SAGES POSITION STATEMENT ON THE MANAGEMENT OF BARRETT'S OESOPHAGUS

This guideline is intended as an educational tool to assist endoscopists treating patients with Barrett's oesophagus (BO). This is not intended as legal standard of care, nor is it meant to encourage, advocate or discourage any particular treatment. Final clinical decision on treatment of BO is a complex issue and remains the prerogative of the treating physician after full assessment of the patient's condition and prognosis with agreement of the patient on the chosen treatment modality.

DEFINITION

BO is the result of replacement of the stratified squamous epithelium that normally lines the oesophagus with columnar epithelium similar to that of the rest of the intestine. If this altered oesophageal segment, which should be longer than 1 cm, contains goblet cells, intestinal metaplasia (IM) is present and this is a prerequisite for the diagnosis of BO. IM increases the risk for the development of dysplasia and subsequent oesophageal adenocarcinoma (OAC)[1].

Implications of BO diagnosis:

BO is associated with increased cellular proliferation that may lead to dysplasia. Dysplasia increases the risk of development of oesophageal adenocarcinoma. The risk of cancer development in BO has been overestimated in previous studies, but current evidence suggests a modest cancer risk of 0.5% per year[2]. Thus, 1 in 200 patients with BO will develop oesophageal cancer each year. Some reports suggest a higher risk for long segment BO and for men[3].

Risk factors for BO include:

- Age 50 and older
- Male sex
- White race
- Smoker
- Overweight
- Family history of oesophageal adenocarcinoma

Diagnosis of BO:

The diagnosis of BO is still made with white light endoscopy, of which the sensitivity and specificity is still 80-90%. BO has a characteristic appearance on white light endoscopy with a typical salmon or pink appearance in contrast to the light grey of normal squamous epithelium. However, the diagnosis of BO is only confirmed on histology[4].

In addition to white light endoscopy, certain advanced, enhancing techniques are used to better identify dysplastic lesions and early oesophageal adenocarcinoma. These include chromo-endoscopy, electrical enhanced imaging, magnification and confocal endoscopy. These modalities are however not widely available in South Africa and are not discussed here.

Thus, for a diagnosis of BO, a patient will undergo white light endoscopy and multiple biopsies taken from the affected distal oesophagus. In addition to the obvious area of BO, suspicious areas of abnormality including nodules, ulcers or areas of mucosal irregularity should be targeted for biopsy. The diagnosis of BO and/or dysplasia cannot be made in the presence of significant reflux oesophagitis. In this instance, the patient should first be treated and rebiopsied at least 3 months later.

Histological grading of BO:

BO is graded:

- Non-dysplastic (NDBO)
- Intermediate dysplasia (IGD)
- Low-grade dysplasia (LGD)
- High grade dysplasia (HGD)
- Intramucosal adenocarcinoma
- Invasive adenocarcinoma

Screening for BO:

Traditional gastroscopy and biopsy remain the gold standard for the diagnosis of BO. Alternative methods have been investigated, but are not freely available in South Africa[5]. Two are discussed below:

1. Oesophageal capsule endoscopy: The sensitivity and specificity of this procedure is 87%. The only limitation is the inability to take biopsy specimens during the procedure. Currently, this procedure is not recommended for screening of BO in South Africa as it will increase cost and patient procedure exposure.
2. Transnasal endoscopy without sedation: This is a useful procedure and limit time off work. Its limitation is that the size of biopsy is small and may influence meaningful interpretation and treatment recommendation. Granted its limitations it can be used in South Africa in certain settings. However, it is not freely available everywhere in the country.

The routine screening of the general population for BO is not recommended. Screening should be targeted for high risk individuals (see above). Patients with three (3) or more risk factors should be targeted as the yield with fewer risk factors is low. In patients with family history oesophageal adenocarcinoma and/or BO,

screening should be escalated even in the presence of low risk factors[6]. Repeat gastroscopy for screening of BO in patients with a previous normal gastroscopy is also not recommended as the yield is low[7].

