Risk of neoplastic progression in Barrett's esophagus diagnosed as indefinite for dysplasia: a nationwide cohort study

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Background and study aims: A histological diagnosis of "indefinite for dysplasia" (IND) in Barrett's esophagus is used when a diagnosis of genuine dysplasia is equivocal. The aim of the present study was to assess the risk of progression to high grade dysplasia (HGD) or esophageal adenocarcinoma (EAC) after a diagnosis of IND in a nationwide cohort of patients with Barrett's esophagus.

Patients and methods: Patients with a first diagnosis of IND in Barrett's esophagus between 2002 and 2011 were selected from a nationwide registry of histopathology diagnoses in The Netherlands. Patients were followed up until treatment for HGD, detection of EAC, or date of last endoscopy contact with biopsy sampling.

Results: In total, 1258 patients met the inclusion criteria, of whom 842 (66.9%) underwent endoscopic follow-up. Patients were followed for a total of 2585 person-years (mean ± SD 3.01±2.6). Median duration until first follow-up endoscopy was 1.2 years (interquartile range 0.3 – 1.8 years). The progression rate from IND to the combined end point of HGD or EAC was 2.0 (95% confidence interval [CI] 1.5 – 2.6) per 100 person-years and progression to EAC was 1.2 (95%CI 0.8 – 1.6). After excluding cases with HGD or EAC within 1 year after IND diagnosis (n = 16), the progression rates were 1.4 (95%CI 1.0 – 1.9) and 0.8 (95%CI 0.5 – 1.2) per 100 person-years for HGD or EAC and EAC, respectively.

Conclusion: In this large, population-based, cohort of patients with Barrett's esophagus, the incidence rate of HGD or EAC following a diagnosis of IND was 1.4 per 100 person-years. The results demonstrate the need for additional studies to select the subgroup of IND patients with an increased risk of neoplastic progression.

Introduction

Barrett's esophagus is a premalignant condition in which squamous epithelium is replaced by columnar-type epithelium containing goblet cells [1]. Barrett's esophagus is a well known risk factor for developing esophageal adenocarcinoma (EAC) [2]. Over the past decades, the incidence of esophageal cancer and particularly EAC has been rising in the Western world [3,4]. EAC is the sixth most lethal cancer type worldwide, with a reported 5-year survival rate of 25% for nonmetastatic disease and a 2-year survival rate of 9% for metastatic disease [4]. In order to achieve higher survival rates, it is important to diagnose EAC at a potentially curable stage when the neoplastic process has not yet invaded the submucosal layer of the esophageal wall [5].

Despite various reports on the application of biomarkers to predict neoplastic progression, a histological diagnosis of dysplasia in Barrett's esophagus has been shown to be the most reliable predictor for cancer risk [6,7]. Neoplastic progression in Barrett's esophagus is known to progress through consecutive histological stages, from no dysplasia to low grade dysplasia (LGD) and high grade dysplasia (HGD) [8,9], which, in fact, represents a morphological continuum, with EAC as the end stage. As not all patients with Barrett's esophagus will develop EAC, several studies have reported the risk of developing EAC starting from the histological stages of no dysplasia, LGD, and HGD, respectively [10 – 14].

The diagnosis "indefinite for dysplasia" (IND) represents a heterogeneous histological group, and is used by pathologists when a diagnosis of genuine dysplasia cannot be made. This is often due to the co-occurrence of inflammatory changes. Reactive cytonuclear changes have similarities to histological changes that are encountered in dysplasia, and evaluation of maturation towards the luminal surface and/or the presence of clonality are not always possible [15]. Treatment of inflammation with acid-inhibiting drugs and endo-

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scopic follow-up after 4–8 weeks of treatment with recurrent biopsy sampling is currently recommended in these patients [8]. From a clinical point of view, it is important to elucidate the risk of progression to HGD or EAC in patients with Barrett's esophagus with IND, as this could enable a tailored surveillance protocol and allow evaluation of its cost-effectiveness. The currently available progression rates for IND are only based on small (sub-)cohort analyses [16, 17].

