Risk of malignant progression in patients with Barrett's oesophagus: a Dutch nationwide cohort study

Pieter J F de Jonge, Mark van Blankenstein, Caspar W N Looman, et al.

Gut 2010 59: 1030-1036
doi: 10.1136/gut.2009.176701

Updated information and services can be found at:
http://gut.bmj.com/content/59/8/1030.full.html

These include:

References
This article cites 59 articles, 15 of which can be accessed free at:
http://gut.bmj.com/content/59/8/1030.full.html#ref-list-1

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To order reprints of this article go to:
http://gut.bmj.com/cgi/reprintform

To subscribe to Gut go to:
http://gut.bmj.com/subscriptions
Risk of malignant progression in patients with Barrett’s oesophagus: a Dutch nationwide cohort study

Pieter J F de Jonge,1 Mark van Blankenstein,1 Caspar W N Looman,2 Mariël K Casparie,3 Gerrit A Meijer,4 Ernst J Kuipers1,5

ABSTRACT

Background Reported incidence rates of oesophageal adenocarcinoma (OAC) in Barrett’s oesophagus (BO) vary widely. As the effectiveness of BO surveillance is crucially dependent on this rate, its clarification is essential.

Methods To estimate the rate of malignant progression in patients with BO, all patients with a first diagnosis of BO with no dysplasia (ND) or low-grade dysplasia (LGD) between 1991 and 2006 were identified in the Dutch nationwide registry of histopathology (PALGA). Follow-up data were evaluated up to November 2007.

Results 42 207 patients with BO were included; 4132 (8%) of them had LGD. Re-evaluation endoscopies at least 6 months after initial diagnosis were performed in 16 365 patients (39%), who were significantly younger than those not re-examined (58±13 vs 63±16 years, p<0.001). These patients were followed-up for a total of 78 131 person-years, during which 666 (4%) high-grade dysplasia (HGD)/OACs occurred, affecting 4% of the surveillance patient population (mean age: 69±12 years, 76% male). After excluding HGD/OAC cases detected within 1 year after BO diagnosis (n=212, 32%), incidence rates per 1000 person-years were 4.3 (95% CI 3.4 to 5.5) for OAC and 5.8 (95% CI 4.6 to 7.0) for HGD/OAC combined. Risk factors for HGD/OAC were increased age (eg, >75 years HR 12; 95% CI 8.0 to 18), male sex (2.01; 1.68 to 2.60) and presence of LGD at baseline (1.91; 1.53 to 2.40).

Conclusion In this largest reported cohort of unselected patients with BO, the annual risk of OAC was 0.4%. Male sex, older age and LGD at diagnosis are independent predictors of malignant progression, and should enable an improved risk assessment in BO.

INTRODUCTION

Barrett’s oesophagus (BO) is an acquired condition, in which the squamous epithelium lining the distal oesophagus is replaced by columnar intestinal-type mucosa.1 It is considered to be a complication of longstanding gastro-oesophageal reflux and constitutes the prime risk factor for oesophageal adenocarcinoma (OAC).2,3 OAC usually has a poor prognosis, with a 5-year survival rate of <15%.4 Hence, in order to detect early-stage cancers suitable for curative treatment, surveillance endoscopy of patients with BO is advised, at intervals dictated by the absence or presence and grade of dysplasia.5

The effectiveness of surveillance of BO is, however, equivocal. Increased survival has been observed in patients with OAC enrolled in BO surveillance programmes. This may have resulted from early detection of cancers. On the other hand, this effect may also have resulted from lead-time bias, as, in particular, young patients without concomitant diseases were included in surveillance programmes.5–11

What is already known about this subject?

► Published estimates of the annual risk of cancer in patients with Barrett’s oesophagus (BO) are highly heterogeneous.

► As the effectiveness of BO surveillance is primarily dependent on this rate, its clarification is essential.

► Large-scale and long-term follow-up studies of unselected patients with BO are lacking.

What are the new findings?

► In this large nationwide cohort of unselected patients with histologically confirmed BO, the annual risk of oesophageal adenocarcinoma (OAC) was 0.4%.

