ORIGINAL ARTICLE

Surveillance endoscopy is associated with improved outcomes of oesophageal adenocarcinoma detected in patients with Barrett's oesophagus

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ABSTRACT

Background The effectiveness of surveillance endoscopy in patients with Barrett's oesophagus (BE) for reducing oesophageal adenocarcinoma (EAC)-related mortality in patients with BE is unclear.

Methods This is a cohort study of patients with BE diagnosed in the National Veterans Affairs hospitals during 2004–2009 excluding those with conditions that affect overall survival. We identified those diagnosed with EAC after BE diagnosis through 2011 and conducted chart reviews to identify BE surveillance programme, and indication for EAC diagnosis, verify diagnosis, stage, therapy and cause of death. We examined the association between surveillance indication for EAC diagnosis with or without surveillance programme and EAC stage and treatment receipt in logistic regression models, and with time to death or cancer-related death using a Cox proportional hazards regression model.

Results Among 29 536 patients with BE, 424 patients developed EAC during a mean follow-up of 5.0 years. A total of 209 (49.3%) patients with EAC were in BE surveillance programme and were diagnosed as a result of surveillance endoscopy. These patients were more likely to be diagnosed at an early stage (stage 0 or 1: 74.7% vs 56.2, p<0.001), survived longer (median 3.2 vs 2.3 years; p<0.001) and have lower cancer-related mortality (34.0% vs 54.0%, p<0.0001) and had a trend to receive oesophagectomy (51.2% vs 42.3%; p=0.07) than 215 patients diagnosed by non-BE surveillance endoscopy (17.2% of whom were BE surveillance failure). BE surveillance endoscopy was associated with a decreased risk of cancer-related death (HR 0.47, 0.35 to 0.64), which was largely explained by the early stage of EAC at the time of diagnosis. Similarly, the adjusted mortality for patients with cancer in a prior surveillance programme for overall death was 0.63 (0.47 to 0.84) compared with patients with cancer not in a surveillance programme.

Conclusions Surveillance endoscopy among patients with BE is associated with significantly better EAC outcomes including cancer-related mortality compared with other non-surveillance endoscopy.

Significance of this study

What is already known on this subject?
- Practice guidelines recommend endoscopic surveillance among patients with Barrett's oesophagus (BE).
- There are few data from cohort studies on the effectiveness of endoscopy in changes the outcomes of patients with oesophageal adenocarcinoma (EAC) diagnosed in Barrett's.

What are the new findings?
- A total of 424 patients who developed EAC were identified in a large cohort of patients with established BE. Of those, 209 (49.3%) patients were diagnosed as a result of BE surveillance endoscopy.
- These patients were more likely to be diagnosed at an early stage, receive oesophagectomy, survived longer and have lower cancer-related mortality than patients diagnosed by non-BE surveillance endoscopy.
- The reduction in cancer-related death was largely explained by the early stage of EAC at the time of diagnosis.

How might it impact on clinical practice in the foreseeable future?
- The study adds an important piece of evidence in support of the effectiveness of endoscopic surveillance for BE.
- Patients with Barrett's who develop cancer that is detected by surveillance do much better than the rest.

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BACKGROUND

Oesophageal adenocarcinoma (EAC) has been increasing in the USA.[1] EAC is a highly fatal cancer with a median overall survival of <1 year following diagnosis. Barrett's oesophagus (BE) is a clinically detectable precursor lesion that offers an opportunity for early diagnosis of EAC.[2] Practice guidelines recommend periodic endoscopic surveillance among patients with BE to detect early neoplastic changes that are amenable to local ablation and/or resection,[3] or detecting early-stage EAC that can be cured by oesophageal resection[4] with or without neoadjuvant chemoradiotherapy.[5]

There is only modest evidence to support the effectiveness of endoscopic surveillance of BE in

improving EAC-related outcomes including detection of early-stage cancer, receipt of potentially curative treatment or reducing cancer-related mortality. There are no data from clinical trials or large prospective cohort studies examining survival or cancer-related mortality among patients with EAC receiving endoscopic surveillance compared with other strategies for diagnosing EAC (eg, diagnostic endoscopy in symptomatic patients, screening asymptomatic patients with BE).[6]

Two types of studies have evaluated the effectiveness of BE surveillance. First, few retrospective studies of patients diagnosed with EAC reported an increased likelihood of early-stage diagnosis or prolonged survival among patients receiving endoscopic surveillance.[7–9] These studies did not follow a well-defined BE population who were eligible for surveillance, and only a small proportion (~15%) of EAC cases had a documented history of BE before EAC diagnosis. The second type are cohort studies of patients with BE. However, these studies were inadequately powered to confirm the effectiveness of endoscopic surveillance given the low incidence rate of EAC in BE. These studies examined a small number of EAC cases (from 16 to 23) diagnosed during BE surveillance reported trends towards a survival benefit among EAC cases that received prediagnosis surveillance.[10] Further, not all studies have reported a survival benefit with BE surveillance. For example, a recent community-based case–control study concluded that endoscopic surveillance of patients with BE was not associated with a decreased risk of death from EAC.[11]

With the emergence of large integrated electronic medical data repositories, it is possible to address some of the lingering comparative effectiveness questions related to endoscopic surveillance of BE. Our objective is to compare the effectiveness of endoscopic surveillance of BE versus non-surveillance strategies for EAC diagnosis and cancer-related outcomes using the full range of clinical, laboratory and pathology data from the national Veteran Affairs (VA) patient electronic medical record in conjunction with VA administrative data.

METHODS

Data sources

We used the national Veterans Health Administration (VHA) Medical SAS Datasets, which include the Outpatient and Inpatient Files, and pharmacy records and lab results from the VHA Decision Support System. Date of death was obtained from the VA Vital Status file. We used the Compensation and Pension Records Interchange and Veterans Health Information Systems and Technology Architecture, a fully electronic health record for all VHA users nationwide, to abstract information from pathology reports, consult notes, referral requests and reports from radiology, procedures and surgery.

