

# Non-goblet columnar epithelium in the distal esophagus: review of recent advances in understanding the origin and neoplastic potential

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**Abstract:** Gastroesophageal reflux disease (GERD) is associated with the replacement of normal squamous epithelium with columnar epithelium in the distal esophagus increasing adenocarcinoma (AC) risk. Two types of metaplastic epithelia have been identified: goblet-cell columnar epithelium (GCE), and non-goblet-cell columnar epithelium (NGCE). GCE, also called Barrett's esophagus (BE), has been associated with an increased risk for neoplasia. Alternatively, few studies have discussed AC risk in NGCE. Some have argued that squamous epithelium transforms to NGCE, which gives rise to GCE. Accordingly, NGCE and GCE may represent different stages in the metaplastic spectrum. Moreover, histological examination of mucosa immediately adjacent to esophageal AC, and molecular findings in NGCE provide additional evidence that this epithelial type may carry a similar risk for developing neoplasia when compared to Barrett epithelium. Therefore, identification of goblet cells, currently a prerequisite for the diagnosis of BE, might not be a sensitive indicator for the evaluation of neoplasia risk in these patients, and a search for more appropriate markers is warranted.

**Key Words:** Barrett esophagus; non-goblet cells epithelium; goblet-cells epithelium; intestinalization; esophageal adenocarcinoma; metaplasia



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## Introduction

Barrett's esophagus (BE) increases the risk of adenocarcinoma (AC), and a precise diagnosis is important. However, BE diagnostic criteria have changed over time. Some groups required long-segment ( $\geq 3$  cm) of columnar epithelium for the diagnosis, to overcome uncertainty of the gastroesophageal junction location, and extension of normal cardiac mucosa (1-3). Later, short segment BE was also found to have increased risk of AC (4).

Also, goblet cells were identified as characteristic of BE, since intestinal metaplasia was associated with AC (5).

Goblet cells columnar epithelium (GCE) increases the risk of AC. However, the influence of non-goblet cells columnar

epithelium (NGCE) remains controversial. Interestingly, while goblet cells are not a prerequisite for BE diagnosis according to the British Society of Gastroenterology (6), the American College of Gastroenterologist (ACG) argues that limited risk for AC exists in NGCE (7). Current research is investigating this controversy. We review past and current NGCE research, its role in esophageal AC, and its implications for BE diagnostic criteria.

## Columnar epithelium at the distal end of esophagus

Some have proposed the concept of cardia; a normal columnar epithelial buffer between the esophagus and the

stomach, when studying esophageal metaplasia. The length of cardia has been debated in the literature, and is reported as ranging from 4 mm to 2 cm (3,8).

Alternatively, some have considered that the presence of any esophageal columnar epithelium is a reflux-related abnormality (1,9). We focus on reflux-related conversion of squamous to columnar epithelium at the distal end of the esophagus and its relationship to neoplasia. Whether the cardia is a normal variation of esophageal mucosa is beyond the scope of this article.

Three types of esophageal columnar epithelia have been described: (I) cardiac, a junctional-type mucosa (CM), composed of mucus glands without parietal cells; (II) oxynto-cardiac, a fundic-type mucosa (FM), composed of chief and parietal cells; and (III) intestinal metaplasia (IM), composed of specialized-type with intestinal features including villiform surface and mucus glands with goblet cells (1,10).

CM is mainly found throughout the columnar esophageal epithelium, while FM and IM are found in the distal and proximal segments, respectively. NGCE refers to CM and FM (1,10). Currently, it is thought that AC rises from IM (11,12) and research is ongoing to determine the relation between NGCE and IM.

### What is the nature of NGCE?

IM increases AC risk, therefore intestinalization features were studied in NGCE.

Intestinal mucosal protein expression (Sucrase-isomaltase, and dipeptidylpeptidase IV) was demonstrated in NGCE. Also, CDX-2 expression in NGCE ranged from 0 to 43% (13-16). Furthermore, intestinal markers expression was studied in non-goblet-cells containing tissue from NGCE *vs.* BE *vs.* normal control groups, and the NGCE group showed intestinal differentiation (14).

Moreover, intestinal markers were increased in non-goblet-cells-containing areas adjacent to goblet-cells-containing areas in the BE group. Previous data supported the metaplasia theory involving transition from squamous epithelium to NGCE, followed by IM (10,17,18). Kerkhof *et al.* showed that CDX-2 expression in NGCE biopsies increases the likelihood of finding goblet-cells in follow-up biopsies (19).

### CDX-2 as a marker of epithelial intestinal differentiation in the esophagus

CDX-2 is a transcription factor that regulates proliferation and differentiation of intestinal epithelial cells (20). Eda *et*

*al.* demonstrated that expression of CDX-2 precedes other intestine-specific genes in gastric IM, and may trigger it. Similar results were obtained in esophageal IM (i.e. BE) using reverse transcriptase-polymerase chain reaction (RT-PCR) and immunohistochemistry (21).

This expression started during esophagitis, and CDX-2 was thought to be a trigger of BE (22). Interestingly, the authors relied on intestinal gene expression for BE diagnosis, rather than histologic appearance, and thus they did not primarily differentiate between NGCE and GCE. They noted 87% concordance between this molecular diagnosis and the traditional histologic diagnosis of IM.

CDX-2 expression have been suggested as a marker for BE when unequivocal goblet cells can not be identified (13,15).

