CHAPTER 1
Definition and Diagnosis of Barrett's Esophagus

Ajay Bansal and Prateek Sharma

Introduction

Diagnosis of Barrett's esophagus is important to identify the subpopulation with gastroesophageal reflux disease (GERD) that not only has an altered quality of life but also is at an increased risk for esophageal adenocarcinoma as compared to the general population. Approximately 10–15% of patients with chronic GERD are diagnosed with Barrett's esophagus, a premalignant lesion for esophageal adenocarcinoma [1,2] This subgroup with Barrett's esophagus may benefit from regular surveillance to identify progression to dysplasia prior to the development of adenocarcinoma. Adenocarcinoma of the esophagus has risen almost fivefold in incidence over the past 20 years in the USA [3–6]. It now accounts for more than 50% of all esophageal cancers in this country [7].

The definition of Barrett's esophagus has evolved from endoscopic findings alone to the use of esophageal manometry and finally now to include a combination of endoscopic and histological findings in the distal esophagus. Novel endoscopic methods including magnification endoscopy, chromoendoscopy, narrow band imaging etc., are being extensively studied to assist in the endoscopic diagnosis of Barrett's esophagus but the studies are far from being conclusive. Application of newer molecular markers like cdx-2, muc-2 and sucrase isomaltase for confirming the intestinal origin of the metaplastic epithelium is being reported. In addition, use of special stains like Alcian blue in biopsies obtained from endoscopically suspected Barrett's esophagus has increased the histologic accuracy of confirming intestinal metaplasia.

Definition

The American Gastroenterological Association workshop in Chicago defined Barrett's esophagus as the displacement of the squamocolumnar junction (SCJ) proximal to the gastroesophageal junction (GEJ) with the presence of intestinal metaplasia [8] (Plate 1.1a,b; color plate section falls between pp. 148–9). The definition of Barrett's esophagus has evolved over many years since the first description in 1950s by N. R. Barrett [9]. All three types of columnar epithelium—fundic mucosa, cardia mucosa and intestinal metaplasia can be detected in the columnar lined distal esophagus [10]. However, currently there is general consensus (although controversial) on using intestinal metaplasia and not the other two types of mucosae, as the histological marker for Barrett's esophagus [8]. The reason for including intestinal metaplasia in the definition as opposed to fundic or cardia mucosa is the observation that dysplasia or cancer is usually associated with the presence of intestinal metaplasia. A review of 14 cases of esophageal adenocarcinoma revealed that 12 (86%) occurred in columnar epithelium as defined by the presence of distinctive intestinal type mucosa (confirmed Barrett's esophagus) [11]. Hamilton and Smith studied biopsy specimens from 14 Barrett's esophagus patients with known dysplasia and 43 esophagectomy specimens from patients with resected adenocarcinoma [12]. They showed that dysplasia was associated with intestinal type mucosa in 11 patients and with cardia type mucosa in three of 14 patients. Also, in the same study, evaluation of 43 esophagectomy specimens revealed that adenocarcinoma most often occurred in Barrett's mucosa of

the intestinal type. Another study identified six patients with dysplastic Barrett's mucosa, four with high-grade dysplasia, and showed that dysplasia arose in five of six cases from foci of intestinal metaplasia [13]. Besides these studies, other investigators have also demonstrated that intestinal metaplasia is associated with an increased risk of malignancy [14,15]. However, the exact malignant potential of each of the epithelia type is yet to be confirmed in a prospective follow-up study.

Endoscopic Recognition of Barrett's Esophagus

Landmarks

Normally, the SCJ should coincide with the GEJ, which is evidenced by the proximal limit of the linear gastric mucosal folds. The lack of this concurrence and the proximal displacement of the SCJ indicate the endoscopic presence of a columnar lined esophagus (i.e. endoscopic or suspected Barrett's esophagus). The GEJ is best visualized when the esophagus is distended minimally to the point at which the proximal ends of the gastric folds appear and coincide with the pinch at the end of the tubular esophagus [16] (Plate 1.1a,b; color plate section falls between pp. 148–9). Once the GEJ is accurately identified, the distance between the proximally displaced SCJ and the GEJ should be measured endoscopically and recorded as the length of the Barrett's esophagus segment [17]. In many situations, the SCJ and the GEJ may coincide for the major portion, but there maybe tongues of columnar mucosa extending for some distance above the GEJ raising a suspicion for Barrett's esophagus.