Study population

The study sampling frame consisted of patients with BE who developed oesophageal cancer subsequent to BE diagnosis (figure 1). The BE cohort was defined by the presence of International Classification of Diseases (ICD)-9 code 530.85 combined with an endoscopy within 1 year before or after the date of the first BE code during fiscal year (FY) 2004–2009 (N=40 239). A structured review of medical records of 400 randomly selected BE cases who fulfilled this definition demonstrated a positive predictive value of 93.3% for BE definition in the administrative data. We included only those who were >18 years of age at BE index date and had at least 1 year of follow-up after the index BE endoscopy as well as before their last VA visit or date of oesophageal cancer. We excluded patients with BE with conditions diagnosed within 5 years prior to and up to the BE index date, which may affect the likelihood of developing EAC (previous oesophageal cancer, gastro-oesophageal resection, bariatric surgery) or overall survival and thus the eligibility to receive endoscopic surveillance (any GI cancer, abdominal cancer, decompensated liver disease, metastatic cancer, cancer therapy); see online supplementary appendix for ICD-9 and CPT codes used to identify these conditions.

We identified patients with ICD-9 codes indicative of oesophageal or gastric cancer and performed structured reviews of the electronic medical record to verify EAC diagnosis and to define the cause of death. EAC was distinguished from tumours limited to the stomach including the cardia based on endoscopic reports and when available resection sample reports.

Indication for EAC diagnosing endoscopy

Trained chart abstractors ascertained the indications for EAC diagnosing endoscopy from procedure request, procedure note or progress note for the procedure. The indication for each of these cases was confirmed by a gastroenterologist (HBE-S). We classified the indication for the EAC diagnosing endoscopy into six distinct categories (figure 1). BE endoscopic surveillance was one broad category that included patients who received surveillance endoscopy for non-dysplastic BE or surveillance endoscopy for BE with dysplasia initially detected as a result of BE surveillance. Non-surveillance was the second broad category and consisted of patients whose EAC was initially detected on diagnostic endoscopy, screening endoscopy, unknown indication for endoscopy or surveillance endoscopy for dysplasia originally detected in non-BE surveillance endoscopy. This latter group of patients, while they may gain benefits of surveillance, was not detected though routine BE surveillance, which is performed in non-dysplastic BE. A diagnostic endoscopy was defined by the presence of symptoms suggestive of gastro-oesophageal malignancy such as dysphagia, anaemia, blood loss, weight loss or abnormal oesophageal imaging. A screening endoscopy was defined as an endoscopy performed to detect possible EAC in the setting of chronic GORD or dyspepsia symptoms (without any of the cancer-suggestive symptoms listed earlier). We defined endoscopic surveillance programme as defined by at least one non-diagnostic oesophagogastroduodenoscopy (EGD) in the three years prior to the cancer diagnosis episode, and for those who met this definition we reclassified diagnostic EGD to surveillance; these definitions exclude BE, dysplasia or EAC diagnosing endoscopies. In patients whose EAC was diagnosed following dysplasia, we reclassified those with at least one EGD prior to the dysplasia diagnosis to surveillance programme; this was done to exclude prevalent dysplasia. We estimated surveillance programme failure rate (ie, per cent who are detected because of symptoms despite being in a surveillance programme).

Study outcomes

EAC stage at diagnosis was determined using the electronic medical record by reviewing tumour board reports for American Joint Committee on Cancer staging[5] or, when absent, by examining reports from pathology, endoscopy, imaging (including CT scans, MRI and PET scans, and endoscopic ultrasound) and consultants (surgery, oncology and gastroenterology). EAC treatment included oesophago or oesophagogastrectomy, ablation (mucosal resection, radiofrequency ablation, cryoablation and photodynamic therapy), chemotherapy (cisplatin, 5 fluorouracil, carboplatin, mitomycin, oxaliplatin, paclitaxel, docetaxel, ironectan, epirubicin, capecitabine and etoposide) or radiation. Chemotherapy or radiotherapy was classified as neoadjuvant

