Carcinogenesis and treatment of adenocarcinoma of the oesophagus and gastric cardia

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Barrett’s oesophagus

Due to long-standing (duodeno)-gastro-oesophageal reflux, the normal squamous mucosa of the oesophagus can be replaced by columnar epithelium. This metaplastic columnar epithelium is called Barrett’s mucosa, after the Australian born surgeon who (erroneously) first described this condition in 1950.\(^1\)

In 1976, Pauli et al. described the intestinal goblet cell as part of the mosaic of oesophageal columnar mucosa along with cardiac and fundic mucosa, thereby offering a histologic classification of Barrett’s oesophagus into cardiac, fundic and specialised/intestinal types.\(^2\) In addition to the relation with reflux, the relation of intestinal metaplasia with adenocarcinoma of the oesophagus became well established in the seventies.\(^3\) By the late eighties, it was clear that it was the specialised intestinal metaplasia, characterised by the presence of goblet cells, that was the epithelial type predisposing patients to cancer development. There was a stepwise irreversible progression from intestinal metaplasia via dysplasia into carcinoma.\(^4,5\) The definition of Barrett’s oesophagus was therefore subsequently restricted to cases showing intestinal metaplasia, which is to be considered an irreversible premalignant condition.

For decades, Barrett’s oesophagus was identified predominantly in patients with severe gastro-oesophageal reflux, based on the finding of long segments of columnar mucosa extending more than 3 cm above the gastro-oesophageal junction. In 1994, specialised intestinal metaplasia was reported in biopsy specimens from short segments of oesophageal columnar epithelium, even in patients with no evidence of reflux disease.\(^6\) The parallel increase in the incidence of adenocarcinoma of the oesophagus and the oesophago-gastric junction and gastric cardia led to an increased interest in this metaplastic process in the junctional area.\(^7\) Recent studies have confirmed the occurrence of dysplasia and carcinoma in short segment Barrett’s oesophagus.\(^8\)\(^9\)\(^10\) Today, it is therefore generally accepted that intestinal metaplasia and the subsequent development of dysplasia and adenocarcinoma can occur in any length of specialised intestinal metaplasia. The present definition of Barrett’s oesophagus therefore includes patients with intestinal metaplasia in a segment of columnar lined epithelium of any length. Patients with segments of specialised intestinal metaplasia in the oesophagus measuring three cm or more have traditional, or long-segment, Barrett’s oesophagus, whereas those with shorter segments have short-segment disease.\(^11\) Whether these two types share the same pathogenesis and natural history, including the risk of malignant degeneration, and whether short segment Barrett develops into long segment disease is yet unclear. Therefore, management of short and long segment Barrett is as yet the same.
Pathogenesis and risk factors

There is a clear relation between the presence of gastro-oesophageal reflux disease (GORD) and adenocarcinoma of the oesophagus and gastric cardia. In a landmark paper by Lagergren, there was a clear and significant correlation between the presence of adenocarcinoma and the frequency of reflux symptoms (>3/week: odds ratio for carcinoma development 16.7 (95% CI 8.7-28.3), the severity of reflux symptoms (4.5-6.5 points: odds ratio for carcinoma development 20.0 (95% CI 11.6 - 34.6)) and the duration of reflux symptoms (> 20 yrs: odds ratio for carcinoma development 16.4 (95% CI 8.3 - 28.4)). However, it is important to realise that although the severity of symptoms is related to the development of Barrett’s oesophagus, there are also individuals experiencing only mild symptoms who develop the lesion.

Not only the severity of symptoms is related to the presence of acid in the oesophagus, but also the presence of complications. This was clearly shown by Vaezi et al. in a paper describing the relation between the presence of acid and bile in the oesophagus and the development of complications of GORD. In patients with uncomplicated GORD the percentage of time at which the oesophageal pH was < 4 was 7%, in patients with oesophagitis this was 15% (range 4-24), in patients with uncomplicated Barrett’s 15% and finally in patients complicated Barrett’s oesophagus (ulcers, strictures, dysplasia or adenocarcinoma) 23%.

