Columnar lined Barrett's oesophagus

Over the past few years, the definition of Barrett's oesophagus has altered with no real agreement on histological understanding. This article highlights the increasing confusion regarding Barrett's oesophagus with a focus on the all-too-frequently ignored aspect of the columnar lined oesophagus.

Globally, there is much controversy regarding the definition of Barrett's oesophagus. In the UK and Japan, the definition focuses on replacement of the normal stratified squamous epithelium with one which is histologically confirmed as columnar in nature and ≥1 cm in extent above the gastro-oesophageal junction (Fitzgerald et al, 2014). However, the American Gastroenterological Association (2011) has stated that the presence of intestinal metaplasia (columnar epithelium with co-existing goblet cells) is essential for the diagnosis of Barrett's oesophagus as this, they conclude, is the only type of columnar lined oesophagus that predisposes to malignancy. This divide in agreement over diagnosis is not new and the controversy is supported by research.

Evidence against the American standpoint comes courtesy of a study of 379 patients with intestinal metaplasia and 309 with glandular mucosa who were followed up over a median of 12 years. Results demonstrated the development of oesophageal adenocarcinoma in 28 patients – 17 in the intestinal metaplasia grouping and 11 in the glandular mucosa group – with no statistically significant difference between the two groups (Kelty et al, 2007). Furthermore on a molecular level, Liu et al (2009) undertook histological evaluation of mucosal biopsies from 68 patients with columnar lined oesophagus – 22 without goblet cells and 46 with. Findings highlighted that patients with columnar epithelium without goblet cells had DNA content results which were statistically similar to those patients with columnar epithelium and goblet cells. In addition there were no key DNA content abnormalities between non-goblet and goblet cell epithelium, indicating that non-goblet columnar epithelium has equal potential for neoplastic progression. A third study from Japan, focusing on the mucosa of 113 oesophageal adenocarcinomas resected endoscopically, highlighted no evidence of intestinal metaplasia in 56.6% of cases with more than 70% of oesophageal adenocarcinomas located adjacent to cardiac or fundic type mucosa (Takubo et al, 2009).

Molecular basis

The molecular basis of columnar lined oesophagus is complex and still not fully understood.

Barrett's metaplasia is subdivided typically as incomplete and complete. The former is characterized by columnar and goblet cells secreting sialomucins and sulfomucins in addition to the expression of MUC2 and MUC3 (seen in intestinal epithelium) as well as MUC1, MUC5AC and MUC6 (seen in gastric epithelium) (McDonald et al, 2015). Complete intestinal metaplasia is associated with absorptive cells, Paneth cells and MUC2 intestinal mucin.

It is widely accepted that Barrett's oesophagus metaplastic glands are derived from multipotential stem cells. The triggering factor is reflux, leading to the change from squamous to columnar epithelium which is thought to provide a form of protective advantage. The sources of Barrett's epithelium are hypothesized as being from stem cells of the squamous epithelium of the oesophagus, stem cells from the gastric cardiac epithelium or submucosal oesophageal glands, or circulating multipotent bone marrow stem cells (McDonald et al, 2015).

An array of genetic influences has also been highlighted with regards to the induction of columnar lined oesophagus. One such example arose from p63 (a member of the p53 family) knock out mice which developed evidence of highly ordered, columnar ciliated epithelium (Daniely et al, 2004). Further work in this model has shown that the development of metaplastic change is secondary to a discrete population of residual embryonic cells at the squamo-columnar junction which migrate towards oesophageal squamous cells following gastro-oesophageal reflux (Wang et al, 2011). Continued genetic evidence has been supplemented by the prevalence of CDX1/2 mRNA expression being significantly higher in Barrett's epithelial mucosa. Furthermore CDX2 mRNA expression was specifically observed during the initial stages of oesophagitis (Eda et al, 2003).

