

# Barrett's oesophagus and columnar metaplasia: saying what we mean

Norman J Carr

*Straightforward, unambiguous terminology can reduce the risk of labelling patients inappropriately*

Whenever the definition of a diagnostic term is changed, a Pandora's box of potential confusion is opened. Are all clinicians and research investigators using the same criteria? If a patient has been given a diagnostic label, does it refer to the old or the new definition? Barrett's oesophagus has changed its definition more than once over the past five decades and is a prime example of how changing definitions causes confusion for clinicians and investigators alike.<sup>1,2</sup> A solution to this problem lies in avoiding the potentially confusing term "Barrett's oesophagus" altogether. Moreover, this is possible by using existing terminology without the need for any new definitions.

## Historical perspective

Barrett's oesophagus takes its name from Norman Barrett, who published on the subject in 1950.<sup>1,2</sup> He observed that, in some individuals, the oesophagus is lined by glandular rather than squamous mucosa, and he assumed, like some earlier investigators, that a congenitally short oesophagus had drawn the stomach into the thorax. However, within a few years studies had shown that this columnar-lined tubular structure was not stomach, but true oesophagus characterised by submucosal glands and muscularis propria typical of the oesophagus. Furthermore, it often had islands of squamous epithelium.

Since it was assumed that the presence of gastric mucosa in the distal oesophagus might be a normal occurrence, early investigators into the phenomenon wished to avoid false positive diagnoses by excluding anyone who might have putatively normal glandular mucosa at the distal end of the oesophagus, and thus ensure that only patients who really did have metaplastic glandular mucosa were included in their studies. They therefore set arbitrary criteria for the length of columnar lining in the tubular oesophagus required for a diagnosis of Barrett's oesophagus; some investigators stipulated 3 cm, others 2 cm.<sup>1</sup> During the 1960s, clinicians adopted these inclusion criteria as literal definitions of Barrett's oesophagus, and considered glandular mucosa in the distal 3 cm or 2 cm of the oesophagus to be normal. However, there is very little evidence that gastric mucosa normally extends proximal to the anatomical gastro-oesophageal junction, and some researchers believe that any such extension is abnormal (ie, columnar metaplasia).<sup>2,3</sup>

These early studies established that glandular metaplasia of the distal oesophagus is caused by reflux, and that the normal mucosa is replaced by a mosaic of glandular epithelium of various types: cardiac, intestinal, and/or gastric fundic with parietal cells.<sup>2,4-7</sup> The general term "columnar metaplasia" is appropriate for all three types. However, in the 1980s it became clear that the risk of developing adenocarcinoma was particularly associated with the intestinal type of epithelium.<sup>8</sup> As a result, researchers whose major focus was the oncogenic potential of the condition defined Barrett's oesophagus as the presence anywhere in the oesophagus of intestinal metaplasia (IM), as shown by the presence of goblet cells

in histological sections.<sup>1</sup> Clinicians again followed the cue of the researchers, and the definition changed once more so that Barrett's oesophagus became synonymous with oesophageal IM. This concept has been refined, and the definition promulgated by a number of international consensus conferences is that Barrett's oesophagus is diagnosed when columnar epithelium containing goblet cells is found in a biopsy from mucosa having the endoscopic features of Barrett's oesophagus.<sup>4,7,9-11</sup>

## Current usage of "Barrett's oesophagus"

Despite this definition, the requirement for goblet cells has not been applied consistently. Some pathologists continue to use the term Barrett's oesophagus for any glandular mucosa in the true oesophagus, whether it be of fundic, cardiac, or intestinal type. This position seems to have been more common in the United Kingdom, and recent guidelines issued by the British Society of Gastroenterology explicitly state that IM is not necessary for the diagnosis.<sup>12,13</sup> The rationale is that sampling errors at endoscopy may miss foci of IM, but that essentially all patients, at least those with long-segment disease, will show IM at some time if enough biopsies are taken.<sup>13</sup> However, there is evidence that this assumption may be erroneous: in a large population-based study in Northern Ireland, patients with columnar metaplasia of the oesophagus had an increased risk of developing adenocarcinoma only if IM was found; furthermore, there was 93% concordance between IM status on the first biopsy and any subsequent biopsy.<sup>14,15</sup> These results suggest that some patients simply do not exhibit IM in their columnar-lined oesophagus, and that biopsies are able to divide patients into well stratified risk groups based on this fact. Consistent with this conclusion are the observations of others that even multiple biopsies, especially in short-segment disease, sometimes contain no goblet cells.<sup>16</sup>

It is unfortunate, to say the least, that doctors in different parts of the world should be using completely different diagnostic criteria. The potential for miscommunication between clinicians and researchers is obvious.

