

# The diagnostic yield of open-access endoscopy of the upper gastrointestinal tract in the Netherlands



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## Bibliography

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## ABSTRACT

**Background and study aims** Since the introduction of open-access esophago-gastroduodenoscopy (OAE) there is an increase in the total number of performed OAEs whilst

the frequency of clinical relevant findings has decreased. The aim of this study was to assess the appropriate use and the diagnostic yield of OAE in the Netherlands and to determine which patient variables are able to predict a malignant finding.

**Patients and methods** A retrospective chart review of all referrals for diagnostic OAE between October 2012 and October 2016 at the Northwest Clinics was performed. The indications were recorded from the referral letter and were classified as “appropriate” or “inappropriate” according to the NHG guideline. Logistic regression was used to detect significant predictive variables for a malignancy.

**Results** A total of 2006 patients were included, of whom 59.6% had an ‘appropriate’ referral indication. The diagnostic yield of finding a clinical relevant finding was significantly higher for OAEs with an “appropriate” referral indication. Independent risk factors for malignancy were alarm symptoms, age and male gender with a combined AUC of 0.868.

**Conclusions** Only 3.8% of the malignancies would be missed by strict adherence to the guideline. This indicates that the open-access system in the Netherlands works well. Further improvement of the system can be achieved by only accepting appropriate indications for OAE and by treating patients under the age of 40 without OAE. We showed that a risk-prediction model based on the variables age, alarm symptoms and male gender is a good predictor of malignant finding.

## Introduction

Open-access esophago-gastroduodenoscopy (OAE) allows the general practitioner (GP) to refer patients for esophago-gastro-duodenoscopy without prior consultation of a gastroenterologist. OAE was introduced to decrease waiting time for patients who require urgent endoscopy, to decrease outpatient workload for gastroenterologists and to decrease costs related to endoscopy by eliminating potentially unnecessary office-based consultations. However, the introduction of OAE has resulted in an increase of the total number of performed endoscopies, leading to waiting list for patients requiring urgent endoscopy, whilst the frequency of clinically relevant findings

has decreased [1–3]. In addition, although an esophago-gastro-duodenoscopy is relatively safe it is associated with potential complications and causes discomfort [4]. Therefore, unnecessary OAEs should be avoided.

To optimize use of an open-access system, guidelines for appropriate referral to OAE have been developed. Most studies of the diagnostic yields of OAE used American or British guidelines to examine the appropriateness of the OAE indication. These guidelines contain more indications than the Dutch College of General Practitioner guideline (NHG guideline) “upper abdominal complaints” [5–8]. The performed studies about the yield of OAE showed widely ranging non-adherence rates and also different rates of clinical relevant findings [3, 4, 8–10].

► **Table 1** Referral indications divided in 4 groups, of which the first three groups are considered appropriate referral indications and the last group is considered inappropriate according to the NHG guideline.

Referral indications			
Alarm symptoms	Follow-up	Other referral indications according to the guideline	Referral indications not mentioned in the guideline
Dysphagia	Follow-up of gastric ulcer healing	Persistent or recurrent dyspepsia older than age 50 with a negative H. pylori status	Dyspepsia younger than age 50 without alarm symptoms
Unexplained weight loss		First-degree relative older than age 40 of a patient with familial gastric cancer	Persistent or recurrent dyspepsia older than age 50 with unknown H. pylori status
Gastrointestinal bleeding			Familial esophageal cancer
Anemia			Reassurance
Persistent vomiting			

Some studies tried to identify subgroups which are at risk of malignant disease. It was shown that age, male gender, smoking and alarm symptoms were independent predictors of malignancy but their accuracy is controversial [11, 12].

Due to the absence of studies wherein the Dutch NHG guideline is used, the uncertainty about the diagnostic yield in the Netherlands and the vagueness about which subgroups in the Netherlands have the largest a priori probability of malignancy. The aim of this study was to assess the following questions; what is the appropriateness of referral according to the NHG guideline ‘upper abdominal complaints’? What is the diagnostic yield of OAE in the Netherlands? Which subgroups have the greatest yield of OAE? An answer to these questions is even more important in the era of evidence-based medicine, growing efficacy and cost-effectiveness. Furthermore, the capacity for endoscopic examinations is limited and therefore the need to avoid unnecessary OAE is of paramount importance.

## Patients and methods

A retrospective chart review of all referrals for diagnostic OAE between October 2012 and October 2016 at the Northwest Clinics, location Alkmaar was performed. All patients who underwent an OAE were included and patients younger than eighteen years or with an incomplete endoscopy (not due to a stenosis) were excluded from further analysis.

The indications for OAE were collected from the referral letter. The NHG guideline “upper abdominal complaints” was used to determine the appropriateness of the indication for endoscopy (► **Table 1**). According to the guideline, reassurance was an appropriate indication for OAE, although in this study it was classified as an inappropriate indication, because all OAEs are performed for some sort of reassurance, for the patient or for the GP.

The referral indications were divided into 4 groups; alarm symptoms, follow-up, other referral indications according to the guideline and referral indications not mentioned in the guideline (► **Table 1**). The first 3 categories are considered appropriate and the last category is considered inappropriate according to the NHG guideline.

Alarm symptoms were considered the most clinical relevant when present and patients with any of these symptoms were classified in the category alarm symptoms, irrespective of any other dyspeptic symptoms.

Referrals were screened by a gastroenterologist and they determined the time frame during which the OAE was performed, but even in the absence of an appropriate indication OAE was performed

The OAEs were performed by an experienced gastroenterologist or by a gastroenterologist in training under the supervision of an experienced gastroenterologist. Endoscopic findings were reported in a digital reporting system (Endobase®, Olympus, Zoeterwoude, The Netherlands) with, whenever possible, internationally accepted terminology and definitions (Forrest classification for ulcer bleeding, Los Angeles classification for erosive esophagitis and the Prague C&M classification for a Barrett’s esophagus).

Endoscopic findings were classified into 3 categories; malignant, benign with clinical relevance and benign without clinical relevance. A finding was considered clinically relevant if there was impact on therapeutic decisions and prognosis, wherein it was assumed that patients used a proton pump inhibitor (PPI) or an H2 receptor antagonist (H2RA) in an adequate dose as described in the NHG guideline “upper abdominal complaints.” Malignancies found during OAE were classified into the category malignant. To classify the other diagnosis, the patient file was reviewed to examine whether the outcome of the OAE changed the therapeutic decisions or prognosis. If that was the case patients were classified into the category benign with clinical relevance.

