ORIGINAL ARTICLE

Oesophageal adenocarcinoma and prior diagnosis of Barrett's oesophagus: a population-based study

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ABSTRACT

Objective Endoscopic surveillance of Barrett's oesophagus (BO) provides an opportunity to detect early stage oesophageal adenocarcinoma (OAC). We sought to determine the proportion of OAC patients with a prior diagnosis of BO on a population basis and to evaluate the influence of a prior diagnosis of BO on survival, taking into account lead and length time biases.

Design A retrospective population-based study of all OAC patients in Northern Ireland between 2003 and 2008. A prior BO diagnosis was determined by linkage to the Northern Ireland BO register. Stage distribution at diagnosis and histological grade were compared between patients with and without a prior BO diagnosis. Overall survival, using Cox models, was compared between patients with and without a prior BO diagnosis. The effect of adjusting the survival differences for histological grade and estimates of lead and length time bias was assessed.

Results There were 716 OAC cases, 52 (7.3%) of whom had a prior BO diagnosis. Patients with a prior BO diagnosis had significantly lower tumour stage (44.2% vs 11.1% had stage 1 or 2 disease; p<0.001), a higher rate of surgical resection (50.0% vs 25.5%; p<0.001) and had a higher proportion of low/intermediate grade tumours (46.2% vs 26.5%; p=0.011). A prior BO diagnosis was associated with significantly better survival (HR for death 0.39; 95% CI 0.27 to 0.58), which was minimally influenced by adjustment for age, sex and tumour grade (adjusted HR 0.44; 95% CI 0.30 to 0.64). Correction for lead time bias attenuated but did not abolish the survival benefit (HR 0.65; 95% CI 0.45 to 0.95) and further adjustment for length time bias had little effect.

Conclusions The proportion of OAC patients with a prior diagnosis of BO is low; however, prior identification of BO is associated with an improvement in survival in OAC patients.

Significance of this study

What is already known on this subject?

- Endoscopic surveillance of Barrett's oesophagus is widely practised in an effort to improve outcomes from oesophageal adenocarcinoma.
- The impact of surveillance on population outcomes from oesophageal adenocarcinoma will depend on the proportion of patients that had previously been diagnosed with Barrett's oesophagus.
- The improved outcomes associated with surveillance may in part be due to lead and length time bias

What are the new findings?

- The proportion of oesophageal adenocarcinoma patients with previously diagnosed Barrett's oesophagus is low.
- Oesophageal adenocarcinoma patients with a prior Barrett's oesophagus diagnosis were diagnosed with earlier stage disease and had improved survival compared with adenocarcinoma patients with no prior Barrett's oesophagus diagnosis.
- The improved survival observed in patients with a prior diagnosis of Barrett's oesophagus remained after correction for lead and length time biases of plausible magnitude.

How might it impact on clinical practice in the foreseeable future?

- The low proportion of patients with a prior Barrett's oesophagus diagnosis suggests that endoscopic surveillance of Barrett's oesophagus, as currently practised, can only have a modest impact on population oesophageal adenocarcinoma outcomes.
- Better methods of identifying patients in the population at greatest risk of developing oesophageal adenocarcinoma are required in order to allow targeted surveillance and improve population outcomes from oesophageal adenocarcinoma.

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INTRODUCTION

The incidence of oesophageal adenocarcinoma (OAC) is rising.[1 2] Once diagnosed, OAC has a poor prognosis with a 5-year survival of less than 20%.[3] Attempts to improve survival have focused on the surveillance of Barrett's oesophagus (BO), the precursor to OAC. The rationale for BO surveillance is that detection of early cancer or dysplasia will result in improved patient outcomes through early treatment.[4 5] The potential impact of endoscopic surveillance of BO on population OAC mortality is constrained by the proportion of OAC patients that have a prior diagnosis of BO,[6] but few population-based studies have examined this

proportion. The largest study to date, which was restricted to patients aged 68 years or older, showed that only 8.1% of OAC patients had a prior diagnosis of OAC.[7] Further population-based studies are required to clarify the proportion of OAC patients with a prior diagnosis of BO in order to assess the likely impact of current BO diagnosis and surveillance strategies on OAC outcomes in populations.

