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Alimentary Tract

Consistency of a high-grade dysplasia diagnosis in Barrett's oesophagus: A Dutch nationwide cohort study

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ABSTRACT

Background: Consistency of high-grade dysplasia in Barrett's oesophagus is incompletely known and the clinical course may vary between patients.
Aims: To evaluate the consistency of high-grade dysplasia diagnosis in a Dutch nationwide cohort and to identify predictors for (re-)detecting high-grade dysplasia or oesophageal adenocarcinoma when ≥1 follow-up evaluations after an initial high-grade dysplasia diagnosis were scored with a lower histological grade.
Methods: In this retrospective cohort study, all patients diagnosed with high-grade dysplasia in Barrett's oesophagus between 1999 and 2008 in the Netherlands were selected using the nationwide histopathology registry. Multivariate analysis was performed to identify predictors for (re-)detecting high-grade dysplasia or oesophageal adenocarcinoma in patients with ≥1 follow-up evaluations scored with a lower grade.
Results: In total, 512 high-grade dysplasia patients were included, of whom 53% had ≥1 follow-up evaluations scored with a lower grade. The (re-)detection risk was increased when follow-up was performed in a university hospital and when endoscopic/surgical resection was performed and decreased with an increasing number of follow-up evaluations scored with a lower grade.
Conclusion: High-grade dysplasia diagnosis was inconsistent in more than half of patients. (Endoscopic) resection in an expert centre is recommended to (re-)detect high-grade dysplasia or oesophageal adenocarcinoma when an endoscopic follow-up protocol with biopsies repeatedly shows a lower histological grade.

1. Introduction

Barrett's oesophagus (BE) is a premalignant condition predisposing to the development of oesophageal adenocarcinoma (EAC) [1,2]. The neoplastic progression is thought to occur through a gradual stepwise process from no dysplasia to low-grade dysplasia (LGD), high-grade dysplasia (HGD) and finally EAC [3,4]. In clinical practice, the histological finding of dysplasia is the most commonly used method to predict progression risk and is used to determine endoscopic surveillance intervals and to decide whether or not there is an indication for treatment. Current guidelines recommend endoscopic treatment when HGD in BE is detected [5–7]. We recently demonstrated that the progression rate to EAC in HGD patients was 4.2 per 100 person years, after excluding prevalent cases [8].

Even though we have gained insight in the progression rates in BE, the consistency of a diagnosis of HGD in BE is incompletely known. In clinical practice, HGD may not be detected in repeat biopsy samples during endoscopic follow-up after an initial HGD diagnosis, unless endoscopic or surgical treatment is performed and the specimen is meticulously histologically evaluated. No data are available indicating that HGD regresses spontaneously, however, this phenomenon can also not be completely excluded. It is more likely that a finding of no dysplasia after previous HGD diagnosis is the result of sampling error during endoscopy or interobserver variability between pathologists during histological evaluation, which to some extent can be due to the co-presence of inflammation [9]. At the lower end of the metaplasia-dysplasia sequence (no dysplasia, indefinite for dysplasia (IFD), LGD) interobserver agreement of the diagnosis has been reported to be poor

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[10–12], but is substantial in case of HGD or EAC, with kappa values ranging from 0.61 to 0.72 [10,11,13]. The interobserver agreement is somewhat lower for distinguishing between HGD and EAC in biopsy samples, and is even further reduced in HGD with a predominant architectural distortion [14].

There is no evidence available indicating which patients are at the highest risk of re-detecting HGD or detecting EAC when HGD is not seen during one or more endoscopic follow-up evaluations. We hypothesized that HGD diagnosis was inconsistent in a considerable proportion of patients and that cases with HGD confirmed by an expert pathologist and undergoing aggressive treatment (resection) were at the highest risk of (re-)detecting HGD or EAC. The aim of this study was therefore to evaluate the consistency of a diagnosis of HGD in BE in a large cohort of patients and to identify predictors for (re-)detecting HGD or EAC, particularly when one or more follow-up evaluations after an initial HGD diagnosis were scored with a lower histological grade.

2. Materials and methods

2.1. Study population

All patients diagnosed with HGD in BE between January 1999 and August 2008 were selected in the PALGA database, which is a Dutch nationwide registry in which all summaries of histo- and cytopathology are centrally archived. Nationwide coverage, including all 64 pathology laboratories in the Netherlands, was accomplished in 1991 [15]. Each pathology report is linked to a diagnostic code, reflecting a topological term and type of the tissue sample in combination with the histo- or cytological finding (e.g. oesophagus × biopsy × high grade dysplasia). These diagnostic codes correspond to the Systematized Nomenclature of Medicine (SNOMED) issued by the college of American Pathologists [16].

