Management of Barrett's oesophagus and intramucosal oesophageal cancer: a review of recent development

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Abstract: Barrett's oesophagus is the most important and recognizable precursor lesion for oesophageal adenocarcinoma, which is the one of the fastest growing cancers in the Western World. The incidence of oesophageal adenocarcinoma has increased 600% in the United States between 1975 and 2001 and is thought to represent a real increase in burden rather than a result of histologic or anatomical misclassification or overdiagnosis. Thus, the cancer risk in Barrett's oesophagus has to be managed and involves prevention (surveillance endoscopy), treating underlying gastroesophageal reflux disease (medically and or surgically) and endoscopic therapy to remove diseased epithelium in appropriate patient subgroups. In the last decade, new developments in imaging and molecular markers as well as an armamentarium of novel and effective endoscopic eradication therapy has become available to the endoscopist to combat this exponential rise in oesophageal adenocarcinoma. Paradoxically, the cancer risk in Barrett's oesophagus gets progressively downgraded which raises fundamental questions about our understanding of the known and unknown risk factors and molecular aberrations that are involved in the Barrett's metaplasia–dysplasia–carcinoma sequence. Future research has to be directed at these areas to fine tune our screening and surveillance programs to identify more accurately the high-risk group of progressors to oesophageal adenocarcinoma who would benefit most from endoscopic therapy.

Keywords: Ablative therapy, Barrett's oesophagus, Barrett's surveillance, GORD, oesophageal cancer

Introduction

Oesophageal adenocarcinoma (OA) has a poor prognosis with a 5-year survival rate of less than 15% [Eloubeidi *et al.* 2002; Pondugula *et al.* 2007]. Barrett's oesophagus (BO) is considered the main risk factor for OA although some consider it an adaptive epithelium in response to chronic damage by gastroesophageal refluxate [Fitzgerald *et al.* 2002; Jankowski, 1993; Orlando, 2006]. Unfortunately, there is no universally accepted definition of BO [Vakil *et al.* 2006; Sharma *et al.* 2004]. It is defined in most countries including the United States as displacement of the squamocolumnar junction proximal to the gastroesophageal junction with specialized intestinal metaplasia on biopsy [Wang and Sampliner, 2008]. The British Society of Gastroenterology definition differs in that it is 'an endoscopically apparent area above the oesophago-gastric junction that is suggestive

of BO (salmon-coloured mucosa) which is supported by the finding of columnar lined oesophagus on histology' [Playford, 2006]. The rationale behind this definition is that sampling errors at the index endoscopy may miss areas of intestinal metaplasia which may preclude patients from entering endoscopic surveillance programmes. Interestingly, in a recent large study involving 8522 patients with BO, it has been shown that there is a lower risk of malignant progression in patients without intestinal metaplasia (0.07% per year) as compared with those with intestinal metaplasia (0.38% per year) on index biopsy [Bhat *et al.* 2011].

Surveillance studies have demonstrated that oesophageal cancer develops through a multistep pathway, the so-called Barrett's metaplasia–dysplasia–adenocarcinoma sequence [Jankowski *et al.* 1999]. Despite endoscopic surveillance, the

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incidence of OA has increased 600% in the United States between 1975 and 2001 (from 4 to 23 cases per million) [Pohl and Welch, 2005]. Paradoxically, there has been a reduction in the risk estimate of cancer in BO over time. Hence, there is no plausible explanation for this exponential rise. Nevertheless, it has been postulated that it is due to increasing prevalence of gastroesophageal reflux disease (GORD) as a result of increasing abdominal adiposity, reduced prevalence rates of *Helicobacter pylori* infection (as a result of widespread eradication) and increased ingestion of refined food with a concomitant reduction in consumption of fruit and vegetables [Rajendra and Sharma, 2011].

Epidemiology and natural history of Barrett's oesophagus

BO affects predominantly White [Corley *et al.* 2009] males [Cook *et al.* 2005] and is associated with age >50 [Bhat *et al.* 2011], chronic GORD [Edelstein *et al.* 2009; Corley *et al.* 2009], hiatal hernia [Westhoff *et al.* 2005] and abdominal adiposity [Edelstein *et al.* 2007]. BO is estimated to affect between 1.6% of the adult Swedish population [Ronkainen *et al.* 2005] and 6.8% of Americans [Rex *et al.* 2003]. In those patients with chronic GORD, the prevalence of BO is 10–15% [Sharma, 2009]. A large proportion of patients with BO are asymptomatic and almost half of patients who develop OA have no history of reflux symptoms. Equally intriguing is the fact that 95% of patients with OA had no prior diagnosis of BO and 80% of oesophageal cancer patients had no prior diagnosis of GORD [Reid *et al.* 2010]. The vast majority of subjects with BO (>90%) never progress to OA [Reid *et al.* 2000]. Previously, the risk of progression to OA in patients with BO was thought to be approximately 1.0% per year (1 case per 125 patient-years) [Shaheen *et al.* 2000]. Since then, this risk has been progressively downgraded to 1 case per 200 patient-years and even 1 case per 300 patient-years [Yousef *et al.* 2008]. Recently, two large population-based studies published in 2011 from Northern Ireland and Denmark have reduced the risk estimate of cancer in nondysplastic Barrett's oesophagus (NDBO) even further to 0.13% (1 case per 769 patient years) and 0.12% (1 case per 860 patient years), respectively [Bhat *et al.* 2011; Hvid-Jensen *et al.* 2011]. Moreover, it has been shown [Bhat *et al.* 2011] that the cancer risk in BO remains relatively constant over time.