Endoscopic surveillance in BO patients is associated with the detection of earlier stage cancers and improved survival.[8 9] However, survival estimates in OAC patients detected at surveillance are susceptible to both lead time and length time bias.[10] Lead time bias occurs where surveillance detects cancers at an earlier time point in their natural history; the lead time between diagnosis due to surveillance and diagnosis due to symptoms contributes to any survival benefit observed. Length time bias occurs where slower growing, less aggressive tumours are more likely to be detected at surveillance; subsequent survival analysis may show a survival advantage in surveillance-detected patients, which is due to their tumour biology rather than earlier instigation of treatment. It is also possible that tumours arising in patients with a prior BO diagnosis have inherent biological differences that may positively influence survival. Although both lead and length time bias are recognised as important in cancer screening,[11–13] no previous study has examined the potential influence of these biases on OAC outcomes in patients with and without a prior diagnosis of BO. Assessment of these issues is crucial to understanding the potential benefits of BO diagnosis and surveillance.

Using unique population data sources, we determined the proportion of OAC patients that have a prior diagnosis of BO and examined the potential influences of lead and length time bias, and differences in tumour grade, on survival in OAC patients with and without a prior diagnosis of BO.

METHODS

Patients

This study used data from the population-based Northern Ireland Cancer registry (NICR) and Northern Ireland Barrett's oesophagus register (NIBR). The NICR has recorded data on all patients diagnosed with cancer in Northern Ireland (population 1.8 million) since 1993. The NICR was used to identify all patients with oesophageal cancer diagnosed between January 2003 and December 2008 in Northern Ireland. The NICR uses the International Classification of diseases V.10 (ICD10) to classify patient tumour type and location based on accompanying clinical information. ICD10 codes were used to identify patients from the NICR with adenocarcinoma or histologically unspecified tumours of the oesophagus (hereafter referred to as OAC) for inclusion in the study. Histologically unspecified tumours were included to ensure complete ascertainment of tumours that may have arisen in patients with BO.

The NIBR is a population-based register of all patients (n=11 626) in Northern Ireland diagnosed with BO between 1993 and 2008. Strict criteria were used for the construction of the NIBR database where BO was defined as columnar epithelium of the oesophagus. The register was constructed by examining all oesophageal biopsy pathology reports from endoscopies carried out in Northern Ireland during this period.[14] The date of the first biopsy report showing columnar epithelium of the oesophagus was used as the date of diagnosis of BO. Pathology reports were also examined for the presence of intestinal metaplasia in each patient. The date of first pathological diagnosis of OAC was used to define the diagnosis date of OAC for the study. OAC patients that had a prior diagnosis of BO were identified by matching the NICR data to the NIBR database using patient forename, surname and date of birth. Cancers that were diagnosed within 6 months of BO diagnosis were assumed to be prevalent cases and were not considered to have a prior BO diagnosis for the purposes of the study. The hospital case records of patients with prior BO were reviewed to determine whether they were within an endoscopic surveillance programme.

Further information relating to OAC patients was obtained through the NICR database. Information relating to tumour stage at diagnosis was obtained through a manual review of the Clinical Oncology Information System (COIS). Cancers were staged in accordance with the American Joint Committee on Cancer manual of TNM cancer staging.[15] Information on surgical resection of the tumours, both a marker of early stage disease and curative intent treatment, was available through hospital episode statistics available through the NICR database. Mortality data (date and cause of patient death) were obtained from the NICR for patients up until 31st December 2010 through linkage with the Northern Ireland Registrar General's Office.

