Diagnosis and treatment of Barrett’s oesophagus

Yean Cheant Lim† and Rebecca C. Fitzgerald‡,*

†Addenbrooke’s Hospital, Hills Road, PO Box 133, Cambridge CB2 0QQ, UK and
‡MRC Cancer Cell Unit, Hutchison/MRC Research Centre, Hills Road, Cambridge, UK

Introduction: Barrett’s oesophagus (BO) is a common premalignant condition, which carries a risk of progression to oesophageal adenocarcinoma. Recent advances include quantifying the risk of neoplasia progression, novel diagnostic tools and development of new endoscopic techniques to treat early Barrett’s cancer.

Sources of data: A selective search was performed on recent advances in BO and this was supplemented with guidelines from the American and British Society of Gastroenterology.

Areas of agreement: All cases of dysplasia should be confirmed by a second expert histopathologist. Endoscopic therapy is the preferred option for high-grade dysplasia and intra-mucosal (T1a) carcinoma using endomucosal resection (EMR) and/or radiofrequency ablation. EMR also provides accurate staging information and any remaining Barrett segment should be ablated to reduce the risk of metachronous lesions.

Areas of controversy: The cell of origin for BO is not certain. The merits and cost effectiveness of endoscopic screening and surveillance still remain controversial. The risk of neoplasia progression in low-grade dysplasia is inconsistently reported. The role of chemoprevention remains unclear.

Growing points: The use of radical endotherapy in early Barrett’s neoplasia is promising with some data supporting long-term durability.

Areas timely for developing research: The development of non-endoscopic diagnostic tools and radical endotherapy to treat early cancer strengthens the argument for surveillance and suggests the possibility of screening in the near future. Identification of a biomarker may help to select high-risk patients.

Keywords: Barrett’s oesophagus/intestinal metaplasia/Barrett’s associated dysplasia/endoscopic therapy/biomarkers/screening/surveillance

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Introduction

The diagnosis and management of Barrett’s oesophagus (BO) is increasingly important, given the rapid rise in the incidence of oesophageal adenocarcinoma (OAC). Early detection of cancer or dysplasia in BO allows intervention at an early stage. This is important as advanced disease with regional or distant spread is associated with a dismal 10–20% 5-year survival rate. BO is common, affects ~2% of the Western population, increasing up to 10% in individuals with reflux symptoms and is the most important risk factor for the development of OAC. Large population-based cohort studies have quantified the risk of progression to dysplasia and early intra-mucosal carcinoma (IMC), which, although lower than previously thought in absolute terms, are still significantly increased compared with the general population. Detection of high-grade dysplasia (HGD) and OAC confined to the mucosa permits radical endoscopic intervention, which carries a favourable risk benefit profile compared with standard oesophagectomy. Nevertheless, important controversies remain such as the role of chemopreventive agents, efficacy of surveillance programmes and the long-term outcome for endoscopic therapy.

Definitions and diagnosis

The diagnosis of BO requires the identification of endoscopically visible metaplastic columnar epithelium in the distal oesophagus, which is confirmed histopathologically. BO is generally a mosaic of different columnar cell types (mucous cells, goblet cells and sometimes absorptive cells). The goblet cells signify the intestinal type and confer the greatest risk of malignancy and in the USA, where BO is defined according to its malignant potential, intestinal metaplasia (IM) is generally a prerequisite for making a diagnosis. However, the presence of IM to make a diagnosis is not universally agreed upon. Gatenby et al. demonstrated that in patients without IM at their index endoscopy, 54.8% will have it detected at 5 years and 90.8% at 10 years. There was no difference in the development of dysplasia or OAC in these two groups. This suggests that most patients with BO are likely to harbour IM, which either develops at some stage after diagnosis or more likely has been missed due to sampling error at the initial endoscopy. Harrison et al. suggested eight biopsies as the optimal number needed to demonstrate IM and this corresponds to a 67.9% yield which increases to 100% with 16 biopsies.