► The annual OAC risk decreased to 0.14%, in case cancer risk for all BO patients was analysed, regardless of whether surveillance endoscopy was performed.

► Male sex, older age and low-grade dysplasia at initial diagnosis of BO are independent predictors of malignant progression.
Consequently, US investigators reported evidence of publication bias in surveillance studies, favouring publication of small studies with high cancer incidence rates.18

As a result of the low degree of ascertainment of BO in the general population,19,26 there is a lack of both large-scale and long-term follow-up studies of patients with BO, providing more reliable risk estimates for malignant progression. Such studies are essential, both in re-appraising the potential value of surveillance endoscopy for patients with BO and in optimising the recommended follow-up intervals. We therefore estimated the progression rate of BO to high-grade dysplasia (HGD) and OAC in a nationwide cohort of patients with BO in The Netherlands, and assessed the value of the factors age, sex and initial histology as predictors of malignant progression in BO.

METHODS
Histopathology database
In The Netherlands all histopathology and cytopathology reports are collected in a national archive (PALGA database), which encompasses all 64 pathology laboratories in The Netherlands. Since 1991, PALGA has had nationwide coverage and currently contains ~42 million excerpts from nearly 10 million patients.21 Every excerpt in the database contains encrypted patient identification, a part of the summary of the original pathology report and diagnostic codes similar to the Systematised Nomenclature of Medicine (SNOMED) issued by the College of American Pathologists.22 This diagnostic code contains a topological term, the type of sample, and a morphological term describing the finding, for example ‘oesophagegus’ biopsy ‘intestinal metaplasia’. The SNOMED morphology codes are identical to the codes in the International Classification of Diseases for Oncology (ICD-O-2; WHO).23 Details with regard to the number and intraoesophageal location of biopsies, or information on the indication for performing an endoscopic procedure, are not uniformly registered. Each pathology report can, however, be traced to an individual patient with a unique identifier, allowing follow-up of subsequent histology, irrespective of where subsequent biopsies were taken or resections were performed.24 For each report, gender, date of birth, date of pathology review, summary text and diagnostic codes were made available. It was not, however, possible to access additional clinical data. The present study was based on data recorded in the PALGA database between 1991 and 2007.

Data collection
All patients registered in the database between 1991 and 2006 with an initial, histological diagnosis of BO with no baseline dysplasia (ND), or maximally low-grade dysplasia (LGD), were identified.25 BO was defined as the presence of intestinal metaplasia in oesophageal biopsies. Codes that were used for identification of our patient cohort were (1) a combination of ‘oesophagegus’ biopsy ‘intestinal metaplasia’ (T62000) and ‘intestinal metaplasia’ (M73320) or (2) ‘Barrett’s metaplasia’ (T6231OM7330) (see appendix). To validate the accuracy of the latter code, we manually reviewed the summary text of a random sample of 700 pathology reports that were coded as ‘Barrett’s metaplasia’, and examined whether the presence of intestinal metaplasia or goblet cells was mentioned. In only 16 of 700 reports (2.3%) were these terms not specifically mentioned. However, in seven of these patients, the presence of intestinal metaplasia could be confirmed in a follow-up pathology report.

Patients with a baseline diagnosis of HGD in BO were excluded, as were patients with either gastric or oesophageal surgery or malignancy, registered prior to, or simultaneously with, the first diagnosis of BO.

For each patient admitted to the cohort, all pathology excerpts concerning oesophageal biopsies from the first diagnosis of BO to the end of the study period (November 2007) were retrieved. Follow-up excerpts were scrutinised for codes indicating HGD and/or OAC. Where present, the pathology reports of the surgical resection specimens were reviewed; only carcinomas of which the bulk was macroscopically located above the gastro-oesophageal junction and those clearly originating from BO were diagnosed as OAC.26,27