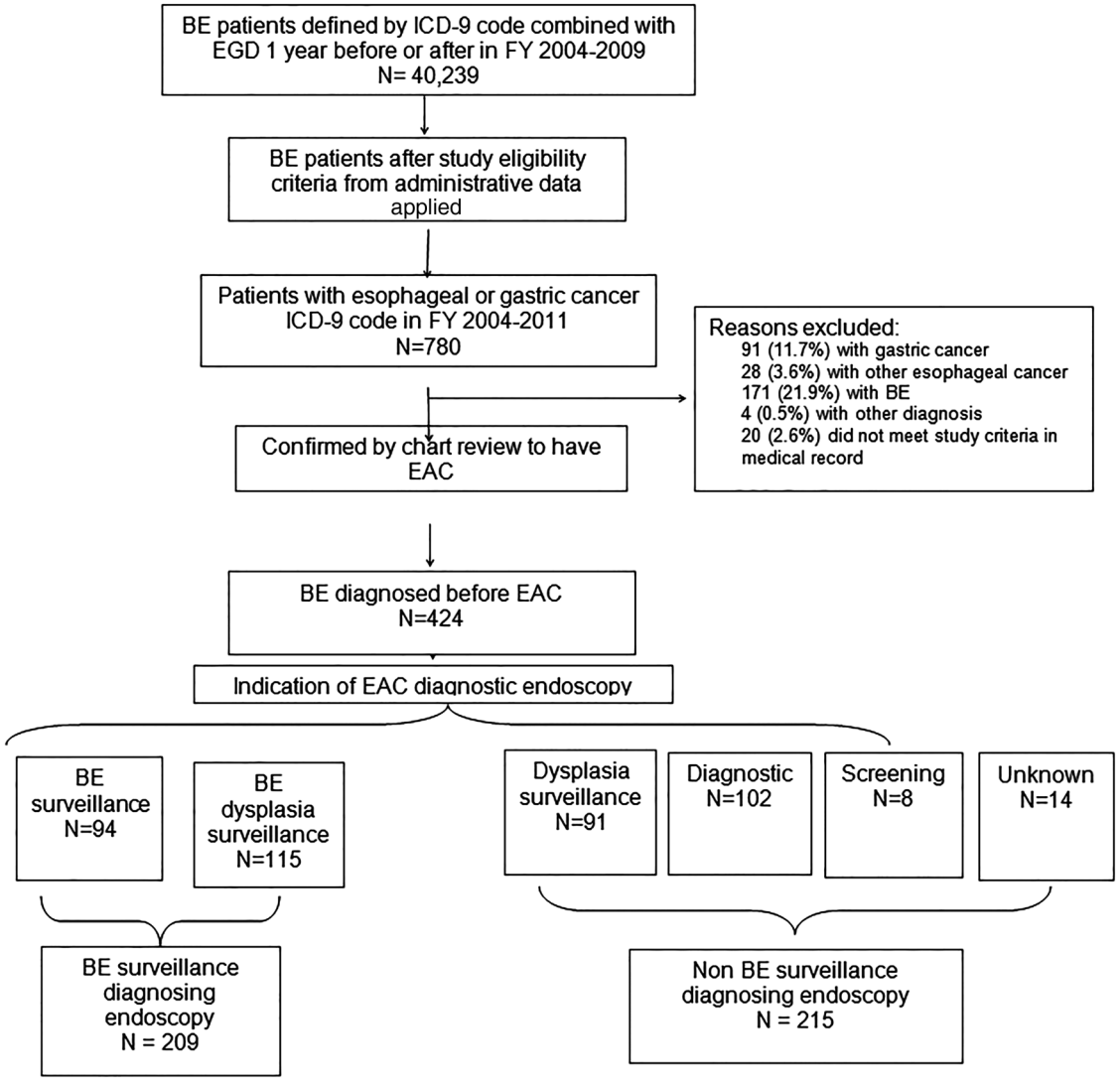

Figure 1 Flow diagram of the study design and inclusion and exclusion criteria. BE, Barrett's oesophagus; EAC, oesophageal adenocarcinoma; EGD, oesophagogastroduodenoscopy; FY, fiscal year; ICD, International Classification of Diseases.

therapy (before oesophagectomy) or adjuvant after oesophagectomy). Death, if any, was identified in medical records and supplemented and verified by the VA Vital Status file. Cause of death was determined by two clinical expert reviewers (HBE-S and MS) blinded to the indication for diagnosis, and defined as EAC-related if caused by local or metastatic complications resulting from the EAC itself or complications from cancer treatment. Survival duration was calculated from the date of EAC diagnosis to the date of death or last contact through the end of the study period, which was 29 March 2013.

Potential confounders and effect modifiers

Several variables were examined as potential confounders. Patient-level variables included age at BE diagnosis, age at EAC diagnosis, race, year of BE diagnosis, year of EAC diagnosis, Deyo comorbidity score, quartile of propensity score to receive endoscopy and number of GI visits between BE and EAC diagnosis. Facility-level variables included endoscopy load per facility and oesophagectomy load per facility during 2004–2010.

Statistical analysis

First, we examined the socio-demographic and clinical features of the patients with EAC stratified by BE surveillance and non-BE surveillance groups. χ^2 tests were used to determine statistical significant differences for categorical variables and t tests for continuous variables. We then compared six subcategories of patients with EAC categorised based on the indication for diagnosing endoscopy with respect to EAC stage and EAC treatment using χ^2 tests and mortality using Cox proportional hazards model.

We evaluated the association between receipt of BE surveillance (compared with all patients diagnosed by non-BE surveillance endoscopy) and the outcomes of early-stage EAC (stage 0 or 1 vs 2, 3, 4 and missing) and receipt of any EAC treatment (surgery, local ablation and/or resection, chemotherapy or radiation) in separate logistic regression models. The cumulative risk of mortality following EAC diagnosis was compared among subgroups of patients with and without BE surveillance in Kaplan–Meier analyses. The association between BE surveillance endoscopy and risk of overall and EAC-related mortality following EAC diagnosis was examined using separate Cox proportional hazards regression models. The demographic and clinical variables listed above were tested as potential confounders. A forward stepwise regression approach was used to reduce the set of predictor variables included in the final models; only predictor variables that remained significant ($p<0.10$) were

retained. Adjusted ORs (or HRs) and their accompanying 95% CIs were estimated in the models.

We examined the possible role of EAC stage as an explanatory variable for the association between BE surveillance and receipt of EAC-specific treatment, as well as the role of EAC stage and treatment as explanatory variables for the association between BE surveillance and time to death and EAC-related death. We included these potential explanatory variables in the respective models and evaluated for an attenuation of the effect of BE surveillance on the outcomes.

We adjusted for estimated lead time in models comparing mortality risk in BE surveillance endoscopy to diagnostic endoscopy. Sojourn time is the time for an undetected cancer to become detected; and estimated in previous studies of oesophageal cancer to be approximately 3 years.[12 13] We assumed an exponential distribution of the sojourn time.[14] The lead time was corrected by subtracting expected additional follow-up time from the observed survival time in the BE surveillance group.

The propensity of the individual patient in the underlying BE cohort (n=29 536) to receive endoscopy before EAC diagnosis was calculated as a score in a logistic regression model taking into consideration the following predictors: year of BE diagnosis, sex, race, age, total VA visits during follow-up, any GI visit in first year after BE diagnosis, rural residence, distance from residence to endoscopy facility, Deyo comorbidity score, GORD, obesity, *Helicobacter pylori*, dysphagia, oesophageal stricture, receiving H2RA or proton pump inhibitor (PPI) and facility characteristics including geographic region, academic affiliation, hospital size and numbers of several endoscopic procedures (endoscopy, oesophagectomy, endoscopic ultrasound) performed in each facility during FY 2004–2010. Only variables with a p<0.10 were retained in the logistic regression model for establishing a propensity score for receiving endoscopy; these variables included year of EAC diagnosis, age, race, propensity for endoscopy, comorbidity score, total number of VA visits and GI clinic visit. The propensity score was classified into quartiles and adjusted for in the analyses of BE surveillance receipt on EAC outcomes (stage, treatment and mortality).