Endoscopic features of BO are described using the Prague criteria, allowing objective measurements and standardization of the classification.
internationally. It is reproducible without significant observer variation in segments >1 cm.\textsuperscript{10} Measurements are made proximal to the top of gastric folds with C denoting the circumferential extent of the columnar epithelium in cm and M, the maximal extent. Thus, C4, M6 denotes a circumferential Barrett’s segment of 4 cm which extends with more proximal tongues of columnar mucosa to a total of 6 cm (Fig. 1). It is important to note the landmarks of the gastro-oesophageal junction, as biopsies from a hiatus hernia or gastric cardia may have IM which cannot be distinguished from IM of the oesophagus histologically. The significance of IM of the cardia and ultrashort Barrett’s (<1 cm) is less clear, but evidence suggests that the malignant risk is very low and follow-up is not generally recommended.\textsuperscript{11}

The gold-standard endoscopic examination to diagnose and monitor BO is performed per-orally. This relies on an endoscopic theatre and trained nursing staff to assist especially in patients opting for conscious sedation. Recently, several techniques have been developed to improve the cost effectiveness and the ease of making a diagnosis in the primary care setting. This includes an office-based ultrathin transnasal approach that does not require sedation.\textsuperscript{12,13} In one study of 82 patients, 48 out of 49 patients with BO were accurately diagnosed (sensitivity 98%, specificity 100%) with a high correlation between transnasal and the standard per oral endoscopy for BO length ($R^2 = 0.97$).\textsuperscript{12} A non-endoscopic cytological collection device called the Cytosponge\textsuperscript{TM} coupled with a biomarker (Trefoil factor 3, TFF3) to detect goblet cells has also been studied in the primary care setting with promising early results.\textsuperscript{13–15} In contrast, the use of another relatively non-invasive technique, video capsule endoscopy, had a lower sensitivity and does not allow tissue sampling.\textsuperscript{16}

Once BO is diagnosed, the aim is to detect dysplasia which may be a harbinger of cancer. This is defined as unequivocal neoplastic epithelium

![Fig. 1 Prague classification for Barrett’s oesophagus (reproduced with permission from Sharma et al.\textsuperscript{10}).](image-url)
which is confined to the basement membrane. As the cytological and architectural abnormalities increase, they are described as low-grade dysplasia (LGD) and hence HGD. Accurate assessment of dysplasia is difficult with inter- and intra-observer variation and accuracy is confounded by inflammatory and regenerative changes which are commonly observed in BO.\textsuperscript{[17,18]} This is particularly the case for LGD with wide variations in concordance and estimates for the likelihood of malignant progression.\textsuperscript{[5,19]} When assessment of dysplasia is not possible due to these artefacts, the features are described by the pathologist as indefinite for dysplasia. This does not mean that there is less dysplasia than low grade, but rather that a grade cannot be assigned. In this case, re-biopsy should be considered after the inflammation has been reduced using acid-suppressant medication to rule out significant dysplasia which could be high grade. Recent studies have suggested that p53 immunostaining can be a useful diagnostic adjunct for dysplasia and this has recently been incorporated into the new British Society of Gastroenterology (BSG) guideline.\textsuperscript{[20–22]} When the tumour invades the lamina propria but is confined to the muscularis mucosae, it is termed IMC or T1a. Tumour present beyond the muscularis mucosae is regarded as invasive. Once the submucosa is breached, there is an increasing risk of lymph node metastasis and hence endoscopic therapy becomes less likely to cure the patient and therefore surgical treatment should be considered. An endoscopic resection of visible lesions thought to be at an early stage can be extremely useful to determine the depth of invasion.\textsuperscript{[23,24]} This procedure should be carried out with a therapeutic intent as discussed later.