The diagnosis of Barrett's esophagus in cases of columnar appearing mucosa extending for greater than 3 cm above the GEJ is usually straightforward [18]—the chances of detecting intestinal metaplasia in this situation are greater than 90% and the recognition of the columnar lined esophagus is usually not an issue. The difficulty arises in two different situations. Firstly, there is presence of columnar mucosa on endoscopy that is at least 2–3 cm in length but histology may show cardiac type mucosa. Secondly, what appears to be a short area of columnar mucosa in the distal esophagus or an irregular Z line can show intestinal metaplasia which may actually represent intestinal metaplasia of the anatomic gastric cardia—i.e., cardia intestinal metaplasia (CIM) leading to misclassification of CIM as short segment Barrett's esophagus. The role of the endoscopist in defining the endoscopic extent of Barrett's esophagus above the GEJ is thus critical, especially in the latter situation as the pathologist will report only intestinal metaplasia that could be either Barrett's esophagus or CIM based on the exact location of the biopsy. This is of importance as Barrett's esophagus and CIM appear to be distinct entities with different demographics, symptoms and dysplasia/cancer risk [19]. Moreover, the presence of a large hiatal hernia, ulcers/erosions, strictures etc., may prevent the accurate assessment of endoscopic Barrett's esophagus, sometimes leading to the overdiagnosis of Barrett's esophagus, especially in the situation of a hernia.

Endoscopic Classification of Barrett's Esophagus

A clinically relevant classification Barrett's esophagus based on the length on endoscopy has proposed to classify the finding of intestinal metaplasia on biopsies into three categories—long segment Barrett's esophagus, short segment Barrett's esophagus, and CIM. Traditionally, long segement and short segment Barrett's esophagus have been distinguished by the length of the endoscopic Barrett's esophagus segment ($\geq$3 cm or $<$3 cm respectively) whereas CIM is diagnosed by the lack of any esophageal columnar mucosa on endoscopy but the presence of intestinal metaplasia, if biopsies are obtained below the GEJ. The "3 cm" rule for traditional Barrett's esophagus was applied in 1970s to avoid an overdiagnosis of Barrett's esophagus resulting from either failure to recognize the tubularized portion of a herniated stomach on endoscopy and, also, because it was felt that the "normal esophagus" could have 1–2 cm of columnar mucosa in its distal portion [20]. Thereafter, it was documented that even short lengths of Barrett's esophagus may undergo progression to dysplasia as well as adenocarcinoma [21,22]. A prospective study showed that although there was a non-significant trend towards increased cancer risk by 1.7-fold for every 5 cm increase in the length of Barrett's esophagus ($P = 0.06$), the length of Barrett's

esophagus was not significantly related to risk for adenocarcinoma ($P > 0.2$) [23]. In view of this, the classification of Barrett's esophagus into long (≥3 cm) and short (<3 cm) segments may be less relevant clinically.

On the other hand, CIM may have a lower risk of neoplastic progression. Sharma *et al.*, in a study of 78 patients with short segment Barrett's esophagus and 34 patients with CIM, reported that dysplasia developed in nine short segment Barrett's esophagus patients and one CIM patient, whereas adenocarcinoma developed in one patient in the short segment Barrett's esophagus group and none in the CIM group [19]. But this issue is far from settled at this time. In a review of 22 resected specimens of adenocarcinoma occuring within 2 cm of the GEJ and 22 matched control specimens of resected esophageal squamous carcinoma, CIM with high- or low-grade dysplasia was associated with 64% of adenocarcinoma compared to 5% of controls ($P < 0.001$) [24]. Moreover, the incidence of cardia adenocarcinoma has increased over the past 15 years [25] and longer follow-up studies are needed to define the exact neoplastic risk of CIM.