The histological grade of tumours was assessed by manual review of all pathology reports relating to the OAC diagnoses of patients in the study. Tumour grade was defined according to the American Joint Committee on Cancer[16] as 'well differentiated', 'moderately differentiated', 'poorly differentiated' or 'undifferentiated'. Patients with 'diffuse type' or 'signet ring carcinoma' were considered to have 'poorly differentiated' tumours. If the pathologist reported a mixed grade of tumour, the least well-differentiated grade mentioned in the report was used. If a pathology report could not be obtained for a patient or the pathologist did not mention the grade of tumour, it was classified as 'unknown'.

Statistical methods

All statistical analyses were conducted using Intercooled Stata V.11.0 (College Station, Texas, USA). Comparisons were made between OAC patients that did or did not have a prior diagnosis of BO using χ^2 test and the Student t test for categorical and continuous variables, respectively. Tumour grade was reclassified for analysis as 'low grade' if reported as well differentiated, 'intermediate grade' if reported as moderately differentiated or 'high grade' if reported as poorly differentiated. Very few tumours were classified as 'undifferentiated', and these were reclassified as 'high grade'. A Cox proportional hazards model was used to conduct survival analysis comparing OAC patients with and without a prior diagnosis of BO. Patients were followed up from date of OAC diagnosis to date of death or 31 December 2010. An event in the survival analysis was defined as death from any cause prior to 31 December 2010. The model was adjusted for age at cancer diagnosis (continuous), sex (categorical) and tumour grade (categorical). The proportional hazards assumption was checked from visual inspection of Kaplan–Meier curves. Sensitivity analyses were conducted, excluding patients with histologically unspecified tumours.

Adjustment for lead and length time bias

The approach suggested by Duffy *et al*[17 18] was used to adjust the survival analysis for lead time bias and conduct a sensitivity analysis around the potential influence of length time bias. To adjust for lead time bias, the sojourn time for OAC, the time where the tumour is asymptomatic but surveillance detectable, was estimated from the difference in mean age at OAC diagnosis between patients with and without a prior BO diagnosis. The

Table 1 Characteristics of oesophageal adenocarcinoma (OAC) patients according to prior Barrett's oesophagus (BO) diagnosis

	Adenocarcinoma and histologically unspecified tumours				Oesophageal adenocarcinoma only			
	All patients (n=716)	Patients with no prior BO diagnosis (n=664)	Patients with a prior BO diagnosis (n=52)	p Value	All patients (n=527)	Patients with no prior BO diagnosis (n=485)	Patients with a prior BO diagnosis (n=42)	p Value
Age at cancer diagnosis (years), mean (SD)	69.7 (12.4)	69.9 (12.3)	67.4 (13.2)	0.18	68.6 (12.3)	68.8 (12.2)	66.6 (13.1)	0.26
Sex, n (%)								
Male	525 (73.3)	484 (72.9)	41 (78.9)	0.35	404 (76.7)	370 (76.3)	34 (81.0)	0.49
Female	191 (26.7)	180 (27.1)	11 (21.1)		123 (23.3)	115 (23.7)	8 (19.0)	
Tumour stage, n (%)								
Stage I	4 (4.8)	25 (3.7)	9 (17.3)	<0.001	32 (6.1)	23 (4.7)	9 (21.4)	<0.001
Stage IIA	43 (6.1)	33 (5.0)	10 (19.2)		39 (7.4)	30 (6.2)	9 (21.4)	
Stage IIB	20 (2.8)	16 (2.4)	4 (7.7)		18 (3.4)	14 (2.9)	4 (9.5)	
Stage III	93 (13.0)	87 (13.1)	6 (11.5)		88 (16.7)	83 (17.1)	5 (11.9)	
Stage IV	183 (25.6)	178 (26.8)	5 (9.6)		136 (25.8)	133 (27.4)	3 (7.1)	
Unknown	343 (47.9)	325 (49.0)	18 (34.6)		214 (40.6)	202 (41.7)	12 (28.6)	
Surgery, n (%)								
Resection	195 (27.2)	169 (25.5)	26 (50.0)	<0.001	185 (35.1)	159 (32.8)	26 (61.9)	<0.001
No resection	521 (72.8)	495 (74.6)	26 (50.0)		342 (64.9)	326 (67.2)	16 (38.1)	
Tumour grade, n (%)								
Low	28 (3.9)	23 (3.5)	5 (9.6)	0.011	28 (5.3)	23 (4.7)	5 (11.9)	0.025
Intermediate	172 (24.0)	153 (23.0)	19 (36.5)		167 (31.7)	148 (30.5)	19 (45.2)	
High	317 (44.3)	301 (45.3)	16 (30.8)		248 (47.1)	235 (48.5)	13 (31.0)	
Unknown	199 (27.8)	187 (28.1)	12 (23.1)		84 (15.9)	79 (16.3)	5 (11.9)	