## The problem of oesophagus versus stomach

A significant practical diagnostic problem arises if Barrett's oesophagus is defined by the presence of IM, because the diagnosis is only correct if the biopsy specimen showing IM comes from the oesophagus (ie, mucosa that was previously squamous) and not from the stomach. This distinction is important because, despite the methodological problems that plague studies in this area, there is evidence that IM of the proximal stomach is different clinically and pathologically from IM in the oesophagus. Therefore, "Barrett's oesophagus" should be avoided if the specimen might have come from the stomach, because the diagnostic label could imply the wrong disease process. In particular, compared with IM in the

gastric cardia, IM in the oesophagus is more likely to be associated with reflux and more likely to become dysplastic.<sup>17</sup> On the other hand, patients with IM of the gastric cardia are more likely to have *Helicobacter pylori* gastritis. Some immunohistochemical markers have been found to show a difference between gastric and oesophageal IM, including DAS-1 and CDX2,<sup>18-20</sup> and differences in expression of the cytokeratins CK7 and CK20 have been described by some researchers (although not all).<sup>21,22</sup>

Unfortunately, despite these and other differences between IM in the oesophagus and IM in the stomach, no histological technique has yet been shown to reliably distinguish IM in the two sites in clinical material.<sup>4,13,18</sup> There is one exception: if the pathologist observes a feature specific for the oesophagus (eg, a submucosal gland or its duct), then origin from the oesophagus can be definitively stated. However, this is only likely if jumbo forceps are used, and even then it only occurs in some cases.<sup>10</sup> In general, the only way in which the pathologist can tell where the biopsy came from is by the endoscopist providing the information.

Hence the problem — clinicians do not always give accurate information on the request form regarding the site of the biopsy. Pathologists may try to get around this problem by making statements such as: “The biopsy appearances would be consistent with Barrett’s oesophagus if the biopsy came from the true oesophagus”. Consequently, there is a risk that patients will be inappropriately labelled with the diagnosis of Barrett’s oesophagus through miscommunication.

There is a controversy regarding the cardiac mucosa that touches on this discussion. Some researchers have suggested that cardiac mucosa (ie, mucosa composed of glands without oxyntic cells at the gastro-oesophageal junction) is always abnormal, and represents a change due to reflux.<sup>2,3</sup> According to this hypothesis, only oxyntic mucosa is normal in the proximal stomach, only squamous mucosa is normal in the oesophagus, and what most people call cardiac mucosa is actually a pathological change (“reflux carditis”). A consequence of this is that finding cardiac mucosa in a biopsy would automatically imply that the specimen came from the oesophagus, not the stomach.<sup>2,3</sup> However, the idea that there is no such thing as normal cardiac mucosa is a minority opinion and is not supported by the conclusions of studies showing that the gastric cardia in individuals defined as normal is usually lined by pure mucous glands or a mixture of mucous and oxyntic glands for up to 4 mm.<sup>23-25</sup>

### The solution

A solution to these problems of inconsistency and confusion is to stop using the term “Barrett’s oesophagus” altogether, and instead use alternative terms that are less ambiguous. A biopsy from the oesophagus showing IM could be diagnosed as “columnar metaplasia with intestinal metaplasia”, while one without IM could be labelled “columnar metaplasia without intestinal metaplasia”. This terminology is based on well established usage and does not depend on subscribing to a particular definition of Barrett’s oesophagus; it avoids the problem of variable definitions, and the risk factor of IM is clearly and unambiguously stated.

In any case, avoiding the term Barrett’s oesophagus should be routine if the biopsy site is unclear, because it implies a risk of neoplasia that would be incorrect if the biopsy came from the stomach. A diagnosis such as “glandular mucosa with intestinal metaplasia” combined with a statement in the pathology report about the uncertainty of the exact site of the biopsy would

eliminate the potential misunderstanding that could arise if the word Barrett’s appeared.

One could argue that a general term to describe the various morphological changes in the vicinity of the gastro-oesophageal junction remains useful. However, using “Barrett’s oesophagus” in this way is inappropriate because it now has precise definitions — even though these definitions have significant regional differences. One could also suggest that appropriate education is all that is required to allow Barrett’s oesophagus to be diagnosed correctly. Nevertheless, we still need to know which definition is being used before we can understand what a colleague means by Barrett’s oesophagus. It would be much simpler just to say what we mean using straightforward words.

Others have suggested this solution before (including Norman Barrett himself),<sup>1</sup> yet it does not seem to have been widely adopted. Although it might take a long time to eliminate a term as entrenched as Barrett’s oesophagus, the medical community has successfully negotiated changes in diagnostic terminology many times before. In this case, no new definitions would be required — simply the application of expressions we already understand.

### Competing interests

None identified.

### Author details

Norman J Carr, MB BS, Professor of Anatomical Pathology  
Graduate School of Medicine, University of Wollongong,  
Wollongong, NSW.

