwise regimen of circumferential and focal RFA for the treatment of Barrett’s esophagus with either low-grade (N=39) or high-grade (N=24) dysplasia, Sharma and colleagues reported a CR-IM rate of 87 percent, and a complete response-dysplasia (CR-D) rate of 95 percent for the low-grade patients, and CR-IM and CR-D rates of 67 and 79 percent for high-grade patients, respectively.36 Similarly, in a multicentre randomized trial comparing stepwise radical endoscopic resection versus focal endoscopic resection followed by RFA for patients with Barrett’s esophagus and high-grade dysplasia or early esophageal cancer, van Vilsteren et al. reported comparably high rates of CR-IM (92% versus 96%) and CR-neoplasia (100% versus 96%) with both procedures.37 Radical endoscopic resection was associated with a higher number of complications and required more therapeutic sessions, leading the investigators to recommend a combined endoscopic approach of focal endoscopic resection followed by RFA. In a comparison of the neosquamous epithelium of patients with high-grade dysplasia or early esophageal cancer pre- and post-RFA, Pouw and colleagues reported that all patients had normal neosquamous epithelium following ablation, with no persistent genetic abnormalities or buried glands.33 Adverse effects associated with RFA include chest pain, esophageal hemorrhage, and upper gastrointestinal bleeding.13,33 As a result of these published findings, we recommend RFA as the standard ablative therapy for the treatment of patients with Barrett’s esophagus with high-grade dysplasia, as well as for select patients with no or low-grade dysplasia and additional risk factors.

3. **Photodynamic therapy.** Photodynamic therapy (PDT) involves the administration of a photosensitizing drug, porfimer sodium (Photofrin ®) that accumulates in the dysplastic tissue and causes tissue destruction when it is activated by an endoscopic light source.38 In a multi-centre, randomized trial comparing 208 patients treated with PDT with porfimer sodium plus a proton pump inhibitor (PPI) versus a PPI alone, Overholt et al. reported that PDT was significantly more effective
than the PPI in eliminating high-grade dysplasia (77% versus 39%, \(p<0.0001\)). In addition, patients in the PDT group had a statistically significant decrease in high-grade dysplasia and adenocarcinoma risk when compared with patients in the PPI group (15% versus 29%, \(p<0.004\)). In a small randomized trial involving 26 patients with Barrett’s esophagus and dysplasia who were treated with either PDT or APC, Ragunath et al. reported that while both therapies were equally effective in eradicating Barrett’s mucosa, PDT was more effective in eradicating dysplasia. PDT has also been used to treat patients with esophageal cancer and local failure after chemotherapy plus radiotherapy, as well as patients with early stage esophageal tumors who refused or were not candidates for esophagectomy. Porfimer sodium remains in the body for up to 2 months, therefore patients treated with PDT are extremely photosensitive, and must be cautioned to avoid any exposure to sunlight. The main adverse effect associated with PDT in patients with Barrett’s esophagus is the formation of strictures, with some series reporting rates as high as 30 percent. The use of biomarkers to predict a response to PDT may help to better identify ideal candidates for this therapy; one recent study reported that the loss of p16 was associated with a decreased response to PDT in patients with high-grade dysplasia or mucosal cancer. The cost-effectiveness of PDT has been assessed in several recent publications, including 2 health technology assessments (HTA) produced by Alberta Health. Both HTAs concluded that PDT offers relatively poor value for money in relation to other endoscopic procedures for Barrett’s esophagus and early esophageal cancer, but that all of the endoscopic therapies have similar incremental cost-effectiveness ratios (ICERs) compared to surveillance alone. The HTAs also highlight the additional human resources required for patients treated with PDT, including patient education with a dietician, follow-up care with a nurse familiar with the PDT procedure, and follow-up appointments with the physician 3 and 6 months after the procedure. In Alberta, PDT is only available at the Royal Alexandra Hospital in Edmonton and the Foothills Hospital in Calgary. At present, we only recommend PDT for patients who:

- are likely to be highly compliant with follow-up procedures (i.e., staying out of the sun for up to 2 months)
- are not surgical candidates
- are not amenable to endoscopic mucosal resection
- are not eligible for radiofrequency ablation (i.e., due to strictures), or
- had treatment failure with radiofrequency ablation or chemoradiation

A special Tumour Board meeting must be called to review each case of potential PDT eligibility; a final approval checklist is included in Appendix B.