adjustment for lead time bias requires an estimate of the additional follow-up time observed purely as a result of lead time for each prior BO cancer patient and was calculated based on the sojourn time for OAC and the observed follow-up time for each patient.[17] A sensitivity analysis was conducted varying the length of sojourn time.

The adjustment for length time bias requires estimates of the proportion of OAC patients with less aggressive tumours (the length bias affected group) compared with those with more aggressive tumours, and the corresponding differences in survival between these groups.[17] As no published data exist providing these proportions, sensitivity analyses, as recommended by Duffy *et al*,[17] were employed examining a range of plausible values for these estimates. In additional analyses, these proportions were estimated from our own data, where low-grade and intermediate-grade tumours are assumed to be less aggressive (affected by length time bias).

RESULTS

There were 716 patients diagnosed with OAC between 2003 and 2008 in Northern Ireland. The majority of tumours included in the study were classified as adenocarcinoma (527 of 716; 73.6%) with the remainder unspecified histological types. Characteristics of patients are shown in table 1. There were 52 OAC patients (7.3%) that had an established diagnosis of BO more than 6 months prior to diagnosis of cancer. The mean interval between diagnosis of BO and diagnosis of cancer was 6.0 (SD±3.8; range 0.6–14.9) years. There was no significant difference in the proportion of cancer patients with a prior BO diagnosis in the first 3 years of the study period (6.8%) compared with the last 3 years (7.7%). In total, 41 of the 52 patients (78.9%) had specialised intestinal metaplasia, 12 (23.1%) had low-grade dysplasia at BO diagnosis and 41 (78.9%) were known to be undergoing endoscopic surveillance.

Age at diagnosis, tumour stage, surgical resection and tumour grade

OAC patients with a prior diagnosis of BO were slightly younger at cancer diagnosis than those without (mean age 67.4 vs 69.9 years; p=0.18) but did not differ in terms of sex distribution (table 1). OAC patients with a prior BO diagnosis had significantly lower stage disease than those without (44.2% vs 11.1% had stage 1 or 2 disease; p<0.001). Surgical resection was performed in a total of 195 patients (27.2%), and patients with a prior diagnosis of BO were significantly more likely to have undergone resection than those without a prior diagnosis (50.0% vs 25.5%; p<0.001). Tumour grade could be determined from pathology reports in 517 (72.2%) patients; no report was available in 110 of the 199 patients in whom grade could not be determined and in the remaining 89 the pathologist did not mention tumour grade. A greater proportion of OAC patients with a prior diagnosis of BO had low-grade or intermediate-grade tumours compared with OAC patients without a previous BO diagnosis (46.2% vs 26.5%; p=0.011). This difference remained significant when patients of unknown tumour grade were excluded (60.0% vs 36.9%; p=0.007).

