

Chronology of the Barrett's metaplasia–dysplasia–carcinoma sequence*

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SUMMARY. The objective of this study was to assess the course over time of the Barrett's metaplasia–dysplasia–carcinoma sequence. The method used was a retrospective analysis of the medical records of a patient series with a median follow-up of 25 months. The study was undertaken in a university hospital foregut laboratory. The progress of seven patients was followed through the sequence of Barrett's esophagus, low-grade dysplasia and high-grade dysplasia to cancer. They all underwent subsequent esophagectomy and were found to have intramucosal adenocarcinoma. The main outcome measure was the time from the first diagnosis of intestinal metaplasia to the development of low-grade dysplasia, high-grade dysplasia and adenocarcinoma. Low-grade dysplasia developed in a median of 24 months, high-grade dysplasia after a median of 33 months and cancer after 36 months. All patients underwent esophagectomy with reconstruction and no patient has had a recurrence at a median follow-up of 25 months (range 10–204 months). Patients on Barrett's surveillance who develop early esophageal adenocarcinoma did so within approximately 3 years after the diagnosis of non-dysplastic Barrett's esophagus.

KEY WORDS: adenocarcinoma, Barrett's esophagus, carcinogenesis, chronology.

INTRODUCTION

The natural history of the metaplasia–dysplasia–carcinoma sequence in Barrett's esophagus remains unknown. This has contributed to great variability in the surveillance frequency of patients diagnosed with Barrett's esophagus.^{1,2} Several reports have shown that surveillance programs can detect esophageal adenocarcinoma at an early stage when the depth of the tumor is limited to the muscularis mucosa. When surgical treatment is applied at this stage the 5-year survival is in excess of 80%.^{3–6} This contrasts strongly with the poor survival of patients with tumors detected at the time symptoms occur. Surveillance for early adenocarcinoma in patients with Barrett's esophagus is possible because of the known progressive sequence from low-grade dysplasia (LGD), to high-grade dysplasia (HGD) to adenocarcinoma.^{7–9}

Low or high-grade dysplasia occurs in approximately 20% of patients with Barrett's esophagus and is currently the most widely available marker for the detection of progression to malignancy.^{10–13} Data on the chronology of the dysplasia to carcinoma sequence in Barrett's esophagus are limited and controversial.^{11,14} High-grade dysplasia has been reported to be present for several years in patients with Barrett's esophagus without progression to cancer and some have stated that the abnormality is reversible.^{13,15–17} However, patients who have undergone surgery for HGD were found to have adenocarcinoma in postoperative histology in up to 30% of cases.¹⁸ The aim of this study is to assess the time course of the dysplasia to carcinoma sequence based on a retrospective analysis of the medical records of patients in whom intramucosal adenocarcinoma was detected by endoscopic surveillance.

PATIENTS AND METHODS

Of the 235 patients who underwent esophagectomy for adenocarcinoma of the distal esophagus or gastroesophageal junction between 1978 and 1997 at the University of California Department of

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Surgery, 28 patients were found who had esophageal adenocarcinoma limited to the lamina propria and this group made up the study population. Of these patients seven went through the entire sequence of intestinal metaplasia (IM), LGD, HGD to cancer. There were five men and two women, with a median age of 65 years ranging from 52 to 76 years at the time of the operation. They were enrolled in a surveillance program after the initial diagnosis of Barrett's esophagus either at the referring institution or our own program. None of the study patients received preoperative radio- or chemotherapy or underwent any type of esophageal or gastric surgery prior to the esophagectomy for cancer. The time taken to develop LGD, HGD and cancer was calculated retrospectively by analysis of our medical records on those retrieved from the various medical facilities that referred the patients to our institution. All patients underwent esophagectomy for either adenocarcinoma or HGD with colon interposition or gastric pull-up, and were followed at our institution. The median follow-up after surgery was 25 months with a range from 10 to 204 months.

Endoscopy

All patients underwent upper gastrointestinal endoscopy with biopsy initially and during the period of surveillance. The frequency varied depending on the histology found on biopsy. The protocol for biopsying the esophagus depended on the suspected length of the metaplastic tissue. Most commonly, multiple biopsies were obtained from the gastroesophageal junction and from any visible tongues of glandular mucosa extending in the esophagus. In patients whose squamocolumnar junction was separated from the gastroesophageal junction, biopsies were taken from four quadrants at 2 cm intervals throughout the length of the columnar lined esophagus.