The Z-line appearance (ZAP) classification has been developed to describe the endoscopic extent of Barrett's esophagus with particular reference to short segment Barrett's esophagus [26]. However, this system also uses a threshold of 3 cm to distinguish between grade II and III Barrett's esophagus making it insufficiently precise to document progression or regression of Barrett's esophagus. A new grading system called the Prague C and M criteria for the endoscopic extent of Barrett's esophagus has recently been put forth [17]. This classification proposes to use the length of circumferential Barrett's esophagus (C) as well as the maximal length (M) including the length of tongues to accurately describe the extent of Barrett's esophagus. This grading system may be useful in clinical practice as well as in multicenter research studies to follow the length of Barrett's esophagus over time in the same patient. Intial validation studies have shown good interobserver agreement using the Prague C and M criteria but they still need to be validated prospectively with respect to further interobserver agreement, clinical relevance and patient outcomes [17].

Histologic Diagnosis of Barrett's Esophagus: the Goblet Cell

The current working definition of Barrett's esophagus necessitates histologic confirmation of intestinal metaplasia on biopsies from the columnar lined esophagus. The "goblet cell" deserves special mention as it is the *sine qua non* for intestinal metaplasia. It is an integral part of the normal small intestinal mucosa and metaplasia in the setting of Barrett's esophagus and is responsible for the secretion of mucus into the gut lumen. On H&E staining, goblet cells have a distended lateral border, compressed basal nucleus and basophilic apical cytoplasm. Goblet cells have acid mucins and stain intensely with Alcian blue (at pH 2.5) [27–29], making it easy to distinguish them from the foveolar cells of gastric type mucosa which stain with periodic acid–Schiff (PAS) but not Alcian blue. The staining with Alcian blue is extremely useful in distinguishing the intestinal metaplasia from cardia mucosa as occasionally some of the gastric cardiac cells may look like goblet cells on routine hematoxylin and eosin (H&E) staining [30]. This may prevent overdiagnosis of Barrett's esophagus and avoid unnecessary enrollment of patients into a surveillance program. Occasionally, Alcian blue may stain the cytoplasm of foveolar cells that are called "columnar blues." However, the distinction from typical goblet cells is usually straightforward as the histology of these columnar blues is distinct from the goblet cells. Also, columnar blues are often seen in groups while goblet cells usually are seen as solitary cells amongst the columnar epithelium.

In summary, despite the usefulness of Alcian blue staining, this technique is laborious, time consuming, and more expensive than routine H&E staining, preventing its wider applicability. At this time, typically, Alcian blue is used if the routine H&E staining is not convincing enough to diagnose the presence of intestinal metaplasia.

Impact of Length on the Diagnosis of Barrett's Esophagus

It is important to understand that intestinal metaplasia is a patchy disease. First and foremost, the

conventional method of four quadrant biopsies from short lengths of the columnar lined esophagus (<3 cm) provides a histologic confirmation of Barrett's esophagus in approximately 35–45% of the patients [31]. Intestinal metaplasia is more often found when the endoscopic Barrett's esophagus segment is >3 cm rather than <3 cm (80% vs. 30%) [32,33]. Secondly, repeat biopsies in these patients may increase the yield of intestinal metaplasia by almost 20% [34].

A prospective study of 177 patients enrolled in a surveillance program showed that the detection of intestinal metaplasia increased markedly with increasing number of surveillance endoscopies, particularly in short segments of columnar mucosa [35]. The cumulative percentage of intestinal metaplasia in endoscopic lengths 1–2 cm and 3–4 cm increased from 30.5% and 44.8% to 63.6% and 88.9% respectively after six endoscopies. Intestinal metaplasia was detected in all patients with greater than 4 cm of the endoscopic Barrett's esophagus segment after 2–4 endoscopies. This raises some very important questions, especially if we define Barrett's esophagus as the presence of intestinal metaplasia. Are biopsies on a single endoscopy sufficiently sensitive to rule out Barrett's esophagus in all patients? Do patients develop new intestinal metaplasia within the endoscopic segment during follow-up? In fact, the increasing yield of intestinal metaplasia on subsequent biopsies may be inferred to suggest that the endoscopic presence of columnar appearing mucosa cannot be ignored even in absence of intestinal metaplasia on biopsies. Some investigators have suggested that repeat endoscopy be considered in patients with endoscopic Barrett's esophagus if the initial biopsies are negative, especially in the short segment of suspected Barrett's esophagus. This may especially be relevant in light of data that dysplasia and adenocarcinoma can be associated with short segment Barrett's esophagus [21,22]. However, clear recommendations are lacking, and further research in this area is surely needed.