Survival analysis

Overall there were 610 deaths by 31st December 2010. The median survival time (estimated from the Kaplan–Meier plots) in patients with prior BO was 29.0 months and in patients with on prior BO was 7.0 months. Figure 1 shows the Kaplan–Meier survival curve comparing overall survival between OAC patients that did or did not have a prior diagnosis of BO. Survival analysis showed that receipt of a prior diagnosis of BO was associated with improved survival; the unadjusted HR for death in OAC patients with prior BO was 0.39 (95% CI 0.27 to 0.58). Adjustment for age at diagnosis, sex and tumour grade did not substantially alter the risk of death; adjusted HR 0.44 (95% CI

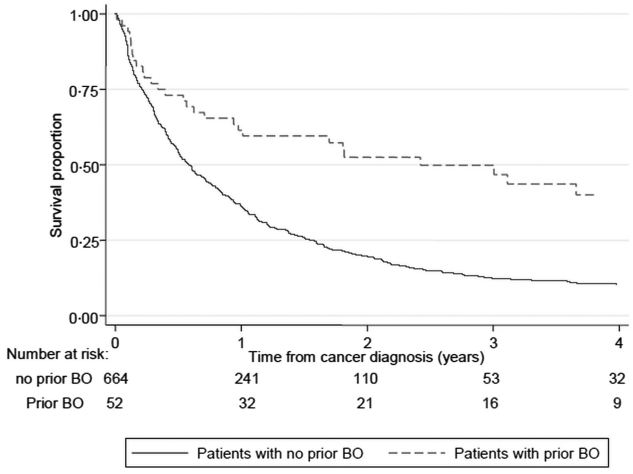

Figure 1 Kaplan–Meier curve comparing survival of patients with or without a prior diagnosis of Barrett's oesophagus.

0.30 to 0.64) (table 2). As expected, patients with high-grade tumours had a significantly higher HR for death than those with low-grade or intermediate-grade tumours, adjusted HR 1.38 (95% CI 1.14 to 1.69). Analysis was also conducted according to surgical resection status. This revealed that a prior diagnosis of BO was associated with improved survival even among patients that did not undergo surgical resection; a prior diagnosis of BO was associated with improved survival with an adjusted HR for death of 0.50 (95% CI 0.32 to 0.79). In patients that underwent surgical resection, the survival benefit was also seen; patients with a prior BO diagnosis had an adjusted HR for death of 0.46 (95% CI 0.22 to 0.96).

Sensitivity analysis

Analysis was repeated in the 527 patients with histologically confirmed OAC. In these patients, 42 (8.0%) had been diagnosed with BO prior to OAC. In this restricted analysis, findings were similar to the main analysis such that a previous diagnosis of BO was associated with significantly lower stage disease, higher surgical resection rates and significantly improved survival (tables 1 and 2).

Adjustment for lead time bias and length time bias

The adjustment for lead time bias employed an estimate of the sojourn time based on the difference in mean age at cancer diagnosis between OAC cases with and without prior BO (2.5 years). Analysis of survival after correcting for lead time bias revealed an attenuated survival benefit for patients with a prior diagnosis of BO (HR 0.65; 95% CI 0.45 to 0.95). In sensitivity analyses, the estimate was attenuated to a greater extent when applying an estimated sojourn time of 3.5 years (HR 0.71; 95% CI 0.49 to 1.04) and to a lesser extent when applying an estimated sojourn time of 1.5 years (HR 0.58; 95% CI 0.40 to 0.85).

Additional adjustment for length time bias was conducted using a suggested range of values[17] for the proportion of patients with length bias affected tumours (ranging from 50% to 90%) together with estimates for the relative rate of fatality in the length bias group (ranging from 0.5 to 0.9). These sensitivity analyses (shown in online supplementary table S1) were based upon the relative risk (RR) of death for prior BO patients compared with no prior BO patients, which at 1.5 years after cancer diagnosis was estimated at 0.72 after adjustment for lead time bias. Further adjustment for length time bias gave a range for the RR of death between 0.72 and 0.81, with a median RR of 0.73. We can refine the length time bias adjustment using our own data if we assume that patients in the study with low-grade or intermediate-grade tumours are the length bias affected group; 27.9% of our tumours would be classified as length bias affected, with a HR of death of 0.69 compared with other tumour grades. This provides a lead and length bias adjusted RR of death at 1.5 years of 0.74, little altered from the lead time bias adjusted RR of 0.72.