The malignancy potential in Barrett's low-grade dysplasia (LGD) is poorly defined [Spechler *et al.* 2011]. The reasons include poor interobserver correlation (reactive changes due to oesophagitis *versus* LGD), biopsy sampling error and regression of LGD as a result of immunosurveillance [Sharma *et al.* 2004, 2006b; Rajendra and Robertson, 2010]. Some authorities have estimated the incidence of OA in LGD to be between 1.7% and 14.6% per annum [Fleischer *et al.* 2010] based on meta-analysis [Wani *et al.* 2009] and individual studies [Skacel *et al.* 2000; Gatenby *et al.* 2009; Lim *et al.* 2007; Veith, 2007]. Nevertheless, in a large multicentre study conducted by one of the authors (PS) revealed that the incidence of OA among patients with Barrett's LGD was even lower at 0.6% per year [Sharma *et al.* 2006b]. More recently, it has been reported that the incidence rate of OA amongst 621 Danish patients with LGD was 0.5% per annum [Hvid-Jensen *et al.* 2011]. In the Northern Ireland Barrett's oesophagus register study, subgroup analysis of 374 patients with LGD followed up for a mean of 7 years, revealed the risk for developing high-grade dysplasia (HGD) or cancer was 1.4% per year [Bhat *et al.* 2011].

In a meta-analysis involving four studies that included patients with HGD but excluded prevalent cancers and those patients with previous endoscopic and/or surgical intervention, the incidence of OA was estimated to be between 5.6% and 6.6% per annum [Rastogi *et al.* 2008]. Older individual studies may have overestimated the risk of Barrett's HGD progressing to cancer (16–60%) [Reid *et al.* 2000; Weston *et al.* 2000; Schnell *et al.* 2001].

Predictors of progression

Currently, dysplasia on histopathology is considered the best (but imprecise) marker of cancer risk in BO. It is defined as neoplastic change of the epithelium that remains confined within the basement membrane of the gland from which it arises [Riddell *et al.* 1983]. The shortcomings of dysplasia as a cancer risk stratification tool especially in LGD have been mentioned above. Hence, a number of biomarkers have been proposed to predict the risk of malignant progression. Chromosome instability (which is the commonest cause of genomic instability) is strongly associated with progression from BO to OA [Reid *et al.* 2010]. A biomarker panel indicating chromosome instability as indicated by detecting the presence

of 9p LOH (inactivation of p16), 17p LOH (inactivation of p53), aneuploidy/tetraploidy (DNA content abnormalities) may be superior to histology alone for risk stratifying patients with Barrett's metaplasia, indefinite dysplasia or LGD [Spechler *et al.* 2011]. In a study involving 243 patients with BO in whom oesophageal biopsies were subjected to the above biomarker panel revealed that those who tested positive for all of the above had a relative risk of progression to OA of 38.7 (95% confidence interval [CI] 10.8–138.5) [Galipeau *et al.* 2007]. BO patients positive for 9p LOH, 17p LOH and DNA content aberrations had a 5-year cumulative incidence for OA of 79.1% *versus* 0% in those without. Nevertheless, the American Gastroenterological Association (AGA) Medical Position Panel suggests against the routine use of molecular biomarkers to confirm dysplasia or risk stratification in BO subjects [AGA, 2011].