It is important to realise that it is not only the total time in which acid is present, but also the pattern of reflux that may be important. In an ex vivo model, it was shown that short pulses of acid decreased differentiation, and increased proliferation, while the continuous presence of acid induced the opposite: a decrease in proliferation and an increase in differentiation.

Also, it is not only the presence of acid, but also of bile and probably pancreatic juice that is deleterious. Paralleling the acid exposure time, the percentage of time the bilirubin absorbance level is over 0.14 increases across the GORD spectrum. In uncomplicated GORD patients this is approximately 3%, in patients with oesophagitis 15%, in patients with uncomplicated Barrett’s 23%, while this reaches 46% in patients with complicated Barrett’s oesophagus. There is also a correlation between the percentage of time the pH is below 4 and the percentage of time bilirubin absorbance level is over 0.14. The vast majority of bile reflux occurs while oesophageal pH is 4-7, which is the normal pH in the oesophagus. Pure bile refluxing in the oesophagus is extremely rare, only approximately 1% of all reflux episodes consists of pure bile.

Bile salts are only toxic when soluble and unionised. In that state they may be able to enter the cell and inflict damage on mitochondria or the cell membrane. At a pH higher than 7, the normal pH in the duodenum, most bile salts are in solution but ionised, and thus harmless. At a pH below 2, the gastric pH, bile salts precipitate irreversibly, and are therefore also harmless. However, at a pH of 4 to 7, some bile salts may be ionised, and some may be unionised and soluble,
thus posing a threat to the mucosa. The vast majority of duodenal reflux occurs at a pH range of 4 to 7, at which bile salts are therefore capable of damaging the oesophageal mucosa.\textsuperscript{16}

Another controversial factor possibly involved in the pathogenesis of Barrett's oesophagus might beHelicobacter pylori (Hp). This bacterium is very common in the Western hemisphere, and even more so in developing countries.\textsuperscript{16,17} Hp infection is clearly associated with gastritis, and virtually all Hp colonised subjects develop chronic gastric inflammation. There is also an association between Hp and gastric carcinoma.\textsuperscript{20} Especially the CagA+ strains of Hp are associated with malignant degeneration in the stomach.\textsuperscript{21}

Hp colonisation and subsequent gastritis may influence the production of acid. Patients with a predominantly corporal gastritis might have a decreased acid production, while patients with a predominantly antral gastritis may have an increased acid production. Also, approximately 50\% of patients eventually develop chronic atrophic gastritis, further decreasing the number of acid producing parietal cells and thus the amount of secreted acid. In this way Hp may partially prevent the development of GORD. This might explain why in some epidemiological studies the prevalence of Hp is lower in patients with oesophagitis or Barrett's oesophagus compared to the reference group.\textsuperscript{22-25}

In contrast with the association of Hp and gastric cancer, some reports suggest a possible protective role of Hp in the development of oesophageal carcinoma: especially cagA+ strains of Hp, which are the most virulent strains in the stomach, may decrease the risk of intestinal metaplasia and/or adenocarcinoma. Although these strains are associated with an increase in gastritis and/or atrophy, cagA+ strains are found less frequently in patients with Barrett's oesophagus, when compared with patients with GORD or control patients.\textsuperscript{26-29} Weston and co-workers even showed a decrease in Hp prevalence along the metaplasia – dysplasia – carcinoma sequence in the oesophagus.\textsuperscript{25} This may be due to the inflammation caused by cagA+ strains depressing the production of acid, and thus the potential reflux. CagA+ strains are highly prevalent in Asians and Blacks, which may partly explain the lower incidence of Barrett's oesophagus and adenocarcinoma of the distal oesophagus in non-western populations.

