Controversies in Barrett's Oesophagus

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Abstract

Barrett's oesophagus (BO) is common in our clinical practice, and it is associated with oesophageal adenocarcinoma. The goal of this article is to review available data regarding BO with a focus on prevalence, racial difference, screening and surveillance of BO, management of high-grade dysplasia and metaplasia at the gastro-oesophageal junction (GOJ). In this regard, a systematic search of the English language literature of BO was performed. Recent studies suggest that the prevalence of BO and racial differences are still controversial. Many societies published guidelines for screening and surveillance of BO, but debate continues regarding the benefit of endoscopic screening and surveillance, and new screening and surveillance tools have been explored. The treatment choice for high grade dysplasia (HGD) should be made based on consideration of patient medical condition and preference, local expertise and the extent of BO. Data regarding intestinal metaplasia of GOJ is very limited and controversial. Debate is continuing on many issues of BO including prevalence, racial difference, diagnosis, treatment, screening and surveillance. Patient's choice may play a critical role in cancer prevention and treatment.

Keywords

Barrett's oesophagus, prevalence, high grade dysplasia, intestinal metaplasia at the gastro-oesophageal junction, racial difference, screening and surveillance

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Barrett's oesophagus (BO) is the replacement of the normal squamous epithelium of the oesophagus with intestinal type epithelium. The diagnosis of BO requires not only the endoscopic appearance of salmon-coloured mucosa above the Z line of the gastro-oesophageal junction (GOJ), but also the pathological confirmation of the presence of intestinal metaplasia.[1]

BO is clinically significant because of its association with oesophageal adenocarcinoma (OAC).[2,3] The incidence of OAC is increasing in the US and the developed world in the past two decades.[4,5] The mortality rate of OAC is very high with a five-year survival rate of less than 20 % for patients with advanced disease.[6] The high mortality rate, combined with late stage diagnosis in a high proportion of patients led to screening for early stage cancer. Although relatively clear guidelines are available for clinicians for diagnosis and treatment of BO, many aspects regarding BO are still controversial, such as prevalence, racial difference, screening and surveillance guidelines, management of high grade dysplasia (HGD) and intestinal metaplasia at GOJ.

Prevalence of Barrett's Oesophagus

The prevalence of BO has been variously reported to be from 1–25 %. Some prospective studies of patients with frequent gastro-oesophageal reflux disease (GORD) symptoms indicated a prevalence of 11–13 %.[7,8] More recent studies reported a lower prevalence rate of about 3–8 % of patients with reflux symptoms having BO.[9–11] The prevalence of BO for patients without GORD symptoms undergoing endoscopy was reported to be about 1–3 %.[11–13] Rex et al. screened for BO among patients undergoing colonoscopy, and reported that the prevalence of BO was 8.3 and 5.6 % for patients with and without GORD symptoms, respectively.[14] In a Veterans' Affairs study with patients undergoing sigmoidoscopy for colon rectal cancer screening, BO was detected in 25 % of asymptomatic male veterans older than 50 years of age.[15] Several factors could have contributed to this high prevalence, including male predominance, older age and a high percentage of Caucasians.

Endoscopic Evaluation has Limitations for the Diagnosis of Barrett's Oesophagus

A poor correlation of 20–50 % was reported between the endoscopic findings and the presence of intestinal metaplasia on biopsy.[17–19] Biopsy sampling error, small size of biopsy sample, endoscopic observational error and errors in histological interpretation may all play a role in this finding, especially in the presence of esophagitis and inflammation. Many new endoscopic techniques including magnification endoscopy, chromoendoscopy, optical coherence tomography, narrow band imaging and autofluorescence endoscopy have the potential to improve detection of BO, but none is used routinely in clinical practice. Alcian blue staining might be able to improve on routine staining with haematoxylin and eosin in the diagnosis of BO.[20]

There is no universal agreement on the inclusion of intestinal metaplasia as diagnosis criteria for BO. Many US societies require its presence, but the British Society of Gastroenterology does not.[21,22] It is well known that a small portion of patients with endoscopically long segment of BO do not have goblet cells in biopsies regardless of the number of the biopsies and the sites of the biopsies.[23] Some patients show waxing and waning of findings of goblet cells in the follow-up

