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Adherence to recommendations of Barrett's esophagus surveillance guidelines: a systematic review and meta-analysis

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ABSTRACT

Background Guidelines aim to reduce treatment variation and improve quality of care. In the literature there is large variation in the reported rates of adherence to recommendations of surveillance for Barrett's esophagus (BE). The aim of this systematic review was to identify explanatory parameters determining these differences in adherence rates.

Methods Embase, Medline Epub, and Web of Science were searched. Studies reporting adherence in at least one of five domains were selected: general domain, surveillance interval, biopsy protocol, landmark identification, and histopathological information. Adherence was expressed as the proportion of endoscopies or endoscopists being in accordance with guideline recommendations. Variation in adherence was evaluated by 1) meta-regression of adherence rates in random effects meta-analysis to define subgroups, and 2) compiling an overview of the most reported explanatory parameters for (non)adherence.

Results 56 studies, including 14 002 BE patients and 4932 endoscopists, were included. Subgroup analysis showed that variation in rates of adherences to surveillance interval recommendations (I^2 = 98 % – 99 %) was explained by difference in country (43 %), by practice type (90 %), and by year of publication (11 %). Variation in adherence to the Seattle protocol was explained by difference in country (14 %). Factors most frequently reported to be associated with better adherence were shorter BE length, salaried employment, surveillance in university hospitals, and dedicated programs.

Conclusions This study provides insight into the variability of rates of adherence to BE surveillance recommendations between studies. Better adherence in university hospitals and dedicated programs indicate that persistent alertness of guidelines is important.

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Introduction

Barrett's esophagus (BE) is a premalignant condition of esophageal adenocarcinoma (EAC), and is associated with gastroesophageal reflux disease. The incidence of EAC has been rising over past decades. In the advanced stage, morbidity and mortality of EAC are high, with a dismal prognosis [1]. Surveillance was introduced to detect early signs of neoplastic progression. Studies have shown repeatedly that BE patients participating in a surveillance program had EAC detected at an earlier stage compared with sporadic (symptomatic) EAC patients [2]. In addition to a better prospect of survival, early detection also offers the possibility to apply minimally invasive treatment, such as endoscopic eradication therapy, in selected cases. The generally accepted recommendation for patients with BE is to undergo regular endoscopic follow-up with biopsies according to the Seattle protocol.

In general, guidelines aim to reduce treatment variation and improve quality of care [3–6]. Adherence to guideline recommendations for surveillance of BE has been shown to be low, with varying consequences [7]. In particular, if impaired cost-effectiveness of surveillance due to shorter surveillance intervals is accompanied by lower detection of dysplasia because of nonadherence to the Seattle protocol and the Prague classification, the healthcare burden of surveillance of BE patients is disproportionate [8]. This may result in increased costs for society and poorer detection of early neoplastic progression in BE patients [9].

The key question is, Why is the gap between guideline recommendations and practice patterns so substantial in studies? As well as low rates of adherence to guideline recommendations, high adherence rates have also been reported [10]. Sources of this between-study variance are unclear. Explanatory factors for adherence may also explain this heterogeneity in adherence rates between studies. Insight into the reason(s) behind adherence may identify areas for improvement.

In this systematic review and meta-analysis we aimed to identify explanatory parameters of (non)adherence by exploring the sources of variation between studies and determining risk factors for (non)adherence as reported in the literature.

Methods

This systematic literature review and meta-analysis was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

Search strategy

An electronic search in Embase, Medline Epub (Ovid), and Web of Science was performed without restrictions in date or language on 3 July 2017. The search strategy included the terms relating to Barrett's esophagus, adherence to the guideline, and surveillance (see **Table 1s** in the online-only supplementary material). Bibliographies of full-text articles assessed for eligibility were handsearched.

Study selection

Five domains within BE surveillance were defined, based on guidelines: general domain, surveillance interval, biopsy protocol, landmark identification, and histopathological information. Within these domains, 19 single guideline recommendations were selected (▶ **Table 1**). The recommended surveillance interval, Seattle protocol, and Prague classification were assigned as primary recommendations because of the expected importance in BE surveillance. Adherence to all of these recommendations was estimated. To estimate adherence to the Prague classification, only studies conducted after 2006 were included, as this was the year of publication of this classification [11].