RESULTS

We identified 29 536 patients who met the study eligibility criteria between 1 October 2003 and 30 September 2009 (figure 1). Of these, 780 had an ICD-9 code for any oesophageal or gastric cancer between FY 2004 and 2011, and 424 were verified to have a new diagnosis of EAC after BE diagnosis upon chart review. All 424 had their BE diagnosis verified based on both endoscopic and histological criteria; and most (78%) were reported as long segment BE. Reasons that patients were excluded are listed in figure 1. The mean duration between BE index date and EAC diagnosis date was 5.0 years (SD 4.3). Most (99.8%) EAC cases were men and of white caucasian race (84.9%), and the mean age at EAC diagnosis was 66.9 years (SD 9.2). EAC was diagnosed as stage 0 in 11.8% of cases, stage 1 in 50.0%, stage 2 in 18.9%, stage 3 in 5.0%, stage 4 in 8.9% and missing stage in only 5.4% of cases. Oesophagectomy was performed in 198 (46.7%) cases, adjuvant or neoadjuvant chemotherapy/radiation was received by 47 (11.1%) cases, endoscopic ablation and/or resection was received by 105 (23.1%) and any type of treatment was received by 283 (66.7%) cases. A total of 207 (48.8%) patients died during the study period. The 1-year, 3-year and 5-year observed survival rates were 83.5%, 58.8% and 48.5%, respectively. Approximately 90.3% of total deaths were judged to be EAC related.

A total of 209 (49.3%) patients with EAC were diagnosed as a result of BE surveillance endoscopy, all of whom were in a surveillance programme (94 had a surveillance endoscopy for non-dysplastic BE and 115 had a surveillance endoscopy for dysplastic BE that was originally diagnosed as a result of BE surveillance), while 215 (50.7%) patients with EAC were diagnosed as a result of non-BE surveillance endoscopy (102 on diagnostic endoscopy, 91 on surveillance of BE dysplasia that was originally diagnosed in a non-BE surveillance endoscopy, 8 on screening endoscopy and 14 with unknown indication). Of 215, 37 (17.2%) subjects were in a BE surveillance programme, and thus potentially represent programme failure. There were significant differences in age, PPI and endoscopy receipt between patients with EAC detected by BE surveillance compared with those detected by non-BE surveillance (table 1). However, there were no significant differences in sex, race, GORD diagnosis, comorbidity scores, frequency of endoscopies between BE and EAC, frequency of VA visits, visit to GI clinic or year of EAC diagnosis by mode of BE diagnosis.

Among patients with EAC diagnosed by non-BE surveillance (n=215), those whose endoscopy was performed for surveillance of dysplasia that was originally detected in a non-BE surveillance endoscopy (n=91) had outcomes that were similar to those of the BE surveillance group (n=209) (see online supplementary appendix 2) (p=0.37 for stage, p=0.81 for any treatment and p=0.40 for death). On the other hand, the group diagnosed by diagnostic endoscopy (n=102) had worse outcomes compared with those in the BE surveillance group (n=209) (p<0.0001 for stage, p=0.0001 for treatment and p<0.0001 for survival). Patients diagnosed with EAC by BE surveillance endoscopy (n=209) had the highest proportions of early stage at EAC diagnosis (74.7% vs 56.2%; p<0.001) and receipt of any EAC treatment (72.2% vs 61.4%; p=0.02), receipt of oesophagectomy irrespective of neoadjuvant or adjuvant chemo or radiation (51.2% vs48.8%; p=0.07) as well as the longest overall survival (3.2 median years vs 2.3 years; p<0.001) compared with patients diagnosed with EAC by non-BE surveillance. The 1-year, 3-year and 5-year observed overall mortality of EAC cases detected by BE surveillance endoscopy were 5.3%, 33.2% and 48.8% compared with EAC cases detected by non-surveillance endoscopy (27.4%, 54.7% and 63.8%) (log-rank p<0.0001) (figure 2). The survival advantage was considerably greater when the patients with EAC diagnosed by BE surveillance were compared with EAC cases detected as a result of diagnostic endoscopy (1-year, 3-year and 5-year cumulative mortality: 38.2%, 67.7% and 71.8, p<0.001 for log-rank test). EAC-related deaths were also significantly lower in the BE surveillance group than the non-surveillance group as a whole (34.0% vs 54.0%, p<0.0001 for χ^2 test), and this reduction was considerable when the BE surveillance group was compared with the diagnostic endoscopy group only (34.0% vs 65.7%, p<0.0001).

In multivariable logistic regression analysis, the significant association between EAC diagnosis as a result of BE surveillance endoscopy and early EAC stage persisted in multivariable models adjusting for potential confounders (OR 2.62, 95% CI 1.67 to 4.11) (table 2). Similarly, the association between BE surveillance endoscopy and receipt of any treatment persisted (adjusted OR 1.71, 95% CI 1.11 to 2.63). The receipt of oesophagectomy, irrespective of adjuvant or neoadjuvant therapy, was associated with BE surveillance endoscopy with an adjusted OR of 1.51 (95% CI 1.00 to 2.30), which was attenuated to 1.18 (95% CI 0.76 to 1.85) when adjusting for stage, which indicates that stage explains the association between surveillance

Table 1 Socio-demographic and clinical features of patients with Barrett's oesophagus (BE) diagnosed with oesophageal adenocarcinoma (EAC) stratified based on the indication of the EAC diagnosing endoscopy