When multiple endoscopic findings were present, patients were included for statistical analysis in the most relevant group, wherein it was assumed that the group malignant was the most relevant.

Besides the referral indication other variables which were possibly associated with the outcome of the endoscopy were collected, such as: age, gender, treatment with PPI or H2RA and Helicobacter pylori status.

## Statistical analysis

Patients with appropriate indications were compared with those with an inappropriate indication to assess the association between the appropriateness of the referral indication and the presence of clinically relevant endoscopic diagnoses (malignant and benign with clinical relevance). The extent of this association was calculated with univariate logistic regression analysis.

Logistic regression analyses were performed on predictor variables with a *P* value < 0.2 in the univariate analysis, using a forward method procedure with a cut-off *P* value of 0.05.

The ability of the NHG guideline to predict relevant endoscopic diagnoses was determined by calculating the relative risk and positive and negative predictive value for each separate referral indication and for all indications combined.

To find out which subgroup of patients has the highest risk of an upper gastrointestinal malignancy a logistic regression analysis was performed, were tested for different factors influencing the finding of a malignancy. The receiver operating characteristics (ROC) curve with the area under the curve (AUC) was used to describe the performance of these factors. The statistical difference between these AUCs of the dependent ROC curves was calculated with the method of DeLong et al. using MedCalc (MedCalc Software, Mariakerke, Belgium).

Internal validation of the prediction model for upper gastrointestinal malignancies found by the logistic regression model was done by bootstrap resampling (1000 bootstrap samples).

Nominal and ordinal variables were described as numbers with percentages. Continuous variables were described as means with standard deviations in case of a normal distribution and as median with interquartile range in case of a skewed distribution. Normality was tested with Kolmogorov-Smirnov test. Independent Student's *t*-tests were used to analyze continuous outcome variables and logistic regression analyses were used for dichotomous outcome variables. Differences were considered significant at a 5% probability level.

Statistical analyses were conducted using Statistical Package for Social Sciences (SPSS®, IBM, New York, United States of America) version 20.

## Results

### Baseline characteristics

A total of 2006 OAEs were performed during the study period. Of these patients, 1088 were women (54.2%) and 918 were men (45.8%). The median ( $\pm$  IQR) age of the participants was 60  $\pm$  20 years (range 18–92 years). In total 1478 (73.7%) used a PPI or H2RA before the OAE was performed. The *H. pylori* status was known for 611 patients prior to the OAE (30.5%) of whom 6 patients tested positive (0.3%). In 100 patients (4.9%) showed the biopsies, or the test done after the endoscopy that they were infected with *H. pylori*. 979 patients had an unknown *H. pylori* status (48.8%). Any form of sedation with midazolam or alfentanil was used in 774 patients (38.6%).

## Referral indication

The indication for OAE was considered appropriate, according to the NHG guideline, in 59.6% of the cases (1195 patients). The main indication in this group was dysphagia in 420 patients (35.1%). The main inappropriate indication was dyspeptic symptoms in 427 patients (52.7%) older than 50 years without a *H. pylori* status. All referral indications are summarized in ► **Table 2**.

### Endoscopic finding

A malignancy in the upper gastrointestinal tract was detected in 104 examinations (5.2%) of which the majority was found to be an esophageal carcinoma (*n* = 82; 4.1%). An endoscopic finding classified as benign with clinic relevance was found in 388 patients (19.3%), of these findings a Barrett's esophagus accounted for 6.4% (129 patients). A not clinically relevant finding and a normal examination occurred in 39.5% and 36% of the cases, respectively. All endoscopic findings are summarized in ► **Table 3**.

### Diagnostic yield

The diagnostic yield was significantly higher for OAEs with a referral indication according to the NHG guideline. Of the 492 patients with clinical relevant endoscopic findings, 74% had an appropriate referral indication (OR 2.337 [95% CI 1.866–2.928]; *P* < 0.0001). Significant predictive variables for a clinical relevant finding at OAE found by multinomial logistic regression analysis were a referral indication according to the NHG guideline, age, male gender and a positive *H. pylori* status (► **Table 4**). A sensitivity analysis with age divided in equal quartiles showed that the significance of age as predictive variable is based on the last quartile (69 years and older) (*P* < 0.0001).

The diagnostic yield of finding a malignancy in the upper gastrointestinal tract was also significantly higher in patients with an appropriate referral indication (OR 18.425 [95% CI 6.754–50.260]; *P* < 0.0001). The relative risk of finding a malignancy in patients with alarm symptoms was 14.26 (► **Table 2**). Especially dysphagia, weight loss and dysphagia with weight loss combined were associated with a malignancy diagnosed with endoscopy. In contrast, the appropriate referral indication: 'dyspepsia in patients > 50 years of age with a negative *H. pylori* status' had a low diagnostic yield of finding a malignancy. 4 patients above 50 years of age with dyspeptic symptoms and an unknown *H. pylori* status had a malignancy (► **Table 2**). The characteristics of these 4 patients with malignant disease are shown in ► **Table 5**.

The sensitivity, specificity, PPV and NPV for all referral indications are summarized in ► **Table 6**.

Besides the malignancies in the upper gastrointestinal tract, more frequently detected findings with clinical relevance in appropriate OAEs were; reflux esophagitis grade D, esophageal candidiasis and hiatal hernia (► **Table 3**).

► **Table 2** Relative risk of finding a malignancy, a benign finding with clinical relevance and a benign finding without clinical relevance for every referral indication. Wherein patients with the referral indication are compared to patients without the referral indication.