Studies reporting adherence to at least one of the 19 recommendations were selected. Studies conducted in the setting of a hospital, freestanding or open-access endoscopy center, or based on the registry of members of a gastroenterological association, were assessed for inclusion. Participants in these studies had to be adults with known BE, with or without histological confirmation, who were enrolled in a surveillance program, or endoscopists performing BE surveillance. No minimum number of participants or duration of follow-up was set for studies to be considered for inclusion. Types of studies eligible for this review were cross-sectional, retrospective, and prospective cohort studies. Conference abstracts were included only if the data were not published in peer-reviewed full-text format.

Studies of patients who had already reached the end point of high grade dysplasia, EAC, or who had undergone previous endoscopic therapy were excluded. If studies only focused on the effect of an intervention to improve adherence, such as a dedicated surveillance program, they were included if baseline data were available in the same or previously published article or abstract.

Records identified by this search strategy were initially screened, after deduplication, on title and abstract by one author (C.A.M.R.), and relevant full-text articles were then selected. A second author (R.D.vdB) reviewed this process. In cases of disagreement, a third independent author (M.C.W.S.) was consulted. All reviewers were working in the field of gastroenterology in both clinical practice and research. The deduplication and management of records was performed using EndNote X7.5 reference manager (Thomson Reuters).

Data extraction and synthesis

The extraction form used to collect the study data was based on the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) statement.

The primary outcome was the variability between studies explained by a specific subgroup, expressed as R^2. This represents the variance in adherence rates, as explained for example by difference in type of practice between studies, expressed as a percentage. To be able to determine this between-study variance, we extracted data concerning adherence to guideline recommendations in individual studies. We defined adherence as a proportion of the number of adherent participants divided by the total number of participants. As subjects could be either

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▶ **Table 1** Guideline recommendations and associated patient, endoscopist, and facility variables, as scored for adherence in this systematic review and meta-analysis.

Domain	Recommendation in the guideline
General	Performance of any form of surveillance
	Total adherence to the guideline
Surveillance interval	Surveillance interval in general*
	Surveillance interval in patients without dysplasia (NDBE)*
	Surveillance interval in patients with low grade dysplasia*
Biopsy protocol	Seattle protocol*
	Use of advanced imaging/high definition/high resolution white-light endoscopy
Landmark identification	Report of indication of endoscopy
	Report of level of squamocolumnar junction
	Report of level of gastroesophageal junction
	Report of level of diaphragm impression
	Report of presence of hiatal hernia
	Report of length of BE using Prague criteria*
	Report of length of BE in general
	Report of presence of inflammation
	Report of presence of visible abnormalities
Histopathological information	Report of presence of intestinal metaplasia
	Report of presence of dysplasia
	Review of second pathologist in cases of suspected dysplasia
Field of association	**Factors of potential association with adherence**
Patient variables	Age
	Sex
	Ethnicity
	Length of BE
Endoscopist variables	Age
	Sex
	Years in practice
	Number of EGDs per week or month
	Reimbursement
	Belief in efficacy
	Surgeon or physician
	Awareness of the guideline
	Agreement with the guideline
Facility variables	Type of practice
Other	Effect of intervention to improve adherence

NDBE, nondysplastic Barrett's esophagus; BE, Barrett's esophagus; EGD, esophagogastroduodenoscopy.
* Primary recommendations of the guideline.

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patients with BE in a study based on data retrieved from endoscopy and pathology reports, or endoscopists in a questionnaire-based study, we referred to them as participants. If only the practice pattern was reported (e. g. the number of endoscopies with an interval of 3 years in nondysplastic patients, rather than the number of adherent endoscopies), these results were compared with the guideline as mentioned in the article. If no guideline was mentioned, recommendations of the most recently issued guideline at the time and location of that publication were used to determine the proportion of adherence [3 – 5, 12 – 29]. In the United States, where multiple guidelines exist, such cases (i. e. only the practice pattern was reported in a study from the USA, but no guideline mentioned), the guideline of the American College of Gastroenterology was used.