	EAC diagnosed by surveillance endoscopy (n=209) n (%)	EAC diagnosed by non-surveillance endoscopy (n=215) n (%)	p Value
Male (%)	208 (99.5)	215 (100.0)	0.49
Race			0.37
White	182 (87.1)	178 (82.8)	
Black	4 (1.9)	8 (3.7)	
Other	23 (11.0)	29 (13.5)	
Age at BE diagnosis in years, mean (SD)	60.6 (9.6)	63.3 (10.0)	0.01
Age at EAC diagnosis in years, mean (SD)	66.0 (9.1)	67.9 (9.4)	0.04
Year of EAC diagnosis			0.41
2004–2006	63 (30.1)	56 (26.1)	
2007–2009	86 (41.2)	102 (47.4)	
2010–2011	60 (28.7)	57 (26.5)	
Number of endoscopies between BE diagnosis and EAC diagnosis, mean (SD)	4.1 (3.6)	3.8 (4.4)	0.34
Number of VA visits between BE and EAC diagnosis (quartile in BE cohort)			0.31
1st quartile (8–36)	18 (8.6)	21 (9.8)	
2nd quartile (37–68)	27 (12.9)	41 (19.0)	
3rd quartile (69–125)	62 (29.7)	61 (28.4)	
4th quartile (126–720)	102 (48.8)	92 (42.8)	
GI visit in the 1st year after BE index date	103 (49.3)	124 (57.7)	0.08
Presence of GORD diagnosis	206 (98.6)	207 (96.3)	0.14
PPI use (between BE and EAC diagnosis)	192 (91.9)	182 (84.7)	0.02
Propensity score to receive any endoscopy after BE diagnosis			0.05
1st quartile (0.06–0.28)	19 (9.1)	28 (13.0)	
2nd quartile (0.29–0.47)	33 (15.8)	49 (22.8)	
3rd quartile (0.48–0.61)	59 (28.2)	63 (29.3)	
4th quartile (0.62–0.87)	98 (46.9)	75 (34.9)	
Comorbidity score at BE diagnosis			0.98
0	98 (46.9)	103 (47.9)	
1	61 (29.2)	62 (28.8)	
2+	50 (23.9)	50 (23.3)	

PPI, proton pump inhibitor; VA, Veteran Affairs.

and treatment. In the multivariate Cox proportional hazards model examining overall and EAC-related mortality risk, the adjusted HR for BE surveillance endoscopy remained significant (HR 0.49, 95% CI 0.37 to 0.66). The latter association was also mostly explained by adjusting for early EAC stage and receipt of EAC treatment (including ablation or resection, surgery, adjuvant and neoadjuvant therapy) in the multivariable model, which reduced the HR to 0.73 (95% CI 0.52 to 1.01) (table 3). In the multivariate Cox PH model examining time to cancer-related death, the adjusted HR for BE surveillance endoscopy persisted in significance (HR 0.47, 95% CI 0.35 to 0.64). The latter association was also mostly explained by early EAC stage and receipt of therapy; adjusting for these two variables in the multivariable model changed the HR to 0.72 (95% CI 0.51 to 1.01). In multivariable analysis examining the effect of surveillance programme, irrespective of the purpose of the EAC diagnosing endoscopy and thus including possible surveillance programme failures, the adjusted HR for overall death was 0.63 (0.47 to 0.84) and when adjusted for stage and treatment was 0.89 (0.65 to 1.22); thus, early-stage and increased receipt of treatment seem to account for almost all of the observed benefits of surveillance on mortality (table 4). Similarly, the adjusted HR for EAC-related death without adjusting for stage or treatment was 0.60 (0.45 to 0.82).

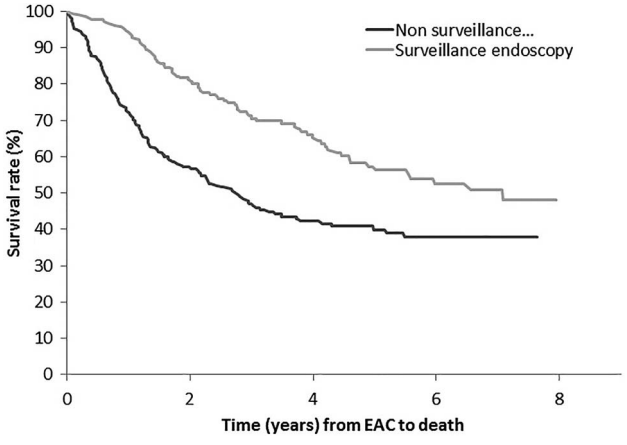

Figure 2 Kaplan–Meier curves showing cumulative mortality among patients with Barrett's oesophagus (BE) and newly diagnosed oesophageal adenocarcinoma (EAC) stratified by the type of cancer diagnosing endoscopy (BE surveillance programme vs. non-BE surveillance). p Value from log-rank test <0.001.

The outcomes of patients with EAC diagnosed with BE surveillance endoscopy were significantly better than those diagnosed with cancer-related signs and symptoms (table 5).

Table 2 Multivariate models predicting the early stage, treatment receipt and mortality in patients diagnosed with oesophageal adenocarcinoma (EAC) in the Veterans Health Administration

	Early stage* OR (95% CI)	Treatment† OR (95% CI)	Overall mortality HR (95% CI)
BE surveillance programme			
No	Ref.	Ref.	Ref.
Yes	2.62 (1.67 to 4.11)	1.71 (1.11 to 2.63)	0.49 (0.37 to 0.66)
BE fiscal year			
2004	Ref.	Ref.	–‡
2005	1.70 (0.88 to 3.31)	1.65 (0.89 to 3.09)	–
2006	1.05 (0.49 to 2.25)	2.20 (1.04 to 4.65)	–
2007	1.15 (0.49 to 2.71)	3.81 (1.53 to 9.46)	–
2008	1.68 (0.59 to 4.78)	3.39 (1.20 to 9.61)	–
2009	2.80 (0.55 to 14.33)	4.36 (0.88 to 21.49)	–
Age at EAC diagnosis			
<60	Ref.	Ref.	Ref.
60–64	0.82 (0.46 to 1.48)	1.30 (0.71 to 2.37)	0.93 (0.59 to 1.46)
65–69	1.13 (0.60 to 2.13)	0.75 (0.41 to 1.34)	1.22 (0.77 to 1.92)
70+	0.90 (0.49 to 1.67)	0.98 (0.54 to 1.77)	1.70 (1.17 to 2.46)
Race			
White	Ref.	Ref.	Ref.
Black	0.69 (0.20 to 2.41)	1.94 (0.49 to 7.65)	1.00 (0.46 to 2.22)
Other	1.68 (0.81 to 3.46)	1.16 (0.60 to 2.24)	0.64 (0.39 to 1.03)
Propensity score (quartiles)			
1	Ref.	Ref.	Ref.
2	1.34 (0.38 to 4.69)	0.98 (0.28 to 3.39)	1.77 (0.99 to 3.16)
3	1.61 (0.41 to 6.35)	1.47 (0.38 to 5.71)	2.33 (1.25 to 4.34)
4	1.72 (0.41 to 7.29)	2.48 (0.59 to 10.42)	1.78 (0.89 to 3.58)
PPI			
No	Ref.	Ref.	–
Yes	0.29 (0.13 to 0.67)	0.45 (0.21 to 0.96)	–
GI visit			
No	Ref.	–	Ref.
Yes	1.52 (0.98 to 2.37)	–	1.25 (0.93 to 1.67)
Comorbidity score at BE diagnosis			
0	–	–	Ref.
1	–	–	1.46 (1.04 to 2.06)
2+	–	–	2.06 (1.42 to 2.99)
Number of VA visits between BE and EAC diagnosis			
1st quartile (8–36)	–	–	Ref.
2nd quartile (37–68)	–	–	0.64 (0.34 to 1.20)
3rd quartile (69–125)	–	–	0.41 (0.21 to 0.79)
4th quartile (126–720)	–	–	0.46 (0.23 to 0.92)
Year of EAC diagnosis			
2004–2006	–	–	Ref.
2007–2009	–	–	1.33 (0.94 to 1.88)
2010–2011	–	–	1.71 (1.14 to 2.55)