Outcome of endoscopy							
Referral indication	N (%)	Malignant		Benign with clinical relevance		Benign without clinical relevance	
		n (%)	RR (95% CI)	n (%)	RR (95%CI)	n (%)	RR (95%CI)
<b>Indication according to the NHG guideline</b>	1195 (59.6%)	100 (5.0%)	17.0 (6.3–45.91) <sup>1</sup>	264 (13.2%)	1.44 (1.19–1.75) <sup>1</sup>	831 (41.4%)	0.83 (0.79–0.87) <sup>1</sup>
Alarm symptoms overall	797 (39.7%)	94 (4.7%)	14.26 (7.48–27.20) <sup>1</sup>	200 (10.0%)	1.61 (1.35–1.93) <sup>1</sup>	503 (25.0%)	0.75 (0.71–0.80) <sup>1</sup>
Dysphagia	420 (20.9%)	38 (1.9%)	2.17 (1.48–3.19) <sup>1</sup>	113 (5.6%)	1.55 (1.28–1.88) <sup>1</sup>	269 (13.4%)	0.82 (0.76–0.88) <sup>1</sup>
Weight loss	104 (5.2%)	10 (0.5%)	1.95 (1.05–3.62) <sup>1</sup>	21 (1.0%)	1.05 (0.71–1.55)	73 (3.7%)	0.93 (0.82–1.05)
Gastrointestinal bleeding	92 (4.6%)	4 (0.2%)	0.83 (0.31–2.21)	22 (1.1%)	1.25 (0.86–1.82)	66 (3.3%)	0.95 (0.83–1.08)
Anaemia	31 (1.5%)	2 (0.1%)	1.25 (0.32–4.84)	9 (0.4%)	1.51 (0.87–2.64)	20 (1%)	0.85 (0.66–1.11)
Dysphagia and weight loss	121 (6.0%)	34 (1.7%)	7.57 (5.25–10.91) <sup>1</sup>	28 (1.4%)	1.21 (0.86–1.70)	59 (2.9%)	0.64 (0.54–0.78) <sup>1</sup>
Weight loss and gastrointestinal bleeding	12 (0.6%)	1 (0.05%)	1.61 (0.24–10.64)	4 (0.2%)	1.73 (0.77–3.87)	7 (0.35%)	0.77 (0.48–1.25)
Dyspepsia >50 years of age, HP negative	383 (19.1%)	6 (0.4%)	0.26 (0.11–0.59) <sup>1</sup>	62 (3.5%)	0.81 (0.63–1.03)	315 (15.2%)	1.11 (1.05–1.18) <sup>1</sup>
Other	32 (1.6%)	5 (0.25%)	3.12 (1.36–7.13) <sup>1</sup>	5 (0.25%)	0.81 (0.36–1.81)	22 (1.1%)	0.91 (0.72–1.15)
<b>Indication not according to the NHG guideline</b>	811 (40.4%)	4 (0.2%)	0.06 (0.02–0.16) <sup>1</sup>	124 (6.2%)	0.69 (0.57–0.84) <sup>1</sup>	683 (34.0%)	1.21 (1.15–1.27) <sup>1</sup>
Dyspepsia <50 years of age	373 (18.6%)	0 (0%)	0.02 (0.00–0.34) <sup>1</sup>	39 (1.9%)	0.49 (0.36–0.67) <sup>1</sup>	334 (16.7%)	1.24 (1.18–1.30) <sup>1</sup>
Dyspepsia >50 years of age, HP unknown	427 (21.3%)	4 (0.2%)	0.15 (0.05–0.40) <sup>1</sup>	82 (4.2%)	0.99 (0.80–1.23)	341 (16.9%)	1.08 (1.02–1.14) <sup>1</sup>
Other	11 (0.5%)	0 (0%)	0.80 (0.05–12.08)	3 (0.1%)	1.41 (0.54–3.73)	8 (0.4%)	0.96 (0.67–1.38)
<b>Total</b>	2006 (100%)	104 (5.2%)		388 (19.3%)		1514 (75.5%)	

Only the indications occurring with a frequency >0.5% were extensively reported  
<sup>1</sup>  $P < 0.05$

## Risk-predictive model

To find out which subgroup of patients has the greatest risk of a malignancy in the upper gastrointestinal tract a multinomial logistic regression analysis (► **Table 7**) was performed, which showed that significant predictive variables for a malignant finding at OAE were; male gender, alarm symptoms and age. A sensitivity analysis with age divided in equal quartiles showed that the significance of age as predictive variable is based on the last 2 quartiles (60 years and older) ( $P < 0.001$ ).

No malignancies were found in patients <40 years of age while it was uncommon in patients under 45 years of age, whereas in this patient group many OAEs were performed

(► **Fig. 1** and ► **Fig. 2**). In women under the age of 50 years no malignancies of the upper gastrointestinal tract were detected (► **Fig. 1** and ► **Fig. 2**).

The ROC curve (► **Fig. 3**) showed that age alone (AUC = 0.729 [95% CI 0.687–0.771]) was significantly ( $P < 0.0001$ ) less accurate in predicting a malignant finding than our risk prediction model (age, male gender and alarm symptoms combined) (AUC = 0.868 [95% CI 0.841–0.894]). Also alarm symptoms alone (AUC = 0.767 [95% CI 0.729–0.805]) was less accurate in predicting a malignant finding than the combination of the 3 factors (► **Fig. 3**).

Internal validation of the predicting model with bootstrap resampling showed a corrected AUC of 0.867.

► **Table 3** Odds ratio of different endoscopic outcomes in OAEs performed for an appropriate referral indication.