The secondary outcome was to search for associations between adherence rates and explanatory parameters that had already been determined in the studies, with regard to patient, endoscopist, or facility variables. The direction of the association (increased or decreased probability of adherence), and the presence or absence of its statistical significance, were extracted.

Quality assessment

Publication bias was assessed separately for each recommendation by funnel plots. In the process of methodological quality assessment of the risk of bias in individual studies, another tool was used for each outcome.

Because adherence to the guideline recommendations was considered a proportion, the methodological quality of studies was evaluated using the Loney Scoring Tool, adjusted to our systematic review. Studies estimating prevalence or incidence of a certain condition can be scored in this tool at a scale from 0 (worst score) to 8 (best score). A score of ≥ 5 was considered good quality.

The quality of methods for associated factors was assessed using the Quality In Prognosis Studies tool (QUIPS) [30]. Each aspect could be scored as low, moderate, or high risk of bias.

Statistical analysis

In order to calculate between-study variance, first the proportions of adherence of individual studies were pooled in a random effects meta-analysis with a log odds transformation to stabilize data. In cases where the proportion of adherence was zero, a continuity correction was applied. This pooled estimate and 95 % confidence interval (CI) was interpreted as the proportion of adherent participants. Heterogeneity was estimated using Cochran's test (Q statistic) and I^2 statistic with a threshold value of 25 %, 50 %, and 75 % for low, moderate, and high, respectively [31]. Only adherence reported as a proportion with absolute numbers could be used in the meta-analysis. Next, for primary recommendations (surveillance interval, Seattle protocol, Prague classification), possible sources of heterogeneity were investigated in a subgroup analysis. We used univariate meta-regression analysis. Prespecified variables that were tested were year of publication and country; post hoc we added type of practice and data collection (i. e. either self-reported surveys or data retrieved from endoscopy and/or pathology reports). In the subgroup type of practice, Veterans Affairs medical facilities were considered as community hospitals, and BE centers and teaching hospitals were considered as university hospitals. The difference between subgroups was reported as an odds ratio (OR). The variability between studies explained by these subgroups was expressed using R^2.

In addition to using the exploration of between-study variance as a potential source of parameters explaining (non)adherence, the associations between adherence rates and explanatory parameters that had already been determined in the included studies were evaluated. Only those explanatory parameters that determined adherence rates to at least two primary recommendations (surveillance interval, Seattle protocol, Prague classification) were plotted separately in a figure. Meta-analysis was not possible because of the limited number of studies per association. If statistical significance was not reported in the studies, the chi-squared test with continuity correction was used where possible to calculate statistical significance of the association.

Statistical calculations were done using R, version 3.4.1 (R Foundation for Statistical Computing, Vienna, Austria; www.R-project.org), using the metafor package for meta-analysis. P values of <0.05 were considered statistically significant.

Sensitivity analysis

Outliers were identified based on a plot of influence diagnostics outliers. Sensitivity analyses by excluding these studies showed the difference compared with the original results. In addition, the effect of excluding studies with a score of methodological quality ≤ 5 was evaluated.

Results

Study selection and characteristics

Initially 684 records were identified. After deduplication, 475 were screened on title and abstract. Out of 86 articles assessed for eligibility, 60 articles containing 56 studies were included for qualitative and 49 articles containing 45 studies for quantitative analyses. In some articles, the same study was conducted with a different sample size, which explains the difference in number of articles and studies included (▶ **Fig. 1**).

The 56 studies (**Table 2s**) could be subdivided into four categories based on type of participants and methods used. In 19 cross-sectional studies, gastroenterologists and surgeons practicing surveillance were surveyed by a questionnaire to determine their practice patterns and factors influencing adherence. In 26 retrospective cohort studies (17 single-center and nine multicenter studies), endoscopy and pathology reports of BE patients under surveillance were reviewed. In six prospective studies, the effect of an intervention to improve adherence rates was evaluated. The other five studies were a combination of the previously mentioned, or other designs.