Full models were adjusted for the variables indicated for each outcome.
*Early stage: 0 and 1 vs 2, 3, 4 and missing.
†Any treatment: surgery, endoscopic ablation/or resection, chemotherapy or radiation versus no treatment.
‡All variables with '–' were not included in multivariable model due to exclusion by stepwise regression.
BE, Barrett's oesophagus; PPI, proton pump inhibitor; VA, Veteran Affairs.

The adjusted OR for early stage was high (OR 6.03, 95% CI 3.40 to 10.72) when comparing patients with BE surveillance endoscopy to those with diagnostic endoscopy. The adjusted OR for receiving EAC treatment was 2.70 (95% CI 1.60 to 4.56) and was almost completely explained by EAC stage (OR adjusted for stage 1.11; 95% CI 0.56 to 2.18). The adjusted overall mortality risk in patients with BE surveillance was 0.28 (95% CI 0.20 to 0.40) compared with diagnostic endoscopy and was partly explained by differences in stage and treatment (HR adjusted for stage and treatment 0.62, 95% CI 0.40 to 0.97). Accounting for lead time in this comparison attenuated the association somewhat, although it remained significant (HR 0.53, 95% CI 0.37 to 0.76) and was mostly explained by stage and treatment (HR adjusted for stage and treatment, 95% CI 0.81 to 2.06). Results for EAC-related mortality were similar to those for overall mortality (table 5).

DISCUSSION

In a cohort of patients with BE, we found those who were diagnosed with EAC while in a BE surveillance programme had

Table 3 Effect of surveillance diagnosing endoscopy on mortality risk of patients with Barrett's oesophagus and newly diagnosed oesophageal adenocarcinoma (EAC)

	HR	95% CI
BE surveillance diagnosing EGD vs non-surveillance		
All EAC cases (n=207/424; 81/209 surveillance and 126/215 non-surveillance)		
Unadjusted	0.52	0.39 to 0.69
Adjusted* (without stage or treatment)	0.49	0.37 to 0.66
Adjusted (including stage)	0.76	0.55 to 1.06
Adjusted (including stage and treatment)	0.73	0.52 to 1.01
EAC-related mortality (n=187/424; 71/209 surveillance and 116/215 non-surveillance)		
Unadjusted	0.50	0.37 to 0.67
Adjusted* (without stage or treatment)	0.47	0.35 to 0.64
Adjusted (including stage)	0.75	0.53 to 1.05
Adjusted (including stage and treatment)	0.72	0.51 to 1.01

*Adjusted for year of EAC diagnosis, age, race, propensity of EGD, comorbidity score, total number of VA visit and GI clinic visit.
EGD, oesophagogastroduodenoscopy; VA, Veteran Affairs.

considerably better outcomes than those diagnosed outside of a surveillance programme, and dramatically better than patients receiving a diagnostic endoscopy for cancer-related symptoms. The improved outcomes with BE surveillance endoscopy included a significantly higher proportion of patients with EAC who were diagnosed with early-stage tumours, received cancer-directed treatment and had significantly longer overall survival as well as lower EAC-related mortality. These findings persisted when adjusting for several demographic and clinical factors as well as multiple sources of potential bias including healthy volunteer bias and lead time bias. The prolonged survival and reduced EAC-related mortality outcomes were primarily accounted for by an increased detection of early-stage cancer combined with receipt of EAC treatment.

This is the largest study of incident EAC diagnosed in a BE cohort, and the only one that examined the comparative effectiveness of BE surveillance endoscopy relative to other confirmed endoscopy indications, and to examine surveillance indication

Table 4 Effect of surveillance programme (irrespective of the purpose of the cancer diagnosing EGD) on mortality risk of patients with Barrett's oesophagus and newly diagnosed oesophageal adenocarcinoma (EAC)

	HR	95% CI
BE surveillance programme versus non-surveillance		
All EAC cases (n=207/424; 106/246 surveillance and 101/178 non-surveillance)		
Unadjusted	0.65	0.49 to 0.85
Adjusted* (without stage or treatment)	0.63	0.47 to 0.84
Adjusted (including stage)	0.90	0.66 to 1.22
Adjusted (including stage and treatment)	0.89	0.65 to 1.22
EAC-related mortality (n=187/424; 94/246 surveillance and 93/178 non-surveillance)		
Unadjusted	0.63	0.47 to 0.84
Adjusted* (without stage or treatment)	0.60	0.45 to 0.82
Adjusted (including stage)	0.87	0.63 to 1.21
Adjusted (including stage and treatment)	0.87	0.63 to 1.20

*Adjusted for year of EAC diagnosis, age, race, propensity of EGD, comorbidity score, total number of VA visit, GI clinic visit.
EGD, oesophagogastroduodenoscopy; VA, Veteran Affairs.