Surveillance in BO:

The primary purpose of surveillance in BO is to identify dysplasia and OAC early enough to offer effective treatment. The natural history of BO is believed to be:

NDBO → LGD → HGD → OAC

However, data suggest that there is a lack of linear progression through the steps outlined above. Thus, OAC can develop in a patient with previous NDBO. Similarly, LGD can at rebiopsy be classified as NDBO, in keeping with regression of the disease[8]. On the basis of available data, international societies recommend surveillance strategies for patients with BO and dysplasia[9, 10]. We agree with these recommendations and below discuss our recommended surveillance strategies for individual patient groups:

1. NDBO:
   Biopsy protocols for NDBO recommend 4-quadrant biopsies every 2cm along the length of the Barrett's mucosa with large capacity/jumbo biopsy forceps. The surveillance interval should be between 3 and 5 years.
2. Indeterminate for dysplasia:
   This condition is not specifically discussed in the management strategy of Barrett's oesophagus. It is a histological diagnosis when some but not all features of LGD is present. This is usually a result of significant inflammation and ulceration in the oesophagus at the time of biopsy. After 6 months of aggressive PPI therapy, repeat gastroscopy and biopsy is indicated for reclassification, either to NDBO or Barrett's oesophagus with LGD.
3. LGD:
   Although the natural history of LGD is unclear, current evidence suggest slightly higher progression rate of LGD to OAC, compared to NDBO. Current rate of progression is estimated at 0.7% per year. The diagnosis of LGD should be made by 2 independent pathologists of which 1 should be a GI pathologist. It is preferable that the confirming pathologist not be based at the same institution. Biopsy protocols presently recommend 4-quadrant biopsies every 1-2cm along the length of the Barrett's mucosa with large capacity/jumbo biopsy forceps. The surveillance interval should be every 6 months to 1 year.
4. HGD:
   Diagnosis of early stage OAC is the main reason for surveillance in HGD. Confirmation of HGD must be made by a second expert GI pathologist, not based at the same institution. 4-quadrant biopsies every 1cm along the length of the Barrett's mucosa with large capacity/jumbo biopsy forceps is currently recommended. As safe and effective endoscopic therapies are now available for the treatment of HGD, continued routine surveillance of HGD should only

be offered to patients unwilling or unfit to undergo these therapies. Surveillance intervals in HGD should be every 3 months.

Endoscopic therapy:

The advent of endoscopic therapy for BE has changed the management of this condition. Endoscopic therapy is generally regarded as safe and effective[11]. However, it has not been shown to reduce surveillance recommendations in BO. Two broad categories of endoscopic therapies are currently in use:

- Ablation
- Mucosal resection

The purpose of endoscopic therapies is the removal of the dysplastic mucosa followed by re-epithelialization of the distal oesophagus with squamous epithelium. Endoscopic therapies are associated with less procedural complications, compared to oesophagectomy.

Endoscopic ablation:

1. Radiofrequency ablation (RFA):
   It is the only modality currently available in South Africa. It involves the direct application of radiofrequency energy to the distal oesophagus. Rare short term complications of this procedure include:
   - Chest pain: settles with simple analgesics over 1 (one) week period.
   - Gastrointestinal bleed: can be managed endoscopically.
   - Oesophageal stricture formation is a medium term complication occurring at a rate of 6%. This can be managed effectively with oesophageal balloon dilation[12].
2. Argon Plasma Coagulation (APC):
   APC is more readily available in South Africa compared to RFA. It is inferior to RFA. APC is a thermal cautery device that involves the transmission of high frequency current at constant flow of ionized argon gas. Tissue destruction with APC is superficial. Hence, after APC, persistent buried glands are present in as high as 44% of patients. There is a high recurrence rate (66%) of Barrett's mucosa in surveillance studies[13]. Furthermore, it offers no protection against development of OAC[14]. Complication rates are low and include: chest pain, fever, acute bleeding, perforation and death. Stricture formation is low at 4.3%. APC should be reserved for NDBO and LGD in South Africa with close follow-up where RFA is not available.
3. Photodynamic therapy (PDT):
   This therapy is not currently available in South Africa. It is inferior to RFA. PDT uses 5-amino-levulinic acid or porfimer sodium as photo-sensitization agent[15]. Disadvantages of this technique include:
   - Inability to eradicate NDBO
   - Skin photosensitivity for up to 1 month, and
   - Stricture formation up to 30%

4. Cryotherapy:
   This treatment modality is not presently available in South Africa. It causes cellular destruction by using freeze-thaw cycles. Using a spray catheter during gastroscopy, either liquid nitrogen or carbon dioxide is sprayed onto the Barrett's mucosa. Major side-effects are rare, but oesophageal perforation has been reported[16].