Outcome of OAE	Number of patients (%)	Appropriate referral indication, n (%)	Inappropriate referral indication, n (%)	OR	95% CI	P value
<b>Malignant</b>	104 (5.2%)	100 (5%)	4 (0.2%)	18.425	6.754–50.260	<0.0001
Esophageal carcinoma	82 (4.1%)	79 (3.9%)	3 (0.2%)	19.066	5.998–60.601	<0.0001
Malignancies of the stomach	21 (1.05%)	20 (1%)	1 (0.05%)	13.787	1.847–102.935	0.011
Malignant tumors of the duodenum	1 (0.05%)	1 (0.05%)	0 (0%)			
<b>Benign with clinical relevance</b>	388 (19.3%)	264 (13.2%)	124 (6.1%)	1.571	1.242–1.987	<0.0001
Reflux esophagitis grade A	12 (0.6%)	5 (0.25%)	7 (0.35%)	0.483	0.153–1.526	0.215
Reflux esophagitis grade B	15 (0.7%)	6 (0.28%)	9 (0.42%)	0.450	0.159–1.268	0.131
Reflux esophagitis grade C	37 (1.8%)	23 (1.1%)	14 (0.7%)	1.117	0.571–2.184	0.746
Reflux esophagitis grade D	29 (1.4%)	25 (1.2%)	4 (0.2%)	4.311	1.495–12.434	0.007
Barrett esophagus	129 (6.4%)	73 (3.6%)	56 (2.8%)	0.877	0.612–1.258	0.476
Esophageal candidiasis	30 (1.6%)	24 (1.3%)	6 (0.3%)	2.750	1.119–6.757	0.027
Hiatal hernia	22 (1.1%)	19 (0.95%)	3 (0.15%)	4.351	1.283–14.753	0.018
Ulcus ventriculi	20 (1%)	16 (0.8%)	4 (0.2%)	2.738	0.912–8.219	0.073
Gastritis	19 (0.9%)	13 (0.6%)	6 (0.3%)	1.476	0.559–3.898	0.432
Ulcus duodeni	17 (0.8%)	12 (0.6%)	5 (0.2%)	1.635	0.574–4.659	0.357
Other	58 (2.9%)	48 (2.4%)	10 (0.5%)	3.352	1.686–6.665	0.001
<b>Benign without clinical relevance</b>	1514 (75.5%)	831 (41.4%)	683 (34.1%)	0.428	0.342–0.536	<0.0001
Reflux esophagitis grade A	152 (7.6%)	79 (3.9%)	73 (3.7%)	0.716	0.514–0.997	0.048
Reflux esophagitis grade B	94 (4.7%)	47 (2.3%)	47 (2.3%)	0.666	0.440–1.007	0.054
Schatzki ring	42 (2.1%)	38 (1.9%)	4 (0.2%)	6.626	2.356–18.638	<0.0001
Hiatal hernia	236 (11.7%)	128 (6.4%)	108 (5.3%)	0.781	0.594–1.026	0.076
Fundic gland polyposis	48 (2.4%)	29 (1.4%)	19 (1%)	1.037	0.577–1.862	0.904
Gastritis	176 (8.7%)	99 (4.9%)	77 (3.8%)	0.861	0.630–1.176	0.348
Duodenitis	40 (2.0%)	22 (1.1%)	18 (0.9%)	0.826	0.440–1.550	0.552
Normal	722 (36.0%)	385 (19.2%)	337 (16.8%)	0.669	0.556–0.804	<0.0001
Other	4 (0.3%)	4 (0.3%)	0 (0%)			
<b>Total</b>	2006 (100%)	1195 (59.6%)	811 (40.4%)			

Only the outcomes occurring with a frequency >0.5% were extensively reported.

## Discussion

Since the introduction of OAE an increase in the number of performed endoscopies has been reported, whilst the frequency of clinically relevant findings has decreased [1, 2]. This results in waiting lists leading to delayed endoscopy for those with a potential malignant disease [3]. The appropriateness of the referral and the diagnostic yield of OAEs is, therefore, an important issue. To our knowledge, this is the first surveys on the diagnostic yield of OAEs in the Netherlands in which the NHG guideline "upper abdominal complaints" was used.

The most prominent finding in our study was the high frequency of malignancies compared to other studies. In our cohort a prevalence of 5.2% was found, whilst in a meta-analysis (57,363 patients) a prevalence of upper GI cancer of 0.8% was found [13]. The high frequency of malignancies in our study cannot be explained by patient selection and the prevalence of upper gastrointestinal cancers in the Netherlands is comparable to other Western countries [14]. We speculate that the difference can be explained by the use of the brief NHG guideline and the good primary health care services in the Netherlands.

In our study the rate of patients referred for OAE with an indication not according to the NHG guideline was 40.4%. In

► **Table 4** Uni- and multivariate logistic regression analysis of possible predictors for a clinical relevant endoscopy outcome.

Clinical relevant endoscopy outcome						
Possible predictors	Univariate analyse			Multivariate analyse		
	OR	95% CI	P value	OR	95% CI	P value
Appropriate referral indication	2.337	1.866–2.928	<0.0001	1.565	1.075–2.280	0.020
Age	1.037	1.029–1.045	<0.0001	1.023	1.010–1.037	0.001
Gender						
▪ Female	Reference					
▪ Male	2.071	1.684–2.547	<0.0001	1.785	1.306–2.438	<0.0001
PPI or H2RA use						
▪ Yes	Reference					
▪ No	1.817	1.445–2.285	<0.0001	1.292	0.877–1.903	0.195
HP status						
▪ Negative	Reference					
▪ Positive	2.724	1.786–4.154	<0.0001	2.767	1.757–4.357	<0.0001
Sedation						
▪ Yes	0.900	0.728–1.113	0.332			
▪ No	Reference					

► **Table 5** Details of the 4 patients with malignant disease without a referral indication according to the guideline.

No	Gender	Age	Sedation	PPI or H2RA use	H. pylori status	Referral indication	Diagnosis
1	Woman	81	No	Yes	Unknown	Nausea	Esophageal carcinoma
2	Man	80	Unknown	Yes	Unknown	Epigastric pain	Esophageal carcinoma
3	Man	69	No	Yes	Unknown	Epigastric pain	Esophageal carcinoma
4	Woman	70	No	Yes	Negative	Cough	Malignancy of the stomach

other studies the rate of inappropriate referrals ranged from 11.7% till 77.2% [4, 9, 10]. The greater guideline compliance in some studies can possibly be explained by a lecture series for the GPs prior to the data collection [8]. This gives the impression that educational programs dedicated to GPs can improve the effectiveness of an open-access system. However, due to the use of different guideline as benchmarks these data are not comparable with our results.

In the present study, the diagnostic yield of OAE was statistically significant higher for endoscopies with a referral indication according to the NHG guideline ( $P < 0.0001$ ). The sensitivity and specificity of the NHG guideline to detect a malignancy was 96.2% and 42.4%. For detecting a clinically relevant finding it was 68.0% and 42.5%, respectively. These data are concordant with a meta-analysis which showed an adjusted sensitivity and specificity of the ASGE guidelines for clinical relevant findings of 85% and 28% [15]. Despite the relatively high sensitivity, the frequency of a clinical relevant finding in patients with an inappropriate referral indication was 15.8% in our study,

which is a low frequency compared to other studies (ranging from 23% till 66%) [16–18].

In our study only 4 (3.8%) of the 104 malignancies would be missed by strict adherence to the guideline, therewith substantially lower than the 8% in the study of Rossi et al. [19]. This can be explained by the high sensitivity (96.2%) of the NHG guideline in our study for detecting malignancies. But the fact remains that by strict adherence to the guideline some malignancies could be missed. That is why some authors were stating that the appropriateness criteria should not be the only factor in the decision-making process [20]. That is the reason that the Dutch NHG guideline states that a GP might consider to perform a OAE for reassurance.