Screening for Barrett's oesophagus

Screening the general population with GORD for BO is not currently recommended and individualized screening has been suggested. GORD is not a reliable marker for BO [Rex *et al.* 2003; Ronkainen *et al.* 2005]. Only 40% of patients with BO report reflux symptoms [Ronkainen *et al.* 2005]. As stated previously, 95% of patients with OA had no prior diagnosis of BO and 80% of oesophageal cancer patients had no prior diagnosis of GORD [Reid *et al.* 2010]. GORD is common, affecting 10–20% of communities in the Western World and approximately 5% of the population in Asia [Dent *et al.* 2005]. This coupled with the number of patients with OA makes screening cost-ineffective [AGA, 2011]. Patients at risk of OA, i.e. age ≥ 50 years, White, male, chronic GORD, hiatal hernia, abdominal adiposity and elevated body mass index should be screened [Spechler *et al.* 2011] although it is not a universal recommendation across gastroenterology societies, unsedated transnasal endoscopy and the ingestible oesophageal sampling device (Cytosponge) aided by immunocytochemistry for trefoil factor 3 may make screening for BO more attractive [Kadri *et al.* 2010]. Compared with gastroscopy, the sensitivity and specificity of the test were 73.3% and 93.8% for ≥ 1 cm circumferential length BO and 90% and 93.5% for ≥ 2 cm segments. Nevertheless, it is pertinent to note that there are no randomized controlled trials demonstrating benefit in terms of decreasing the

incidence or mortality of OA or cost-effectiveness in screening for BO.

Endoscopic surveillance of Barrett's oesophagus

Significant resources are allocated to identify and survey BO in an attempt to detect cancer at an early and potentially curable stage to curb the exponential rise in OA. Paradoxically, the cancer risk in BO gets progressively downgraded [Hvid-Jensen *et al.* 2011; Bhat *et al.* 2011]. Peter Kahrilas argues that the problems with screening and surveillance strategy in BO lie with the numbers and not the logic [Kahrilas, 2011]. The probability that OA will be detected endoscopically is 1 in 1460 screening endoscopic examinations, and concurrently 146 patients with BO will be detected [Kahrilas, 2011]. He rightly points out that patients with BO have the same life expectancy as does the general population [Sharma *et al.* 2004] and oesophageal cancer is an uncommon cause of death in patients with BO [van der Burgh *et al.* 1996]. Are other unknown risk factors to blame [Rajendra and Sharma, 2011]? Pohl and Welch suggest that to explain a rise of oesophageal adenocarcinoma of this magnitude, the prevalence of a strong risk factor must also rise exponentially—as was the case for smoking and lung cancer. Such a risk factor has not been identified and defining it should be a priority? [Pohl and Welch, 2005]. Our screening and surveillance programs need to be improved so as to identify the high-risk population of progressors.

Nevertheless, the association of BO with OA through the metaplasia–dysplasia–carcinoma sequence as well as the poor prognosis of advanced adenocarcinoma makes endoscopic surveillance an attractive option for BO patients [Tomizawa and Wang, 2009]. The current recommendations for surveillance in BO are to perform two endoscopies with biopsy within a year and then endoscopy every 3–5 years [Wang and Sampliner, 2008; Spechler *et al.* 2011]. The absence of dysplasia on the first two endoscopies does not preclude NDBO from progressing to HGD or OA [Sharma *et al.* 2006b]. Patients with LGD should undergo endoscopic surveillance at intervals of 6–12 months and those with HGD in the absence of eradication therapy at 3-monthly intervals. The AGA recommends endoscopic eradication therapy rather than surveillance for treatment of patients

with HGD [AGA, 2011]. The finding of dysplasia needs to be confirmed by an independent second pathologist to reduce interobserver variation. Patients with dysplasia should be on proton- pump inhibitor (PPI) therapy to reduce inflammatory changes which could make histopathological interpretation difficult.

Barrett's oesophagus evaluation

The diagnosis of BO is suspected during endoscopy, when columnar lining is seen to extend above the gastroesophageal junction which itself is defined as the most proximal extent of the gastric folds [McClave *et al.* 1987]. BO has been defined as long segment (LSBO; >3 cm) and short segment (SSBO; ≤3 cm). The risk of cancer is said to vary with the length of oesophageal intestinal metaplasia (0.57% in LSBO *versus* 0.26% in SSBO) [Sharma *et al.* 1998; Yousef *et al.* 2008] although this is not a universal finding [Rudolph *et al.* 2000]. The Prague C and M criteria identifies both the circumferential extent (C) and the maximum extent (M) of Barrett's metaplasia and has been demonstrated to have excellent interobserver agreement among endoscopists [Sharma *et al.* 2006a]. This is the case for columnar epithelium extending at least 1 cm above the gastroesophageal junction. Endoscopic evaluation of the columnar lined oesophagus should be carefully performed using high-definition white-light endoscopy (HD-WLE) [Spechler *et al.* 2011]. Four-quadrant biopsy specimens should be obtained every 1–2 cm as well as targeted biopsies of apparent lesions from patients with BO [Provenzale *et al.* 1994; Sharma *et al.* 2006a]. In patients with known or suspected Barrett's dysplasia, four-quadrant biopsy specimens should be obtained every 1 cm [Spechler *et al.* 2011]. Specific biopsy specimens of any mucosal irregularity should be sent separately to the pathologist for evaluation [Sharma *et al.* 2006a; Reid *et al.* 2000].