Histology

The diagnosis of Barrett's mucosa required the presence of IM of any length in a cardiac-type mucosa at the gastroesophageal junction or above. Intestinal metaplasia was identified by the presence of goblet cells on hematoxylin-eosin staining and confirmed by staining with Alcian blue at pH 2.5. Low-grade dysplasia was defined by the presence of nuclear enlargement, hyperchromasia and spare mitotic figures. High-grade dysplasia was defined by the presence of marked nuclear enlargement, pleomorphism, hyperchromasia and the presence of mitosis including atypical mitotic figures. A single pathologist reviewed all biopsies and postoperative specimens. The diagnosis of HGD required the confirmation by a second pathologist.

Postoperative analysis of the specimen

The location of the primary tumor was recorded and a detailed histological evaluation was performed to identify the depth of invasion. Only patients with primary tumors that invaded the lamina propria but did not extend through the muscularis mucosa were included in the study.

RESULTS

All patients complained of typical symptoms suggestive of gastroesophageal reflux disease (GERD), which are heartburn and/or regurgitation prior to the first diagnosis of IM and were treated either with H2-blockers, proton-pump inhibitors or over-the-counter antacids prior to the initial diagnosis of Barrett's esophagus and during the surveillance.

Barrett's esophagus was diagnosed for the first time at a median of 11 years after the onset of symptoms with a range from 7 to 46 years.

During the period of surveillance an average of seven endoscopies were performed per patient with a range of 4–11. The median interval of endoscopies was 6 months ranging from 1 to 48 months. (Table 1)

Low-grade dysplasia was detected at a median of 24 months after the initial diagnosis of IM with a range of 69 months. In three patients IM was diagnosed several times before LGD was found on biopsy. The remaining four patients were found to have LGD at their second endoscopy. It took a total of 33 months to progress from Barrett's esophagus via LGD to HGD with a range of 89 months. Only a median of 11 months was needed to progress from LGD to HGD (Fig. 1).

Three patients underwent surgery for intramucosal adenocarcinoma. They were found to have cancer on biopsy three months after the first diagnosis of HGD. The remaining four patients underwent esophagectomy for HGD and had intramucosal cancer in the surgical specimen.

During the surveillance period one patient underwent a Nissen fundoplication after the first diagnosis of LGD in addition to medical therapy. There was no proof of failure by 24-hour pH monitoring. This patient demonstrated IM on the

Table 1 Demographics and endoscopic data for the patients under surveillance who went through the entire sequence ($n = 7$)

	Age	Duration of symptoms before first diagnosis of IM (years)	Number of endoscopies	Interval for endoscopies (months)
Median	65	11	7	11
Range	52–76	7–46	4–11	2–26

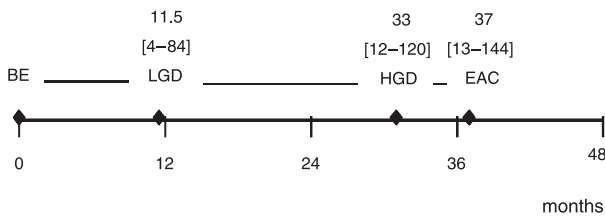


Fig. 1 Cumulative time taken for each step of the sequence in months (BE, Barrett's esophagus; LGD, low-grade-dysplasia; HGD, high-grade-dysplasia; EAC, esophageal adenocarcinoma).

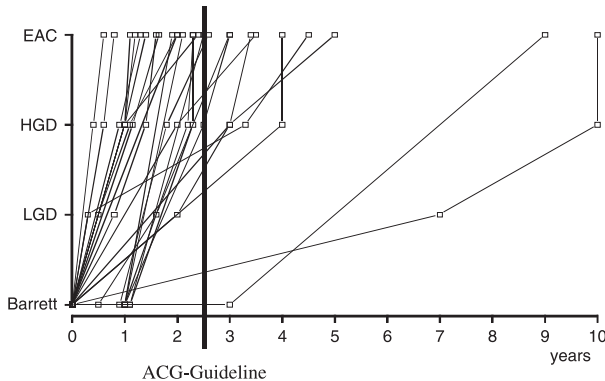


Fig. 2 Time lines for each individual patient in months (ACG-Guideline, American College of Gastroenterologists guideline; EAC, esophageal adenocarcinoma; LGD, low-grade-dysplasia; HGD, high-grade-dysplasia).

first postoperative biopsy, but nevertheless progressed to cancer subsequently.