In work focused on thrombospondin 1 knockout mice, Crawford and colleagues (1998) noted evidence of low levels of transforming growth factor-β resulting in areas of columnar lined epithelium within the oesophagus. Castillo et al (2012) concluded from a human model of gastro-oesophageal reflux disease that BMP4 mRNA levels were significantly greater in non-specialized columnar metaplasia than in squamous oesophageal epithelium. In keeping with cytokine-based theories, work from

Dr Neel Sharma *is Visiting Clinical Research Fellow and* **Professor Khek Yu Ho** *is Senior Consultant in the Division of Gastroenterology and Hepatology, National University Hospital Singapore, 119228, Singapore_*

Correspondence to: Dr N Sharma (drneelsharma@outlook.com)

a transgenic mouse model of Barrett's oesophagus highlighted that overexpression of interleukin-1β led to the evolution of oesophagitis, Barrett's-like metaplasia and later oesophageal adenocarcinoma (Quante et al, 2012).

p53 gene mutations have been noted in oesophageal adenocarcinoma and furthermore in the progression from metaplasia to dysplasia and beyond (Keswani et al, 2006). Younes et al (1997) undertook immunohistochemistry evaluation of p53 in patients with Barrett's oesophagus and concluded that p53 accumulation is more specific and has greater predictive value for the development of high grade dysplasia or oesophageal adenocarcinoma than the histological diagnosis of low grade dysplasia. Functionally p53 is responsible for cellular function regulation such as cell cycle progression, senescence, differentiation and apoptosis (Keswani et al, 2006).

It has also been suggested that extracellular matrix proteins may be pathologically implicated following evidence that mouse embryonic stem cells seeded on hensin or laminin led to the development of columnar or squamous-type epithelium respectively (Takito and Al-Awqati, 2004).

From a translational perspective, Bird-Lieberman and colleagues (2012) targeted cell surface glycans which have been shown previously to be altered in pancreatic, colon and gastric cancer. Glycan changes can be determined using lectins and work by this group highlighted the value of a fluorescently labelled lectin to detect changes in glycan expression from Barrett's oesophagus to dysplasia and beyond during endoscopy.

Diagnostic approaches

The diagnosis of Barrett's oesophagus currently relies on the use of high resolution white light endoscopy and both a random and targeted biopsy approach of visible lesions. The Seattle Barrett's Oesophagus Project undertook 1458 endoscopies on 705 patients from 1983 to 1997 where multiple biopsies were obtained from lesions as well as at 1–2 cm intervals throughout the Barrett's segment. They concluded that this approach was safe and did not lead to the subsequent induction of oesophageal perforation or bleeding (Levine et al, 2000). With regards to diagnosis, however, sampling errors have long been a concern among endoscopists, with a study of 125 patients with columnar lined oesophagus noting that the optimum number of biopsies required to diagnose intestinal metaplasia was eight per endoscopy, a mean yield of 67.9%. If four were taken only 34.7% were diagnosed with intestinal metaplasia. If 16 or more were taken the diagnostic yield of intestinal metaplasia was 100% (Harrison et al, 2007). In addition results from a study of 1751 patients with columnar lined oesophagus demonstrated that 54.8% of patients had evidence of intestinal metaplasia after 5 years and 90% after 10 years, emphasizing yet again that detection of intestinal metaplasia relies significantly on adequate biopsy sampling (Gatenby et al, 2008).

With regards to diagnosis at endoscopy, various classification systems have been put forward as the potential gold standard. The Prague C and M classification was cemented following an international working group agreement in 2006 where videos of patients with columnar lined oesophagus were assessed in terms of circumferential and maximum segment extent above the gastro-oesophageal junction. The overall reliability coefficients were 0.95 and 0.94 respectively. In addition, the reliability coefficient for the endoscopic recognition of columnar lined oesophagus ≥1 cm was 0.72 and 0.22 for <1 cm (Sharma et al, 2006).

Advancing this approach further comes courtesy of the Paris classification system which is advocated for the endoscopic description of superficial neoplastic lesions. Here iodine potassium iodide solution or indigo carmine solution for the stratified squamous or columnar lined epithelium respectively is applied to determine the lesion type with type 0 being the primary nomenclature for an endoscopic superficial lesion. Subdivision of type 0 has been described with three categories: protruding (0–I), non-protruding and non-excavated (0–II), and excavated (0–III). Type 0–II lesions are then further classified into slightly elevated (IIa), flat (IIb) or depressed (IIc), with non-protruding depressed lesions associated with a higher risk of submucosal invasion (Endoscopic Classification Review Group, 2005).