Careful examination of Barrett's oesophageal mucosa is important to detect high grade dysplasia and OA. In a prospective randomized trial, 112 patients with a mean Barrett's length of 3.7 cm were subjected to endoscopy [Gupta *et al.* 2011]. The mean Barrett's inspection time (BIT) with HD-WLE was 3.8 minutes. A total of 57 patients had lesions detected with HD-WLE and 38 patients had a final diagnosis of HGD/OA. Patients whose BIT was less than 5 minutes had fewer visible lesions and were less likely to receive

a diagnosis of HGD/OA compared with patients whose BIT was at least 5 minutes or longer. This finding was independent of the length of BO. It is recommended that endoscopists who evaluate patients for BO using HD-WLE spend an average of 1 min/cm of BO prior to obtaining biopsies. It is unclear whether inspection time is directly responsible for improved detection rates. It may be a surrogate marker for more obsessive and observant endoscopists.

Chromoendoscopy refers to endoscopic tissue staining using chemicals, e.g. Lugol's solution, methylene blue, indigo carmine and acetic acid to highlight surface characteristics of the gastrointestinal tract to detect epithelial changes, e.g. dysplasia. A meta-analysis of 9 studies (450 patients) found that methylene blue staining and four-quadrant biopsy techniques have similar rates for detecting intestinal metaplasia and dysplasia [Ngamruengphong *et al.* 2009]. Indigo carmine chromoendoscopy was again not superior to HD-WLE in detecting early neoplasia in BO [Kara *et al.* 2005]. Furthermore, electronic chromoendoscopy also has not been shown to be superior to HD-WLE which remains the standard of care. Not surprisingly, The AGA Medical Position Statement on the management of BO suggests against requiring chromoendoscopy or advanced imaging techniques (narrow-band imaging or confocal laser microscopy) for the routine surveillance of patients with BO at this time. Chromoendoscopy is time consuming, subject to technical issues (achieving uniform dye spraying), potentially hazardous (methylene blue), poorly standardized and suffers from inter-observer variability [Spechler *et al.* 2011].

Management objectives in Barrett's oesophagus

The three main objectives in managing BO are cancer prevention (including the abovementioned surveillance endoscopy), treating GORD (medically and or surgically) and endoscopic therapy to remove diseased epithelium in appropriate patient subgroups.

Manage underlying GORD

A decrease in quality of life in patients with BO may be related to underlying GORD as well as stress due to increased life- and health-insurance premiums. PPIs are the mainstay of treatment but the addition of H2-receptor antagonists may

be required to combat nocturnal acid breakthrough. Prokinetic therapy may be of use if volume regurgitation is a problem. The vast majority of studies involving medical therapy for BO use either resolution of reflux symptoms or normalization of oesophageal acid exposure as the endpoint. Symptom control alone may be a poor predictor of persistent acid reflux in patients with BO [Gerson *et al.* 2004]. Nevertheless, there is insufficient data advocating oesophageal pH monitoring to optimize PPI therapy to control reflux symptoms fully [Spechler *et al.* 2011]. Furthermore, the AGA recommends against attempts to eliminate oesophageal acid exposure for the prevention of OA [AGA, 2011]. It is pertinent to note that neither surgery nor medical therapy have been shown to prevent OA [Spechler *et al.* 2011].

Regressing and preventing progression of Barrett's metaplasia to dysplasia and, hence, cancer

Indirect evidence exists to support the use of PPIs as a chemopreventative agent in BO. In a randomized control trial involving BO patients treated with PPI *versus* histamine type II-receptor blockers, there was a 8% regression in BO surface area in the former group [Peters *et al.* 1999]. An inverse correlation has been established between long-term use of PPIs and the incidence of dysplasia and adenocarcinoma in BO [El Serag *et al.* 2004; Cooper *et al.* 2006; Nguyen *et al.* 2009]. Conversely, in a nested case control study involving 11,823 patients with a first-time BO diagnosis (116 with incident OA and 696 matched controls without OA) there was no dose-response effect of PPIs on the prevention of progression to OA [Nguyen *et al.* 2010]. This could have been due to the small number of cases (5%) and controls (6%) with no PPI use. Moreover, it is difficult to investigate PPIs as chemopreventative agents in epidemiological studies given significant confounding by indication. Nevertheless, there are no prospective clinical studies demonstrating that PPI therapy prevents the development of dysplasia and progression to cancer.