Molecular Markers for the Diagnosis of Intestinal Metaplasia (Barrett's Esophagus)

The intestinal columnar cell, the histological marker of Barrett's esophagus, shares a common lineage with the small intestinal epithelial cell. This may represent a novel method to diagnose Barrett's esophagus as the small intestinal columnar cell has some unique molecular signatures. The ability to identify these molecular markers characteristic for the intestinal cell type of Barrett's esophagus thus offers great promise, and given that intestinal metaplasia is patchy, these markers may confirm the presence of Barrett's esophagus on random biopsies.

Cdx-2 is a transcription factor whose expression in normal tissues is restricted to intestinal type epithelium. In a study of 90 patients with suspected short segment Barrett's esophagus, (45 with and 45 without intestinal metaplasia), all intestinal metaplasia (100%) cells stained for cdx-2 in the goblet cell and adjacent columnar cells while only 38% of columnar tissue without intestinal metaplasia stained for cdx-2 [36]. Moreover, none of the 25 samples of gastric cardiac mucosa (controls) and none of the "columnar blues" stained for cdx-2. This suggests that cdx-2 staining to detect cells of intestinal origin may allow for a more accurate diagnosis of Barrett's esophagus and, perhaps, a newer molecular classification of the columnar lined distal esophagus could be envisioned in the future.

Another study correlated the expression of cdx-2 and muc-2 (a type of acid mucin specific to the goblet cell) in patients suspected to have intestinal metaplasia in the esophagus [37]. They reported that all patients with histologic intestinal metaplasia had cdx-2 protein and mRNA expression as opposed to none of the 26 patients with gastric metaplasia and the 40 reflux esophagitis patients without Barrett's esophagus. Interestingly, cdx-2 mRNA was also detected in the squamous mucosa of 30% of the Barrett's esophagus patients suggesting that cdx-2 transcription may play a role in development of Barrett's esophagus. If this is shown to be the case, it may help identify GERD patients predisposed to the development of Barrett's esophagus in the future. The detection of cdx-2 mRNA also correlated with the

expression of goblet cell specific Muc-2 mRNA in Barrett's esophagus patients. Another study also showed that MUC-2 was expressed in goblet cells and occasionally in columnar cells but not in cardiac type mucosa, also suggesting that MUC-2 expression could be a useful tool for the accurate detection of intestinal metaplasia [37].

Is it possible to distinguish intestinal metaplasia in the esophagus from that in the stomach? The use of cytokeratins 7 and 20 in initial studies showed that the pattern of CK7/CK20 immunoreactivity was found in both long and short segment Barrett's esophagus but not in CIM [38,39]. Barrett's esophagus was characterized by superficial and deep CK7 staining and superficial band like CK20 staining in the areas of intestinal metaplasia. However, other studies have yielded conflicting results [40–42]. More prospective studies are needed to define the exact role of these biomarkers for the diagnosis of Barrett's esophagus.

Diagnosis of Barrett's Esophagus: the Future

The cost associated with standard upper endoscopy is one of the major limiting factors in its application for the diagnosis of Barrett's esophagus. Newer techniques may help overcome this barrier.

One such technique to diagnose esophageal pathology is capsule endoscopy. A feasibility study from Israel [43] showed that in 17 patients (five with normal findings and 12 patients with erosive esophagitis on upper endoscopy), capsule endoscopy was able to identify all the 12 patients with esophageal pathology on upper endoscopy. Our center is currently involved in a prospective, double blind, multicenter study to correlate the findings on esophageal capsule studies to those on standard endoscopy.

