Current Diagnostic Pathology (2006) **12**, 127–135

Current
DIAGNOSTIC
PATHOLOGY

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REVIEW

# Oesophageal pathology following ablation of Barrett's mucosa

**M. Hage[a,b], P.D. Siersema[b], H. van Dekken[a,*]**

[a]*Department of Pathology, Erasmus Medical Centre, Josephine Nefkens Institute, Dr. Molewaterplein 50, 3015GE, Rotterdam, The Netherlands*
[b]*Department of Gastroenterology and Hepatology, Erasmus Medical Centre, Dr Molewaterplein 50, 3015GE, Rotterdam, The Netherlands*

**KEYWORDS**
Barrett's oesophagus;
Intestinal metaplasia;
Dysplasia;
Photodynamic therapy;
Argon plasma coagulation;
Histopathology

**Summary** Barrett's oesophagus (BO) is a major risk factor for the development of oesophageal adenocarcinoma. Oesophageal adenocarcinoma is preceded by pre-malignant epithelial changes, i.e. low-grade dysplasia and high-grade dysplasia. Endosocopic surveillance programmes have been implemented to monitor these pre-malignant changes. In the last decade, much effort has been invested in non-invasive, low-risk, ablative techniques for elimination of BO as an alternative for oesophagectomy, which confers substantial morbidity and mortality. The rationale for ablative elimination of BO is to reduce or abolish the risk of malignant progression. However, at present, there is no convincing evidence that this risk is truly diminished. Residual or recurrent glands are commonly found after ablation and can be detected next to or underneath (neo)squamous epithelium. Moreover, molecular abnormalities associated with malignant progression have been detected in these glands. This review addresses histopathological aspects of oesophageal biopsy specimens after ablation of BO.


## Introduction

Barrett's oesophagus (BO) is the major precursor of oesophageal adenocarcinoma and is endoscopically characterized by a salmon-pink, velvety-like appearance of the distal oesophageal lining. Histopathologically, BO is defined by the presence of a specialized columnar epithelium with the presence of goblet cells, which is referred to as intestinal metaplasia.[1,2] Initially, three types of BO were discerned: gastric-fundic-type epithelium with parietal and chief cells, junctional-type epithelium with cardiac mucous glands, and specialized columnar epithelium with intestinal-type goblet cells. Presently, cancer risk in BO is considered to be restricted to patients with intestinal metaplasia. The transformed mucosa may have a foveolar,

*Corresponding author. Tel.: +31 10 4087901; fax: +31 10 4089487.
*E-mail address:* h.vandekken@erasmusmc.nl (H. van Dekken).

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doi:10.1016/j.cdip.2005.12.002

sometimes villous, pattern with irregular-spaced pits, crypts and glands. Non-specific inflammation is often found, occasionally ulcerating. The metaplastic epithelium mainly consists of two cell types, i.e. columnar cells and goblet cells. Furthermore, a few neuro-endocrine and Paneth cells may be discerned. Intestinal metaplasia of the distal oesophagus is thought to be the result of long-standing gastro-oesophageal reflux.[3,4] Histopathologically, the development of an adenocarcinoma appears to be preceded by epithelial dysplasia. Dysplasia is defined as neoplastic proliferation within epithelial glands without affecting the basement membrane. Dysplastic changes can often be found surrounding an adenocarcinoma in BO. In addition, longitudinal follow-up studies have documented the gradual increase in severity of dysplasia, eventually resulting in adenocarcinoma. These observations suggest that dysplastic changes may be taken as early indicators of incipient malignancy. This is important because, on the one hand, patients with BO have a 30–40-fold increased risk for esophageal adenocarcinoma, but, on the other hand, only a low percentage of BO patients eventually develop cancer.[1,2]

The incidence of adenocarcinoma is rising rapidly in the Western world.[5] The development of adenocarinoma follows a multistep sequence from intestinal metaplasia to low-grade dysplasia (LGD), high-grade dysplasia (HGD) and, finally, adenocarcinoma[1,6,7] (Fig. 1 and Table 1). Most patients known to have BO are offered endoscopic surveillance with biopsies to detect dysplastic changes at an early stage.[8] These endoscopic surveillance programmes are costly and also have an impact on the patient's well-being. The (cost) effectiveness of these programmes is under discussion for several reasons: (1) the grading of dysplasia is subject to intra- and interobserver variation;[9,10] (2) it is not possible to differentiate between non-dysplastic and dysplastic Barrett's mucosa using endoscopy; and (3) there is no clear evidence whether early detection of dysplasia prolongs the survival of patients with BO.[11,12] LGD is rather indolent and is not a reliable hallmark for malignancy.[13,14] Moreover, dysplastic BO is often multifocal within the Barrett's segment.[15] There is no doubt that HGD is an indication for surgery or endoscopic mucosectomy, as it confers a high risk of developing into adenocarcinoma. However, some controversy concerns the extent of HGD and the risk of adenocarcinoma.[16] Buttar et al.[17] investigated whether a limited extent of HGD had the same potential for cancer development as diffuse HGD. They found that patients with focal HGD are less likely to develop adenocarcinoma than those with diffuse HGD. Weston et al.[18] followed the fate of patients with focal HGD. Approximately 50% of these patients progressed to multifocal HGD or cancer. Only limited information is available for the prognosis of patients with early adenocarcinoma of the oesophagus (T1 stage). Five-year survival rates of 100% for T1 tumours limited to the mucosa have been reported, with rates declining to 60% for T1 tumours invading the submucosa.[19–22]

Endoscopic mucosal resection (EMR) of HGD and early cancer in BO is associated with low morbidity and mortality rates, and offers an alternative to surgical resections. However, Ell et al.[23] reported recurrent or metachronous carcinomas in 14% of patients after EMR for HGD or early adenocarcinoma. In the last decades, several groups have applied photo-ablative techniques to remove Barrett's epithelium. The aim of these techniques is to destroy the pre-neoplastic mucosa and to restore the normal squamous lining in an anacid environment. By doing so, the pre-malignant potential is expected to decrease. Ablating all of the Barrett's mucosa may completely abolish the risk of neoplastic progression.

## Ablation methods

The most commonly used techniques are thermal destruction by argon plasma coagulation (APC) and photochemical destruction by photodynamic therapy (PDT). Other techniques are multipolar electrocoagulation (MPEC) and destruction of the Barrett's mucosa by liquid nitrogen or ultrasonic energy.[24] PDT and APC are most widely used and seem equally effective and safe. Photochemical ablation using PDT is based on the intracellular accumulation of a photosensitizer in tissue. There are different photosensitizers. The most commonly used are an enriched form of haematoporphyrin (Photophrin) and 5-aminolevolinic acid (ALA). ALA is a precursor molecule in the haem biosynthetic pathway that induces an endogenous production of protoporphyrin IX (PpIX). Photophrin is given intravenously to patients, whereas ALA is administered orally. PpIX is activated by photo-irradiation using laser light with an appropriate wavelength. This generates singlet oxygen production, resulting in tissue destruction. APC employs a cautery probe that transfers electrical energy through an ionized, electroconductive plasma of argon gas to the tissue surface, again resulting in tissue destruction.

The choice of therapy is largely dependent on the depth of tissue penetration. Barrett's mucosa is approximately 0.5-mm thick and dysplastic mucosa