Of all studies included, the setting was reported as follows: 9 community hospitals and 16 university hospitals; 20 studies reported data collection from a combination of these types of centers, and in 11 studies the type of practice was unclear. The earliest study was published in 1997, the most recent in 2017.

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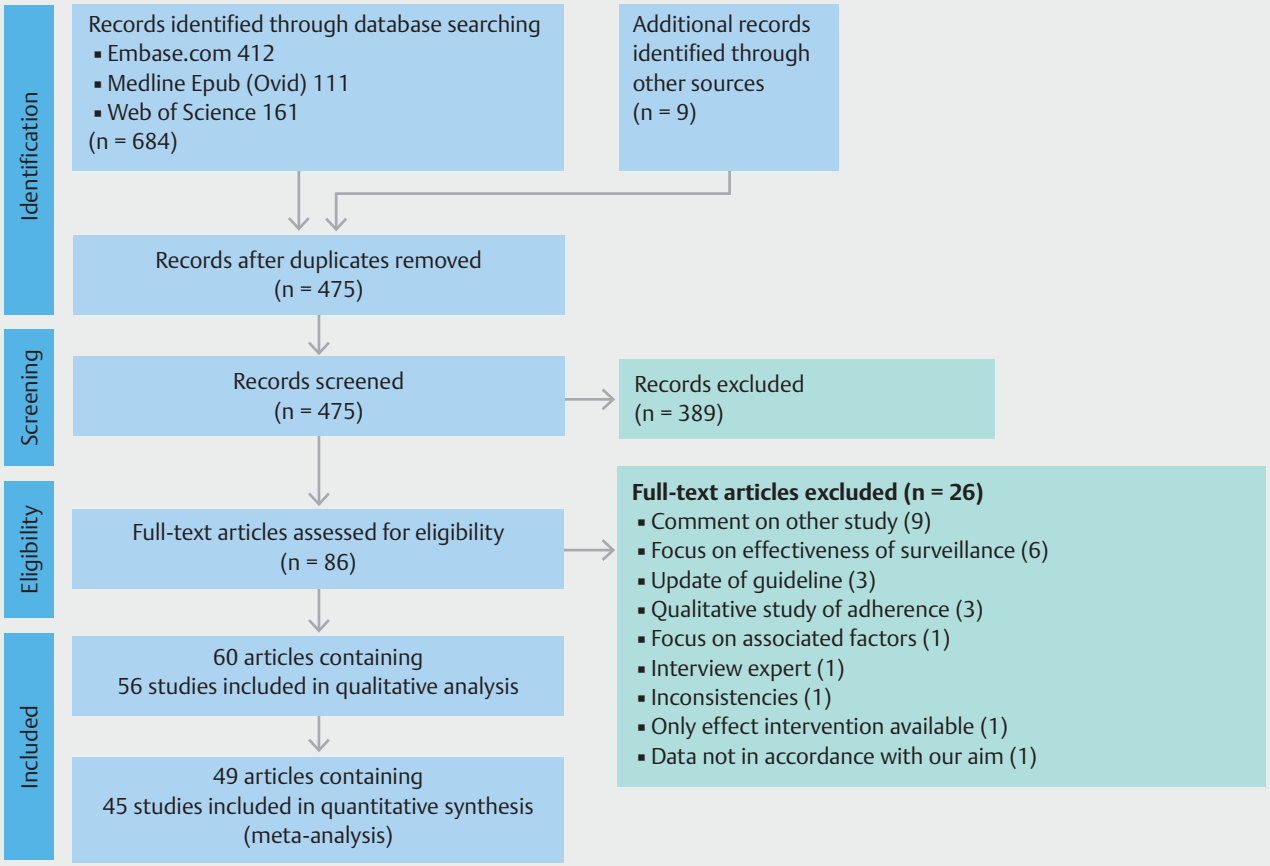

▶ **Fig. 1** Study flow diagram.