Balloon cytology has been reported as a cost-effective method for the diagnosis and surveillance of Barrett's esophagus patients. Falk *et al*. compared balloon cytology with biopsies and brush cytology in patients with Barrett's esophagus [44]. They were able to obtain adequate columnar epithelium in 83% patients with balloon cytology in comparison with 97% with brush cytology. The costs associated with balloon cytology were six times less than that of endoscopy, in part due to lack of sedation. Other results have not been as promising. In a study of 10 unselected patients with known Barrett's esophagus, balloon cytology was unable to identify goblet cells in any of the patients. This area needs further study before balloon cytology can be recommended for the diagnosis of Barrett's esophagus [45].

In summary, more research is needed to validate current methods and identify other techniques, non-invasive methods and serologic markers to diagnose Barrett's esophagus reliably and in a cost-effective manner.

Conclusion

Approximately, 10–15% of people with chronic GERD are diagnosed with Barrett's esophagus, a premalignant condition for esophageal and gastroesophageal adenocarcinoma. The diagnosis of Barrett's esophagus is based on a combination of endoscopic and histologic criteria. The displacement of SCJ proximal to the GEJ should raise the suspicion for Barrett's esophagus and lead to biopsies to confirm intestinal metaplasia. Barrett's esophagus has been classified into long and short segment based on the endoscopic extent. A new system called the Prague C and M criteria for the endoscopic diagnosis of Barrett's esophagus, if validated, may simplify the description of endoscopic findings of Barrett's esophagus both for clinical and research studies. The single most important histologic finding is the presence of goblet cells that confirms the presence of intestinal metaplasia. Special stains like Alcian blue, if used judiciously in conjunction with H&E staining may avoid the overdiagnosis of intestinal metaplasia. Intestinal metaplasia is a patchy lesion that may be missed on a single endoscopy and, although the yield of intestinal metaplasia increases on repeat endoscopies, the number of endoscopies a patient with should undergo to avoid false negative results is unclear. This problem may be overcome by application of newer techniques like magnification, chromoendoscopy, narrow band imaging, and optical coherence tomography to help focused biopsies from areas suspected to represent intestinal metaplasia. Application of molecular techniques to identify cdx-2,

muc-2, sucrase-isomaltase etc., in biopsy specimens may increase the sensitivity of the diagnosis of Barrett's esophagus. In the future, newer methods like capsule endoscopy and balloon cytology may help screen for Barrett's esophagus in a cost-effective manner.

Acknowledgement

Supported by the Veterans Affairs Medical Center, Kansas City, MO.