A meta-analysis of 9 clinical studies has shown a 43% decreased rate of oesophageal cancer in patients who use nonsteroidal anti-inflammatory drugs (NSAIDs) [Corley *et al.* 2003]. A 50% reduction of oesophageal malignancy was seen

with aspirin use. In a prospective study involving 350 patients with BO followed up for a median of 65.5 months there was a reduced risk of OA in current users of NSAIDs (hazard ratio, 0.20; 95% CI 0.10–0.41) *versus* subjects who had never used these drugs [Vaughan *et al.* 2005]. A negative study involving a cyclooxygenase-2 selective NSAID and BO was reported by Heath and colleagues [Heath *et al.* 2007]. They randomized 100 patients who had either low- or high-grade Barrett's dysplasia to receive either celecoxib or placebo for 48 weeks. There was no significant difference in the percentage of oesophageal biopsies demonstrating cancer or dysplasia between the two groups. Inhibition of cyclooxygenase-2 by NSAIDs has been postulated as the mechanism for the prevention of progression of BO to adenocarcinoma [Jankowski and Zagorowicz, 2006].

Another mode of action involves modulation of human leukocyte expression (HLA). A negative association has been noted for NSAIDs and HLA class I downregulation and class II upregulation which are early events in carcinogenesis [Rajendra, 2006], suggesting that immunomodulatory effects reduce the risk of malignant progression in BO [Rajendra *et al.* 2006]. The Aspirin Esomeprazole Chemoprevention Trial (ASPECT) in BO is currently investigating whether treating with aspirin and high-dose PPIs can reduce progression from metaplasia–dysplasia–adenocarcinoma and, hence, reduce mortality. The results of this trial are eagerly awaited. Currently, it is appropriate to consider prescription of low-dose aspirin for BO subjects (who are already on a PPI) with concomitant risk factors for cardiovascular disease [Spechler *et al.* 2011].

Complete eradication of dysplasia and hence reducing progression to OA. This can be achieved by endoscopic means or via surgery. Elimination of metaplastic/dysplastic cells involves ablation, endoscopic mucosal resection (EMR) and oesophagectomy. Ablation can take the form of heat injury [multipolar electrocautery (MPEC), argon plasma coagulation (APC) laser, neodymium-doped yttrium aluminium garnet (Nd:YAG), radiofrequency ablation (RFA)], cold injury (cryotherapy) and photochemical injury (PDT). Postablation/EMR, antisecretory therapy in the form of PPIs is prescribed, so the oesophageal mucosa heals with the growth of new squamous epithelium (neosquamous epithelium).

Non-dysplastic Barrett's oesophagus

Some authorities have suggested that all patients with BO irrespective of the presence of dysplasia should be treated with RFA [Fleischer *et al.* 2010]. This may be related to the availability of endoscopic therapeutic options, the high cost of surveillance and the difficulty in identifying the high-risk progressors to OA. An uncontrolled US multicentre prospective clinical trial involving 70 patients with long-segment NDBO were subject to stepwise circumferential and focal ablation. At 1 year, 70% of patients had no residual intestinal metaplasia in any oesophageal biopsy. At 2.5-year follow up after application of focal RFA, complete eradication of intestinal metaplasia was achieved in 98% of patients. At 5-year follow up, 92% were free of intestinal metaplasia as per protocol analysis. Nevertheless, by intention-to-treat analysis of the same patient population, the eradication rate of intestinal metaplasia was 66%. This result compares favourably with the multicentre sham-controlled randomized trial in which complete eradication of intestinal metaplasia was achieved in 77% of RFA-treated dysplastic BO patients *versus* 2% of sham-treated patients (intention-to-treat analysis) [Shaheen *et al.* 2009]. A multicentre, community-based gastroenterology practices study enrolled 326 NDBO patients to undergo RFA. At the end of a mean follow up of 20 months, complete eradication of intestinal metaplasia was achieved in 76% of patients. Strictures occurred in 1.1% of patients and no serious adverse events were reported [Lyday *et al.* 2010].

It is the authors' opinion that the use of invasive ablative therapies in NDBO is hard to justify given the low risk for cancer development in Barrett's metaplasia [Rajendra and Sharma, 2011], the inadequately understood natural history of this condition as well as an inability to identify a high-risk population of progressors. There is no data from controlled trials demonstrating that ablative therapy is more efficacious or cost-effective than long-term endoscopic surveillance in patients with NDBO.

Low-grade dysplastic Barrett's oesophagus

Dysplasia must be confirmed by at least two expert pathologists preferably one of whom is an expert in oesophageal histopathology [AGA, 2011] prior to contemplating surveillance or eradication of the diseased mucosa.

A number of trials using various ablative modalities [argon plasma coagulation (APC), photodynamic therapy (PDT) and RFA] have been studied in this group of patients. Unfortunately, most of the data on the efficacy of ablative therapy in LGD has been obtained from subgroup analysis of eradication trials involving primarily nondysplastic *versus* HGD.