Correspondence: ncarr@uow.edu.au

### References

- 1 Spechler SJ, Goyal RJ. The columnar-lined esophagus, intestinal metaplasia, and Norman Barrett. *Gastroenterology* 1996; 110: 614-621.
- 2 Chandrasoma P. Controversies of the cardiac mucosa and Barrett’s oesophagus. *Histopathology* 2005; 46: 361-373.
- 3 Chandrasoma PT, Der R, Dalton P, et al. Distribution and significance of epithelial types in columnar-lined esophagus. *Am J Surg Pathol* 2001; 25: 1188-1193.
- 4 Offerhaus GJ, Correa P, van Eeden S, et al. Report of an Amsterdam working group on Barrett esophagus. *Virchows Arch* 2003; 443: 602-608.
- 5 Goldblum JR. Barrett’s esophagus and Barrett’s-related dysplasia. *Mod Pathol* 2003; 16: 316-324.
- 6 Fléjou JF. Barrett’s oesophagus: from metaplasia to dysplasia and cancer. *Gut* 2005; 54 Suppl 1: i6-i12.
- 7 Werner M, Fléjou JF, Hainaut P. Tumours of the oesophagus. Adenocarcinoma. In: Hamilton SR, Aaltonen LA, editors. World Health Organization classification of tumours: pathology and genetics of tumours of the digestive system. Lyon: IARC Press, 2000: 20-26.
- 8 Skinner DB, Walther BC, Riddell RH, et al. Barrett’s esophagus. Comparison of benign and malignant cases. *Ann Surg* 1983; 198: 554-565.
- 9 Sampliner RE. Practice guidelines on the diagnosis, surveillance, and therapy of Barrett’s esophagus. The Practice Parameters Committee of the American College of Gastroenterology. *Am J Gastroenterol* 1998; 93: 1028-1032.
- 10 Armstrong D. Review article: towards consistency in the endoscopic diagnosis of Barrett’s oesophagus and columnar metaplasia. *Aliment Pharmacol Ther* 2004; 20 Suppl 5: 40-47.
- 11 Faller G, Borchard F, Ell C, et al. Histopathological diagnosis of Barrett’s mucosa and associated neoplasias: results of a consensus conference of the Working Group for Gastroenterological Pathology of the German Society for Pathology on 22 September 2001 in Erlangen. *Virchows Arch* 2003; 443: 597-601.
- 12 Playford RJ. New British Society of Gastroenterology (BSG) guidelines for the diagnosis and management of Barrett’s oesophagus [commentary]. *Gut* 2006; 55: 442-443.

- 13 Hellier MD, Shepherd NA. Diagnosis of columnar-lined oesophagus. In: Watson A, Heading RC, Shepherd NA, editors. Guidelines for the diagnosis and management of Barrett's columnar-lined oesophagus. A report of the Working Party of the British Society of Gastroenterology. August 2005. [http://www.bsg.org.uk/pdf\\_word\\_docs/Barretts\\_Oes.pdf](http://www.bsg.org.uk/pdf_word_docs/Barretts_Oes.pdf) (accessed Jan 2007).
- 14 Murray L, Watson P, Johnston B, et al. Risk of adenocarcinoma in Barrett's oesophagus: population based study. *BMJ* 2003; 327: 534-535.
- 15 Murphy SJ, Johnston BT, Murray LJ. British Society of Gastroenterology guidelines for the diagnosis of Barrett's oesophagus: are we casting the net too wide [letter]? *Gut* 2006; 55: 1821-1822.
- 16 Riddell RH. The genesis of Barrett esophagus: has a histologic transition from gastroesophageal reflux disease-damaged epithelium to columnar metaplasia ever been seen in humans? *Arch Pathol Lab Med* 2005; 129: 164-169.
- 17 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: 9-13.
- 18 Rogge-Wolf C, Seldenrijk CA, Das KM, et al. Prevalence of mabDAS-1 positivity in biopsy specimens from the esophagogastric junction. *Am J Gastroenterol* 2002; 97: 2979-2985.
- 19 DeMeester SR, Wickramasinghe KS, Lord RV, et al. Cytokeratin and DAS-1 immunostaining reveal similarities among cardiac mucosa, CIM, and Barrett's esophagus. *Am J Gastroenterol* 2002; 97: 2514-2523.
- 20 Phillips RW, Frierson HF, Moskaluk CA. Cdx2 as a marker of epithelial intestinal differentiation in the esophagus. *Am J Surg Pathol* 2003; 27: 1442-1447.
- 21 Liu GS, Gong J, Cheng P. Distinction between short-segment Barrett's esophageal and cardiac intestinal metaplasia. *World J Gastroenterol* 2005; 11: 6360-6365.
- 22 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 M1. *Am J Surg Pathol* 2001; 25: 87-94.
- 23 Odze RD. Unraveling the mystery of the gastroesophageal junction: a pathologist's perspective. *Am J Gastroenterol* 2005; 100: 1853-1867.
- 24 Kilgore SP, Ormsby AH, Gramlich TL, et al. The gastric cardia: fact or fiction? *Am J Gastroenterol* 2000; 95: 921-924.
- 25 De Hertogh G, Van Eyken P, Ectors N, et al. On the existence and location of cardiac mucosa: an autopsy study in embryos, fetuses, and infants. *Gut* 2003; 52: 791-796.

(Received 8 Jan 2007, accepted 5 Jul 2007)

□