To minimize the risk of missing incorrectly coded oesophageal HGD cases, patients with all types of dysplasia and atypia in both the oesophagus and stomach were identified in the database. For each patient, the summaries of all pathology reports with regard to the oesophagus and stomach were retrieved. Patients with HGD in BE were selected by searching and reviewing the reports for HGD synonyms. Cases with HGD, severe dysplasia or carcinoma in situ diagnosed in a segment with intestinal metaplasia in the oesophagus were included. Exclusion criteria were mild and moderate dysplasia, LGD, HGD in squamous epithelium or stomach (including gastro-oesophageal junction), EAC prior to or simultaneously (in the same set of biopsies) detected with a first diagnosis of HGD and carcinoma of the gastro-oesophageal junction. In case of detection of EAC in a resection specimen only patients in whom the bulk of the tumour was located above the gastro-oesophageal junction were included.

2.2. Data collection

Of the selected HGD cases, all retrieved pathology reports were reviewed by two reviewers (RV and PS), with consultation of a pathologist (FK) in doubtful cases. The following data were extracted from these reports, i.e., gender, age, number of histological evaluations and intervals, diagnosis and type of sample (biopsy or resection specimen), year of HGD diagnosis, type of hospital of HGD diagnosis and follow-up (general/university), extent of HGD, conclusion of a second opinion by an expert pathologist, follow-up strategy, date of (re-)detection of HGD or EAC when HGD was not seen during one or more follow-up evaluations and date of last follow-up. Unifocal HGD was defined as only one focus of HGD in at most one biopsy, in line with the Mayo Clinic definition [17].

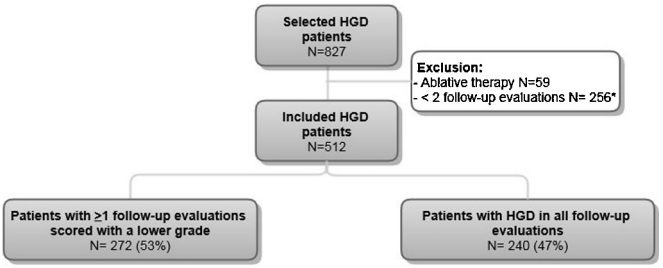

Fig. 1. Identification of the high-grade dysplasia study cohort in the nationwide registry of histo- and cytopathology. * 128 patients had no follow-up and 128 only one follow-up evaluation. HGD, high-grade dysplasia.

In order to evaluate the consistency of a diagnosis of HGD, patients treated with ablative therapy and with <2 histological follow-up evaluations were excluded. Patients were assumed to have undergone ablative therapy if this was either explicitly stated in the pathology report or when the presence of neosquamous epithelium or eradication of Barrett epithelium in the absence of an (endoscopic) resection specimen was stated.

Subsequently, patients with one or more histological follow-up evaluations (biopsies as well as resection specimens) after an initial HGD diagnosis scored with a lower histological grade and patients with HGD detected in all follow-up evaluations until HGD was resected were identified.

2.3. Statistical analysis

Characteristics of HGD patients were analyzed using standard descriptive statistics. Multivariate Cox proportional hazards regression analysis was performed to identify independent determinants for (re-)detection of HGD or EAC after a period with evaluations scored as less severe than HGD. Censoring was applied at the moment of (re-)detecting HGD or EAC or at the last follow-up evaluation. Two-sided p-values < 0.05 were considered statistically significant. SPSS software version 15.0 for Windows was used for the statistical analyses.

3. Results

3.1. Consistency of HGD diagnosis

For this study on the consistency of a diagnosis of HGD in BE, 512 patients were included (Fig. 1). Mean age (±SD) of the study cohort was 64 (±11) years and 80% (n = 410) was male. The median duration of follow-up was 1.9 (interquartile range (IQR) 0.3–4.3) person years.

In 31% (160/512) of the total cohort, the initial HGD diagnosis was evaluated by a second (expert) pathologist. HGD diagnosis was confirmed in 94% (150/160) of the revisions, downgraded in 5% (8/160) and upgraded to EAC in 1% (2/160). In 240 (47%) patients, HGD was found after the initial HGD diagnosis in all histological follow-up evaluations until HGD was resected (n = 98; 19%), or until EAC was detected (n = 142 (28%), which was in 113 patients ≤6 months and in 29 patients >6 months). In total, 272 (53%) patients had ≥1 follow-up evaluation after an initial HGD diagnosis scored with a lower histological grade (Fig. 1).

3.2. Re-detection of HGD or EAC

In 272 patients with an initial HGD diagnosis and with ≥1 evaluations scored with a lower histological grade, the (re-)detection rate of HGD or EAC was determined. The median number of follow-up evaluations scored as less severe than HGD was 3 (IQR 1–5), with a maximum of 18. In 66% (151/272) of these patients, HGD was no