Vallböhmer *et al.* using laser capture microdissection, quantitatively measured CDX-2 mRNA isolated from different epithelial types in patients with GERD symptoms and found stepwise increase in gene expression starting at squamous epithelium, followed by NGCE (40-70 times), leading to BE (400 times). These results support the two-step theory of esophageal IM. They concluded that CDX-2 may be a potential biomarker to detect the early transition to BE (23).

### Where does dysplasia end and subsequent carcinoma start?

Neoplasia arises from the less differentiated, rather than the highly differentiated goblet cells (24).

It has been suggested that IM is the precursor lesion of esophageal AC (11,12). However, recent studies have suggested that goblet cells are not a sensitive indicator for increased risk of neoplasia. Kelty *et al.* reviewed surveillance biopsies, taken over a 14-year follow-up, and did not report significant carcinoma rate differences in BE *vs.* NGCE, respectively (37% *vs.* 30%, P=NS) (25). Similarly, Gatenby *et al.* reported that the majority of patients who present initially with NGCE will develop IM on follow up (26). There was no significant difference in dysplasia or AC rates in goblet-cells *vs.* non-goblet cells containing biopsies.

Histological evidence suggests that the neoplasia risk of NGCE is at least comparable to IM. Chaves *et al.* studied the expression of gastric (MUC5AC and MUC6) and intestinal (MUC2) mucin markers in NGCE, GCE, and neoplastic cells. MUC6 was identified in NGCE as expected. However, it was also detected in neoplastic cells, and in GCE adjacent to neoplasia but not in GCE without neoplasia. This suggests that gastric differentiation, usually seen in NGCE, is present in neoplastic cells and epithelium

adjacent to it. The authors concluded that malignancy is not exclusively associated with the presence of intestinal differentiation (27). In a different study, Takubo *et al.* (24) examined epithelium adjacent to esophageal AC. The rate of exclusively finding NGCE epithelium immediately adjacent to neoplasia was higher than that of GCE (71% *vs.* 22%, respectively). They concluded that neoplasia arises in NGCE more frequently than IM, and thus the diagnosis of BE should not require the presence of goblet cells.

They acknowledge the possibility of neoplasia arising initially in GCE, with subsequent destructive obliteration of goblet cells, but argue that it is unlikely, since all cases were small, early excised ACs.

However, Takubo *et al.* did not mention whether these patients had BE (goblet cells), at some point during follow-up. If so, their malignancy appears to have started in a setting of intestinalized epithelium with goblet cells, justifying the practice of goblet-cells identification for BE diagnosis. In response, the authors reported that 57% of patients had goblet cells (24).

Molecular findings also suggest similar risk of neoplasia in NGCE and IM. Data have shown that DNA abnormalities, measured by image cytometry and high-fidelity histogram, correlate with neoplastic progression of BE (28,29). Liu *et al.* investigated these parameters in NGCE, and demonstrated that they occur with equal frequency in NGCE and IM (30). Additionally, they showed that goblet cells density in BE does not correspond to DNA alterations. They concluded that NGCE and GCE have similar neoplastic potential, and that further studies were warranted.

In summary, these studies have shown that BE malignancy factors (mainly, intestinalization and DNA abnormalities) are present in NGCE, and the rate of malignancy is similar between NGCE and GCE. However, these studies had several shortcomings, mainly the cross-sectional, as well as retrospective nature.

ACG definition of BE uses goblet cells as the only feature of intestinalization. DNA-abnormal NGCE giving rise to neoplasia, representing an advanced state of intestinalization, is not part of the definition. Future studies are required to determine whether histologic intestinalization (goblet-cells containing) is not an essential risk of neoplasia, and therefore not essential in BE diagnosis.

### Proposal for future research and modification of BE definition

Markers that predict risk of neoplasia provide a valid clinical

assessment for high-risk patients, but since some of these markers are not yet determined, less optimal approaches can be applied.

It is important to recognize that columnar epithelium in the distal esophagus is a result of reflux induced injury, regardless of goblet cells presence. With years of follow up, the majority of these patients will develop IM.

Accordingly, two patients who had NGCE for 2 and 10 years, respectively are not at the same stage of disease, and their neoplasia risk may not be similar. Unfortunately, most studies addressing risk of neoplasia in NGCE do not take this issue into consideration. It may be appropriate to stratify NGCE cases depending on molecular intestinal features (genes and/or markers). If future research shows that patients with NGCE (with or without intestinal differentiation) are at risk of neoplasia, then definition of BE should not require the presence of goblet cells. Subsequent surveillance may be warranted in such patients. However, if NGCE associated with neoplasia is found to be at an advanced degree of intestinalization, then the association of intestinalized epithelium and neoplasia is appropriate. Accordingly, identification of an intestinalization marker, one that would be more consistent than the presence of goblet cells, is important to modify BE definition. Cost-effectiveness may be increased, since surveillance would not be initiated in patients that do not show the required degree of intestinalization.

### Conclusions

Studies show that NGCE may be a transition between squamous and intestinal epithelia, provoked early by esophageal injury, and the risk of developing goblet cells increases with continued injury.

NGCE may still display alarming factors of neoplasia (e.g., DNA changes) even without goblet cells on histology. However, features other than goblet cells may better define intestinalization. Future studies are required to recognize additional non-histologic features of intestinalization, as well as recognizing the degree of intestinalization. Moreover, further research could demonstrate new markers for intestinalization, allowing the modification of BE definition. Optimally, these markers could stratify neoplasia risk regardless of the epithelium displayed on presentation and follow up.

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