In this study 20.8% of the referral indication were classified as 'inappropriate' due to an unknown H. pylori status in patients with dyspepsia above the age of 50. Of these patients 4 (0.2%) had a malignant finding and 82 (4.0%) a benign finding with clinical relevance. Epidemiologic studies have shown that individuals infected with H. pylori have an increased risk of gastric adenocarcinoma and an decreased risk of esophageal ade-

► **Table 6** Sensitivity, specificity, positive and negative predictive value of every referral indication for different endoscopic outcome categories.

Referral indication	Outcome of endoscopy	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Indication according to the NHG guideline	Malignant	96.2% (90.4%-98.9%)	42.4% (40.2%-44.7%)	8.4% (8.0%-8.8%)	99.5% (98.7%-99.8%)
	Benign with clinical relevance	68.0% (63.2%-72.7%)	42.5% (40.0%-44.9%)	22.1% (20.8%-23.5%)	84.7% (82.6%-86.6%)
	Benign without clinical relevance	54.9% (52.3%-57.4%)	26.0% (22.2%-30.1%)	69.5% (68.1%-71.0%)	15.8% (13.8%-18.0%)
Alarm symptoms overall	Malignant	90.4% (83.0%-95.3%)	63.0% (60.8%-65.2%)	11.8% (10.9%-12.7%)	99.2% (98.5%-99.5%)
	Benign with clinical relevance	51.6% (46.5%-56.6%)	63.1% (60.7%-65.5%)	25.1% (23.0%-27.3%)	84.5% (83.0%-85.8%)
	Benign without clinical relevance	33.2% (30.9%-35.7%)	40.2% (35.9%-44.7%)	63.1% (60.7%-65.5%)	16.4% (14.9%-18.0%)
Dysphagia	Malignant	36.5% (27.3%-46.6%)	79.9% (78.0%-81.7%)	9.1% (7.1%-11.5%)	95.8% (95.2%-96.4%)
	Benign with clinical relevance	29.1% (24.6%-33.9%)	81.0% (79.0%-82.9%)	26.9% (23.4%-30.7%)	82.7% (81.7%-83.6%)
	Benign without clinical relevance	17.8% (15.9%-19.8%)	69.3% (65.0%-73.4%)	64.1% (60.0%-67.9%)	21.5% (20.5%-22.6%)
Weight loss	Malignant	9.6% (4.7%-17.0%)	95.1% (94.0%-96.0%)	9.6% (5.4%-16.5%)	95.1% (94.8%-95.4%)
	Benign with clinical relevance	5.4% (3.4%-8.2%)	94.9% (93.7%-95.9%)	20.2% (13.7%-28.8%)	80.7% (80.3%-81.1%)
	Benign without clinical relevance	4.8% (3.8%-6.0%)	93.7% (91.2%-95.7%)	70.2% (61.0%-78.0%)	24.2% (23.7%-24.7%)
Gastrointestinal bleeding	Malignant	3.9% (1.1%-9.6%)	95.4% (94.3%-96.3%)	4.4% (1.7%-10.8%)	94.8% (94.6%-95.0%)
	Benign with clinical relevance	5.7% (3.6%-8.5%)	95.7% (94.6%-96.6%)	23.9% (16.5%-33.4%)	80.9% (80.5%-81.3%)
	Benign without clinical relevance	4.4% (3.4%-5.5%)	94.7% (92.4%-96.5%)	71.7% (62.0%-79.8%)	24.4% (23.9%-24.8%)
Anemia	Malignant	1.9% (0.2%-6.8%)	98.5% (97.8%-99.0%)	6.5% (1.6%-22.2%)	94.8% (94.7%-95.0%)
	Benign with clinical relevance	2.3% (1.1%-4.4%)	98.6% (98.0%-99.2%)	29.0% (16.0%-46.9%)	80.8% (80.6%-81.1%)
	Benign without clinical relevance	1.3% (0.8%-2.0%)	97.8% (96.0%-98.9%)	64.5% (46.7%-79.0%)	24.4% (24.1%-24.6%)
Dysphagia and weight loss	Malignant	32.7% (23.8%-42.6%)	95.4% (94.4%-96.3%)	28.1% (21.7%-35.5%)	96.3% (95.8%-96.7%)
	Benign with clinical relevance	7.2% (4.9%-10.3%)	94.3% (93.0%-95.3%)	23.1% (16.7%-31.2%)	80.9% (80.4%-81.4%)
	Benign without clinical relevance	3.9% (3.0%-5.0%)	87.4% (84.1%-90.2%)	48.8% (40.3%-57.3%)	22.8% (22.2%-23.4%)
Weight loss and gastrointestinal bleeding	Malignant	1.0% (0.02%-5.2%)	99.4% (99.0%-99.7%)	8.3% (1.2%-41.1%)	94.8% (94.7%-94.9%)
	Benign with clinical relevance	1.0% (0.3%-2.6%)	99.5% (99.0%-99.8%)	33.3% (13.1%-62.3%)	80.7% (80.6%-80.9%)
	Benign without clinical relevance	0.5% (0.2%-1.0%)	99.0% (97.6%-99.7%)	58.3% (30.9%-81.5%)	24.4% (24.3%-24.6%)
Dyspepsia > 50 years of age, HP negative	Malignant	5.8% (2.2%-12.1%)	80.2% (78.3%-82.0%)	1.6% (0.7%-3.4%)	94.0% (93.7%-94.3%)
	Benign with clinical relevance	16.0% (12.5%-20.0%)	80.2% (78.1%-82.1%)	16.2% (13.1%-19.9%)	79.9% (79.1%-80.7%)
	Benign without clinical relevance	20.8% (18.8%-22.9%)	86.2% (82.8%-89.1%)	82.3% (78.4%-85.5%)	26.1% (25.3%-27.0%)
Other	Malignant	4.8% (1.6%-10.9%)	98.6% (97.9%-99.1%)	15.6% (6.8%-32.0%)	95.0% (94.8%-95.2%)
	Benign with clinical relevance	1.3% (0.4%-3.0%)	98.3% (97.6%-98.9%)	15.6% (6.7%-32.3%)	80.6% (80.4%-80.8%)
	Benign without clinical relevance	1.5% (0.9%-2.2%)	98.0% (96.3%-99.0%)	68.8% (51.2%-82.2%)	24.4% (24.2%-24.7%)
Indication not according to the NHG guideline	Malignant	3.9% (1.1%-9.6%)	57.6% (55.3%-59.8%)	0.5% (0.2%-1.3%)	91.6% (91.2%-92.0%)
	Benign with clinical relevance	32.0% (27.3%-36.9%)	57.5% (55.1%-60.0%)	15.3% (13.4%-17.4%)	77.9% (76.5%-79.3%)
	Benign without clinical relevance	45.1% (42.6%-47.7%)	74.0% (69.9%-77.8%)	84.2% (82.0%-86.2%)	30.5% (29.0%-32.0%)
Dyspepsia < 50 years of age	Malignant	0%	80.4% (78.5%-82.2%)	0%	93.6% (93.5%-93.8%)
	Benign with clinical relevance	10.1% (7.3%-13.5%)	79.4% (77.3%-81.3%)	10.5% (7.9%-13.8%)	78.6% (77.9%-79.3%)
	Benign without clinical relevance	22.1% (20.0%-24.2%)	92.1% (89.3%-94.3%)	89.5% (86.2%-92.2%)	27.7% (27.0%-28.5%)
Dyspepsia > 50 years of age, HP unknown	Malignant	3.9% (1.1%-9.6%)	77.8% (75.8%-79.6%)	0.94% (0.36%-2.42%)	93.7% (93.4%-93.9%)
	Benign with clinical relevance	21.1% (17.2%-25.5%)	78.7% (76.6%-80.7%)	19.2% (16.1%-22.7%)	80.6% (79.7%-81.5%)
	Benign without clinical relevance	22.5% (20.4%-24.7%)	82.5% (78.9%-85.8%)	79.9% (76.2%-83.1%)	25.7% (24.8%-26.7%)