### Risk factors and neoplastic progression

The columnar transformation of squamous oesophagus observed in BO is related to oesophageal acid and bile exposure, which is generally predicted by low oesophageal sphincter pressure and a hiatus hernia. Recent animal models have proposed novel and controversial theories for the cells of origin of the BO mucosa including the expansion of an embryonic columnar cell remnant in the context of injury inflammation, and these require further elucidation in humans.\textsuperscript{[25–27]} While prolonged acid exposure is associated with a longer Barrett’s segment, the segment does not appear to extend further during surveillance, suggesting a stable squamocolumnar boundary.\textsuperscript{[28]} BO is more prevalent in Caucasian populations in the Western world, whereas in the Asian population, BO is uncommon and the segment length tends to be shorter. However, there is some evidence that the prevalence may be increasing in the developing world.\textsuperscript{[29]} Although symptoms of gastroesophageal reflux are common, it can be silent and it is, therefore, an unreliable indicator of prevalent BO and
bears no clear relationship with progression to dysplasia. There is also some evidence of genetic susceptibility in sporadic cases due to multiple low penetrance alleles, whereas in familial cases of BO and OAC, a dominant pattern of inheritance is reported, although no predisposing monogenic mutations have been identified.\textsuperscript{30,31} In cases with a strong family history (one or more first degree relatives with BO or OAC), there may be a rationale for endoscopic screening, though this cannot be advocated on a routine basis.\textsuperscript{22,32}

In one of the first large cohort studies to assess the risk of neoplastic progression in patients with BO, Sharma et al. demonstrated rates of 4.3, 0.9 and 0.5\% per year incidence for LGD, HGD and OAC, respectively.\textsuperscript{5} In the 156 patients with LGD, followed up for a mean of 5 years, 10.3\% developed HGD and 3.2\% developed OAC (Table 1).

However, the incidence of HGD/OAC was significantly lower in a 2010 Dutch nationwide cohort study, which reported a combined HGD/OAC incidence rate of 5.81 per 1000 patient-years.\textsuperscript{4} Patients with non-dysplastic BO had a combined HGD/OAC incidence rate of 5.15 per 1000 patient-years and patients with LGD had double the incident rate at 10.6 per 1000 patient-years. Old age, male gender and LGD were independently associated with progression to HGD/OAC.

A 2011 Danish population study based on pathological retrieval of reports of IM in oesophageal biopsies reported an overall OAC incidence rate of 1.2 per 1000 patient-years. When assessed by degree of dysplasia, patients with non-dysplastic BO or LGD at index endoscopy had HGD incidence rates of 1.6 and 8.6 per 1000 patient-years, respectively. The incidence of OAC in patients with non-dysplastic BO or LGD at index endoscopy was 1.0 and 5.1 per 1000 patient-years.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Incidence of HGD/OAC in BO.</th>
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<tr>
<td></td>
<td>Incidence of LGD</td>
</tr>
<tr>
<td>Sharma et al.\textsuperscript{5}</td>
<td>4.3% per year</td>
</tr>
<tr>
<td>618 patients</td>
<td>2546 patients per year</td>
</tr>
<tr>
<td>42 207 patients</td>
<td>78 131 patients per year</td>
</tr>
<tr>
<td>11 028 patients</td>
<td>67 105 patients per year</td>
</tr>
<tr>
<td>8533 patients</td>
<td>59 784 patients per year</td>
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</table>
Hence, the estimates for the risk of progression to cancer vary between studies and seem to be less in recent publications. Overall, for patients with a baseline non-dysplastic BO, the incidence of HGD/OAC is 1–5.15 per 1000 patient-years and a recent meta-analysis estimated it at 0.33% per year.\textsuperscript{33} The risk appears higher in male gender, older age and presence of dysplasia. In addition, patients with IM and longer segments are also at higher risk.\textsuperscript{7,34} Thus, it is possible to start risk stratifying patients and this may be reflected in the surveillance regimen.\textsuperscript{22} Furthermore, patient fitness for surveillance should be carefully assessed before embarking on repeated endoscopies, since pulmonary and cardiac disease were a more common cause of death in this elderly male population with BO.\textsuperscript{35}

