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Long-Term Follow-Up in Patients with Indeterminate Barrett Esophagus

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Key Words
Barrett esophagus · Adenocarcinoma · Endoscopy · Histopathology

Abstract
Background: Barrett esophagus (BE) is a major risk factor for adenocarcinoma of the distal esophagus. Reliable detection of BE during upper endoscopy is therefore mandatory. According to most guidelines, diagnosis of BE requires both endoscopy and histology for confirmation. However, since adenocarcinomas were also described in patients with indeterminate BE, i.e. endoscopic visible columnar metaplasia but no histological confirmation of goblet cells or vice versa, debate has risen on the risk of malignancy and the need for endoscopic surveillance in such patients. ***Patients and Methods:*** The study was aimed to assess long-term follow-up data on 209 patients with indeterminate BE (on histopathology or endoscopy) initially examined between 1999 and 2000. Patients or referring physicians were contacted concerning the most recent endoscopic and histopathological results. ***Results:*** Follow-up data could be assessed in 149/209 patients (65.1%) after a mean follow-up period of 9.4 years (SD ±2.4 years). Neoplasia was not reported for any patient. The previous endoscopic-histopathological diagnoses could be confirmed in 3 patients only. In the group with endoscopic diagnosis of BE but no histopathological confirmation, BE was described histopathologically in 1 patient during follow-up. ***Conclusion:*** Persistence of indeterminate BE is poor during long-term follow up. The risk of cancer appears to be negligible. Hence, surveillance of these patients appears equivocal.

Background

Barrett esophagus (BE) is a major risk factor for adenocarcinoma of the distal esophagus [1]. The frequency of BE varies widely between 0.9% [2] and >10% [3], depending on the country and the respective definition used. In the last decades, histopathological diagnosis of BE was directly connected to columnar epithelium with the presence of goblet cells [4]. Since neoplastic potential is also discussed in nongoblet columnar epithelium, debate has risen on the risk of malignancy and the need for endoscopic surveillance in indeterminate BE, i.e. endoscopic visible columnar metaplasia but no histological confirmation with goblet cells or vice versa [5]. Although recommended by the British guidelines [6], taking these patients into life-long endoscopic surveillance programs might affect healthcare resources and costs tremendously.

In addition, endoscopic and histopathological detection and diagnosis is prone to sampling error and in-

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terobserver variability and long-time follow-up data are sparse. Furthermore, intestinal metaplasia (IM) of the cardia might be misdiagnosed as histological BE without endoscopic evidence. This study aimed to assess the neoplastic potential and endoscopic-histological persistence during long-term follow-up in patients with indeterminate BE.

Patients and Methods

Patients with indeterminate BE (on histopathology or endoscopy) initially examined between 1999 and 2000 within the framework of a multicenter study were analyzed [7]. Patients with symptoms of gastroesophageal reflux disease (GERD) or dyspepsia were recruited at eight gastroenterological centers. Patients aged between 18 and 80 years without a previous history of BE or neoplasia of the upper gastrointestinal tract were included. Exclusion criteria were: known malignant disease, previous gastrectomy, severe comorbidity or any coagulation disorders. Initial upper endoscopy and histopathological examination was performed as described previously [7].

Based on the previous results, patients with endoscopic visible columnar metaplasia but no histological confirmation of goblet cells or vice versa were identified. Patients or referring physicians were contacted by telephone or e-mail. The most recent endoscopic and histopathological results were transferred by e-mail or fax to our study center and were evaluated for the presence of BE based either on endoscopy and/or the histopathological reports. The time interval from the initial endoscopic examination to the most recent procedure was calculated. Intermediate results were not analyzed due to variable time intervals. Patients were also asked about symptoms of GERD and the use of proton pump inhibitors (PPIs).

Statistical Analysis

Data are described by means, standard deviation, range and frequencies, respectively. For all calculations, IBM SPSS Statistics for Windows 18 (SPSS Inc., Chicago, Ill., USA) was used.