The aims of the current study were to evaluate the progression rate to HGD or EAC from pathology reports, and to report the currently employed surveillance patterns in a large group of patients with Barrett's esophagus and IND.

Patients and method

Data collection

The PALGA database is a nationwide database that collates data from all pathology laboratories in The Netherlands. It was established in 1971 and has had nationwide coverage since 1991. The PALGA database was set up to facilitate communication between histopathology and cytopathology laboratories, and to provide data to health care researchers [18]. All histopathology reports in the database are registered as written conclusions from pathologists, combined with the diagnostic code derived from the Systemized Nomenclature of Medicine (SNOMED) [19]. It includes sample type, and topological and morphological codes. Patient identification is encrypted, and only details of patient age, sex, and site of pathological assessment are available to researchers.

For the current study, all histopathological reports from January 2002 to December 2011 were reviewed. The database was searched for all patients with a diagnostic code for Barrett's esophagus. Detailed information on diagnostic codes can be found in **Table e1** (available online). For all patients in this cohort, written conclusions were evaluated for synonyms and misspellings (in both the English and Dutch languages) of the word "indefinite." All histopathological reports related to the esophagus, both before and after an index IND diagnosis, were collected. Reports of selected cases were manually reviewed to confirm the final diagnosis (C.K., P.S.). Exclusion criteria were gastric type Barrett's esophagus, a history of Barrett's esophagus with any form of dysplasia or EAC, and dysplasia in the same set of biopsies as the diagnosis of IND.

The study was approved by the Review Board of the PALGA foundation.

Data analysis

The primary end point was the incidence of progression to HGD or EAC, calculated for patients with at least one follow-up endoscopy with biopsy sampling after an initial diagnosis of IND. Secondary end points included progression rates to dysplasia in general, follow-up according to the general practice for IND in The Netherlands, and risk factors for progression to HGD or EAC. To avoid an effect of the co-presence of undetected HGD or EAC in the same set of biopsies during initial diagnosis, prevalent HGD or EAC was distinguished from incident HGD or EAC. Prevalent HGD or EAC was defined as occurring within the first year after the index IND diagnosis. A final diagnosis was defined as the highest grade of dysplasia in the same set of biopsies. The date of the last follow-up was equal to the date of EAC diagnosis, ablation or resection of HGD, or date of the last histopathology report in the database.

Statistical analysis

Baseline characteristics were analyzed by calculating means or medians for continuous variables and frequencies or percentages for categorical variables. Comparisons between groups for baseline characteristics and secondary end points were calculated using the chi-squared test, Mann-Whitney U test, or Student's *t* test when appropriate. The neoplastic progression rate was calculated per 100 person-years of follow-up. Kaplan-Meier curves were used to evaluate progression-free survival. Univariable and multivariable Cox regression analysis was used to identify independent risk factors for progression to dysplasia, HGD, or EAC. Estimates of relative risks are shown in hazard ratios (HR) with a 95 % confidence interval (CI).

Statistical analyses were performed using SPSS version 20.0 (IBM Corp., Armonk, New York, USA). A two-sided P value of <0.05 was considered to be statistically significant.

Results

In total, 2482 patients with Barrett's esophagus and with "indefinite" in the written conclusion of the pathology report were identified from the PALGA database. As shown in **Fig. 1**, 1258 patients were included following application of the inclusion and exclusion criteria, of whom 842 had endoscopic follow-up with biopsy sampling. Of these, 586 (69.6 %) were male, 148 (17.6 %) were diagnosed in an academic center, and in 59 patients (7.0 %) the final diagnosis was the result of a histological revision (second report on same slides) (**Table 2**). In 395 patients (46.9 %), a diagnosis of no dysplasia in Barrett's esophagus was present prior to the index IND diagnosis, over a median duration of 3.8 years (interquartile range [IQR] 1.85–7.01 years).