4. Argon plasma coagulation. Argon plasma coagulation (APC) therapy involves the use of a high-frequency monopolar current which is conducted to the tissue by ionized argon gas. In a 5-year follow-up study of 40 patients with Barrett’s esophagus (20 treated with APC, 20 with surveillance), Bright and colleagues reported that 14 of 20 APC patients continued to have at least 95% of their previous Barrett’s esophagus replaced by neosquamous mucosa, with 8 of these patients having complete microscopic regression of the Barrett’s esophagus. In comparison, 5 of the 20 surveillance patients had more than 95% regression of their Barrett esophagus, and 4 of these had complete microscopic regression. The major complications associated with APC are pain and dysphagia; strictures have been reported in 5 to 10 percent of patients. APC is easy to use for small lesions (<4cm), and has a reasonable safety profile; the major concern with this therapy is the heightened risk of buried glands, which may be more common in patients treated with APC versus other ablative techniques.

5. Multipolar electrocoagulation. Multipolar electrocoagulation (MPEC) involves the delivery of thermal energy to the abnormal Barrett’s mucosa through a probe passed through the endoscope that delivers
the current between two or more electrodes. In a study involving 139 patients with Barrett’s esophagus and no dysplasia who were followed over 10 years, Allison and colleagues reported a recurrence of Barrett’s esophagus in less than 5 percent of patients, and no adenocarcinoma or high-grade dysplasia of the esophagus developed in any of the patients. The major complications associated with MPEC include painful swallowing, chest pain, fever, gastrointestinal bleeding, and stricture. One of the disadvantages of MPEC is that multiple procedures are required to achieve ablation, and only small amounts of esophageal mucosa can be treated at one time (<4cm). MPEC has been compared directly with APC in 2 randomized trials, both of which reported equal efficacy for both therapies with respect to complete eradication of Barrett’s esophagus.

The use of other ablative therapies such as cryoablation are only recommended in the context of research and clinical trials.

Follow-up

Ongoing ablative therapy should be continued with a goal of eliminating all visible and histologic Barrett’s esophagus (CR-IM), allowing for neo-squamous epithelial regrowth. If not possible, then eradication of any Barrett’s with dysplasia (CR-D) is a secondary aim. While the evidence for surveillance is inconclusive at this time, expert opinion for surveillance is as follows:

1. For patients with nondysplastic, indefinite or low-grade dysplasia Barrett’s esophagus treated with ablation, follow-up should include a 4-quadrant biopsy every 1cm of the entire previous Barrett’s esophagus segment within 12 months of CR-IM or CR-D. Surveillance endoscopy should take place every 6 months for the first year, then annually, with continuance based on clinical judgment and the individualized plan of care for each patient.

2. For patients with high-grade dysplasia treated with ablation, follow-up should include a 4-quadrant biopsy every 1cm of the entire previous Barrett’s esophagus within 12 months of CR-D. Surveillance endoscopy should take place every 3 months for 1 year, then every 6 months for the second year, then annually, with continuance based on clinical judgment and the individualized plan of care for each patient.

3. For patients with early esophageal cancer treated with ablation, follow-up should include a 4-quadrant biopsy every 1cm of the entire previous Barrett’s esophagus within 12 months of CR-D. Surveillance endoscopy should take place every 3 months for 1 year, then every 6 months for the second year, then annually, with continuance based on clinical judgment and the individualized plan of care for each patient. A CT-PET scan is also recommended for patients with early esophageal cancer 12 months following ablation.
Treatment Algorithms

Figure 1. Initial Management

Referral for Barrett’s Esophagus (BE) Screening

Chronic GERD ≥ 10 years plus 2 or more additional risk factors:
- > 50 years of age
- Male sex
- White race
- Hiatal hernia
- BMI ≥ 30
- Intra-abdominal distribution of fat: waist circumference >35 inches (women) or >40 inches (men)
- Family history of BE or esophageal cancer

Endoscopically Suspected Esophageal Metaplasia (ESEM)?