In a trial involving the use of APC to ablate low-grade Barrett's dysplasia, all 19 patients with this condition had complete eradication of dysplasia after a median follow up of a year [Familiari *et al.* 2003]. A head-to-head trial involving the use of PDT with porfimer sodium *versus* APC in the treatment of patients with LGD resulted in lower rates of eradication, i.e. 77% for PDT *versus* 62% for APC [Ragunath *et al.* 2005].

RFA is at least equally efficacious as PDT in eradicating dysplasia. RFA therapy in patients with LGD restores normal appearing squamous epithelium in >90% of subjects [AGA, 2011]. A number of studies have evaluated the safety and efficacy of RFA in patients with Barrett's LGD. A multicentre randomized sham-controlled trial of RFA in Barrett's LGD and HGD was carried out by Shaheen and colleagues [Shaheen *et al.* 2009]. At 12 months, in the intention-to-treat analysis of the patients with LGD, complete eradication was achieved in 90.5% in the ablation group ($n = 42$) as compared with 22.7% in the control group ($n = 22$) ($p < 0.001$).

The above trials have demonstrated short-term benefit in eliminating LGD but there is no long-term data to show cancer prevention. As mentioned earlier, the definition of dysplasia is fraught with difficulties and without a well-defined uniform natural history compounded by widely varying risk estimates for progression to cancer of 0.6–1.6% [Lim *et al.* 2007; Sharma *et al.* 2006b; Dulai *et al.* 2005; Shaheen *et al.* 2000]. Therefore, it is difficult to be definite about ablative therapy in this group at this time although it in the future it can be considered as a therapeutic option especially if the high-risk population of progressors could be identified.

High-grade dysplasia and intramucosal oesophageal adenocarcinoma

Patients with HGD (whereby the glandular crypts are significantly distorted and may include

Figure 1. Intramucosal Barrett's adenocarcinoma (T1) subclassification. Lymph node metastases in intramucosal cancer is <1% and that involving the upper third of the submucosa is between 0–8% [Pech, 2009; Liu *et al* 2005].

branching, which is not present in LGD) are at highest risk for progression to cancer. Therefore, this epithelium should be eradicated provided that the biopsies have been independently reviewed by two expert histopathologists preferably one with special expertise in oesophageal diseases. Intramucosal adenocarcinoma is defined as neoplasia that penetrates the basement membrane but does not extend below the muscularis mucosae. The TNM classification (extent of tumour, spread to lymph nodes and presence of metastasis) developed by the American Joint Committee on Cancer defines intramucosal adenocarcinoma confined to the mucosa as T1m, that penetrating deeper into the submucosa as T1sm (Figure 1).

Historically, the gold standard for treatment of HGD and intramucosal cancer was oesophagectomy, especially given the risk of a synchronous cancer in the former. Moreover, the entire segment is removed including occult adenocarcinoma and local lymph nodes although endoscopic surveillance may still be required postsurgery [Dresner *et al.* 2003]. The 5-year survival rate in patients postoesophagectomy is between 90% and 95%. Significant morbidity occurs in approximately 40–50% including pulmonary complications, anastomotic leak, dysphagia, loss of appetite, early satiety, fatigue and loss of functional oesophagus [Rice *et al.* 1993; Heitmiller *et al.* 1996; Nigro *et al.* 1999]. It is important that oesophagectomies are performed by an experienced surgeon in a high-volume centre to minimise morbidity and mortality (4.9% at a centre performing >50 oesophagectomies) [Van Lanschot *et al.* 2001].

Endoscopic ultrasound (EUS) utilizing the TNM classification is useful in deciding whether patients with Barrett's high-grade neoplasia/

adenocarcinoma are offered endoscopic therapy or oesophagectomy. Nevertheless, EUS has its limitations in differentiating HGD from a T1m or T1sm lesion [Larghi *et al.* 2005]. Diagnostic EMR and CT scanning are useful tools in further fine-tuning staging of HGD/OA. Diagnostic EMR is superior to conventional biopsies and can result in a significant bidirectional alteration in diagnosis [Nijhawan and Wang, 2000]. Most patients with HGD (70–80%) can be successfully treated with endoscopic eradication therapy [AGA, 2011] and this shall be discussed in greater detail in the following section.

Ablative therapy for high-grade Barrett's dysplasia

Photodynamic therapy

This eradication therapy involves the use of a photosensitizing agent delivered either intravenously or orally, i.e. porfimer sodium (approved for use in the USA) or 5-aminolevulinic acid (5-ALA, rest of the world) followed 48 hours later by delivery of laser light to the Barrett's epithelium. Upon contact with laser light, cells containing the photosensitizer form highly reactive oxygen metabolites that destroy tissue.