Table 5 Effect of surveillance endoscopy on stage, treatment, survival and cancer-related mortality in patients with Barrett's oesophagus and newly diagnosed oesophageal adenocarcinoma (EAC), compared with EAC detected by *diagnostic endoscopy* in symptomatic patients

	OR/HR*	95% CI
Early stage (n=148/198 surveillance and 36/97 diagnostic)		
Unadjusted	5.02	2.98 to 8.45
Adjusted† (without treatment)	6.03	3.40 to 10.72
Receipt of any treatment (n=151/209 surveillance and 51/102 diagnostic)		
Unadjusted	2.60	1.59 to 4.26
Adjusted† (without stage)	2.70	1.60 to 4.56
Adjusted with stage	1.11	0.56 to 2.18
Overall mortality (n=81/209 surveillance and 73/102 diagnostic)		
Unadjusted	0.33	0.24 to 0.46
Adjusted† (without stage or treatment)	0.28	0.20 to 0.40
Adjusted (including stage)	0.64	0.41 to 0.99
Adjusted (including stage and treatment)	0.62	0.40 to 0.97
Overall mortality corrected for lead time (n=81/209 surveillance and 73/102 diagnostic)		
Unadjusted	0.54	0.39 to 0.74
Adjusted† (without stage or treatment)	0.53	0.37 to 0.76
Adjusted (including stage and treatment)	1.29	0.81 to 2.06
EAC-related mortality (n=71/209 surveillance and 67/102 diagnostic)		
Unadjusted	0.32	0.23 to 0.45
Adjusted† (without stage or treatment)	0.28	0.20 to 0.41
Adjusted (including stage and treatment)	0.63	0.39 to 1.00
EAC-related mortality corrected for lead time (71/209 surveillance and 67/102 diagnostic)		
Unadjusted	0.51	0.37 to 0.71
Adjusted† (without stage or treatment)	0.52	0.36 to 0.75
Adjusted (including stage and treatment)	1.27	0.78 to 2.07

*HRs were used for all mortality-related outcomes. ORs were used for remaining outcomes.
†Adjusted for year of EAC diagnosis, age, race, propensity of EGD, comorbidity score, total number of VA visit and GI clinic visit.
EGD, oesophagogastroduodenoscopy; VA, Veteran Affairs.

of the EAC diagnosing endoscopy rather than pre-diagnosis surveillance patterns. For example, a recent study from Kaiser Permanente did not compare patients whose EAC was detected during BE surveillance to those with EAC detected during non-surveillance endoscopy; rather, they compared 39 deceased patients with EAC to 101 living controls with BE.[11] Due to limited power, the results could not detect a small to moderate benefit for surveillance as evidenced by the lower bound of the 95% CI (0.99; 0.36 to 2.75). Our study combined the large sample size of automated VA national data sets coupled with structured electronic chart reviews for several key variables including the indication of the EAC diagnosing endoscopy, EAC diagnosis, stage, receipt of treatment and cause of death. These are key strengths that set our study apart from previous ones and further confirm the importance of pre-cancer BE diagnosis as a marker of improved survival.[15] Further, while the proportion receiving treatment was low, this is not much different from what was reported in non-VA studies.[16 17]

We made several exclusions that may limit the generalisability of the findings to all patients with BE, but these exclusions were intended to create a study sample that is fairly representative of the BE population that is eligible for endoscopic surveillance.[18] Moreover, patients with BE were not 'healthy otherwise'; approximately 53% had a Deyo comorbidity index score ≥1,

indicating a higher likelihood of death. We do not believe that BE surveillance would be effective or should be practised among patients with a short life expectancy and/or major comorbidities. Some information loss may have happened for patients who received care outside the VA; however, our inclusion criteria combined with chart reviews have minimised this effect.

We considered the main threats to the validity of an observational study of cancer surveillance effectiveness; these included healthy volunteer bias, length bias and lead time bias.[19] We limited our sampling frame to patients with known BE who were devoid of major comorbidities. We also adjusted for a variety of demographic and clinical features including a validated disease comorbidity score, but the effect of endoscopic surveillance remained significant. Beyond concrete demographic or clinical features, some patients are more likely to receive endoscopy for other reasons (eg, requesting endoscopy, complaining of more frequent/severe symptoms and physicians at some facilities performing more endoscopies). Therefore, we constructed and subsequently adjusted for propensity score; this adjustment also did not affect the observed association. Lastly, the fact that most differences in survival between those who received or did not receive surveillance were accounted for by adjusting for stage and treatment argues against a large effect for healthy patient bias.

We analysed data for all tumours that were diagnosed after BE diagnosis, and we further adjusted for the calendar year of BE diagnosis. The BE surveillance endoscopy benefit was observed independent of the year of BE diagnosis, thus reducing the likelihood that length bias had a large role in explaining the results.

For lead time bias, we adjusted for the sojourn time, previously estimated to be approximately 3 years,[12 13] and found a persisting significant effect when surveillance is compared with diagnostic endoscopy. We also hypothesised, and our analytic technique has demonstrated, that any improvement in survival would be mediated by detection of early-stage tumour and subsequent application of curative therapy. This observation argues against selection bias as the main reason for differences in survival. Lastly, we measured cancer-related mortality rates, which are the 'gold standard' for measuring the effect of early screening and treatment.