Data analysis
Person-years of follow-up were calculated for each member of the cohort. Here we distinguished between patients who underwent one or more re-evaluation endoscopies with biopsy sampling and patients without further histology after BO diagnosis. The former group was censored at the date of either HGD or OAC diagnosis or of last patient contact with biopsy sampling, the latter at date of death. The date of death of patients registered in the PALGA database is, however, not uniformly recorded, unless an autopsy has been performed, reports of which are also registered in the system, but are fairly rare in The Netherlands. Therefore, for the latter cohort, censoring was imputed to evaluate the number of person-years at risk, as they were unlikely to have developed symptomatic OAC throughout the study period. As the ascertainment of symptomatic OAC in The Netherlands is presumed to be very high,26,27 the disease practically always results in histological analysis, which is registered in the PALGA archive. Survival data from the general Dutch population were collected, starting from age and gender of the patients, and calendar year (Dutch Cancer Registry 2007). A data set with an approximately unbiased number of person-years at risk was subsequently created, by drawing from a binomial distribution for every year, as was done previously.29,30 Multiple imputation did not significantly change the results. Finally, imputed survival estimates were corrected for an assumed 16% risk of excess mortality in patients with BO, based on previous reports.31

Within the first analysis, OAC risk and combined HGD/OAC risk were calculated for those patients with actual documented follow-up in the PALGA registry. Within the second analysis, OAC risk was calculated for the whole cohort of patients, including those who did not receive one or more follow-up endoscopies with biopsies after initial BO diagnosis. Additional analyses of OAC risk based on survival estimates for the general Dutch population without a correction for an assumed mortality excess in patients with BO were also performed. To avoid misclassification of prevalent cases of HGD/OAC, only those cases that were detected at least 1 year after initial BO diagnosis were included in cancer risk analysis. Crude OAC and combined HGD/OAC incidence rates are presented as number of cases per 1000 patient-years of follow-up. Kaplan–Meier survival analysis was performed to evaluate the interval between initial BO diagnosis and occurrence of HGD/OAC. Survival curves for patients with BO without baseline dysplasia were compared with those with baseline LGD, using the log-rank test, at the p<0.05 level of significance. Cox regression analyses were performed to identify independent risk factors for progression of BO to HGD/OAC. Estimates of relative risks are expressed as HRs with 95% CIs. Statistical analyses were conducted using S-PLUS (S-PLUS 6.0; Insightful, Seattle, Washington, USA) and SPSS software (SPSS 16.0; SPSS, Chicago, Illinois, USA).
RESULTS

Study cohort

In total, 42,207 patients with a first diagnosis of BO were identified in the PALGA database, with a 1.0/0.6 male to female ratio (table 1). Of those, 4132 (9.8%) were classified with LGD at baseline. Patients with LGD were significantly older than patients without dysplasia (mean age ± SD: 64 ± 14 vs 61 ± 15 years, p < 0.001) and more often male (65% vs 61%, p = 0.005). In addition, men were also significantly younger than women at initial diagnosis of BO without dysplasia (58 ± 15 vs 65 ± 15 years, p < 0.001) and BO with LGD (61 ± 14 vs 67 ± 15 years, p < 0.001).

Follow-up endoscopies with biopsy sampling

Follow-up upper gastrointestinal endoscopy with biopsy sampling, at least 6 months after the initial diagnosis, was performed in 16,565 patients with BO (39%). Mean length of total follow-up in these patients was 4.8 years (SD 3), for a total of 78,151 patient-years. In total, 43,568 re-evaluation endoscopies were performed, with an average of 3 (range 1–22) endoscopies per patient. Patients with histological follow-up were significantly younger than those not undergoing follow-up (58 ± 13 vs 65 ± 16 years, p < 0.001), and more often male (65% vs 59%, p < 0.001). Only 38% of patients without dysplasia at baseline underwent at least one histological follow-up, as compared with 52% after a diagnosis of baseline LGD (p < 0.001). The mean interval between initial and follow-up endoscopy was 2.0 ± 2 years for patients with BO without baseline dysplasia and 1.4 ± 2 years for those with LGD at baseline (p < 0.001).

Diagnosis of HGD and/or OAC

Malignant progression was observed in 666 (1.6%) patients (HGD, 161; OAC, 505). Five additional patients were diagnosed with an adenocarcinoma of which the bulk was located below the gastro-oesophageal junction. These cases were excluded from the analysis. Mean age of patients at HGD/OAC diagnosis was 69.0 years (SD 12) and the majority of HGD/OACs occurred in males (76%). Male patients were significantly younger at diagnosis of HGD/OAC than females (67 ± 11 vs 74 ± 11, p < 0.001). This overall male predominance gradually disappeared with increasing age, as the rise in incidence rate of HGD/OAC in males levelled off over age 85, whereas in women, especially in those aged >85, it continued to rise with age (figures 1 and 2).