► **Table 6** (Continuation)

Referral indication	Outcome of endoscopy	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Other	Malignant	0%	99.4% (99.0%-99.7%)	0%	94.8% (94.8%-94.8%)
	Benign with clinical relevance	0.8% (0.2%-2.2%)	99.5% (99.0%-99.8%)	27.3% (9.1%-58.5%)	80.7% (80.6%-80.9%)
	Benign without clinical relevance	0.5% (0.2%-1.0%)	99.4% (98.2%-99.9%)	72.7% (41.5%-90.9%)	24.5% (24.4%-24.7%)

Only the indications occurring with a frequency >0.5% were extensively reported.

► **Table 7** Uni- and multivariate logistic regression of possible predictors for upper gastrointestinal malignancy.

Malignancy of the upper gastrointestinal tract						
Possible predictors	Univariate analyse			Multivariate analyse		
	OR	95% CI	P value	OR	95% CI	P value
Alarm symptoms	16.032	8.298 – 30.974	<0.0001	10.488	5.276 – 20.849	<0.0001
Age	1.071	1.052 – 1.090	<0.0001	1.051	1.032 – 1.071	<0.0001
Gender						
▪ Female	Reference					
▪ Male	4.481	2.796 – 7.183	<0.0001	3.942	2.401 – 6.473	<0.0001
PPI or H2RA use						
▪ Yes	Reference					
▪ No	1.828	1.193 – 2.802	0.006	0.769	0.484 – 1.221	0.266
HP status						
▪ Negative	Reference					
▪ Positive	0.825	0.191 – 3.569	0.797			
Sedation						
▪ Yes	0.810	0.541 – 1.214	0.308			
▪ No	Reference					

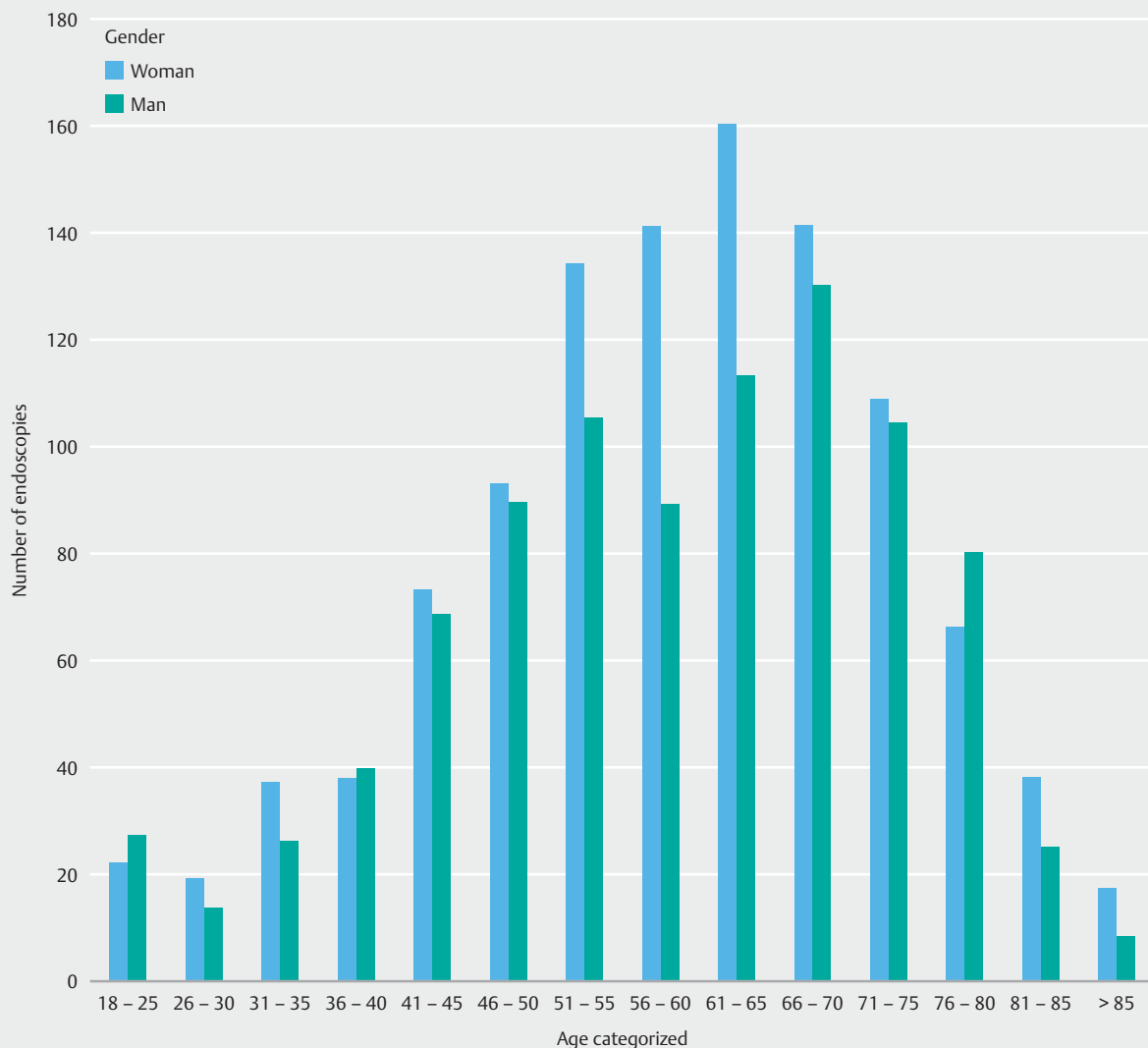
nocarcinoma [21,22]. However, dramatic increases in gastric and esophageal adenocarcinoma rates in several Western countries parallel the declines in *H. pylori* infection rates [22]. Due to the retrospective nature of this study and the discrepancy in the literature we could only speculate what the role of a *H. pylori* infection was in the observed malignancies. If dyspepsia above the age of 50 is considered an appropriate indication no malignancies would be missed, however, the cost effectiveness of OAE would rapidly decrease. Before any changes in the NHG guideline are made, more prospective studies are needed addressing the relationship between a *H. pylori* infection and a malignant finding in OAE.