Surveillance patterns

A total of 3947 endoscopies with biopsy sampling were performed, with a median of 4 biopsies per patient (IQR 3–6). A total of 308 patients (36.6 %) underwent endoscopy with biopsies within 6 months after the index IND diagnosis (**Fig. 2**). The median duration until first follow-up endoscopy was 1.2 years (IQR 0.3–1.8 years). Total duration of follow-up was 2585 person-years (mean ± SD per patient 3.01 ± 2.6). Patients who were not followed up were significantly older compared with those who underwent follow-up (65.2 vs. 60.9 years; $P<0.001$).

Progression rates

In the total cohort, 189 patients (22.4 %) progressed to dysplasia or EAC (138 LGD, 21 HGD, 30 EAC), resulting in a progression rate of 7.3 per 100 person-years (95 %CI 6.3–8.4). HGD and/or EAC were seen in 6.1 % with a mean age of 60.9 years at IND diagnosis. The progression rate was 2.0 (95 %CI 1.5–2.6) for developing HGD and/or EAC and 1.2 (95 %CI 0.8–1.6) for EAC per 100 person-years. After the initial IND diagnosis, 492 (58.4 %) patients were found to have nondysplastic Barrett's esophagus during follow-up. **Table 3** shows the different rate of progression for patients who had no dysplasia, IND, or LGD at the first follow-up endoscopy after IND diagnosis. As expected, the progression rate to HGD or EAC was higher for patients with LGD during the first follow-up endoscopy compared with patients with nondysplastic Barrett's esophagus. **Fig. 3** shows the HGD and/or EAC progres-

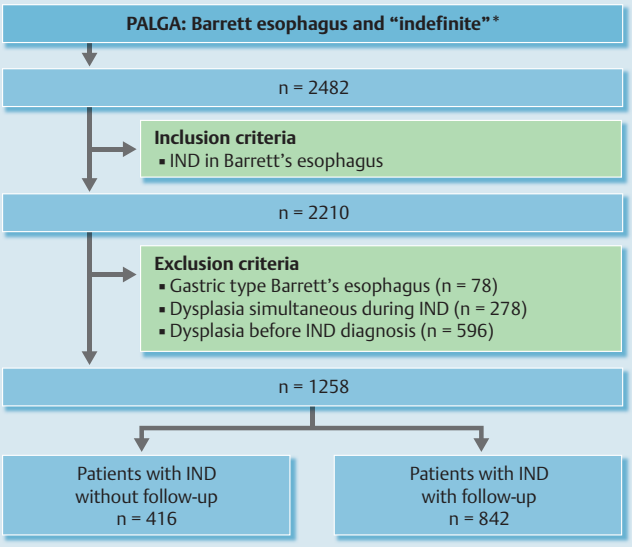

Fig. 1 Identification of patients with a diagnosis of "indefinite for dysplasia" in Barrett's esophagus from the PALGA database between 2002 and 2011. *All synonyms and misspellings were used.

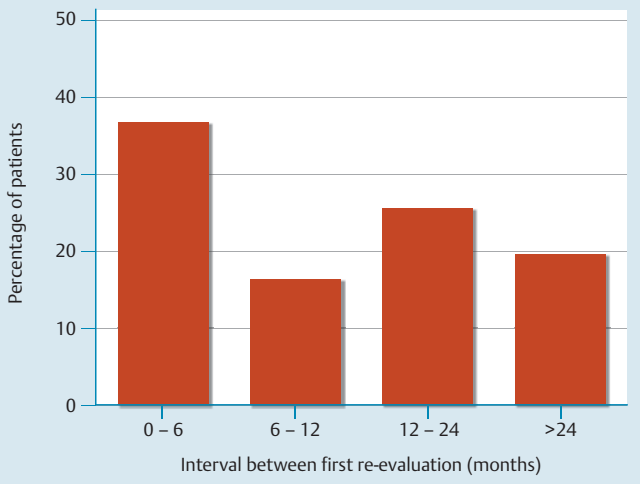

Fig. 2 Difference in time until first follow-up endoscopy with biopsy sampling in Barrett's esophagus patients who were indefinite for dysplasia (n = 842) during the study period 2002 – 2011. A total of 416 patients did not undergo follow-up.

sion-free survival in the total cohort of IND patients. The interval and pathology results of the follow-up endoscopies in the patients with EAC (n = 30) are shown in **Fig. e4** (available online). After excluding prevalent cases of HGD and EAC (n = 16) the progression rates were 1.4 (95 %CI 1.0 – 1.9) and 0.8 (95 %CI 0.5 – 1.2) per 100 person-years for HGD or EAC, and EAC, respectively.