• Refer back to Family Physician for symptom management

Endoscopic Mucosal Resection (EMR) if:
1. Visible mucosal irregularities (flat or raised nodules) suspicious for dysplasia or early carcinoma

EMR preferred over standard endoscopic biopsy

Diagnostic Endoscopy

Refer back to Family Physician for symptom management

Yes

Endoscopically Suspected Esophageal Metaplasia (ESEM)?

Biopsy

- 4-quadrant biopsy specimens obtained every 1cm
- Biopsies submitted separately (per level) to pathology
- All biopsies revealing dysplasia should be reviewed and confirmed by 2 pathologists, one of whom is an expert in esophageal histopathology

Treatment with once daily PPI

Repeat Endoscopy

- Within 6-12 months
- Preferred method: white light, high definition endoscopy

NO DYSPLASIA

INDEFINITE FOR DYSPLASIA

LOW-GRADE DYSPLASIA

HIGH-GRADE DYSPLASIA

EARLY ESOPHAGEAL CARCINOMA

INVASIVE CARCINOMA

See algorithm: No Dysplasia

See algorithm: Low-Grade Dysplasia

See algorithm: High-Grade Dysplasia

See algorithm: Carcinoma

“Using proper “Bread Loaf” technique with samples pinned & mapped to esophageal location

“PPI dose increased to twice daily, repeat endoscopy within 3-6 months

www.albertahealthservices.ca
Figure 2. No Dysplasia

Patients with poor prognostic factors should be discussed at a multidisciplinary Tumour Board.
Figure 3. Low-Grade Dysplasia

**Low Grade Dysplasia**
- Surveillance Endoscopy
  - Every 6-12 months
  - Preferred method: white light, high definition endoscopy
  - 4-quadrant biopsies every 1cm

**One or more risk factors present?**
- Age ≤30 years at diagnosis
- Circumferential BE segment ≥6cm
- Family history of BE or esophageal cancer

**Follow Algorithm for No Dysplasia**

- Single focus
- Multifocal or multi-level

**Visible mucosal irregularities (flat or raised nodules) suspicious for dysplasia or early carcinoma?**

**Endoscopic Mucosal Resection (EMR)**
- Follow-up and Surveillance
  - **Endoscopy:** every 6 months x 2, then annually
  - **Biopsy:** by 12 months after complete response, a full 4-quadrant biopsy every 1 cm of previous segment of BE

**Follow-up and Surveillance**

- **Radiofrequency Ablation (RFA)**
  - Repeat ablation every 2-3 months until complete response
  - If patient is not a candidate for RFA, or RFA is not successful, an alternate ablative therapy could be considered:
    - Argon Plasma Coagulation
    - Multipolar Electrocoagulation
    - Photodynamic Therapy (requires local Tumour Board approval)

**Patients with poor prognostic factors should be discussed at a multidisciplinary Tumour Board**
Figure 4. High-Grade Dysplasia

Patients with poor prognostic factors should be discussed at a multidisciplinary Tumour Board

HIGH GRADE DYSPLASIA

Refer to Tertiary Centre

Endoscopic Mucosal Resection (EMR)
- If visible mucosal irregularities (flat or raised nodules) suspicious for dysplasia or early carcinoma are present

Radiofrequency Ablation (RFA)
- Repeat ablation every 2-3 months until complete response

If patient is not a candidate for RFA, or RFA is not successful, an alternate ablative therapy should be considered:
- Argon Plasma Coagulation
- Multipolar Electrocoagulation
- Photodynamic Therapy (requires local Tumour Board approval)

Follow-up and Surveillance
Endoscopy: every 3 months x 1 year, then every 6 months x 2, annually
Biopsy: by 12 months after complete response, a full 4-quadrant biopsy every 1cm of previous segment of BE