The geographical setting was developed countries in all studies: Argentina, Australia, several countries in Europe, and North America. A total of 14 002 BE patients were included, with a median sample size of 210 (interquartile range [IQR] 103 – 367), and 4932 endoscopists participated, with a median sample size of 203 (IQR 123 – 260).

Data from the original papers were not included in the analysis in cases of: 1) lack of report of numbers, results were only described in words (four studies) [supplementary references 47, 50, 73, 97]; 2) report of mean surveillance interval, mean number of biopsies, or mean biopsy percentage, instead of proportions (eight studies) [supplementary references 42, 51, 54, 58, 70 ,84, 87, 96]; 3) separate reporting of adherence to four-quadrant biopsies and biopsies every 2 cm (three studies) [supplementary references 58, 60, 67]; and 4) separate reporting of adherence in participating centers (one study) [supplementary reference 50].

Subgroups explaining between-study variance

Pooled proportions of adherence ranged from 18 % to 89 % (▶ **Fig. 2**). For recommendations with pooled estimates based on ≥ 20 studies, forest plots were constructed (▶ **Fig. 3**, **Fig. 1s**, **Fig. 2s**). Adherence to surveillance interval was 55 % for nondysplastic Barrett's esophagus (NDBE) (95 %CI 44 % – 66 %), 50 % for low grade dysplasia (LGD) (95 %CI 38 % – 62 %), and 49 % to the Seattle protocol (95 %CI 36 – 62 %). In **Table 3s**, the details of other pooled estimates are shown.

In addition to providing information concerning the proportion of adherence, which was pooled in the meta-analysis, several studies also showed whether intervals were too short or too long. For the recommendation "interval NDBE," 13 studies reported an interval that was too short [supplementary references 41, 47, 51, 53, 60, 62, 67, 70, 77, 78, 90, 91, 95], and only one study reported an interval that was too long among the nonadherent participants [supplementary reference 56]; one study reported an equal proportion of endoscopies with surveillance intervals that were too short or too long [supplementary reference 74]. For "interval LGD," 12 studies reported an interval that was too short [supplementary references 41, 47, 53, 60, 62, 67, 75, 77, 88, 90, 91, 95], and in four studies the interval was too long [supplementary references 70, 56, 74, 78]. For the recommendation "Seattle protocol," 12 studies reported that fewer biopsies than expected were taken [supplementary references 42, 54, 56, 58, 70, 73 – 75, 84, 91, 95, 96], and one study reported a surplus [supplementary reference 77].

Heterogeneity was high (≥ 75 %) for all pooled estimates. For "surveillance interval general," 90 % of heterogeneity could be explained by difference in type of practice between studies

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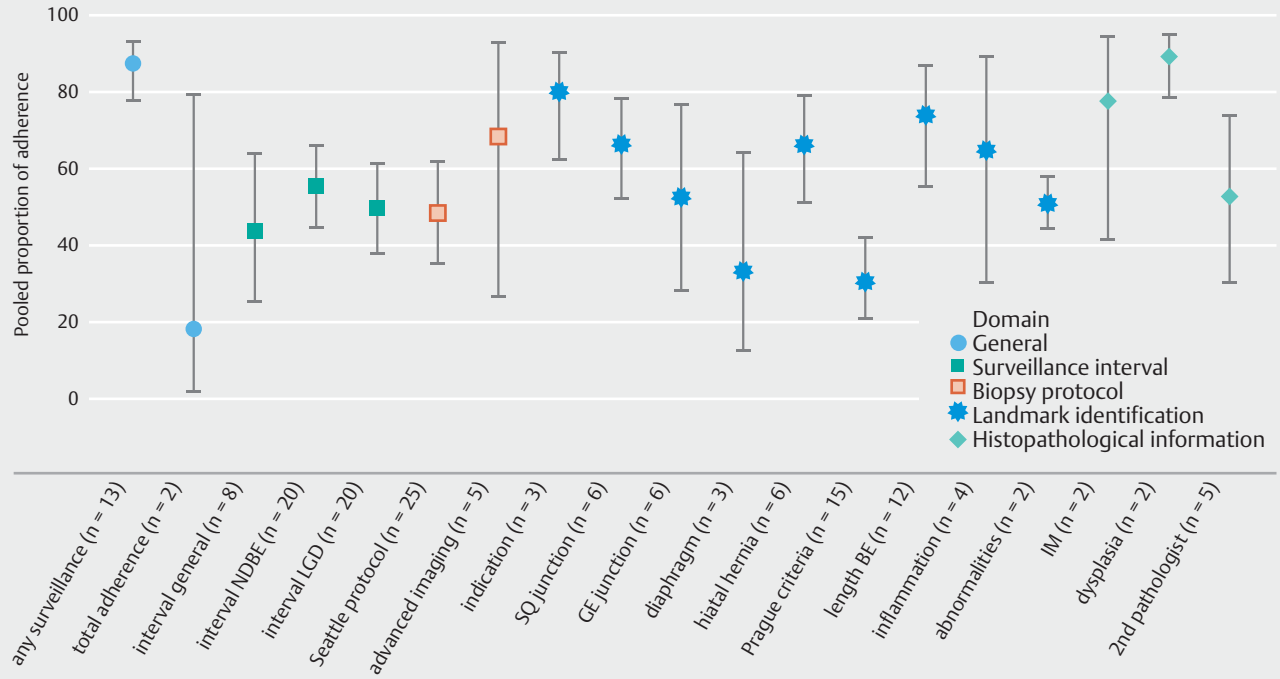