Amano and colleagues (2006) set about determining which landmark was most appropriate in the diagnosis of columnar lined oesophagus and aimed to compare the use of gastric folds with use of the palisade vessels. In this study, 84 endoscopists classified 30 patients with results giving an overall kappa value for identification of the distal oesophagus as 0.14 for the palisade vessel approach, indicating that this approach is a poor way of measuring the extent of Barrett's oesophagus. This finding further supported the use of the Prague C and M criteria.

As mentioned previously, the currently agreed viewpoint for diagnosis is the presence of columnar lined oesophagus ≥1cm above the gastro-oesophageal junction. Interestingly, however, findings from a study of 166 patients noted the existence of specialized intestinal metaplasia from an irregular Z line, namely columnar lined oesophagus shorter than 1 cm, in 43.5% of cases (Sharma et al, 2006). Despite this finding, there is at present no obvious movement towards an altered diagnostic agreement. Further research is certainly warranted in this regard.

Screening for columnar lined oesophagus

In terms of screening, evidence highlights chronic gastro-oesophageal reflux disease as a significant risk factor, with a meta-analysis demonstrating an odds ratio of 2.90 (95% confidence interval 1.86–4.54), with a strong and homogenous association with long segment columnar lined oesophagus (Taylor and Rubenstein, 2010). Edelstein et al (2009) observed that an increasing age, male gender and smoking enhanced the risk of intestinal metaplasia. Central adiposity was strongly linked to the risk of visible columnar lined epithelium and long segment columnar lined oesophagus, but an increasing body

mass index was less so. On the whole there is minimal literature focused on symptom and demographic association comparisons between patients with columnar lined oesophagus and those with intestinal metaplasia. Liu et al (2014) undertook a prospective cohort study of 1603 patients and noted that age, gender, smoking, heartburn, acid reflux, chest or abdominal pain and the use of anti-reflux medication were associated with both columnar lined oesophagus and intestinal metaplasia >2 cm, with acid reflux and chest pain for intestinal metaplasia borderline significant (P=0.07). These eight factors were subsequently used to develop a risk prediction model with age, gender, chest or abdominal pain and anti-reflux medication selected for both columnar lined epithelium and intestinal metaplasia >2 cm. Heartburn was determined a predictor for intestinal metaplasia >2 cm, with acid reflux a predictor for columnar lined epithelium.

Surveillance

Progression of columnar lined oesophagus to adenocarcinoma is of particular interest in determining surveillance strategies. Evidence points in the most part to a higher risk of malignancy in patients with intestinal metaplasia. A study of 8522 patients with Barrett's oesophagus, with or without intestinal metaplasia, followed up over a 7-year period, noted the occurrence of adenocarcinoma in 79 patients. For those with intestinal metaplasia, the combined incidence of oesophageal or gastric cardia cancer or high grade dysplasia was 0.38% per year, with the risk of cancer being statistically significant in patients with *vs* without intestinal metaplasia (0.38% *vs* 0.07%, P<0.001) (Bhat et al, 2011).

The length of the Barrett's segment has also long been investigated with regards to cancer progression. Desai et al (2012) undertook a meta-analysis of 57 studies and noted that in patients with Barrett's oesophagus, defined strictly as the presence of intestinal metaplasia, the annual incidence of adenocarcinoma in those with short segment disease (<3 cm) was 0.19% as opposed to 0.33% overall. A 597-patient study focused on the presence of columnar lined oesophagus noted no evidence of adenocarcinoma in a segment length <3 cm with a mean length of 7.2 cm for those with adenocarcinoma occurrence (Bani-Hani et al, 2005). By and large, there are limited data on cancer incidence in reference to columnar lined oesophagus segment length with large patient cohort studies in the main focused purely on analysis of the progression of intestinal metaplasia (Bhat et al, 2011; Sikkema et al, 2011; Wani et al, 2011).

Based on current research findings general consensus advocates a repeat endoscopy 3–5-yearly for patients with no dysplasia (Fitzgerald et al, 2014). However, with such a low annual risk of cancer progression in patients with only columnar lined oesophagus and those with intestinal metaplasia, this broad surveillance approach may appear rather ill defined and cost ineffective. Furthermore, it has been advised that patients with a Barrett's oesophagus segment length >3 cm should undergo endoscopic assessment every 2–3 years, which again highlights the potential lack of clarity in view of the actual cancer risk (Fitzgerald et al, 2014).