References

1. Reid BJ. Barrett's esophagus and esophageal adenocarcinoma. *Gastroenterol Clin North Am* 1991;**20**(4):817–34.
2. Haggitt RC. Barrett's esophagus, dysplasia, and adenocarcinoma. *Hum Pathol* 1994;**25**(10):982–93.
3. Brown LM, Devesa SS. Epidemiologic trends in esophageal and gastric cancer in the United States. *Surg Oncol Clin N Am* 2002;**11**(2):235–56.
4. Devesa SS, Blot WJ, Fraumeni JF, Jr. Changing patterns in the incidence of esophageal and gastric carcinoma in the United States. *Cancer* 1998;**83**(10):2049–53.
5. Pera M, Cameron AJ, Trastek VF, Carpenter HA, Zinsmeister AR. Increasing incidence of adenocarcinoma of the esophagus and esophagogastric junction. *Gastroenterology* 1993;**104**(2):510–3.
6. Pohl H, Welch HG. The role of overdiagnosis and reclassification in the marked increase of esophageal adenocarcinoma incidence. *J Natl Cancer Inst* 2005;**97**(2): 142–6.
7. Blot WJ, Devesa SS, Fraumeni JF, Jr. Continuing climb in rates of esophageal adenocarcinoma: an update. *JAMA* 1993;**270**(11):1320.
8. Sharma P, McQuaid K, Dent J *et al*. A critical review of the diagnosis and management of Barrett's esophagus: the AGA Chicago Workshop. *Gastroenterology* 2004;**127**(1):310–30.
9. Barrett NR. Chronic peptic ulcer of the oesophagus and 'oesophagitis'. *Br J Surg* 1950;**38**(150):175–82.
10. Paull A, Trier JS, Dalton MD *et al*. The histologic spectrum of Barrett's esophagus. *N Engl J Med* 1976; **295**(9):476–80.
11. Haggitt RC, Tryzelaar J, Ellis FH, Colcher H. Adenocarcinoma complicating columnar epithelium-lined (Barrett's) esophagus. *Am J Clin Pathol* 1978;**70**(1):1–5.
12. Hamilton SR, Smith RR. The relationship between columnar epithelial dysplasia and invasive adenocarcinoma arising in Barrett's esophagus. *Am J Clin Pathol* 1987;**87**(3):301–12.
13. Lee RG. Dysplasia in Barrett's esophagus. A clinicopathologic study of six patients. *Am J Surg Pathol* 1985; **9**(12):845–52.
14. Thompson JJ, Zinsser KR, Enterline HT. Barrett's metaplasia and adenocarcinoma of the esophagus and gastroesophageal junction. *Hum Pathol* 1983;**14**(1): 42–61.
15. Skinner DB, Walther BC, Riddell RH *et al*. Barrett's esophagus. Comparison of benign and malignant cases. *Ann Surg* 1983;**198**(4):554–65.
16. Sharma P, Morales TG, Sampliner RE. Short segment Barrett's esophagus—the need for standardization of the definition and of endoscopic criteria. *Am J Gastroenterol* 1998;**93**(7):1033–6.
17. Armstrong D. Review article: towards consistency in the endoscopic diagnosis of Barrett's oesophagus and columnar metaplasia. *Aliment Pharmacol Ther* 2004;**20**(suppl 5):40–7; discussion 61–2.
18. Eloubeidi MA, Provenzale D. Does this patient have Barrett's esophagus? The utility of predicting Barrett's esophagus at the index endoscopy. *Am J Gastroenterol* 1999;**94**(4):937–43.
19. Sharma P, Weston AP, Morales T *et al*. Relative risk of dysplasia for patients with intestinal metaplasia in the distal oesophagus and in the gastric cardia. *Gut* 2000;**46**(1):9–13.
20. Hayward J. The lower end of the oesophagus. *Thorax* 1961;**16**:36–41.
21. Hirota WK, Loughney TM, Lazas DJ *et al*. Specialized intestinal metaplasia, dysplasia, and cancer of the esophagus and esophagogastric junction: prevalence and clinical data. *Gastroenterology* 1999;**116**(2):277–85.
22. Schnell TG, Sontag SJ, Chejfec G. Adenocarcinomas arising in tongues or short segments of Barrett's esophagus. *Dig Dis Sci* 1992;**37**(1):137–43.
23. Rudolph RE, Vaughan TL, Storer BE *et al*. Effect of segment length on risk for neoplastic progression in patients with Barrett esophagus. *Ann Intern Med* 2000;**132**(8):612–20.
24. Cameron AJ, Souto EO, Smyrk TC. Small adenocarcinomas of the esophagogastric junction: association with intestinal metaplasia and dysplasia. *Am J Gastroenterol* 2002;**97**(6):1375–80.
25. Pera M. Trends in incidence and prevalence of specialized intestinal metaplasia, barrett's esophagus, and adenocarcinoma of the gastroesophageal junction. *World J Surg* 2003;**27**(9):999–1008; discussion 1006–8.
26. Wallner B, Sylvan A, Stenling R, Janunger KG. The esophageal Z-line appearance correlates to the preva-