Table 1: Guidelines for Screening and Surveillance of Barrett's Oesophagus from US Societies

	American College of Gastroenterology[21]	American Society of Gastrointestinal Endoscopy[27]	American Gastroenterological Association[1]
Screening	Recommendations should be individualised to the patients	Consider for patients with chronic GORD	Might be useful for patients aged over 50 and GORD
Surveillance, no dysplasia	Two OGDs with biopsy within 1 year, then every 3 years	Two OGDs with biopsy within 1 year, then every 5 years	Two OGDs with biopsy within 1 year, then every 3 years
Surveillance, low grade dysplasia	Repeat OGD within 6 months, then yearly until no dysplasia is found on two consecutive annual endoscopies	Repeat OGD within 6 months, then annually if dysplasia persist	Repeat OGD within 1 year if dysplasia is confirmed by two pathologists
Surveillance, high grade dysplasia	Repeat OGD within 3 months, continued surveillance every 3 months or intervention depending on the results and patient characteristics; EMR should be performed for irregular mucosa	Diagnosis should be confirmed by a pathologist; surgical candidate can choose to have surgery or endoscopic ablation; follow up patients who choose to have surveillance every 3 months for 1 year with biopsies every 1 cm; surveillance interval can be prolonged if no cancer detection in 1 year	Diagnosis should be confirmed by two pathologists; patients should be treated with either oesophagectomy or endoscopic ablation; surveillance every 3 months with a minimum of eight biopsies every 2 cm

EMR = endoscopic mucosal resection; GORD = gastro-oesophageal reflux disease; OGD = oesophagogastroduodenoscopy.

biopsies from the endoscopically suspected BO, some even convert to the non-goblet cell phenotype.[24] These patients without goblet cells in the biopsies will not be considered as BO according to current US society standard, but it could be a false negative BO, and possibly with increase risk of cancer.

Racial Differences

The racial differences in the prevalence of BO are controversial. One recent retrospective study of 2,100 patients undergoing oesophagogastroduodenoscopy (OGD) for any indication found that the prevalence of BO was higher in whites than Hispanics (p=0.0002) or blacks (0.004).[25] The other recent retrospective study of 4,457 patients undergoing OGD for any reason showed a trend for higher prevalence among Caucasians than African-Americans and a similar prevalence among Hispanics, but no significant differences were found among different racial groups (p=0.29).[11] An earlier study reported that the prevalence of BO was similar between Caucasians and Hispanics (p=0.304).[26] The available racial difference data of BO are conflicting. Geographical variation, the diversities among Hispanics, environmental factors and bodyweight could all contribute to the puzzle.

Screening and Surveillance

Debate continues about the screening and surveillance of BO. The rapid increase in incidence of oesophageal cancer, and the increased risk of cancers for patients with BO led to the effort of screening and surveillance of BO. Several professional organisations released guidelines supporting screening and surveillance (see *Table 1*). They appear to be simple guidelines for screening and surveillance of BO, but many have questioned the screening and surveillance programme with the following arguments:

- the large number of patients with chronic GORD symptoms (the cost of endoscoping all these patients would be enormous);
- the small cancer risk of BO (approximately 0.5 % per year);
- more than 40 % of patients with BO do not report GORD symptoms[11,16] and will not seek any medical attention;
- the cost-effectiveness of endoscopic screening and surveillance is unknown;[27] and
- there is no proof that endoscopic surveillance improves patient survival.[28,29]

Capsule endoscopy has been assessed as a possible method for screening for the presence of BO. A recent meta-analysis of nine studies with a total of 618 patients, reported the pooled sensitivity and specificity of capsule endoscopy for the diagnosis of BO using conventional OGD as the reference standard were 78 and 90 %, respectively; using histologically confirmed BO as the reference standard, the pooled sensitivity and specificity were 78 and 73 %.[30] But conventional OGD is still the preferred method for screening of BO compared to capsule endoscopy because of sensitivity, specificity and cost-effectiveness.[31]

The clinic-based non-sedated transnasal endoscopy could provide a low-cost screening method for BO. In a 121 patients' cross-over study comparing it with conventional OGD, 70 % of the patients prefer the small calibre non-sedated endoscopy. The prevalence of BO was similar between the two groups, and the agreement between the two group was moderate (κ=0.59).[32] However, the small biopsy sample may give further difficulty for histological diagnosis of BO as well as the grade of dysplasia.