Risk factors for neoplastic progression

Older age (per 10 years) was found to be a risk factor for developing HGD or EAC, with a hazard ratio of 1.5 (95 %CI 1.10 – 2.04), whereas a diagnosis in an academic setting, histological revision, sex, and a history of nondysplastic Barrett's esophagus were not (**Table 4**). Furthermore, the duration of nondysplastic Barrett's esophagus prior to baseline did not affect the risk of developing HGD or EAC. As age was the only independent risk factor for progression to HGD, no multivariable Cox regression was performed. As for the progression to HGD or EAC, older age was the only independent risk factor for progression to dysplasia in general (LGD, HGD or EAC), with a hazard ratio of 1.37 (95 %CI 1.20 – 1.57).

Discussion

This is the first large, population-based, cohort study (n = 842) in patients with Barrett's esophagus diagnosed as IND. The risk of progression in this group of IND patients was 1.4 (95 %CI 1.0 – 1.9) per 100 person-years for the combined end point of HGD or EAC and 0.8 (95 %CI 0.5 – 1.2) per 100 person-years for EAC. Only older age was an independent risk factor for progression to HGD or EAC.

The natural history of the histological category IND in Barrett's esophagus is largely unknown. In studies investigating the risk of neoplastic progression in different histological stages of Barrett's esophagus, a diagnosis of IND was mostly combined with LGD. When progression rates to HGD or EAC for IND were discussed separately from LGD, these were mostly based on small subcohort analyses [13, 16, 17, 20, 21]. Moreover, most previous studies did not report on the progression rates per person-years, which makes comparison with the current data difficult, if not impossible. In the previous studies, the reported percentages of IND patients who developed EAC ranged from 11 % to 18 % [16, 17, 20, 21]. One multicenter cohort study reported a progression rate of 0.33 per 100 person-years for developing EAC in IND [13]. This is lower than the progression rate of 0.8 per 100 person-year

	Total population n = 842	Prevalent dysplasia		*P* value
		Yes n = 16	No n = 826	
Sex, n (%)				
Male	586 (69.6)	13 (81.3)	573 (69.4)	0.4
Female	256 (30.4)	3 (18.8)	253 (30.6)	
Age, mean ± SD, years	60.9 ± 11.65	63.6 ± 12.1	60.9 ± 11.6	0.3
History of no dysplasia Barrett's esophagus, n (%)	395 (46.9)	7 (43.8)	388 (47.0)	0.8
Hospital of IND diagnosis, n (%)				
Academic	148 (17.6)	3 (18.8)	145 (17.6)	0.6
General	694 (82.4)	13 (81.3)	681 (82.5)	
Reviewed IND diagnosis	59 (7.0)	2 (12.5)	57 (6.9)	0.3

IND, indefinite for dysplasia.

Table 2 Baseline characteristics of patients with Barrett's esophagus diagnosed as indefinite for dysplasia who underwent endoscopic follow-up.

Table 3 Risk of progression in patients (n = 732) with no dysplasia, indefinite for dysplasia, or low grade dysplasia during the first follow-up endoscopy after a diagnosis of indefinite for dysplasia. Remaining patients (n = 110) had no Barrett's esophagus, gastric type Barrett's esophagus, Barrett's esophagus and high grade dysplasia or esophageal adenocarcinoma during the first follow-up endoscopy.