lence of intestinal metaplasia. *Scand J Gastroenterol* 2000;**35**(1):17–22.
27. Peuchmaur M, Potet F, Goldfain D. Mucin histochemistry of the columnar epithelium of the oesophagus (Barrett's oesophagus): a prospective biopsy study. *J Clin Pathol* 1984;**37**(6):607–10.
28. Lee RG. Mucins in Barrett's esophagus: a histochemical study. *Am J Clin Pathol* 1984;**81**(4):500–3.
29. Jass JR. Mucin histochemistry of the columnar epithelium of the oesophagus: a retrospective study. *J Clin Pathol* 1981;**34**(8):866–70.
30. Weinstein WM, Ippoliti AF. The diagnosis of Barrett's esophagus: goblets, goblets, goblets. *Gastrointest Endosc* 1996;**44**(1):91–5.
31. Kim SL, Waring JP, Spechler SJ *et al*. Diagnostic inconsistencies in Barrett's esophagus. Department of Veterans Affairs Gastroesophageal Reflux Study Group. *Gastroenterology* 1994;**107**(4):945–9.
32. Spechler SJ, Zeroogian JM, Antonioli DA, Wang HH, Goyal RK. Prevalence of metaplasia at the gastro-oesophageal junction. *Lancet* 1994;**344**(8936):1533–6.
33. Iftikhar SY, James PD, Steele RJ, Hardcastle JD, Atkinson M. Length of Barrett's oesophagus: an important factor in the development of dysplasia and adenocarcinoma. *Gut* 1992;**33**(9):1155–8.
34. Jones TF, Sharma P, Daaboul B *et al*. Yield of intestinal metaplasia in patients with suspected short-segment Barrett's esophagus (SSBE) on repeat endoscopy. *Dig Dis Sci* 2002;**47**(9):2108–11.
35. Oberg S, Johansson J, Wenner J *et al*. Endoscopic surveillance of columnar-lined esophagus: frequency of intestinal metaplasia detection and impact of antireflux surgery. *Ann Surg* 2001;**234**(5):619–26.
36. Groisman GM, Amar M, Meir A. Expression of the intestinal marker Cdx2 in the columnar-lined esophagus with and without intestinal (Barrett's) metaplasia. *Mod Pathol* 2004;**17**(10):1282–8.
37. Lopes CV, Pereira-Lima JC, Hartmann AA. Correlation between Alcian blue-periodic acid-Schiff stain and immunohistochemical expression of mucin 2 in Barrett's oesophagus. *Histopathology* 2004;**45**(2):198–9.
38. Couvelard A, Cauvin JM, Goldfain D *et al*. Cytokeratin immunoreactivity of intestinal metaplasia at normal oesophagogastric junction indicates its aetiology. *Gut* 2001;**49**(6):761–6.
39. Ormsby AH, Vaezi MF, Richter JE *et al*. Cytokeratin immunoreactivity patterns in the diagnosis of short-segment Barrett's esophagus. *Gastroenterology* 2000;**119**(3):683–90.
40. El-Zimaity HM, Graham DY. Cytokeratin subsets for distinguishing Barrett's esophagus from intestinal metaplasia in the cardia using endoscopic biopsy specimens. *Am J Gastroenterol* 2001;**96**(5):1378–82.
41. Glickman JN, Wang H, Das KM *et al*. Phenotype of Barrett's esophagus and intestinal metaplasia of the distal esophagus and gastroesophageal junction: an immunohistochemical study of cytokeratins 7 and 20, Das-1 and 45 MI. *Am J Surg Pathol* 2001;**25**(1):87–94.
42. Mohammed IA, Streutker CJ, Riddell RH. Utilization of cytokeratins 7 and 20 does not differentiate between Barrett's esophagus and gastric cardiac intestinal metaplasia. *Mod Pathol* 2002;**15**(6):611–6.
43. Eliakim R, Yassin K, Shlomi I, Suissa A, Eisen GM. A novel diagnostic tool for detecting oesophageal pathology: the PillCam oesophageal video capsule. *Aliment Pharmacol Ther* 2004;**20**(10):1083–9.
44. Falk GW, Chittajallu R, Goldblum JR *et al*. Surveillance of patients with Barrett's esophagus for dysplasia and cancer with balloon cytology. *Gastroenterology* 1997;**112**(6):1787–97.
45. Fennerty MB, DiTomasso J, Morales TG *et al*. Screening for Barrett's esophagus by balloon cytology. *Am J Gastroenterol* 1995;**90**(8):1230–2.