*All patients should undergo a full nutritional assessment prior to referral to surgery

Consider EUS and/or chest CT for early workup

Refer to thoracic/foregut surgeon for esophagectomy if ablative therapy is contraindicated or continuously unsuccessful*
Figure 5. Early Esophageal Cancer or Invasive Carcinoma

Patients with poor prognostic factors should be discussed at a multidisciplinary Tumour Board

**CONFIRMED OR SUSPECTED EARLY ESOPHAGEAL CARCINOMA**

- Refer to Tertiary Centre

**Work-up:**
- Endoscopic ultrasound
- CT scan
- Thoracic/foregut surgery consult

**Staging**

- Tis or T1a
  - Therapeutic EMR
    - **Radiofrequency Ablation (RFA)**
      - After all visible mucosal irregularities resected
      - Repeat ablation every 2-3 months until complete response
    - **RFA successful?**
      - Yes
        - Follow-up and Surveillance
          - **Endoscopy:** every 3 months x 1 year, then every 6 months x 2, then annually
          - **Biopsy:** by 12 months after complete response, a full 4-quadrant biopsy every 1cm of previous segment of BE
          - Consider CT scan at 1 year
      - No
        - **RFA contra-indicated?**
          - Option 1: Refer to thoracic/foregut surgeon for esophagectomy*
          - Option 2: Photodynamic Therapy (PDT)
            - GI Tumour Board Approval Required
            - **PDT successful?**
              - Yes
              - No

**INVASIVE CARCINOMA (T2+, Any N)**

- Referral to Surgery and/or Oncology discussion of treatment options*

  - See Esophageal Cancer Clinical Practice Guideline GI-009

  - T1b or higher
    - Metastatic Disease
    - Diagnostic Endoscopic Mucosal Resection (EMR)

  - Tis or T1a
    - Therapeutic EMR
      - **Radiofrequency Ablation (RFA)**
        - After all visible mucosal irregularities resected
        - Repeat ablation every 2-3 months until complete response
      - **RFA successful?**
        - Yes
        - **PDT successful?**
          - No
          - **RFA contra-indicated?**
            - Option 1: Refer to thoracic/foregut surgeon for esophagectomy*
            - Option 2: Photodynamic Therapy (PDT)
              - GI Tumour Board Approval Required
              - **PDT successful?**
                - Yes
                - No

**Follow-up and Surveillance**

*All patients should undergo a full nutritional assessment prior to referral to surgery

---

*All patients should undergo a full nutritional assessment prior to referral to surgery
GLOSSARY OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGA</td>
<td>American Gastroenterological Association</td>
</tr>
<tr>
<td>APC</td>
<td>argon plasma coagulation</td>
</tr>
<tr>
<td>BE</td>
<td>Barrett's esophagus</td>
</tr>
<tr>
<td>CI</td>
<td>95% confidence interval</td>
</tr>
<tr>
<td>CR-D</td>
<td>complete response – dysplasia</td>
</tr>
<tr>
<td>CR-IM</td>
<td>complete response – intestinal metaplasia</td>
</tr>
<tr>
<td>CT</td>
<td>computed tomography scan</td>
</tr>
<tr>
<td>EMR</td>
<td>endoscopic mucosal resection</td>
</tr>
<tr>
<td>ESEM</td>
<td>endoscopically suspected esophageal metaplasia</td>
</tr>
<tr>
<td>GERD</td>
<td>gastroesophageal reflux disease</td>
</tr>
<tr>
<td>GI</td>
<td>gastrointestinal</td>
</tr>
<tr>
<td>HTA</td>
<td>health technology assessment</td>
</tr>
<tr>
<td>ICER</td>
<td>incremental cost effective ratio</td>
</tr>
<tr>
<td>MPEC</td>
<td>multipolar electrocoagulation</td>
</tr>
<tr>
<td>PDT</td>
<td>photodynamic therapy</td>
</tr>
<tr>
<td>PET</td>
<td>positron emission tomography scan</td>
</tr>
<tr>
<td>PPI</td>
<td>proton pump inhibitor</td>
</tr>
<tr>
<td>RFA</td>
<td>radiofrequency ablation</td>
</tr>
<tr>
<td>RR</td>
<td>risk ratio</td>
</tr>
</tbody>
</table>

DISSEMINATION

- Present the guideline at the local and provincial tumour team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services website.
- Send an electronic notification of the new guideline to all members of CancerControl Alberta.