DISCUSSION

This study is one of the largest population-based studies to examine patients with OAC and assess the proportion that had an established diagnosis of BO prior to development of cancer. We showed that the proportion of OAC patients with a prior diagnosis of BO was very low at only 7.3%. The low prevalence of a prior diagnosis of BO in OAC patients agrees with other studies,[6 7 10] although the largest of these studies included only elderly patients and did not identify BO diagnosis more than 3 years before cancer diagnosis. Our finding suggests that

Table 2 Survival analysis of oesophageal adenocarcinoma (OAC) patients according to prior Barrett's oesophagus (BO), sex and tumour grade categories

	Adenocarcinoma and histologically unspecified tumours				Oesophageal adenocarcinoma only			
	All patients (n=716)	Number of deaths (n=610)	Unadjusted HR (95% CI)	Adjusted* HR (95% CI)	All patients (n=527)	Number of deaths (n=435)	Unadjusted HR (95% CI)	Adjusted* HR (95% CI)
Prior BO diagnosis, n (%)								
No	664	582 (87.7)	1.00	1.00	485 (92.0)	416 (95.6)	1.00	1.00
Yes	52	28 (53.8)	0.39 (0.27 to 0.58)	0.44 (0.30 to 0.64)	42 (8.0)	19 (4.4)	0.32 (0.20 to 0.51)	0.34 (0.21 to 0.54)
Sex, n (%)								
Male	525	440 (83.8)	1.00	1.00	404 (76.7)	326 (74.9)	1.00	1.00
Female	170	241 (89.0)	1.31 (1.09 to 1.56)	1.13 (0.94 to 1.35)	123 (23.3)	109 (25.1)	1.30 (1.05 to 1.62)	1.15 (0.92 to 1.44)
Tumour grade, n (%)								
Low or intermediate	189	144 (76.2)	1.00	1.00	142 (26.9)	142 (32.6)	1.00	1.00
High	303	266 (87.8)	1.46 (1.19 to 1.78)	1.38 (1.14 to 1.69)	246 (46.7)	212 (48.7)	1.32 (1.07 to 1.63)	1.25 (1.01 to 1.55)
Unknown	224	200 (89.3)	1.84 (1.49 to 2.29)	1.56 (1.25 to 1.95)	94 (17.8)	81 (18.6)	1.39 (1.05 to 1.84)	1.17 (0.88 to 1.55)

*Adjusted for age at cancer diagnosis (years, continuous), sex (categorical) and tumour grade (categorical).

diagnosis and surveillance of BO as currently practised can only modify outcomes in a minority of OAC patients.

No randomised controlled trial has been conducted to examine the effectiveness of BO surveillance at improving OAC outcomes. A trial in the UK is currently underway; however, it will not report findings for several years.[19] The few studies that have examined survival in OAC patients with respect to a previous BO diagnosis have all demonstrated a survival advantage for patients with a previous history of BO[9 10 20] but have not considered the influence of lead and length time bias on observed survival benefits.[10 21] In this study, we demonstrate substantial survival benefits in OAC patients who had a prior diagnosis of BO compared with those without such a diagnosis. Much of this survival benefit is likely to result from the detection of cancer at an earlier stage, with a corresponding higher surgical resection rate in patients with a prior BO diagnosis, presumably reflecting detection of cancer within surveillance (80% of patients with a prior BO diagnosis were participating in surveillance). Indeed, our data confirmed an increased proportion of lower stage tumours and a higher surgical resection rates in patients with a prior BO diagnosis. However, alternative explanations for the improved survival in prior BO patients need to be considered. The lower mean age (by 2.5 years) at cancer diagnosis in patients with a prior BO diagnosis suggests that lead time bias contributes to the survival benefit we observed. We also showed, for the first time, that a prior BO diagnosis was associated with lower histological tumour grade. Tumour histological grade is known to influence outcomes for OAC patients,[22 23] and we confirmed that lower grades of OAC were associated with better survival. Potential explanations for the survival differences between OAC patients with and without a prior BO diagnosis therefore include inherent differences in tumour biology in prior BO patients, or lead and length time bias related to surveillance of these patients. The reduction in risk of death when we restricted the analysis to patients who did not undergo surgery suggests that inherent tumour biological differences between these two patient groups may be important.