Results

In total, 209 patients with indeterminate BE (on histopathology or endoscopy) initially examined between 1999 and 2000 could be identified. Follow-up data could be assessed in 149 patients (65.1%). Mean follow-up period was 9.4 years (SD ±2.4 years) (fig. 1). For the remaining patients (34.9%), either the respective patient or referring physicians could not be contacted. Characteristics of the patients followed-up are shown in table 1. There were no significant differences observed between patients with indeterminate BE either by histology or endoscopy. In total, 1,368 patient years were analyzed.

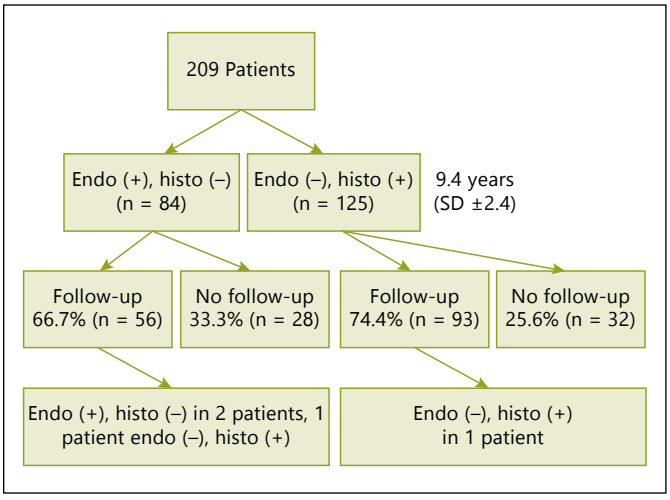

Fig. 1. Study design. Patients in both groups were asked for their most recent endoscopic (Endo) and histopathological (histo) results in order to be able to evaluate the presence of BE. Negative (–); positive (+).

Table 1. Patient characteristics

	Endoscopy: positive histopathology: negative (n = 56)	Endoscopy: negative histopathology: positive (n = 93)
Age, years		
Mean	63.2	64.6
Gender		
Male	51.7%	52.6%
PPI intake	57.1%	50.5%
Reflux symptoms	41.0%	43.0%

In patients with an endoscopic diagnosis of BE but no histopathological confirmation, follow-up data could be assessed in 56 of 84 patients (fig. 1). Neoplasia was not reported to occur in any of them. Initial diagnosis was confirmed in 2 patients. In 1 patient with endoscopically normal distal esophagus, BE was described histopathologically. A regular intake of PPI was reported by 57.1% of the patients and 41.0% indicated GERD symptoms.

In patients with an endoscopically normal distal esophagus but a histopathological diagnosis of BE in biopsies obtained from the Z-line, follow-up data could be assessed in 93 of 125. Neoplasia was not reported for any patient. Initial histopatholigcal diagnosis was confirmed in 1 patient. A regular intake of PPI was reported by 50.5% of the patients and 43% indicated GERD symptoms.

Discussion

We aimed to assess long-term follow-up data in patients with indeterminate BE to evaluate the risk of malignancy and the need for endoscopic surveillance. The endoscopic and histological results during follow-up examinations were not very consistent, but the risk of malignancy seemed to be very low. Neoplasia was not reported in any patient. Our study therefore indicates that endoscopic follow-up examination in patients with indeterminate BE is dispensable.

It is known that BE is a strong risk factor for esophageal adenocarcinoma. However, in current studies, cancer risk in non-neoplastic BE is reported to be much lower than was assumed in earlier data [8]. In a current, large, population-based study in patients with endoscopically and histopathologically confirmed BE, the annual risk of adenocarcinoma is 0.12% or 1 case of adenocarcinoma per 860 patient-years [9]. So far, there is only a very limited number of studies evaluating cancer risk in patients with indeterminate BE. In a follow-up study of patients with short-segment BE or IM of the cardia, neoplasia risk was significantly lower in IM compared to short-segment BE patients [10]. In agreement with our data, no neoplasia has been detected in IM. However, the mean follow-up period was only 24 months (range 8–100 months), significantly shorter than in our data.