Histology	No. of patients	HGD or EAC cases, n (%)	EAC cases, n (%)	Incidence rate per 100 person-years [95 %CI]	
				HGD or EAC	EAC
No dysplasia	530	7 (1.3)	3 (0.6)	0.43 [0.19 – 0.85]	0.18 [0.05 – 0.50]
IND	101	3 (3.0)	3 (3.0)	1.10 [0.28 – 2.99]	1.10 [0.28 – 2.99]
LGD	101	13 (13.0)	4 (4.0)	3.39 [1.88 – 5.64]	1.04 [0.33 – 2.51]

HGD, high grade dysplasia; EAC, esophageal adenocarcinoma; CI, confidence interval; IND, indefinite for dysplasia; LGD, low grade dysplasia.

in the current study, but it was based on only 42 patients with a diagnosis IND in Barrett's esophagus. More studies that evaluate the risk of progression to HGD or EAC in IND are needed to confirm the current results.

Progression from Barrett's esophagus to EAC has been studied extensively. The progression rate from nondysplastic Barrett's esophagus to EAC has been reported to be 0.3 – 0.4 per 100 person-years [10,11]. Not surprisingly, the progression rate in patients with dysplastic Barrett's esophagus has been reported to be higher, at 0.4 – 0.8 [11 – 14] and 4.2 [14] per 100 persons-years for LGD and HGD, respectively. It is important to keep in mind that these progression rates are based on studies without histological revision by a second (expert) pathologist. When HGD and EAC are combined, the progression rates are 0.4 – 0.5 and 1.1 – 1.3 per 100 person-years for no dysplasia and LGD, respectively [11,22]. This suggests that the progression rates for IND to HGD or EAC are not different from the reported progression rates for patients with LGD [11 – 13]. The current study supports the common practice of combining patients with IND and LGD into one category, as was done in previous studies reporting on progression rates to HGD or EAC in Barrett's esophagus [12,13,22].

Increasing age was an independent predictor for neoplastic progression, which is in line with other studies [11,14]. Histological assessment in an academic setting was not found to be associated with progression to HGD or EAC. It has been shown that the risk of progression to HGD or EAC is increased when a diagnosis of LGD is confirmed by an expert pathologist. As a result, it is recommended that a diagnosis of LGD is confirmed by a second (expert) pathologist to determine the real risk of neoplastic progression [21,23]. Surprisingly, this could not be confirmed in the current IND cohort. This may be due to the fact that a second pathologist reviewed the slides in only 7 % of IND diagnoses. We are currently performing a study in which two expert pathologists review a selection of IND cases to evaluate whether a subgroup of patients with an increased risk of neoplastic progression can be identified.

The results from the current study raise several questions regarding the meaning of an IND diagnosis. An IND diagnosis probably represents a heterogeneous subgroup of patients with Barrett's esophagus; while in some cases the uncertainty is due to inflammatory changes, in others this category is used because changes cannot be reliably recognized as genuine dysplasia, for example when the cytonuclear features are limited to the lower part of the gland [14,24]. This may represent basal crypt dysplasia [25, 26], but this can be difficult to discriminate from an expanded proliferative compartment as seen in inflammation. This so-called basal crypt dysplasia is rarely seen and is currently not considered as a distinctive form of dysplasia. In general, dysplastic lesions show reduced or even absent surface maturation, which is a feature that is not found in crypt dysplasia and may

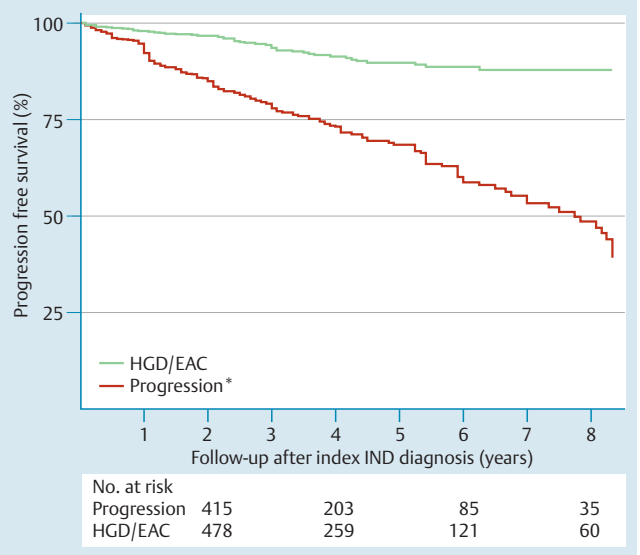

Fig. 3 Progression-free survival of 842 patients with Barrett's esophagus who were indefinite for dysplasia, calculated for progression and high grade dysplasia (HGD) or esophageal adenocarcinoma (EAC). *Progression defined as any form of dysplasia and/or EAC.