In a long-term randomized multicentre trial, Overholt and colleagues assessed the safety and efficacy of photodynamic therapy (PDT) treatment in patients with Barrett's HGD. They randomized 138 patients to PDT plus omeprazole and 70 subjects to omeprazole alone ($n = 70$) for a 2-year period. At 5-year follow up, HGD was eradicated in 77% of those treated with PDT and omeprazole *versus* 37% on PPI alone. Cancer progression which was a secondary outcome was lower in the PDT group (15%) as compared

with the omeprazole group (29%) ($p = 0.004$) [Overholt *et al.* 2007].

PDT achieves a relatively uniform depth of ablation and a significantly greater depth of penetration (with tissue necrosis >5 mm) as compared with other ablative techniques [Tokar *et al.* 2006]. In addition, longer segments of tissue can be treated because it is a noncontact ablative technique. Efficacy rates of 57–100% have been achieved with porfimer sodium (deeper tissue penetration than 5-ALA) with mean follow-up intervals of 10–51 months [Vij *et al.* 2004]. The drawbacks of PDT are its high cost, complications and limited availability. It has been reported that 27–34% of patients treated with PDT end up with strictures. Cutaneous phototoxicity is also common, occurring in 30–69% of patients [Wolfsen *et al.* 2004; Overholt *et al.* 2005].

Radiofrequency ablation

RFA is a relatively new endoscopic treatment modality for BO consisting of a balloon-based bipolar radiofrequency ablation catheter, sizing catheters and a radiofrequency energy generator (BaRRx, Inc, Sunnyvale, CA). Several groups have reported high rates of complete eradication of dysplasia (and metaplasia) using radiofrequency ablation for dysplastic BO [Shaheen *et al.* 2009; Sharma *et al.* 2008; Pouw *et al.* 2008]. Importantly, RFA treatment for patients with HGD has been shown to reduce progression to cancer [Shaheen *et al.* 2009].

The landmark AIM Dysplasia Trial mentioned previously randomized 127 patients (64 LGD, 63 HGD) in a 2:1 ratio into RFA and endoscopic surveillance or endoscopic surveillance alone [Shaheen *et al.* 2009]. A total of 117 participants completed a year's follow up. At 1 year, complete eradication of HGD (intention-to-treat analysis) occurred in 81% of those in the ablation group as compared with 19% in the control group ($p < 0.001$). Moreover, 2- and 3-year outcomes of the trial confirmed durability of the treatment effect after allowing for focal touch up RFA [Shaheen *et al.* 2011]. In the HGD group, columnar eradication of dysplasia (CE-D) was achieved in 50/54 patients (95%) at 2 years and 23/24 (96%) at 3 years.

Pouw and colleagues recruited 44 patients (12 HGD, 16 early cancer) and using EMR in most patients ($n = 31$) followed by step-wise RFA in all

achieved CE-D and complete eradication of intestinal metaplasia (CE-IM) in 43/44 subjects (98%) [Pouw *et al.* 2008]. Again, at 21 months, durability of response was evident, i.e. no recurrence of dysplasia. Combination therapy of EMR and RFA is highly effective for HGD and intramucosal cancer and may well represent the gold standard ablation technique. Reported complications with RFA include transient fever, mild dysphagia, odynophagia, oesophageal stricture and perforation. Buried metaplasia appears to occur infrequently after RFA [Shaheen *et al.* 2009; Sharma *et al.* 2008].

Endoscopic mucosal resection

EMR is the removal of affected mucosa and submucosa by resection through the middle or deeper part of the submucosa. Unlike other ablative methods, EMR permits histological assessment of the whole lesion permitting definition of lateral extent and depth. It alters the pathological staging in BO in 26–37% of patients [Conio *et al.* 2005; Mino-Kenudson *et al.* 2005]. EMR is suitable for short segments of BO, early OA and particularly useful for visible lesions. Mucosally confined oesophageal carcinoma has a very low risk of metastatic lymphadenopathy (1–2%) which makes endoscopic resection feasible. In one study involving 41 patients with Barrett's adenocarcinoma, 350 resected lymph nodes were analysed. The risk of lymph node metastasis was 0% in patients with intramucosal (m1–4) cancers compared with 16% in patients with submucosal infiltration [Holscher *et al.* 1997]. Intramucosal (m1–4) Barrett's cancers less than 2 cm, unifocal and macroscopically type I, IIa, IIb and IIc are ideal for EMR.