The presence of prevalent dysplasia as a risk is worth particular mention because the outcome for patients with LGD is heterogeneous. For example, in the Sharma \textit{et al.} study, 66% regressed to non-dysplastic BO.\textsuperscript{5} A large Dutch multicentre study involving non-university hospitals demonstrated that only 15\% of patients had definite LGD on review of the histopathology by experts.\textsuperscript{19} However, those with a consensus diagnosis carried a startling 13.4\% per patient per year risk of progression to HGD or OAC. Surprisingly, this was contradicted in a study that reported an incidence rate for HGC/OAC of 0.18\% for LGD when assessed by a local pathologist increasing to only 0.21\% when agreed by a central pathologist.\textsuperscript{36} This likely reflects the importance of diagnostic accuracy, since the kappa value for agreement between the pathologists was very low in the second study. In a recent biomarker study, using a robust nested case:control design in a Northern Ireland population cohort, the presence of a consensus of LGD was associated with a relative risk of 11.8.\textsuperscript{37} Overall, LGD is a difficult diagnosis to make but when agreement is reached between pathologists, it should be taken seriously and in this context, a p53 immunostain may be useful.\textsuperscript{38}

\section*{Management}

\textit{Chemoprevention and anti-reflux surgery}

Proton pump inhibitors (PPIs) are widely prescribed in the management of BO. They are useful for managing acid reflux symptoms and reducing oesophageal inflammation to allow accurate assessment for dysplasia. The role of PPIs in preventing neoplastic progression is less clear despite acid reflux being implicated in the development of BO. In a small cohort study, Wilkinson \textit{et al.} demonstrated regression of BO length and increased squamous island formation in patients treated with Omeprazole 40 mg daily.\textsuperscript{39} These findings were also seen in two other
retrospective studies. A recent prospective Dutch study, with a median follow-up of 5.2 years and 7% incident case of HGC/OAC, showed that use of PPI at baseline (hazard ratio, HR 0.41) or during follow-up (HR 0.21) was associated with a reduced risk of dysplasia. A Cochrane review in 2010 concluded that both medical and surgical intervention to reduce acid reflux does not eradicate BO or prevent neoplastic progression. At present, both the American and the British guideline do not recommend the routine use of PPI as a chemopreventive agent. The results of the prospective, randomized AspECT trial, which includes low- and high-dose PPI arms, are awaited to clarify this issue.

It has been suggested that aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) reduce the risk of neoplastic progression in BO. A randomized controlled trial (RCT) comparing celecoxib and placebo in 100 patients with 48 weeks of follow-up did not show any difference in dysplasia or length of BO. A retrospective analysis of the UK Barrett’s registry similarly demonstrated no difference with aspirin or NSAIDs usage. However, a recent Dutch observational study showed a significant reduction in neoplastic progression with NSAIDs and statin (HR 0.47 and HR 0.46) but not low-dose aspirin, and the effects were additive when both were prescribed together. At the moment, no recommendation can be made for the use of NSAIDs, but high-dose Aspirin will also be evaluated in the AspECT trial described earlier.

The role of anti-reflux surgery is mainly limited to patients with severe refractory symptoms, individuals intolerant of PPIs or those wishing to avoid long-term medication. Although the benefit of reducing acid and bile reflux through such a procedure is theoretically attractive, there is no evidence that surgery reduces the risk of neoplastic progression. In the only RCT so far, no patients developed OAC and the rates of incidence of HGD in the two arms were not significantly different. A systematic review in 2007 concluded that anti-reflux surgery is associated with regression of BO and/or dysplasia but no reduction in OAC. The LOTUS study in 2008 compared treatment outcome between 28 patients who were treated with Esomeprazole and 32 patients with laparoscopic anti-reflux surgery and found no difference in symptom control, although acid reflux control (as evidenced by pH monitoring) was better in the surgical group. Overall, anti-reflux surgery has a place for symptom control, but should not be used as a cancer prevention strategy in BO.