Risk of HGD and/or OAC

The distribution of detected HGD/OAC cases in relation to the duration of follow-up is shown in figure 3. During the study period, 180 (0.4%) patients with BO developed HGD/OAC within 6 months, and 32 patients (0.08%) within the subsequent 6 months after BO diagnosis. Another 215 patients (0.5%) progressed to HGD/OAC between the second and fifth year after BO diagnosis, and the remaining 239 (0.6%) patients after 5 years. In the majority (n = 357, 54%) of patients with malignant progression, HGD/OAC was already detected at the second endoscopy. In 53% of these patients, this second investigation with biopsy sampling was performed after >1 year following initial BO diagnosis, and in 21% after >5 years. The remaining 509 (46%) patients with malignant progression underwent one or more surveillance endoscopies with biopsies yielding negative for HGD/OAC, before being diagnosed with HGD/OAC. Patients with prior negative endoscopies were significantly younger at BO diagnosis than those in whom HGD/OAC was diagnosed at the second endoscopy (60 ± 12 vs 67 ± 11, p < 0.001). Furthermore, the mean latent period from BO to HGD/OAC was significantly longer in those with prior intermittent endoscopies as compared with those without (7.0 ± 4 vs 2.5 ± 3, p < 0.001).

After excluding prevalent cases of HGD/OAC (detection <1 year after BO diagnosis), crude OAC and combined HGD/OAC incidence rates among 16,333 patients with BO with at least one re-evaluation endoscopy were calculated, on the basis of a total of 78,105 patient-years of follow-up (table 2). Overall incidence rates per 1000 patient-years at risk were 4.3 (95% CI 3.4 to 5.5) for OAC and 5.8 (95% CI 4.6 to 7.2) for HGD/OAC combined. Survival curves for patients with BO (n = 16,333) with or without baseline LGD are shown in figure 4. Within 2, 5 and 10 years of follow-up after initial diagnosis, HGD/OAC was diagnosed in 1, 2 and 6%, respectively of patients with BO without baseline LGD. In those with LGD at baseline, HGD/OAC was diagnosed in 1, 2 and 11% of patients after 2, 5 and 10 years of follow-up.

Table 1 Baseline characteristics of the study population

<table>
<thead>
<tr>
<th>Total</th>
<th>No dysplasia</th>
<th>Low-grade dysplasia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients with BO (%)</td>
<td>42,207</td>
<td>38,075 (90%)</td>
</tr>
<tr>
<td>Male/female</td>
<td>1.0/0.6</td>
<td>1.0/0.6</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>62.1</td>
<td>61.8</td>
</tr>
<tr>
<td>10th–90th percentile</td>
<td>41–80</td>
<td>41–80</td>
</tr>
</tbody>
</table>

BO, Barrett’s oesophagus.

Figure 1 Age distribution of 666 detected cases of high-grade dysplasia (HGD)/oesophageal adenocarcinoma (OAC) in 42,207 patients with Barrett’s oesophagus during the study period January 1991 to November 2007.

Figure 2 Age-specific incidence rates of high-grade dysplasia (HGD)/oesophageal adenocarcinoma (OAC) for males and females with a first diagnosis of Barrett’s oesophagus (BO).
without baseline dysplasia, and in 2, 4 and 13%, respectively, of patients with BO with baseline LGD (p < 0.001) (figure 4). Men with baseline LGD experienced a faster progression to HGD/OAC as compared with women (both p < 0.001). The same difference was observed between men and women without baseline dysplasia (p < 0.001).