Mucosal resection:

Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) are techniques used to remove superficial (EMR) and large, deeper strips (ESD) of oesophageal mucosa. While EMR is performed at a few specialised centres in South Africa, ESD is not currently practised. EMR is indicated for shorter segment BO, nodular BO and early stage (T1a) OAC. Complications of EMR include:

- Bleeding,
- perforation and
- stricture formation.

These complications have steadily been decreasing and a recent single centre study noted complications rates of 1-1.5%[17]. They can all be managed endoscopically. Often, EMR is followed by RFA, to ensure complete eradication of the dysplastic Barrett's segment. The combined procedure is not associated with more complications compared to the single intervention of RFA alone[18]. As no long term data are available for the maintenance of neo-squamous epithelium following EMR, annual surveillance gastroscopy and biopsy is indicated indefinitely.

<u>RFA as endoscopic therapy:</u>

1. NDBE:
   The idea of RFA in the very early stages of BO seems attractive. This will avoid progression of disease, obviate need for surveillance and eliminate development of OAC. However, only one study by Fleischer *et al* of 50 patients in 2010 showed complete reversal of IM in 92% of patients in 5 years' follow-up after a single treatment with RFA. No patient progressed beyond NDBO[19]. A number of meta-analysis reviewed this topic and found RFA in NDBO to be a safe and cost-effective form of treatment. However, the long term outcome and reconversion rates are not clear. Therefore, the treatment of NDBE with RFA should be individualized and reserved for the patient with family history of oesophageal cancer[20]. The routine treatment of NDBE with RFA cannot be recommended at this time until more evidence become available.

2. LGD:

The treatment of LGD with RFA is now routinely recommended by most international health authorities and societies. However, certain provisos should remain in place:

- Diagnosis confirmed by a second expert GI pathologist.
- Prior to treatment, the diagnosis of LGD should be confirmed on a second biopsy 6 months after the first.

Data are fast accumulating for the effective treatment of LGD with RFA. A retrospective study by Small *et al* published in 2015 showed decreased development of HGD and OAC in 45 patients treated with RFA over 20 years. 125 patients in the surveillance group developed HGD or OAC at an annual rate of 6.6% over the same period[21].

Another study by Phoa *et al* published 2014 showed reduced development of HGD or OAC to 1% in 68 patients with LGD treated with RFA over a 3-year period. However, 25% of patients in the surveillance arm developed HGD or OAC[22].

From the above, SAGES recommends RFA therapy for LGD if the above criteria have been fulfilled.

3. HGD:
   Routine surveillance for HGD in 2016 is only recommended in the conditions mentioned above. All patients with confirmed HGD should be scheduled for elective gastroscopy and RFA[23, 24].

Special group surveillance:

Surveillance is not recommended for patients with IM at the gastric cardia or with an irregular z-line regardless of the presence of IM.

In patients with short segment BO (<3cm), regardless of the presence of IM, a repeat gastroscopy and biopsy is recommended. In the absence of IM, it is recommended that the patient is discharged from active surveillance as the risk (and cost) of surveillance outweighs the benefit.

Patients with short segment BO and IM should be surveyed every 3-5 years.

<u>In summary</u>; in light of the available data, SAGES recommends the following regarding treatment and surveillance in patients with BO:

- Patients with NDBO should have surveillance gastroscopy and biopsy every 3-5 years. Treatment with RFA is not routinely recommended, but is certain exceptional cases may be considered.
- In patients with LGD, if confirmed on repeat gastroscopy and histology, at least 6 months apart, treatment with RFA is recommended as first line. Following RFA, patients should undergo surveillance gastroscopy and biopsy every 6 months for 1 year, followed by annual gastroscopy and biopsy.

- In patients with HGD, RFA is now considered standard of care and should be offered to all patients. Post-treatment surveillance is similar to that in LGD.
- In patients with nodular BO, EMR, where available, is recommended. This may be followed by RFA depending on expertise. Following these procedures, annual surveillance gastroscopy and biopsy is suggested.

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