The increase in incidence of adenocarcinoma of the distal oesophagus and gastric cardia over the last decade has been paralleled by the increased use of potent anti-acids, particularly proton-pump inhibitors (PPI). PPIs decrease the production of acids, and thereby symptoms. However, it is as yet not totally clear how this affects reflux of duodenal and non-acid gastric contents into the oesophagus. One possibility is that the decrease in volume leads to a decrease in refluxate, including acid and non-acid reflux. However, even the most potent regimes of PPIs are often not able to abolish reflux all together, and short bursts of acid may still reach the oesophagus. Also, although the pH in the oesophagus may increase, it is as yet uncertain whether this increase in beneficial. Bile salts are most toxic at a pH of 4-7, and it may well be that by increasing the oesophageal pH, while not abolishing (bile) reflux, the bile salts may become more toxic. This was confirmed in animal experiments, in
which there was a progressive increase in the prevalence of adenocarcinoma as less gastric juice was permitted to reflux with duodenal juice.\textsuperscript{29} This may explain why approximately 20\% of GORD patients go on to develop complications such as Barrett's oesophagus, despite optimal medical treatment with PPIs.\textsuperscript{30,31} In a recent study from our institution 50\% of patients with Barrett's oesophagus used PPIs, versus 17\% of patients with intestinal metaplasia at the gastro-oesophageal junction and 21\% of patients in the reference group.\textsuperscript{32} Alterations in the gastric pH environment caused by potent acid suppression therapy may therefore potentiate oesophageal injury and induce malignant degeneration. However, further clinical data supporting this theory are lacking.

Although symptoms are relieved, there has not been convincing evidence for the regression of Barrett's oesophagus after treatment with PPIs. Although some regression of the Barrett's segments have been reported, this regression is rarely clinically significant, let alone complete.\textsuperscript{31} In a review of the prospective studies regarding this subject, only 3 out of 123 patients showed complete regression of their Barrett's segments.\textsuperscript{32} Although regeneration of squamous epithelium does occur frequently in the form of island of squamous epithelium, there is a considerable risk of "buried Barrett", that is Barrett's mucosa overgrown by squamous mucosa. This "buried Barrett" may even be more dangerous, as it can be missed easily endoscopically.

Motor and sensory changes of the oesophagus and lower oesophageal sphincter are also clearly related to the development of complications. Castell and co-workers showed that mean lower oesophageal sphincter pressure in patients with daily heartburn is four mmHg, while this was 12 mmHg in patients with monthly heartburn.\textsuperscript{33} An increase in both the prevalence and size of a hiatal hernia has been found in GORD patients developing Barrett's oesophagus.\textsuperscript{34-36} An increase in transient lower oesophageal sphincter relaxations may result in an increased exposure of the oesophagus to acid and bile, leading to fibrosis and oesophageal shortening. This may lead to the formation of a hiatal hernia, which may stretch the diaphragmatic crural sling, thereby further impairing the lower sphincter competence. This reduction in lower oesophageal sphincter pressure across the GORD spectrum has been confirmed by many studies.\textsuperscript{37,38,39}

\textit{Malignant degeneration}

The metaplasia-dysplasia-carcinoma sequence occurring in Barrett's oesophagus parallels that occurring in the colon. The average age at which Barrett's oesophagus develops is 40 years, while the average age for the development of adenocarcinoma of the oesophagus lies at 60.\textsuperscript{40} This may suggest that the average time between the development of Barrett's oesophagus and the development of adenocarcinoma would be approximately 20 years. The presence of specialised columnar epithelium confers a 30-125 fold increased risk for oesophageal adenocarcinoma compared with the normal population.\textsuperscript{41} However, there might be a publication bias: there is an inverse correlation between the
number of patients involved and the reported cancer risk.\textsuperscript{42} Most recent risk estimates suggest a cancer incidence among patients with a Barrett’s segment of approximately 1 per 200 patient years.\textsuperscript{43} Several molecular genetic changes are necessary for the transformation of a normal cell into a malignant tumour cell. At least five to ten genetic alterations are necessary to generate the malignant phenotype, and most tumours are characterised by genomic instability facilitating the accumulation of mutations. There are two main routes leading to an uncontrolled cellular proliferation: 1) the activation of oncogenes (e.g. c-erbB-2, cyclin D1 and c-myc).\textsuperscript{44-48} These are dominant genes involved in cellular proliferation or inhibition of apoptosis and/or the increased expression of growth factors (such as EGF) and 2) the inactivation of tumour suppressor genes which under normal conditions prevent proliferation (e.g. p53).\textsuperscript{49-51} These are recessive genes, which implies that both gene copies have to be inactivated to contribute to tumourigenesis. Inactivation of tumour suppressor genes may occur by genetic as well as epigenetic phenomena such as mutation, deletion and hypermethylation of the promotor region.