The findings show favourable comparative effectiveness of surveillance endoscopy among patients who developed EAC and even more benefit among those who were as apart of successful programme (ie, EAC diagnosis was a result of surveillance). However, residual confounding in the overall mortality analyses was possible. We did not examine the possible harms, costs or cost effectiveness of surveillance endoscopy among all patients with BE.[20 21] Nevertheless, we believe that proving effectiveness is an essential building block in the debate around BE endoscopic surveillance. The effect of endoscopic ablation using radiofrequency and/or endoscopic mucosal resection,[22] both of which are recent advances,[18 20] may not have been adequately examined in our study period. Endoscopic ablation is now frequently used for and preferred by patients with BE with[23 24] precancerous low-grade and high-grade dysplasia where it successfully prevents the development of EAC.[25] Lastly, we did not examine the use of medications such as statins that could influence post-EAC diagnosis survival.[26]

In summary, EACs detected among patients in a BE surveillance programme were associated with improved survival compared with symptom-detected EACs. This demonstrated effectiveness was higher compared with patients with EAC diagnosed by endoscopy for cancer-related symptoms and was mostly related to higher detection of early-stage EAC and increased receipt of EAC treatment. These results support further evaluations regarding whether surveillance is associated with a net survival benefit among all patients with BE and on improving surveillance tools.[27]

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Appendix 1.

Variable	ICD9 Code or CPT Code
Barrett's esophagus	530.85
Esophageal adenocarcinoma	150.0-150.5, 150.8-150.9, 230.1, V100.3
Gastrointestinal cancers	151.0-151.6, 151.8-151.9, 152.0-152.3, 152.8, 152.9, 159.9, 209.00-209.03, 209.23, 230.2, 230.7,
Other abdominal cancer	156.0-156.2. 156.8, 156.9, 158.0, 158.8, 158.9, 159.1, 159.8
Other malignancy	140.0-149.9, 1510-1729, 174.0-195.9, 200.00-208.99, 209.00-209.39, 230.0-234.9, 258.02-258.03, 795.0-795.13, 796.70-796.76
Metastatic cancer	196.0-196.3, 196.5, 196.6, 196.8-197.8, 198.0-198.7, 198.81, 198.82, 198.89, 209.71-209.74, 511.81, 789.51
Decompensated liver disease	155.0, 348.3, 348.30-348.31, 348.39, 456.0-456.2, 572.2-572.4, 572.8, 789.5, 570.0; 573.4
Bleeding gastroesophageal varices	42.91
Gastroesophageal surgery	42.01, 42.09-42.12, 42.19, 42.21, 42.22, 42.25, 42.29, 42.31, 42.32, 42.39-42.42, 42.51-42.56, 42.58, 42.59, 42.61-42.66, 42.68-42.70, 42.82-42.87,42.89, 42.99, 43.00, 43.3, 43.42, 43.49, 44.0-44.03, 44.2, 44.21, 44.29, 44.31, 44.39-44.42, 44.5, 44.61, 44.63-44.67, 44.69, 44.91, 44.92, 44.99, 45.30, 50.0, 50.14, 50.21-50.26,50.29, 50.3, 50.4 50.91-50.94, 50.99, 51.01-51.04, 51.13, 51.19, 51.31-51.37, 51.39, 51.61-51.64,51.69, 51.71, 51.72, 51.79, 51.81-51.89, 51.91-51.96, 51.98, 51.99, 52.01, 52.09, 52.11, 52.12,52.20- 52.22, 52.30, 52.40, 52.51-52.53, 52.59, 52.60, 52.70, 52.92, 52,95, 52.96, 52.99, 54.12, 54.19, 54.23-54.25, 54.29, 54.40, 54.61, 54.62, 54.64, 54.73-54.75, 54.92-54.97, 54.99, 96.08, 96.24, 96.27, 96.28, 96.36, 96.41-96.43, 97.05, 97.54-97.56, 97.59, 97.82, 97.86, 176.3
Bariatric surgery	44.68, 44.38, 44.95-44.98
GE resection	43.5-43.7, 43.81, 43.89, 43.91, 43.99, 45.61 (43620-43634, 43638-43639)
Percutaneous gastric tube	431.0, 431.1, 431.9, 432.0, 443.2 (43246, 43653, 43750, 43760, 43830-43832, 44373, 49440, 49450, 49452, 56346)

Appendix 2. The distribution of EAC stage, treatment and overall mortality following diagnosis among EAC cases diagnosed in BE patients categorized by 6 indications for the diagnosing endoscopy.

	BE Surveillance			Non-BE Surveillance				
	Total (n=209)	BE Surveillance (n=94)	BE Dysplasia Surveillance (n=115)	Total (n=215)	Diagnostic (n=102)	Dysplasia Surveillance (n=91)	Screening (n=8)	Unknown indication (n=14)
EAC Treatment*								
None	58 (27.7)	26 (27.7)	32 (27.8)	83 (38.6)	51 (50.0)	24 (26.4)	3 (37.5)	5 (35.7)
Any cancer targeted treatment	151 (72.3)	68 (72.3))	83 (72.2)	132 (61.4)	51 (50.0)	67 (73.6)	5 (62.5)	9 (64.3)
EAC Stage[±]								
0	29 (13.9)	7 (7.5)	22 (19.1)	21 (9.8)	4 (3.9)	15 (16.5)	0 (0.0)	2 (14.3)
1	119 (56.9)	53 (56.4)	66 (57.4)	93 (43.2)	32 (31.4)	54 (59.3)	4 (50.0)	3 (21.4)
2	44 (21.1)	24 (25.5)	20 (17.4)	36 (16.7)	17 (16.7)	13 (14.3)	3 (37.5)	3 (21.4)
3	3 (1.4)	2 (2.0)	1 (0.9)	18 (8.4)	15 (14.7)	1 (1.1)	1 (12.5)	1 (7.2)
4	3 (1.4)	1 (1.1)	2 (1.7)	35 (16.3)	29 (28.4)	4 (4.4)	0 (0.0)	2 (14.3)
Missing	11 (5.3)	7 (7.5)	4 (3.5)	12 (5.6)	5 (4.9)	4 (4.4)	0 (0.0)	3 (21.4)
Overall Mortality[†]								
n (%)	81 (38.8)	33 (35.1)	48 (41.7)	126 (58.6)	73 (71.6)	40 (44.0)	5 (62.5)	8 (57.1)

*p=0.02 for BE surveillance vs. non-BE surveillance groups

[±] p<0.0001 for BE surveillance vs. non-BE surveillance groups for early (0-1) vs. other stages[†]p<0.0001 for BE surveillance vs. non-BE surveillance groups