Some investigators have reported that the upper third of the submucosa (sm1) has a very low risk of lymph node metastasis [Stein *et al.* 2005; Buskens *et al.* 2004]. Others have reported a risk of lymph node involvement of between 0% and 8% in sm1 OA [Westerterp *et al.* 2005; Liu *et al.* 2005], although one study from the Mayo Clinic has found that up to 12.9% of cancers confined to the first third of the submucosa have lymph node metastasis [Badreddine *et al.* 2010]. There is debate as to whether sm1 cancers might be eligible for endoscopic resection with a curative intent. One study has revealed that EMR in submucosal cancers with low-risk criteria have favourable outcomes. These include invasion confined to sm1, absence of lymphovascular infiltration, macroscopic appearance type I/II

Figure 2. Paris classification of the endoscopic appearance of superficial neoplastic lesions of the digestive tract mucosa.

and histological grade G1/2 [Manner *et al.* 2008]. Nevertheless, more trial data is required before recommending EMR for sm1 lesions (Figures 1 and 2).

In a nonblinded, nonrandomized study, the Wiesbaden group performed EMR in a total of a 100 patients with early OA and complete remission was obtained in 99% after a mean of 1.47 endoscopic mucosal resections without major complications. Nevertheless, there was a cancer recurrence rate of 11% at 36.7 months follow up [Ell *et al.* 2007]. Piecemeal resection, long-segment BO, multifocal neoplasia and non-use of ablative therapy after complete remission of BO are risk factors for recurrence of malignancy [Pech *et al.* 2008]. Circumferential endoscopic mucosal resection (removal of the entire BO segment) results in complete remission of early OA and Barrett's epithelium in the vast majority of patients (75–100%) [Seewald *et al.* 2003; Giovannini *et al.* 2004; Peters *et al.* 2006; Larghi *et al.* 2007]. In a study involving 37 patients with early OA, successful eradication of cancer was achieved in all patients. Complete removal of BO was reported in 89% of patients [Peters *et al.* 2006]. Reported complications of EMR include early bleeding (within 12–24 hours), perforation (0.06–5%) and stricture formation particularly after circumferential resection (30–40%) [Rembacken *et al.* 2001; Peters *et al.* 2006].

Cryotherapy

Endoscopic spray cryotherapy ablation uses liquid nitrogen (–196°C, CSA system) or rapidly

expanding carbon dioxide gas (–78°C at flow temperature of 6–8 l/min, PolarWand) to produce rapid freezing and slow thawing of a defined volume of tissue causing injury. Nonrandomized and uncontrolled studies show success rates comparable to other ablative modalities for the treatment of Barrett's HGD, with complete eradication of dysplasia seen in 87–96% and complete elimination of intestinal metaplasia in 57–96% of treated patients. In early-stage oesophageal cancer, spray cryotherapy, eliminates mucosal cancer in 75% of patients [Greenwald and Dumot, 2011]. In an uncontrolled, nonrandomized, retrospective study, 98 patients with BO and HGD underwent a mean of 3.4 CRYO treatments. Sixty subjects completed all planned CRYO treatments, of which 58 patients (97%) had complete eradication of HGD [Shaheen *et al.* 2010]. Fifty-two patients (87%) had complete eradication of all dysplasia with persistent nondysplastic intestinal metaplasia, and 34 (57%) had complete eradication of all intestinal metaplasia. Reported adverse events included strictures in three subjects and severe chest pain in two patients. One subject was hospitalized for bright red blood per rectum. Buried glands were found in two subjects (3%).

Conclusion

Current and future exciting innovations in imaging and endoscopic treatment modalities may offer the real possibility of detecting, surveying and treating more patients with BO and dysplasia at an early stage in the disease sequence well before it progresses to cancer (Figure 3). In a few short years, the combination

Figure 3. Algorithm for the management of Barrett's oesophagus [adapted from Singh *et al.* [2011]].

of EMR and ablative therapy, e.g. RFA, has replaced oesophagectomy as the standard of care in the management of HGD and oesophageal intramucosal cancer.

Sadly, despite screening, surveillance, new developments in imaging and molecular markers as well as the armamentarium of ablative therapy being available to the endoscopist, the exponential rise in OA in the Western World continues. Paradoxically, the cancer risk in BO gets progressively downgraded [Rajendra and Sharma, 2011; Bhat *et al.* 2011; Hvid-Jensen *et al.* 2011]. Obviously, there is a missing link that is yet to be identified. It raises fundamental questions about our understanding of this fascinating but potentially lethal premalignant condition especially at

molecular level and lack of attention to possible interactions with other as yet unidentified risk factors, e.g. viruses [Rajendra and Robertson, 2010]. Future research has to be directed at these areas to fine tune our screening and surveillance programs to identify more accurately the high-risk group of progressors to OA who would benefit most from ablative therapy.

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Conflict of interest statement

The authors declare no conflicts of interest in preparing this article.

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