Table 4 Risk factors for neoplastic progression to dysplasia or to high grade dysplasia or esophageal adenocarcinoma (identified using univariable Cox regression analysis) with the exclusion of prevalent cases, for patients with Barrett's esophagus diagnosed as indefinite for dysplasia.

	HR	95 %CI
Sex		
Male	1.06	0.72 – 1.54
Female	–	–
Age		
Increasing/10 years	1.50	1.10 – 2.04
History of nondysplastic Barrett's esophagus		
Yes	1.06	0.55 – 2.06
No	–	–
Hospital of IND diagnosis		
Academic	1.57	0.73 – 3.35
Non-academic	–	–
IND diagnosis reviewed		
No	–	–
Yes	1.83	0.71 – 4.71
Surveillance prior to IND diagnosis		
No	–	–
Yes	1.44	0.65 – 3.16

HR, hazard ratio; CI, confidence interval; IND, indefinite for dysplasia.

lead inexperienced pathologist to a diagnosis of IND. It would be interesting to evaluate the natural history of basal crypt dysplasia but this was not possible within the current study.

Some limitations of this study warrant consideration. First, because a SNOMED code for IND does not exist, only cases with some phrasing corresponding to "indefinite" were selected from the database. Cases may have been missed if the pathologist used "indefinite" in another phrasing. The 2482 cases with IND in the written conclusion of the pathological reports came from 97 % of all histopathological laboratories in The Netherlands, which suggests that the term IND is generally used among Dutch pathologist. Second, the PALGA database only contains histological data and therefore no clinical data were available. As a result, the progression rates of HGD or EAC could not be adjusted for known risk factors, such as the number of biopsies taken, the extent of dysplasia (unifocal vs. multifocal), the length of the Barrett's segment, presence of a hiatal hernia and/or esophagitis, smoking history, or medication use. Furthermore, results from immunohistochemical staining of p53, which may help to stratify patients at risk for progression to HGD or EAC [27 – 29], were not available for all IND cases. Third, no standardized endoscopy protocol was used because of the retrospective nature of this study. However, in The Netherlands it is general practice to follow international guidelines and take biopsies according to the Seattle protocol [30]. In 33 % of the patients in the current cohort, no follow-up endoscopy with biopsy sampling was performed, which may at least be partially due to older age and/or co-morbidity. Given the design of this study, the reasons why these patients did not receive follow-up remain unknown. As this latter group was relatively large, the risk of progression could have been influenced by indication bias, which makes the actual risk lower if symptomatic patients underwent an endoscopy more frequently.

This study has some unique features that may overcome some of these drawbacks. To our knowledge, it is the first large, population-based, cohort study of IND in Barrett's esophagus. In The Netherlands, patients have free access to health care, which largely eliminates diagnostic bias. As a result, the generalization of the results is high, as this cohort involves patients of all ages and both sexes with Barrett's esophagus treated in primary, secondary, and tertiary settings.

In conclusion, in this large, nationwide, cohort study of patients with Barrett's esophagus with a histological diagnosis of IND, the annual risk of progression to HGD or EAC seems to be more or less the same as the progression risk in LGD and suggests that repeat endoscopy with biopsy sampling is mandatory. Particular attention should be paid to older patients with Barrett's esophagus as they have a higher risk of developing HGD or EAC compared with younger patients. Nonetheless, additional studies are needed in order to select the subgroup of IND patients with an increased risk of neoplastic progression.

Competing interests: None

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Table e1 and Figure e4

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