Recommendations for endoscopic surveillance as proposed by the current guideline from the American Gastroenterological Association are based on the annual cancer incidence of 0.5% [11]. Even using this comparatively high number of cancer incidence in non-neoplastic BE, endoscopic surveillance programs are probably not cost-effective [12]. According to our data and the results of the Sharma study group [11], cancer risk in indeterminate BE appears to be much lower than in non-neoplastic BE. It can therefore be assumed that endoscopic surveillance programs in patients with indeterminate BE are neither promising nor cost-effective. Guidelines that establish a diagnosis of BE based only on endoscopic results might transfer a higher number of patients with indeterminate BE to endoscopic surveillance programs [6]. Considering the negligible cancer risk of indeterminate BE, it must be assumed that there is a relevant number of patients in surveillance programs without any substantial risk of neoplasia. In addition, surveillance is associated with a considerable psychological burden.

The reason for the discrepancies between initial examination and follow-up can be explained in different ways. The preknown 'sampling error' and the intraobserver and interobserver bias of the pathologist and endoscopist might explain any inconsistent results [13, 7]. Furthermore, previous studies have shown that identifying the gastroesophageal junction accurately during endoscopy is challenging. It is still a matter of debate which reference points should be used. The 'Prague criteria' suggest the proximal extent of rugal folds, whereas Japanese data prefer the palisade vessels. However, interobserver studies show low agreement in identification of the gastroesophageal junction for either the palisade vessel or the 'Prague criteria' [14]. For the histopathologist, identifying the gastroesophageal junction is essential, because it might be difficult to distinguish IM in the esophagus from IM in the cardia. They share many characteristics including expression of certain antigens. Even slight respiratory movements made by patients during endoscopic examination might lead to 'false' biopsies. The pathomechanism of IM of the cardia is completely different and is associated with reflux. It is most likely associated with *Helicobacter pylori* gastritis as well as IM in other parts of the stomach. Prevalence of IM of the cardia varies between 5 and 23% in routine upper endoscopy. Surveillance is not recommended in IM of the cardia [10].

Another reason for the discrepancies might be long-term PPI use, which is discussed to reduce the risk of neoplastic progression or might even lead to regression in BE. Observational studies indicate that reducing the intraesophageal acid exposure decreases cellular proliferation and the risk of neoplasia [15]. However, in the presented data, approximately half of the patients reported regular PPI use. Potentially, regression of BE might partly be associated with the use of PPIs. Use of statins and NSAIDS, which might also be causal for regression in BE were not analyzed due to missing initial data.

A limitation of our study is the multicenter setting with several endoscopists and histopathologists, which can lead to less consistent data than in a single-center study with one reference endoscopist/histopathologist. However, in contrast, such a setting represents regular outpatient care in daily practice. Furthermore, follow-up data were assessed only in 149 of 209 patients (65.1%). However, taking into account the lack of long-term follow-up studies under consideration, we think that a mean follow-up period of 9.4 years (SD ±2.4 years) can be regarded as an acceptable number. In addition, initial patient data are limited. Unfortunately, there is no information about length or total area of BE, numbers of biopsies taken or suspicious lesions for the respective patient. Due to variable time intervals or missing intermediate endoscopic procedures, data were not analyzed. Therefore, it

is not possible to determine at what time point changes occurred. To overcome these limitations, more prospective, longer-term studies are needed.

The Clinical approach for patients with indeterminate BE reflects an everyday clinical problem and has not yet been adequately addressed. New imaging techniques like chromoendoscopy are not ready to significantly improve the diagnosis of BE compared to standard endoscopy with random biopsies [16]. Potentially, molecular markers might have the potential to improve diagnosis and evaluation of cancer risk in BE in the future. Meanwhile, there is an increasing number of molecular alterations, e.g. in tumor suppressor genes p16 and TP53 [17]. Unfortunately, in carcinoma arising from BE, there are considerable genetic heterogeneities and the clinical significance of the genetic alterations is still unclear.

In summary, irrespective of endoscopic or histopathological confirmation, the reproducibility of indeterminate BE is poor during long-term follow-up. The risk of cancer appears to be negligible. According to our data, endoscopic surveillance programs for patients with indeterminate BE cannot be recommended.

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