For patients who did not undergo re-evaluation and were unlikely to have developed symptomatic OAC throughout the study period, life expectancy based on general survival data of the Dutch population was imputed. This rendered a total follow-up of 234821 patient-years for the whole cohort of 42207 patients with BO. Overall incidence rates of OAC per 1000 patient-years were 1.4 (95% CI 1.2 to 1.6) for both sexes combined, 1.9 (95% CI 1.7 to 2.1) for males and 0.8 (95% CI 0.7 to 1.0) for females. For patients with BO with baseline LGD, the OAC incidence rate rose to 3.6 per 1000 patient-years (95% CI 2.5 to 4.2) versus 1.2 (95% CI 1.1 to 1.5) for those without baseline dysplasia (p < 0.001). Additional analyses of annual OAC risk based on survival estimates for the general Dutch population without a correction for an assumed mortality excess in patients with BO did not significantly alter the results.

**Risk factors for malignant progression**

Multivariate Cox regression analysis showed that male sex was independently associated with an increased risk of progression to HGD/OAC (HR 2.12, 95% CI 1.70 to 2.65) (table 3). In addition, older age as well as the presence of LGD at initial BO diagnosis were independently associated with development of HGD/OAC.

**DISCUSSION**

In this, to our knowledge, largest reported cohort of patients with BO, the overall annual risk of cancer in BO was 0.4% (95% CI 0.3 to 0.6), and the annual risk of cancer and HGD combined only 0.6% (95% CI 0.5 to 0.7). These figures are lower than previously published estimates. In fact, the annual cancer risk decreased to 0.14%, in case cancer risk for all BO patients was analysed, regardless of whether any follow-up was performed. Against this background, male sex, older age and LGD at initial BO diagnosis were identified as independent predictors for malignant progression.

To date, there have been four published systematic reviews on the incidence of cancer in BO. Our finding of an annual cancer risk of 0.4% in BO is lower than those reported in these studies. Several explanations may account for this discrepancy. First, the population of our BO cohort consisted of a large number of unselected patients with BO with long-term follow-up, from all hospitals in The Netherlands. Our cohort therefore reflects daily clinical ascertainment and management of BO. This nationwide registry minimises selection bias, which is a particular drawback of small retrospective studies. This obviously differs from previous studies describing referral-based cohorts and from small studies with short follow-up, which may have included a biased selection of patients with BO with high cancer risk. For instance, only three studies with >1000 patient-years of follow-up were included in a review from the USA. A large study size results in lower reported cancer risks, as was also previously demonstrated in two systematic reviews. Another explanation for variations in outcome can be found in our strict exclusion of HGD and OAC cases occurring within the first year after initial BO diagnosis, and the exclusion of patients with BO with HGD at baseline. Only two reviews excluded incident cancers occurring within the first year after initial BO diagnosis. The inclusion of prevalent cancers will obviously inflate cancer risk for patients with uncomplicated BO. In the most recently published review, annual cancer incidence decreased to 0.41%, after limiting the analysis to the occurrence of only incident cancers, which is in line with our estimate of annual cancer risk.

Several authors have used mathematical models to explore the cost-effectiveness of BO surveillance. US researchers concluded that, for a cancer risk of 0.5% per annum, surveillance every 4 years was indicated and, if the annual risk was 0.4%, surveillance every 5 years was the only strategy that increased quality of life. Others reported that screening 50-year-old men with gastro-oesophageal reflux disease (GORD), followed by surveillance of those with dysplasia only, is probably cost-effective, but that surveillance of BO, even at 5-yearly intervals,
is very expensive even though more quality-adjusted life years (QALYs) may be gained.15 According to a British study using an economic model, an annual cancer risk of 0.5% would mean that surveillance conferred less benefit and more costs than no surveillance at all, irrespective of the surveillance interval used.14 The overall annual cancer risk obtained from our study is even lower than those incorporated in these models, especially with regard to the annual cancer risk of the whole cohort of patients with BO (0.14%), including those who did not receive any histological follow-up, and who did not in all probability develop symptomatic OAC. Our findings indicate that both quality of life benefit and cost-effectiveness of surveillance of BO are highly questionable unless it can be targeted at those patients with BO who are at the highest risk of cancer.