A third mechanism contributing to genetic instability is impairment in DNA repair. This mismatch repair deficiency leads to genome-wide accumulation of mutations, also in proto-oncogenes and tumour suppressor genes.

\textit{Incidence of oesophageal carcinoma}

While the incidence of carcinoma of the distal stomach has been declining in the Western world over the last decades, the incidence of carcinoma of the proximal stomach (cardia) and adenocarcinoma of the oesophagus have been rising sharply.\textsuperscript{52,53,54} A recent study from Wijnhoven and co-workers confirmed this trend also for the Netherlands.\textsuperscript{55} The age-adjusted incidence and mortality rates for oesophageal cancer in males increased over the last two decades from 2.4 to 4.8 and from 2.7 to 5.6 per 100,000 person years respectively.

At the beginning of the study period, the incidence of adenocarcinoma was much lower than that of squamous cell carcinoma in men, but at present the incidence of adenocarcinoma and the incidence of squamous carcinoma are comparable (2.2 and 2.3 per 100,000 person years resp.). In females the incidence rates for squamous cell carcinomas appeared to increase faster than that of adenocarcinoma. When looking at the different subsites, the steep rise in incidence is mainly due to an increase in lower 1/3 carcinomas, which are mainly adenocarcinomas.\textsuperscript{55} The mechanisms responsible for this upward trend in adenocarcinomas of the oesophagus and gastric cardia are as yet unclear.
Carcinoma of the oesophagus is a highly lethal disease. Surgery is still considered by many as the best option for cure, but even after potentially curative surgery, five-year survival rates rarely exceed 25%. Wide surgical resection of the (thoracic) oesophagus is difficult due to its anatomical position between trachea, main bronchi, pericardium and aorta. This position also leads to early ingrowth in surrounding tissues. Although tumours of the proximal and middle oesophagus tend to metastasise to the cervical lymph nodes and tumours of the distal oesophagus and gastric cardia to the coeliac lymph nodes, early lymphogenic metastases may occur at a large distance from the primary tumour due to its longitudinal submucosal lymphatic drainage. The presence of distant tumour positive lymph nodes is considered as distant metastasis (M1a and M1b) in the TNM classification.

**Primary Tumour (T)**

- **Tis**: Carcinoma in situ/high grade dysplasia
- **T1**: Infiltration into lamina propria (T1im) or into submucosa (T1sm)
- **T2**: Infiltration into muscularis propria
- **T3**: Infiltration into adventitia
- **T4**: Infiltration into adjacent structures

**Regional Lymph Nodes (N)**

- **N0**: No regional lymph node metastasis
- **N1**: Regional lymph node metastasis

**Distant metastasis**

- **M0**: No distant metastasis
- **M1**: Distant metastasis

**Tumours of the upper thoracic oesophagus**

- **M1a**: Metastasis in cervical nodes
- **M1b**: Other distant metastasis

**Tumours of the midthoracic oesophagus**

- **M1b**: Non regional lymph nodes and/or other distant metastasis
Tumours of the lower thoracic oesophagus

M1a  Metastasis in coeliac lymph nodes
M1b  Other distant metastasis

Stage I  T1N0M0
Stage IIa  T2/3N0M0
Stage IIb  T1/2N1M0
Stage III  T3N1M0, T4N0/1M0
Stage IV  Any T, Any N, M1a/b

When the diagnosis has been established, surgery is the first option for cure. However, due to the magnitude of the surgical procedure and its related morbidity and mortality, an oesophageal resection should probably not be performed on a palliative basis. After having assessed the patient’s general condition and thereby operability, pre-operative staging to assess local resectability and the presence of distant metastases therefore becomes essential.