Management of High Grade Dysplasia

Three treatment options are available for the management of HGD:

- endoscopic intensive surveillance programme;
- endoscopic ablative therapy; and
- oesophagectomy.

The most appropriate management of patients with HGD is still controversial. Surgical pathology of oesophageal resections reported 10–50 % occult cancer rate in patients with HGD.[33,34] Oesophagectomy is certainly a curative therapy, but the procedure is highly operator-dependent, with the 30 days' mortality rate ranging from less than 5 % in a high volume centre to up to 20 % in a low volume centre.[35,36] Most of the oesophagectomies are performed at low volume centres.[37]

The endoscopic ablation of HGD is rapidly evolving. Multipolar electrocoagulation, laser therapy, argon plasma coagulation, photodynamic therapy, cryotherapy and radiofrequency ablation (RFA) have been used to eradicate the intestinal metaplasia. After endoscopic ablation of the intestinal metaplasia and the help of acid

suppression with proton pump inhibitor (PPI), the normal squamous epithelial cells typically can be regenerated. Photodynamic therapy uses a photosensitive drug and an activating non-thermal light to generate reactive oxygen species resulting in mucosa damage and has been reported to reduce the risk of cancer in patients with HGD.[38] The RFA system uses thermal energy provided by a set of electromagnetic coils on the surface of a balloon to destroy cells. RFA has been shown to effectively eradicate HGD and reduce the risk of disease progression.[39] Endoscopic mucosal resection (EMR) can be used alone to remove nodular mucosa or combined with other endoscopic treatment options.[40,41] However, the long-term benefit of these procedures is still limited and the prevalence of residual BO buried under re-epithelialised mucosa and their cancer risk are conflicting.[42,43]

The natural history of BO with HGD is not well defined. The annual incidence rate for oesophageal cancer was reported to be 2.2, 4 and 11.8 % in different studies.[44–46] Because of the mortality rate of oesophagectomy and the side effects and controversies with endoscopic therapy (the intensive endoscopic surveillance for HGD), oesophagectomy reserved for biopsy proven cancer could be the best option for some centres. The treatment choice for HGD should be made based on consideration of patient medical condition, patient preference, local expertise and the extent of BO.

Intestinal Metaplasia of the Gastro-oesophageal Junction and Gastric Cardia

Oesophageal cancers are now arising from more distal oesophagus. Ultra short BO, oesophagogastric junction specialised intestinal metaplasia (SIM) and SIM of the cardia are present in as high as 10–36 % of the healthy population.[47–49] Currently, there are no guidelines for managing SIM of the cardia; moreover, it is not an area that is routinely biopsied when performing OGD. It is possible that SIM in this area has a lower risk for cancer, but because of its high prevalence, this may represent a large portion of OAC and gastric cardia cancer.

GOJ tumours were classified into three types based on their anatomical location.[50] Risk factors and morphological characteristics are different between these three types of GOJ tumours. Eighty one per cent of the patients with type 1 GOJ tumour have BO identified, while only 11 % of the patients with type 2 GOJ tumour have BO identified.[50] A recent study in 165 patients with OAC reported that only 19 % of the GOJ tumour associated with identifiable BO, while 96 % of the oesophageal body tumour associated with identifiable BO.[51] An earlier pathology study reported that the coexistence of BO and OAC at the distal oesophagus is 3 % and at the oesophageal body is 20 %.[52] Although it is possible that tumour overgrows BO,[53] it is likely that tumours at GOJ may have other risk factors for cancer development. Recently reported Paget cells associated with poorly differentiated OAC suggested that SIM may not be the only precursor for OAC.[54]

Conclusion

BO is common in our clinical practice. Debate is continuing on many issues of BO including prevalence, racial difference, diagnosis, treatment, screening and surveillance. Many of these controversies may not be resolved in the near future. Patients should be well educated about the disease and its surrounding controversies. Patient's choice may play a critical role for cancer prevention and treatment. ■

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