Despite the development of new cancer biomarkers, the presence and grade of dysplasia in random oesophageal biopsies obtained at BO surveillance still remain the best indicators of cancer risk.34 This was confirmed in our study by the fact that, despite its generally criticized lack of reproducibility, the initial diagnosis of LGD by a large variety of pathologists proved to have been a predictor of a twofold increased risk of malignant progression as compared with patients with BO without dysplasia. This was consistent with other studies.35–41 It is likely that an even better accuracy of risk prediction may be achieved by a consensus LGD diagnosis of more than one pathologist.42

Some limitations of our study warrant consideration. First, as both sampling error and interobserver variability in the interpretation of dysplasia between non-expert and expert gastrointestinal pathologists exist,56 misclassification of baseline dysplasia status in our patients could have influenced our results. Nevertheless, differential misclassification to absence of baseline dysplasia would bias the difference between non-dysplastic and dysplastic patients with BO towards the null value, thereby understimating rather than overestimating cancer risk in patients with BO with baseline LGD without affecting the overall cancer risk. In addition, overclassification of BO by community pathologists could have led to underestimation of reported cancer risks. However, reproducibility of intestinal metaplasia is high, with agreement rates between community pathologists could have led to underestimation of dysplastic patients with BO towards the null value, thereby understimating rather than overestimating cancer risk in patients with BO with baseline LGD without affecting the overall cancer risk. In addition, overclassification of BO by community pathologists could have led to understimation of reported cancer risks. However, reproducibility of intestinal metaplasia is high, with agreement rates between community pathologists of up to 88%.57 Secondly, some patients with intestinal metaplasia of the cardia could have been misclassified as having BO in our cohort, as endoscopic data were not available. We believe, however, that such misclassifications would only have played a minor role, as only pathology excerpts were included. In addition, obtaining biopsy specimens from the gastric cardia is not routine practice during oesophagogastroduodenoscopy or in the diagnosis of BO in The Netherlands. Thirdly, as data on the length of the Barrett’s segment, presence of hiatal hernia, presence of oesophagitis, body mass index and use of selected medications were not available, cancer risk could not be stratified for these factors. Unfortunately, it was also impossible to collect information with regard to the indication of performing re-evaluation endoscopies in these patients. As a result, no clear distinction could be made between patients participating in a surveillance programme and those undergoing re-evaluation endoscopies for investigation of symptoms. This could have led to an underestimation of our reported annual risk of cancer and HGD combined, as asymptomatic HGD cases might have been overlooked in this cohort. Nevertheless, we think that this has had only little influence on our findings, as a recent systematic review reported an incidence rate of cancer and HGD combined of 7.7 per 1000 person-years, which is only slightly higher compared with our findings.55 Fourthly, we could not provide data on the stage of cancers diagnosed in our cohort, as these data are not uniformly registered in the database. The younger age at diagnosis of cancer within the group receiving follow-up as compared with the group without follow-up

Table 3  Risk factors for malignant progression in Barrett’s oesophagus (n=16 333)

<table>
<thead>
<tr>
<th>HR univariate</th>
<th>95% CI</th>
<th>HR multivariate</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1.00</td>
<td>—</td>
<td>1.00</td>
</tr>
<tr>
<td>Male</td>
<td>1.58</td>
<td>1.27 to 1.96</td>
<td>2.12</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;40 years</td>
<td>1.00</td>
<td>—</td>
<td>1.00</td>
</tr>
<tr>
<td>40–48 years</td>
<td>1.77</td>
<td>1.03 to 3.05</td>
<td>1.81</td>
</tr>
<tr>
<td>50–59 years</td>
<td>2.56</td>
<td>1.54 to 4.30</td>
<td>2.64</td>
</tr>
<tr>
<td>60–69 years</td>
<td>3.32</td>
<td>2.00 to 5.51</td>
<td>3.57</td>
</tr>
<tr>
<td>70–79 years</td>
<td>8.77</td>
<td>5.27 to 14.6</td>
<td>10.0</td>
</tr>
<tr>
<td>&gt;80 years</td>
<td>16.38</td>
<td>8.70 to 30.9</td>
<td>21.0</td>
</tr>
<tr>
<td>Histopathology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BO with ND</td>
<td>1.00</td>
<td>—</td>
<td>1.00</td>
</tr>
<tr>
<td>BE with LGD</td>
<td>2.24</td>
<td>1.80 to 2.80</td>
<td>1.92</td>
</tr>
</tbody>
</table>