Management

Owing to the triggering factor of gastro-oesophageal reflux disease in the pathogenesis of columnar lined oesophagus, patients are advised to take proton pump inhibitor therapy. El-Serag et al (2004) noted, during a 20-year study of 236 patients, that the cumulative incidence of dysplasia was significantly lower among those who had received proton pump inhibitors compared to those who did not, either having had no therapy or H_2-receptor-based antagonists (P<0.001). van Pinxteren et al (2006) further confirmed the benefit of proton pump inhibitor therapy following analysis of 31 randomized controlled trials involving 9457 patients, noting the relative risk of heartburn remission for proton pump inhibitors as 0.37 (95% confidence interval 0.32–0.44), for H_2-receptor-based antagonists as 0.77 (95% confidence interval 0.60–0.99) and for prokinetics as 0.86 (95% confidence interval 0.73–1.01).

Current consensus highlights the value of endoscopic intervention specifically in cases of Barrett's-related dysplasia and early neoplasia. (Further details on this aspect are outside the scope of this review.) However, El Serag and Graham (2011) highlighted a potential discourse between non-dysplastic Barrett's oesophagus and colorectal polyps, stating that endoscopic therapy in the latter is not simply limited to malignant-type polyps. Further advocates for endoscopic-based therapy in non-dysplastic disease have remarked that loss of cell cycle control, molecular aberrations and further neoplastic features also exist in the former. In addition early crypt dysplasia is plagued by detection-based limitations during pathological analysis, therefore signalling a need for intervention such as radiofrequency ablation across all subtypes of Barrett's oesophagus (Fleischer et al, 2010a). Outcomes from the multicentre AIM II trial of 50 patients who underwent radiofrequency ablation for non-dysplastic Barrett's oesophagus demonstrated no evidence of dysplasia after a 5-year follow up (Fleischer et al, 2010b). One could therefore certainly advocate the potential value of early intervention at the inflammatory stage. However, further prospective studies are needed to confirm such policy.

Conclusions

This article summarizes the significant complexities of columnar lined Barrett's oesophagus. There is still disagreement as to the true definition of Barrett's oesophagus and how best to monitor this particular epithelial change. The BOSS multicentre randomized controlled trial hopes to shed light on the efficacy and cost effectiveness of screening patients with Barrett's oesophagus for oesophageal adenocarcinoma (Old et al, 2015). Management strategies are continually debated and the limited understanding of how columnar lined oesophagus develops in the first instance

emphasizes that we still have a long way to go. Until the true nature of this disease is fully understood, clinicians will not be able to promote effective treatment. **BJHM**

Conflict of interest: none.

American Gastroenterological Association (2011) American Gastroenterological Association Medical Position Statement on the Management of Barrett's Esophagus. *Gastroenterology* **140**(3): 1084–91 (doi: 10.1053/j.gastro.2011.01.030)

Amano Y, Ishimura N, Furuta K et al (2006) Which landmark results in a more consistent diagnosis of Barrett's esophagus, the gastric folds or the palisade vessels? *Gastrointest Endosc* **64**(2): 206–11

Bani-Hani KE, Bani-Hani BK, Martin IG (2005) Characteristics of patients with columnar-lined Barrett's esophagus and risk factors for progression to esophageal adenocarcinoma. *World J Gastroenterol* **11**(43): 6807–14

Bhat S, Coleman HG, Yousef F, Johnston BT, McManus DT, Gavin AT, Murray LJ (2011) Risk of malignant progression in Barrett's esophagus patients: results from a large population-based study. *J Natl Cancer Inst* **103**(13): 1–9 (doi: 10.1093/jnci/djr203)

Bird-Lieberman EL, Neves AA, Lao-Sirieix P et al (2012) Molecular imaging using fluorescent lectins permits rapid endoscopic identification of dysplasia in Barrett's esophagus. *Nat Med* **18**(2): 315–21 (doi: 10.1038/nm.2616)

Castillo D, Puig S, Iglesias M et al (2012) Activation of the BMP4 pathway and early expression of CDX2 characterize non-specialized columnar metaplasia in a human model of Barrett's esophagus. *J Gastrointest Surg* **16**(2): 227–37; discussion 237 (doi: 10.1007/s11605-011-1758-5)