The current study showed that the PPV of alarm symptoms for detecting a malignancy is considerably higher compared to other studies (11.8% versus 5.9%). Especially patients with the alarm symptoms dysphagia and weight loss combined had a relatively high PPV of 28.1% (► **Table 5**). The NPV is 99.2% which is corresponding with a meta-analysis which showed a pooled

NPV for alarm symptoms of 99.4% [23]. Our analysis showed that age, male gender and alarm symptoms are significant predictive variables for upper gastrointestinal malignancies. The combination of these variables resulted in an AUC of 0.868 for detecting upper GI malignancies, therewith higher than a similar Finnish study (AUC=0.72) [24]. Our risk-prediction model (age, alarm symptoms and male gender) gives the same AUC as the risk-prediction model made by Khademi et al. (AUC=0.85) which was based on different independent variables (age, alarm symptoms and smoking) [25]. Due to missing data, we could not include cigarette smoking in our risk prediction model, but this previous study suggests that our AUC could possibly become even higher by including this variable. Our study suggests that in female patients without alarm symptoms the age threshold for performing OAE could be safely raised compared to male patients.

The aim of OAE is to ensure rapid detection of upper gastrointestinal malignancy and to provide an effective way of mana-



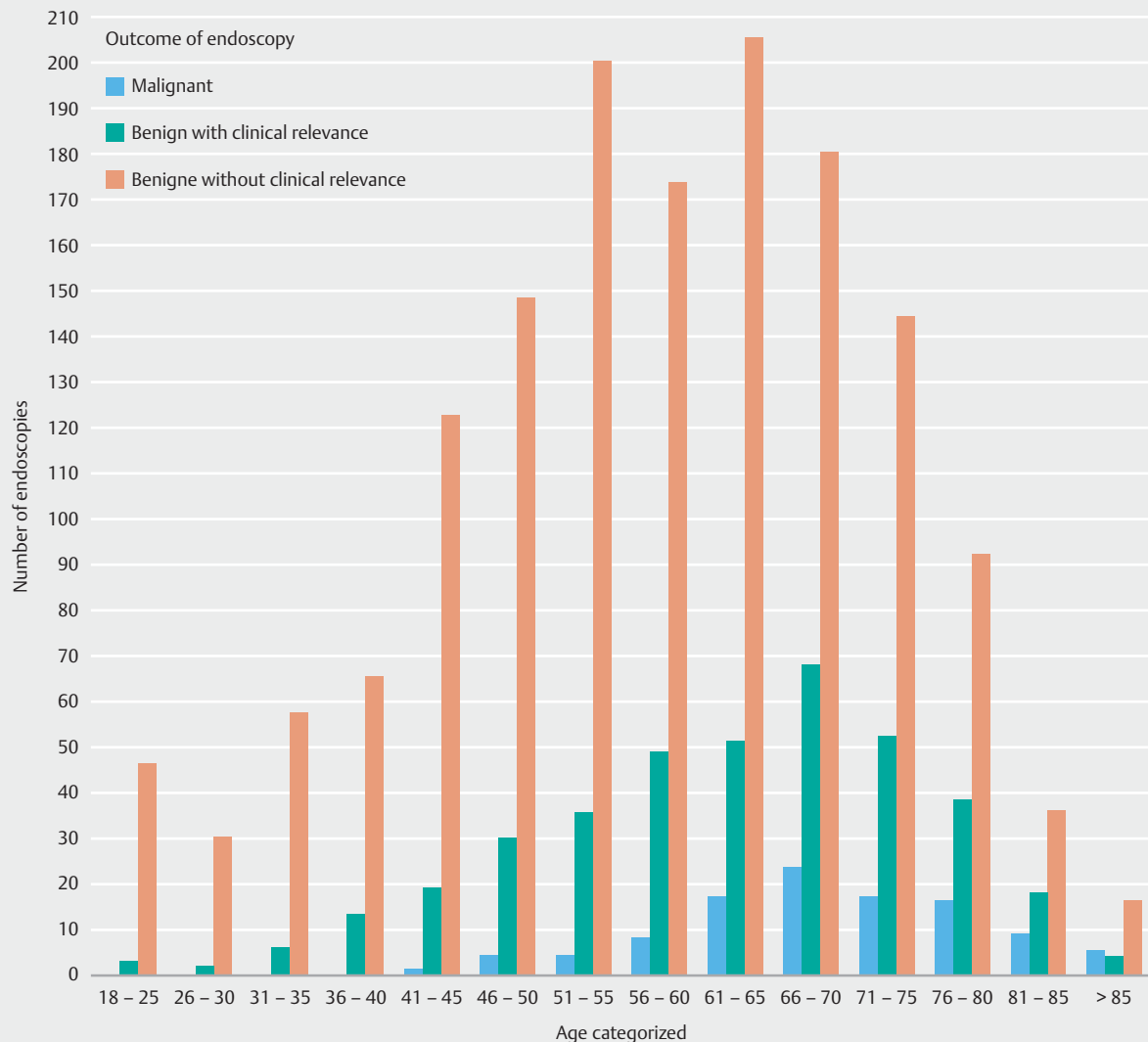


► **Fig. 1** Number of OAEs performed in different age groups.