We adjusted the survival estimates for tumour biology differences (tumour grade) and corrected for lead time and length time bias according to the method of Duffy *et al*.[17] Adjustment for tumour grade had little effect on the survival estimates, and although the survival benefit was attenuated after adjustment for lead time bias, there remained a 35% reduction in the risk of death in the prior BO group. Adjustment for length time bias used a range of possible proportions of OAC patients with length bias affected tumours and corresponding mortality reductions. This additional adjustment had little effect on the lead time bias adjusted estimate. The median estimate of the RR for death in the prior BO group was 0.73 (range 0.72–0.81) after adjusting for tumour biology/grade, lead and length time bias, indicating a persistent survival advantage in patients in this group. This is the first study to attempt to correct for a marker of tumour biology and lead and length time bias in OAC patients with prior BO. It appears that a previous diagnosis of BO confers a true survival benefit among those patients who will develop OAC, presumably through endoscopic surveillance, early detection and early instigation of treatment.

Strengths of the current study are its size and population-based nature, enabling capture of all cancer and BO cases in a defined area, with low migration rates.[24] The availability of data on prior diagnosis of BO up to 15 years before cancer diagnosis is also a substantial strength. Limitations of the study include the lack of complete staging data; staging data were available for 52.1% of patients. However, the observation of a significant increase in lower stage tumours in prior BO patients was also present when analysis was restricted to patients with known tumour stage (data not shown). Other potential benefits of BO diagnosis and surveillance cannot be determined from this study, including the ascertainment of HGD cases that may be amenable to endoscopic therapy. It is therefore possible that our results have underestimated the potential benefits of a BO diagnosis and surveillance. It is not clear to what extent the approaches we employed adequately deal with the issues of lead and length time bias. Apparent residual survival benefits may result from inadequacies in these methods or from inaccuracy in the estimates of sojourn time or the proportion with length bias affected tumours, although survival differences remained when we conducted sensitivity analyses around these estimates.

In conclusion, this study has shown that the proportion of OAC patients with an established previous diagnosis of BO is small. This suggests that current approaches to diagnosis and surveillance of BO can only achieve modest improvements in population outcomes from OAC. Patients that were previously diagnosed with BO had a survival advantage compared with those without prior BO, which was not fully explained by differences in tumour biology and lead and length time bias. Although the true benefits or harms of BO diagnosis and surveillance cannot be conclusively determined by observational studies, our results indicate that prior identification of BO results in an improvement in survival in those patients who develop OAC.

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Contributors SKB had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: LJM, DTM and BTJ. Acquisition of data: HGC, SKB, DTM, BH, GK and ATG. Analysis and interpretation of data: SKB, HGC, DTM, CRC, FB and LJM. Drafting of the manuscript: SKB and LJM. Critical revision of the manuscript for important intellectual content: HGC, DTM, BTJ, CRC, FB, ATG, SKB and LJM. Statistical analysis: SKB, FB, HGC, DTM and CRC. Study supervision: LJM.

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Ethics approval Research ethics was obtained for the Northern Ireland Barrett's oesophagus register from the Office for Research Ethics Committees (NI). REC number 09/NIR02/53.

Provenance and peer review Not commissioned; externally peer reviewed.

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