Crawford SE, Stellmach V, Murphy-Ullrich JE et al (1998) Thrombospondin-1 is a major activator of TGF-β1 in vivo. *Cell* **93**(7): 1159–70 (doi: 10.1016/S0092-8674(00)81460-9)

Daniely Y, Liao G, Dixon D et al (2004) Critical role of p63 in the development of a normal esophageal and tracheobronchial epithelium. *Am J Physiol Cell Physiol* **287**(1): C171–81

Desai TK, Krishnan K, Samala N, Singh J, Cluley J, Perla S, Howden CW (2012) The incidence of oesophageal adenocarcinoma in non-dysplastic Barrett's oesophagus: a meta-analysis. *Gut* **61**(7): 970–6 (doi: 10.1136/gutjnl-2011-300730)

Eda A, Osawa H, Satoh K et al (2003) Aberrant expression of CDX2 in Barrett's epithelium and inflammatory esophageal mucosa. *J Gastroenterol* **38**(1): 14–22

Edelstein ZR, Bronner MP, Rosen SN, Vaughan TL (2009) Risk factors for Barrett's esophagus among patients with gastroesophageal reflux disease: a community clinic-based case-control study. *Am J Gastroenterol* **104**(4): 834–42 (doi: 10.1038/ajg.2009.137)

El-Serag HB, Graham DY (2011) Routine polypectomy for colorectal polyps and ablation for Barrett's esophagus are intellectually the same. *Gastroenterology* **140**(2): 386–8 (doi: 10.1053/j.gastro.2010.12.019)

El-Serag HB, Aguirre TV, Davis S, Kuebeler M, Bhattacharyya A, Sampliner RE (2004) Proton pump inhibitors are associated with reduced incidence of dysplasia in Barrett's esophagus. *Am J Gastroenterol* **99**(10): 1877–83

Endoscopic Classification Review Group (2005) Update on the Paris classification of superficial neoplastic lesions in the digestive tract. *Endoscopy* **37**(6): 570–8 (doi: 10.1055/s-2005-861352)

Fitzgerald RC, di Pietro M, Ragunath K et al ; British Society of Gastroenterology (2014) British Society of Gastroenterology guidelines on the diagnosis and management of Barrett's oesophagus. *Gut* **63**(1): 7–42 (doi: 10.1136/gutjnl-2013-305372)

Fleischer DE, Odze R, Overholt BF et al (2010a) The case for endoscopic treatment of non-dysplastic and low-grade dysplastic Barrett's esophagus. *Dig Dis Sci* **55**(7): 1918–31 (doi: 10.1007/s10620-010-1218-1)

Fleischer DE, Overholt BF, Sharma VK et al (2010b) Endoscopic radiofrequency ablation for Barrett's esophagus: 5-year outcomes from a prospective multicenter trial. *Endoscopy* **42**(10): 781–9 (doi: 10.1055/s-0030-1255779)

Gatenby PA, Ramus JR, Caygill CP, Shepherd NA, Watson A (2008) Relevance of the detection of intestinal metaplasia in non-dysplastic columnar-lined oesophagus. *Scand J Gastroenterol* **43**(5): 524–30 (doi: 10.1080/00365520701879831)

Harrison R, Perry I, Haddadin W et al (2007) Detection of intestinal metaplasia in Barrett's esophagus: an observational comparator study suggests the need for a minimum of eight biopsies. *Am J Gastroenterol* **102**(6): 1154–61 (doi: 10.1111/j.1572-0241.2007.01230.x)

Kelty CJ, Gough MD, Van Wyk Q, Stephenson TJ, Ackroyd R (2007) Barrett's oesophagus: intestinal metaplasia is not essential for cancer risk. *Scand J Gastroenterol* **42**(11): 1271–4 (doi: 10.1080/00365520701420735)

Keswani RN, Noffsinger A, Waxman I, Bissonnette M (2006) Clinical use of p53 in Barrett's esophagus. *Cancer Epidemiol Biomarkers Prev* **15**(7): 1243–9 (doi: 10.1158/1055-9965.EPI-06-0010)

Levine DS, Blount PL, Rudolph RE, Reid BJ (2000) Safety of a systematic endoscopic biopsy protocol in patients with Barrett's esophagus. *Am J Gastroenterol* **95**(5): 1152–7 (doi: 10.1111/j.1572-0241.2000.02002.x)