ging patients without a malignancy. In our study, there was no malignancy found in patients under the age of 40 years and more than 90% of the patients with a malignancy had 1 or more alarm symptoms (► **Fig. 2**). Our study is consistent with others who found that upper gastrointestinal cancer was rare in patients under the age of 45 and all patients had alarm symptoms at presentation [26]. In contradiction, 1 study showed that 0.3% of the malignancies were detected in patients under the age of 45 who presented with uncomplicated dyspepsia [27]. However, it is uncertain whether an earlier diagnosis would alter clinical outcome, as studies showed that patients with a malignancy under the age of 55 years presented with uncomplicated dyspepsia had lymph node metastasis at diagnosis [27, 28]. The authors concluded that increasing the age limit of OAE to 55 years in patients with uncomplicated dyspeptic symptoms would unlikely affect clinical consequences, given the inoperable stage of the tumors in this younger patient group [27, 28]. These and our results support the opinion that

patients without alarm symptoms under the age of 50 year can be treated without OAE, which is concordant with the indications mentioned in the NHG guideline [24]. It even suggests that you can treat patients under the age of 40 without OAE, irrespectively of alarm symptoms. This with a low risk of missing a curable malignancy of the upper gastrointestinal tract. Important to notice is that this age threshold is only applicable to the Dutch community because it is determined by local epidemiological factors (ethnic background and prevalence of *H. pylori*).

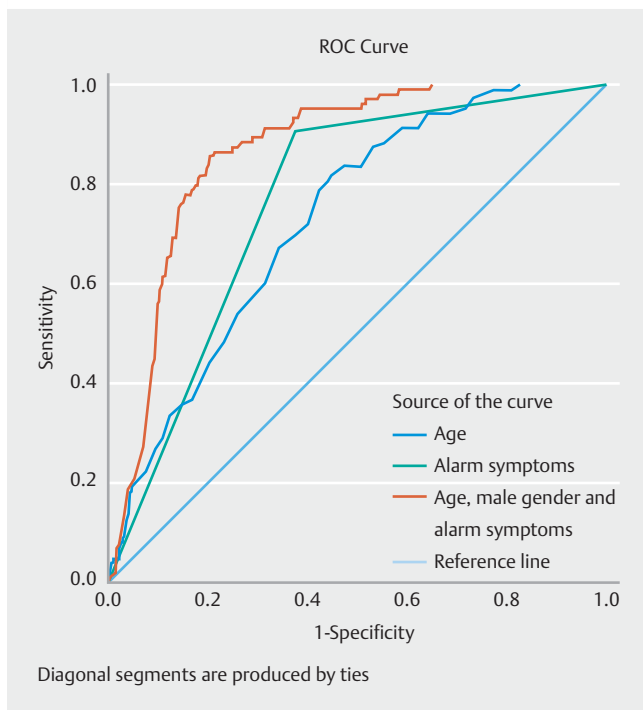
In our study OAE is unnecessary (no clinical relevant finding) in 88.3% of dyspeptic patients under the age of 45, even 50% had a normal endoscopy. Our results were consistent with studies which found that OAE is unnecessary in approximately 75% of young dyspeptics [29, 30]. Yet, in our study 16% of the OAE are performed in this age group, in other studies this number rises to even a third of all endoscopies [26, 31]. A reduction of this number of unnecessary OAEs can be crucial to the cost ef-



► **Fig. 2** Outcome of endoscopy in different age groups.

fectiveness of the open-access system. In addition, evidence suggest that most patients with reflux symptoms are, regardless of the endoscopic findings, switched to acid suppressive therapy [32,33]. This may suggest that the management of symptoms is hardly influenced by the OAE. However, a normal endoscopy cannot simply be devalued, it may have changed the treatment course of some patients. 1 study showed that 67% of the normal endoscopies assisted the caring physicians whether to continue with medication or to proceed with other investigations, and to help reassure patients [34]. Furthermore, some studies demonstrated that a normal endoscopy led to a better quality of life and patient satisfaction [17, 35]. In contradiction, other studies showed that quality of life was only improved during a short period after a negative endoscopy and there was no difference in experienced quality of life between prompt endoscopy or empirical treatment with acid suppressive therapy after 1 year [36, 37].

Our retrospective study had certain limitations. Firstly, indications for OAE were based on information provided by the GP, consequently, appropriateness of the indication could be underestimated or overestimated. This is, nevertheless, always the case in an open-access system. Secondly, because of the sometimes brief referral letter some data were missing. For example, it is unclear how long in advance the acid inhibition has been stopped and whether it has been stopped at all. This could, possibly, have masked some organic disorders. We think, however, that clinically relevant findings would still be detected by OAE, irrespectively of PPI use. Lastly, we did not include histological analysis of normal mucosa, which could lead to a diagnosis of celiac disease, and therefore clinical relevance.



► **Fig. 3** Receiver operating characteristic (ROC) curve comparing the accuracy of age alone (AUC = 0.729), alarm symptoms alone (AUC = 0.767) and age, alarm symptoms and male gender combined (AUC = 0.868) in predicting a malignant finding in OAE.

## Conclusion

In conclusion, we found a high rate of malignant findings and only 3.8% of the malignancies would be missed by strict adherence to the guideline. This indicates that the open-access system in the Netherlands works well. Further improvement of the open-access system can be achieved by streamlining of the referrals by the endoscopy unit by only accepting appropriate indications for OAE. Our results even suggest that patients under the age of 40 can be treated without OAE, irrespectively of alarm symptoms, with a very low risk of missing a curable malignancy. We showed that a risk-prediction model based on the variables age, alarm symptoms and male gender is a good predictor of malignant finding. This suggests that gender should be adopted in guidelines besides age and alarm symptoms which may lead to a different age cut-off point for performing OAEs in men and women.

## Competing interests

None

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