Ingrowth in surrounding tissues is considered a contra-indication for surgical resection, just as the presence of distant metastases. The presence of surgically resectable tumour positive lymph nodes does not have to be a contra-indication for surgery. Probably, this also holds true for resectable lymph nodes near the coeliac axis, while cervical tumour positive lymph nodes in patients with a mid/distal oesophageal tumour are generally considered a contra-indication for surgery. This early and fairly random lymphogenic metastatic potential in combination with the early ingrowth in adjacent structures explains the generally dismal prognosis of oesophageal cancer patients and might have consequences for the surgical approach.

As the tumour penetrates deeper into or even outside the muscular wall of the oesophagus, the incidence of lymph node metastases increases. While for T1im tumours the incidence of lymph node metastasis is <5%, the incidence of tumour positive lymph nodes in T1sm tumours reaches up to 20%. In T3 tumours the incidence of positive lymph nodes is even up to 80%. The presence of lymph node metastasis and the lymph node ratio are one of the strongest prognostic factors for survival.

From these findings different attitudes towards lymph node dissection have emerged. One option is to perform an extended lymph node dissection in abdomen, chest and possibly neck as well, to try and obtain long term survival. The other option aims at decreasing early morbidity and mortality by performing a less extensive procedure. Proponents of this second strategy argue that lymph node metastases are indicators rather than governors of long term survival. Major question, and thereby the central theme of this thesis, is whether the possible long-term survival benefits of an extended procedure outweigh the expected increase in early post-operative morbidity and mortality and costs.
Improvements in the surgical treatment of oesophageal carcinoma can be achieved in different ways: by early diagnosis and patient selection, by optimising surgical care, and by optimising (neo)adjuvant treatment modalities. Finally, further insight in the development along the metaplasia – dysplasia – carcinoma sequence might enable us further to improve treatment of this highly lethal disease. This thesis mainly deals with surgical aspects of Barrett’s carcinoma, but also includes work on the pathogenesis of Barrett’s oesophagus and adenocarcinoma of the oesophagus and gastric cardia.

References

8) 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: 1033-6


18) Blaser MJ. Epidemiology and pathophysiology of Campylobacter pylori infections. Rev Inf Dis 1990; 129: 44-59


29) Ireland AP, Peters JH, Smyrk TC, DeMeester TR, Clark GWB, Mirvish SS. Gastric juice protects against the development of esophageal adenocarcinoma in the rat. Ann Surg 1996; 224: 358-71


36) Cameron AJ. Barrett’s esophagus: prevalence and size of hiatal hernia. Am J Gastroenterol 1999; 94: 2054-9


39) Singh P, Taylor RH, Colin-Jones DG. Esophageal motor dysfunction and acid exposure in reflux esophagitis are more severe if Barrett’s metaplasia is present. Am J Gastroenterol 1994; 89: 349-56

40) Haggitt RC. Barrett’s esophagus, dysplasia, and adenocarcinoma. Hum Pathol 1994; 25: 982-93

41) Cameron AJ. Epidemiologic studies and the development of Barrett’s esophagus. Endoscopy 1993; 25: 635-6


50) Yacoub L, Goldman H, Ozde RD. Transforming growth factor-alpha, epidermal growth factor receptor, and MiB-1 expression in Barrett’s-associated neoplasia: correlation with prognosis. Mod Pathol 1997; 10: 105-12
55) Wijnhoven BPL, Louwman WJ, Tilanus HW, Coebergh JWW. Increased incidence of adenocarcinomas of the gastro-oesophageal junction in Dutch males since the 1990’s. Eur J Gastroenterol Hepatol 2002; 14: 115-22