LGD, high-grade dysplasia; ND, no dysplasia.
suggests the detection of cancers at an earlier stage. In addition, we could not suggest the effect of the migration rate on our results. As the migration out of The Netherlands during the study period was small, with an average of 0.6% of the population annually, and there has been a predominant migration of populations with similar esophageal cancer rates towards The Netherlands, we expect that these rates have only marginally affected the reported cancer rates. Finally, in order to calculate progression rates to QAC for the whole cohort of patients, a virtual life expectancy was calculated for all patients without follow-up until November 2007, based on the life expectancy of the general population. This assumption may have led to a slight underestimation of cancer risk, as there is conflicting evidence of increased co-morbidity and mortality in patients with BO as compared with the general population. However, as we assumed a high, 16%, increased risk of all-cause mortality in patients with BO, as reported by Cook et al., it is highly unlikely that this caused underestimation of our incidence rates.

In conclusion, in this large nationwide cohort of unselected patients with histologically confirmed BO, the annual risk of malignant progression was lower than previously reported. This further underestimates the cost-effectiveness of generalised BO surveillance, from which an even smaller minority of patients than previously estimated is likely to benefit. However, we have demonstrated three independent predictors of neoplastic progression enabling tailoring of surveillance programmes towards a better selection of high-risk patients. Future large studies from other unselected populations should be performed to develop further risk stratification. A multicentre trial with randomisation of patients to varying surveillance intervals based on age, sex and the presence and grade of dysplasia is urgently needed.

Competing interests GAM is a member of the executive board of the PALGA registry. The other authors have no conflict of interest to disclose.

Ethics approval This study was conducted with the approval of the Stichting PALGA.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

When to leave a stone unturned …

CLINICAL PRESENTATION
A 16-year-old, 41 kg boy with chronic granulomatous disease presented with fever, chills, and diaphoresis. CT showed necrotising mediastinal lymphadenitis and a contracted but otherwise normal gallbladder (figure 1A). The patient was started on intravenous antibiotics and clinically improved. Culture of the lymphadenitis obtained by CT-guided aspiration started on intravenous antibiotics and clinically improved. One month later a follow-up CT scan showed improvement in the mediastinal lymphadenitis, and a new enhancing mass in the gallbladder (figure 1B), which was consistent with a gallstone on ultrasound. The patient had no abdominal symptoms and liver-associated blood tests were all in the normal range.

QUESTION
What antibiotic did the patient receive?
See page 1100 for answer

Figure 1 (A) CT scan showing a contracted but otherwise normal gallbladder. (B) CT scan 1 month later reveals a calcified calculus in the gallbladder.

Editor’s quiz: GI snapshot

Oesophagus


APPENDIX
PALGA diagnosis codes used in the analysis: Barrett’s oesophagus: T62310M73330, M73320
Low-grade dysplasia: M74000, M74006, M74007
High-grade dysplasia and esophageal adenocarcinomas: M74008, M80003, M80011, M80101, M80102, M80103, M80104, M80105, M80123, M80193, M80203, M80213, M80413, M81403, M81453, M81454, M82003, M82113, M82603, M84303, M84803, M85603
PALGA terminology: http://www.palga.nl/palga/thesaurus.rdf

Erik C von Rosenvinge, Christopher Koh, Steven M Holland, Theo Heller

National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland, USA

Correspondence to Dr Erik C von Rosenvinge, Digestive Diseases Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Building 10, Room 9C-101, Bethesda, MD 20892-1804, USA; vonroe@yahoo.com

Competing interests None.

Patient consent Obtained from the patient’s guardian.

Ethics approval This study was conducted with the approval of the Institutional Review Board of the National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland, USA.

Contributors All authors made a substantial contribution to the manuscript according to the Uniform Requirements for Manuscripts Submitted to Biomedical Journals.

Provenance and peer review Not commissioned; externally peer reviewed.

Published Online First 10 June 2010

Gut 2010;59:1036. doi:10.1136/gut.2009.188276