All together there were three patients who did not show a progressive sequence in their biopsies. One was found to have LGD after HGD was diagnosed, the second patient showed IM after a Nissen fundoplication for LGD and the third patient went through a reverse sequence before finally being diagnosed with HGD. The remaining patients went through the sequence progressively. The individual time-courses of all 28 patients are depicted in months in Figure 2.

DISCUSSION

Barrett's esophagus develops as a complication of chronic GERD. Its significance lies in a 30–40-fold increase in the risk of developing esophageal adenocarcinoma. Classic long-segment Barrett's esophagus develops in approximately 15% of patients with GERD,¹⁹ and studies have suggested that about 2.6 million Americans are likely to develop Barrett's esophagus.²⁰ Once present, Barrett's epithelium is at risk for developing adenocarcinoma of the esophagus.^{10,11,20}

The natural history of Barrett's esophagus is not very well understood. The current study supports the theory that a stepwise progression from non-

dysplastic Barrett's esophagus to LGD to HGD to esophageal adenocarcinoma occurs.^{8,9,11,14}

Little attention, however, has been paid to the length of time this sequence takes to develop. The analysis of a well-defined group of patients with early esophageal adenocarcinomas provides an excellent opportunity to determine the timing of these mucosal changes. Cancer confined to the muscularis mucosa is currently the earliest detectable form of cancer in the distal esophagus and therefore marks a well-defined endpoint for a longitudinal study. However the long duration of symptoms of 11 years in our study group leads to the assumption that the metaplastic tissue has been there for an unknown time. Because of the moving target at the beginning of the study an interpretation of the timing between Barrett's esophagus and LGD has to be done carefully. Acknowledging that we do not know exactly how long Barrett's tissue had been present in these patients, it is striking that in the subset of patients with Barrett's esophagus who do develop cancer the time taken to progress through the sequence, once Barrett's esophagus is diagnosed, is very short, namely within 3 years. This subgroup accounts for about 30–40% of all patients with Barrett's esophagus. This is supported by the findings of a large study by Schnell *et al.*¹⁷ These authors found a mean 7.3-year surveillance period before cancer was detected. However, this included advanced cancer as well. Looking at the subgroup of patients with early lesions in this study the time decreased to about 4 years for the development of cancer, which is similar to our results. This indicates that some patients can move through the sequence at a fairly high speed. The detection of cancer in HGD with extensive biopsies as shown by Schnell *et al.* within the first year demonstrates the likelihood of sampling error with regular protocols. We also observed a rapid progression from HGD to cancer in a median of 3 months, clearly suggesting the possibility of sampling error, rather than a progression effect. These tumors might have been picked up by extensive examinations, such as extra endoscopies with additional biopsies.

Hameeteman *et al.* showed in a prospective study that it took between 1.5 and 4 years for patients to progress from LGD to cancer,¹¹ and demonstrated that HGD might be present for as long as 3.5 years before it progressed to cancer. The present study made similar findings in a patient who was diagnosed with HGD on biopsies for almost 2 years before the diagnosis of cancer was made in the surgical specimen.

McDonald *et al.* demonstrated that after a failed antireflux procedure the progression of patients to cancer occurred during the first 3 years.²¹ The one patient in our study group who developed cancer after a Nissen fundoplication showed a similar time

course with an interval of 2 years between the operation and the diagnosis of cancer. Even so most patients with Barrett's esophagus never develop cancer,^{16,17} but a subset of them do and once HGD is present these patients need to be followed closely to exclude invasive cancer. To date, no convincing predictors are known to identify this subset of patients who are likely to run through the sequence of Barrett's esophagus–LGD–HGD–invasive cancer. To further increase the accuracy of prediction future studies should be aimed at identifying this subset of patients with Barrett's esophagus who carry the risk of rapid progression towards cancer.

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