Liu W, Hahn H, Odze RD, Goyal RK (2009) Metaplastic esophageal columnar epithelium without goblet cells shows DNA content abnormalities similar to goblet cell-containing epithelium. *Am J Gastroenterol* **104**(4): 816–24 (doi: 10.1038/ajg.2009.85)

Liu X, Wong A, Kadri SR et al (2014) Gastro-esophageal reflux disease symptoms and demographic factors as a pre-screening tool for Barrett's esophagus. *PLoS One* **9**(4): e94163 (doi: 10.1371/journal.pone.0094163)

McDonald SA, Lavery D, Wright NA, Jansen M (2015) Barrett oesophagus: lessons on its origins from the lesion itself. *Nat Rev Gastroenterol Hepatol* **12**(1): 50–60 (doi: 10.1038/nrgastro.2014.181)

Old O, Moayyedi P, Love S et al; BOSS Trial Team (2015) Barrett's Oesophagus Surveillance versus endoscopy at need Study (BOSS): protocol and analysis plan for a multicentre randomized controlled trial. *J Med Screen* **22**(3): 158–64 (doi: 10.1177/0969141315575052)

Quante M, Bhagat G, Abrams JA et al (2012) Bile acid and inflammation activate gastric cardia stem cells in a mouse model of Barrett-like metaplasia. *Cancer Cell* **21**(1): 36–51 (doi: 10.1016/j.ccr.2011.12.004)

Sharma P, Dent J, Armstrong D et al (2006) The development and validation of an endoscopic grading system for Barrett's esophagus: the Prague C & M criteria. *Gastroenterology* **131**(5): 1392–9

Sikkema M, Looman CW, Steyerberg EW et al (2011) Predictors for neoplastic progression in patients with Barrett's Esophagus: a prospective cohort study. *Am J Gastroenterol* **106**(7): 1231–8 (doi: 10.1038/ajg.2011.153)

Takito J, Al-Awqati Q (2004) Conversion of ES cells to columnar epithelia by hensin and to squamous epithelia by laminin. *J Cell Biol* **166**(7): 1093–102 (doi.org/10.1083/jcb.200405159)

Takubo K, Aida J, Naomoto Y et al (2009) Cardiac rather than intestinal-type background in endoscopic resection specimens of minute Barrett adenocarcinoma. *Hum Pathol* **40**(1): 65–74 (doi: 10.1016/j.humpath.2008.06.008)

Taylor JB, Rubenstein JH (2010) Meta-analyses of the effect of symptoms of gastroesophageal reflux on the risk of Barrett's esophagus. *Am J Gastroenterol* **105**(8): 1729, 1730–7; quiz 1738 (doi: 10.1038/ajg.2010.194)

van Pinxteren B, Sigterman KE, Bonis PA, Lau J, Numans ME (2006) Short-term treatment with proton pump inhibitors, H2-receptor antagonists and prokinetics for gastro-oesophageal reflux disease-like symptoms and endoscopy negative reflux disease. *Cochrane Database Syst Rev* (**3**): CD002095 (doi: 10.1002/14651858.CD002095.pub3)

Wang X, Ouyang H, Yamamoto Y et al (2011) Residual embryonic cells as precursors of a Barrett's-like metaplasia. *Cell* **145**(7): 1023–35 (doi: 10.1016/j.cell.2011.05.026)

Wani S, Falk G, Hall M et al (2011) Patients with nondysplastic Barrett's esophagus have low risks for developing dysplasia or esophageal adenocarcinoma. *Clin Gastroenterol Hepatol* **9**(3): 220–7; quiz e26 (doi: 10.1016/j.cgh.2010.11.008)

Younes M, Ertan A, Lechago LV, Somoano JR, Lechago J (1997) p53 Protein accumulation is a specific marker of malignant potential in Barrett's metaplasia. *Dig Dis Sci* **42**(4): 697–701

KEY POINTS

- Disagreement continues to exist as to the actual definition of Barrett's oesophagus.
- Further research is needed to ascertain the molecular basis.
- More prospective studies are needed to determine whether endoscopic therapy proves advantageous for columnar lined oesophagus.