MAINTENANCE

A formal review of the guideline will be conducted at the Annual Provincial Meeting in 2015. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

CONFLICT OF INTEREST

Participation of members of the working group in the development of this guideline has been voluntary and the authors have not been remunerated for their contributions. There was no direct industry involvement in the development or dissemination of this guideline. CancerControl Alberta recognizes that although industry support of research, education and other areas is necessary in order to advance patient care, such support may lead to potential conflicts of interest. Some members of the Alberta Provincial Tumour Teams are involved in research funded by industry or have other such potential conflicts of interest. However the developers of this guideline are satisfied it was developed in an unbiased manner.
REFERENCES


APPENDIX A – EMR Specimen Handling ("Bread Loaf" Technique)

Images courtesy of Dr. R. McLean
APPENDIX B – Final Approval Checklist for Photodynamic Therapy

1. Terms of Reference
   a. Board comprised of 3 members:
      - Provincial GI Tumour Team Leader, or delegate
      - AHS Medical Director of Pharmacy, or delegate
      - Senior gastroenterologist
   b. Board to meet on a case-by-case basis.
   c. Case material to be provided 1 week in advance of meeting by referring physician.
   d. PDT checklist used by the Board to determine a patient’s eligibility for photodynamic therapy.

2. Case Material
   a. Letter from referring physician requesting PDT.
   b. Report detailing previous therapies and outcomes.
   c. Copy of current blood work (HCG level) if patient female.
   d. Signed patient letter consenting to procedure and acknowledging risks and compliance necessary.

3. Criteria Checklist

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Met (please check)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Patient has confirmed dysplasia or intramucosal carcinoma</td>
<td></td>
</tr>
<tr>
<td>2. Patient does NOT have porphyria</td>
<td></td>
</tr>
<tr>
<td>3. Patient NOT pregnant – confirmed with bloodwork</td>
<td></td>
</tr>
<tr>
<td>4. Patient able to comply with contraceptive use during therapy</td>
<td></td>
</tr>
<tr>
<td>5. Patient aware and agrees to compliance regarding 6 weeks of photosensitivity</td>
<td></td>
</tr>
<tr>
<td>6. Tertiary centre access arranged (accommodations for out-of-town patients)</td>
<td></td>
</tr>
<tr>
<td>7. Patient has failed other therapies – list of therapies provided</td>
<td></td>
</tr>
<tr>
<td>8. Patient is a poor operative candidate – letter from referring physician</td>
<td></td>
</tr>
<tr>
<td>9. Patient does NOT have:</td>
<td></td>
</tr>
<tr>
<td>- a tracheoesophageal or bronchoesophageal fistula</td>
<td></td>
</tr>
<tr>
<td>- esophageal or gastric varices</td>
<td></td>
</tr>
<tr>
<td>- a tumour eroding into a major blood vessel</td>
<td></td>
</tr>
<tr>
<td>- no esophageal ulcers &gt;1cm in diameter</td>
<td></td>
</tr>
<tr>
<td>10. Drug coverage for Photofrin is available or the patient will pay</td>
<td></td>
</tr>
</tbody>
</table>

4. Final Approval
   a. All criteria must be met and checked off.
   b. No other reasonable options are considered appropriate
   c. Submission of checklist with Board Member signatures must be submitted to: (AHS Provincial Medical Director of Pharmacy)
   d. Patient to be contacted regarding final decision of Board by referring physician.

5. Signatures

______________________________  ________________________
Provincial GI Tumour Team Leader  Date

______________________________  ________________________
AHS Provincial Medical Director of Pharmacy  Date