**Surveillance**

The stepwise neoplastic progression in BO suggests a role for surveillance programmes to detect HGD or early OAC. No data from RCTs have
been published so far; however, several retrospective studies suggest that surveillance programmes identify early-stage disease with some studies suggesting a survival benefit.\textsuperscript{55–56} The largest so far was from the Surveillance Epidemiology and End Results database, which identified 2754 patients with OAC. 11.5\% had an oesophagogastroduodenoscopy (OGD) performed 3 years to 6 months prior to diagnosis, of which 8.1\% had BO. The median number of OGDs was 4, suggesting enrolment in a surveillance programme. In a multivariate analysis, a diagnosis of BO carries the strongest association with early stage OAC (odds ratio, OR, 3.68).\textsuperscript{56} However, there are important practical challenges, for example, in an audit of BO surveillance programmes, 98 (50.3\%) out of 195 patients discontinued surveillance of which 21 (21.4\%) were due to non-attendance and 20 (20.4\%) from non-OAC related death.\textsuperscript{54} Such studies highlight the issues with compliance for this relatively invasive surveillance programme with the benefits needing to be balanced against the risks and the fiscal costs.

Several cost-effective models have been developed with heterogeneous result.\textsuperscript{57,58} The UK Health Technology Assessment in 2006 suggested that Barrett’s surveillance may cause more harm than benefit from operative complication, mortality and early recurrence.\textsuperscript{57} This together with a paucity of data may partly be the reason why surveillance is not performed to protocol with only 41\% of clinicians subscribing to quadrantic biopsies every 2 cm.\textsuperscript{59} It should also be borne in mind that these studies are retrospective in nature and conducted on a background of evolving diagnostic standardization, inconsistent adherence to the Seattle protocol and a changing practice towards radical endotherapy compared with oesophagectomy. Only one study included ablative therapy to HGD and found BO surveillance to be cost effective.\textsuperscript{60} The AspECT study and the ongoing BOSS study, which compares a BO surveillance programme with on demand endoscopy will be very informative. Nevertheless, improvements have been made in all these aspects and at the current time, all of the major societies favour surveillance.\textsuperscript{22,32} The new BSG guidelines will suggest that surveillance protocol be tailored to the individual and take into account the presence of IM and length of BO. In order to maximize the efficacy of surveillance, practical issues need to be attended to; surveillance endoscopy should be performed with a high-resolution endoscope and with strict adherence to the Seattle protocol in conjunction with expert histopathological review for all cases of suspected dysplasia.\textsuperscript{61}

\textbf{Endoscopic assessment and staging}

While HGD or OAC may be picked up with strict Seattle protocol biopsies, evidence suggests that high-resolution endoscopes or a combination
of autofluorescence and narrow band imaging are likely to detect subtle endoscopic lesions in the hands of an experienced endoscopist. These are described according to the Paris classification with Type 0-IIa (37%) or 0-IIb (28%) being the most common findings (Fig. 2). Retrospective analysis of endomucosal resection (EMR) samples suggests that Type 0-1 or Type 0-IIc is more likely to be associated with submucosal invasion. All detectable lesions should be staged with EMR to determine the risk of lymph node metastasis and hence the need for oesophagectomy with lymph node clearance rather than endotherapy. OAC limited to the mucosa is amenable to endotherapy and staged as T1a, whereas invasion to the submucosal is staged as T1b and above (Table 2).

Patients with T1b disease should be treated with oesophagectomy, although surgical fitness may dictate that they undergo radical endotherapy and there is some evidence for this in ‘low-risk’ T1b patients, for example with sm1 disease and well-differentiated tumours. In patients with T1a disease, radical endotherapy provides a superior risk benefit profile compared with oesophagectomy, which should be reserved in patients with involvement of the deep resection margin or failed endotherapy.

The use of endoscopic ultrasound (EUS) to locally stage disease unfortunately differs significantly from surgical or EMR staging with a systematic review suggesting only 65% concordance. In a retrospective study of 109 cases with EUS staging, 84% were over staged (≥T1a) and 3.4% were under staged (≤T1b). This was also observed in a further study leading to the authors concluding that EUS had no clinical impact and that diagnostic EMR was superior. At the moment, there is no

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**Fig. 2** Paris classification for superficial neoplastic lesion.
standardization on the use of EUS in staging early Barrett’s neoplasia. Overall, there is a risk of over-staging and its role is more defined in visible invasive lesions.

Management of dysplasia

The risk of OAC increases significantly when dysplasia is detected and hence there is a requirement to deliver some form of intervention. As described earlier, there is significant inter-observer variation in the grading of dysplasia, especially so in the case of LGD where inflammation can make accurate assessment difficult. In general, any forms of dysplasia should be re-assessed and confirmed by a second expert pathologist. If dysplasia cannot be accurately graded, such as in indefinite for dysplasia, the patient should have their acid suppression optimized and undergo a repeat surveillance biopsy. If no dysplasia is identified then the patient’s surveillance interval reverts to that for non-dysplastic BO.

When a diagnosis of LGD is made, the risk of HGD/OAC progression is likely to increase significantly. The AGA advises that ‘radiofrequency ablation (RFA) should also be a therapeutic option’ while the new BSG guideline recommends that ‘endotherapy … cannot be recommended on a routine basis’, both likely reflecting the heterogeneous nature of LGD. It may be possible to individualize risk assessment in this case, for example taking into account, age, gender, length of BO, family history and presence of multifocal LGD.

Endoscopic therapy has advanced over the past few years and are summarized below as a major review is beyond the scope of this article. Endotherapy in BO is mainly in the form of RFA, EMR or a multimodal approach combining RFA and EMR. Photo-dynamic therapy (PDT) is now performed less frequently due to the side-effects of photo-sensitivity and oesophageal strictures.

Table 2  Early Barrett’s neoplasia staging and risk of lymph node metastasis.

<table>
<thead>
<tr>
<th>Disease staging</th>
<th>Description</th>
<th>Risk of lymph node metastasis</th>
<th>Westerterp et al.84</th>
<th>Leers et al.85</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1a</td>
<td>Carcinoma in situ or with questionable invasion beyond the basement membrane</td>
<td>0/13, 0%</td>
<td>0/18, 0%</td>
<td>0/18, 0%</td>
</tr>
<tr>
<td>m2</td>
<td>Invasion into the lamina propria</td>
<td>0/23, 4.3%</td>
<td>1/57, 1.3%</td>
<td></td>
</tr>
<tr>
<td>m3</td>
<td>Invasion into the muscularis mucosa</td>
<td>1/20, 5.0%</td>
<td>0/18, 0%</td>
<td></td>
</tr>
<tr>
<td>T1b</td>
<td>Invasion into the upper third of the submucosa</td>
<td>6/23, 26.1%</td>
<td>4/19, 21.0%</td>
<td></td>
</tr>
<tr>
<td>sm1</td>
<td>Invasion into the middle third of the submucosa</td>
<td>1/9, 11.1%</td>
<td>0/25, 0%</td>
<td></td>
</tr>
<tr>
<td>sm2</td>
<td>Invasion into the lower third of the submucosa</td>
<td>12/18, 66.7%</td>
<td>6/23, 26.1%</td>
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</tr>
</tbody>
</table>

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Endoscopic therapy has advanced over the past few years and are summarized below as a major review is beyond the scope of this article. Endotherapy in BO is mainly in the form of RFA, EMR or a multimodal approach combining RFA and EMR. Photo-dynamic therapy (PDT) is now performed less frequently due to the side-effects of photo-sensitivity and oesophageal strictures.
In a cohort study of 40 patients with LGD treated with PDT, all patients achieved eradication at 1 month, which was maintained over a median follow-up of 53 months. One patient developed OAC but in an untreated BO segment. However, Ragunath et al. compared PDT with argon plasma coagulation in 26 patients (23LGD, 3HGD) and achieved dysplasia eradication of 77% in the PDT group and 62% in the APC group at 12 months. In addition, there were sub-squamous IM and one patient went on to develop OAC under the neo-squamous epithelium. 15% developed stricture in both arms and an additional 15% developed photo-sensitivity in the PDT group.

Shaheen et al. reported the results of a randomized controlled trial of RFA in 2009 where 127 patients (64 LGD, 63 HGD) achieved a 90% dysplasia eradication for LGD and 81% for HGD with an intention to treat basis at 1 year. These increased to 95 and 90% for those who completed the treatment protocol. In addition, IM was also eradicated in 77%. Following crossover from the sham group and further follow-up over a mean 3.05 years, 98 and 93% with initial LGD and HGD, remained free of dysplasia. The rate of OAC progression in this high-risk group was 0.55% per patient-year. In contrast to PDT, only 3.4% significant adverse events were reported (post-procedure chest pain and bleeding) and 7.6% had stricture formation.

The on-going SURF trial compares surveillance to RFA in patients with a consensus diagnosis of LGD and may address further the role of ablation in this specific group.

As HGD or OAC may associate with an endoscopically visible lesion, EMR is generally the first step and provides staging information and initial resection of the highest grade dysplastic focus. Limiting EMR to just the dysplastic foci has been shown to leave a 30% risk of metachronous lesions and hence the remaining BO should also be eradicated. In BO segments <3 cm, Moss et al. showed that stepwise EMR eradicated BO in 94% of cases. This was subsequently extended to C3M5 lesions in a study involving 77 patients where 95% achieved complete neoplasia eradication and 82% achieved IM eradication over a median of two resection sessions. However, oesophageal dilatation was required in 33% of cases over a median follow-up of 20 months. Similarly, a Dutch retrospective analysis of 169 patients with BO ≤ 5 cm, with an intention to treat analysis, achieved complete eradication of neoplasia in 97.6% and complete eradication of IM in 85.2%. This was sustained at a median of 32 months (95.3 and 80.5%). However, 49.7% developed symptomatic stenosis.

The use of RFA has been described earlier as having a favourable efficacy and side effect profile especially with regard to stricture formation. It is also effective in long-segment BO including ≥ 8 cm, although this is associated with a higher IM recurrence. Patients with flat or non-visible
lesions may proceed straight to RFA but commonly, the presence of a macroscopic lesion requires EMR staging first. This combined approach has been shown to be effective and safe. 77,78 In a recent randomized study comparing stepwise radical endoscopic resection (SRER) vs. RFA in BO ≤ 5 cm, both procedures were equally efficacious; however, SRER was associated with a significantly higher stenosis rate (88% vs. 14%), severe complications (6/25 vs. 0/22) and more therapeutic sessions (median of 6 vs. 3).79

The use of all ablative techniques requires complete eradication of IM to prevent risk of recurrence including under the neo-squamous epithelium described as sub-squamous IM.80,81 In a retrospective analysis, Yuan et al. found sub-squamous IM in patients while undergoing RFA treatment; however, these were completely eradicated upon treatment completion. 82 Despite this, there are case reports of sub-squamous neoplasia (2 OAC, 1 HGD) in patients after successful RFA treatment.83 Currently, all patients who undergo endoscopic therapy should remain under a surveillance programme until further data are available.

For management of dysplasia, a multi-disciplinary approach is required in an expert centre. This should include input from pathologists, radiologists, endoscopists and surgeons to ensure that the correct histopathological and staging diagnoses have been made and all treatment options considered. The patient should be fully informed about their disease and the treatments available with opportunity to discuss this in a multi-disciplinary clinic if necessary.

Conclusions

The management of this common premalignant condition has significantly evolved with a greater understanding of the risk of neoplasia progression and the development of a well-tolerated and effective endoscopic therapy to treat early OAC. Multimodal treatment with EMR and RFA is effective and appears safest for patients with HGD and IMC, although patients will need to remain under surveillance post-treatment. For patients with more advanced disease, extending into the submucosa surgical management remains the mainstay. Several on-going studies such as the BOSS and AspECT trials are likely to address key clinical unresolved issues about surveillance and the role of chemoprevention. In the meantime, with the increasing incidence and poor outcomes for invasive OAC, better ways to identify high-risk patients are required. Non-endoscopic diagnostic tools bring us the possibility of a screening programme in the future and this may be further advanced with identification of risk-stratifying biomarkers.
Conflict of interest

R.C.F. has developed the Cytosponge technology. This is in the process of being licensed, but it is not yet commercially available. R.C.F. has no financial relationships to declare.

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