▶ **Fig. 2** Summary of pooled proportions and 95 % confidence intervals of adherence to guideline recommendations, subdivided per domain. n, number of studies included in the meta-analysis; BE, Barrett's esophagus; GE, gastroesophageal; IM, intestinal metaplasia; LGD, low grade dysplasia; NDBE, nondysplastic Barrett's esophagus; SQ, squamocolumnar.

and 11 % by year of publication (▶ **Table 2**). For "interval NDBE," 43 % could be explained by differences in country. For "Seattle protocol," 14 % of the between-study variance was explained by differences in country. And for the "Prague classification," 12 % of heterogeneity was due to differences in data collection.

Factors associated with surveillance guideline adherence

An overview was compiled of reported factors that influence adherence to primary recommendations of the surveillance guideline (▶ **Fig. 4**). The following factors were reported most frequently to be associated with better adherence: shorter BE segments (Seattle protocol); salaried employment instead of productivity-based employment of the endoscopists (surveillance intervals); university hospitals (Seattle protocol and Prague classification); the introduction of dedicated surveillance programs, often reported as "interventions" (surveillance intervals, Seattle protocol, and Prague classification). The type of interventions reported to improve adherence were participation in a trial, pooling patients on a dedicated list, and formalized and multifaceted intervention programs. Only the implementation and dissemination of guidelines were not reported as often to improve adherence to guideline recommendations. Other factors less frequently reported to be associated with better adherence to guideline recommendations were more belief in the efficacy of surveillance, and awareness and agreement of the endoscopists with the guideline (surveillance interval), younger age of the endoscopists (surveillance interval and Seattle protocol), and physicians compared with surgeons (Prague criteria). Only 10 out of 29 studies performed multivariable analysis to identify factors associated with better adherence.

Quality assessment

Methodological quality concerning the between-study variance was good for 34 studies (scored ≥ 5, **Table 4s**), while 15 scored < 5. Biased data collection using self-reported surveys, inadequate response rate, and a lack of adequate description of participants led to reduced quality scores most frequently. Studies with a low score on aspect 5 of the Loney Scoring tool also scored low on aspect 4 of the QUIPS (**Table 5s**) within the context of the methodological quality of the secondary objective. The maximum score was low for 1 study, medium for 14 studies, and high for 15 studies. Reduced quality was often attributable to the lack of correction for confounders and self-reported outcome measurement. Funnel plots were rather symmetric, providing no evidence of publication bias (**Fig. 3s**).

Sensitivity analysis

The exclusion of outliers or low quality studies showed similar results in assessing adherence rates. The results of sensitivity analyses of adherence to guideline recommendations are shown in **Table 6s**.

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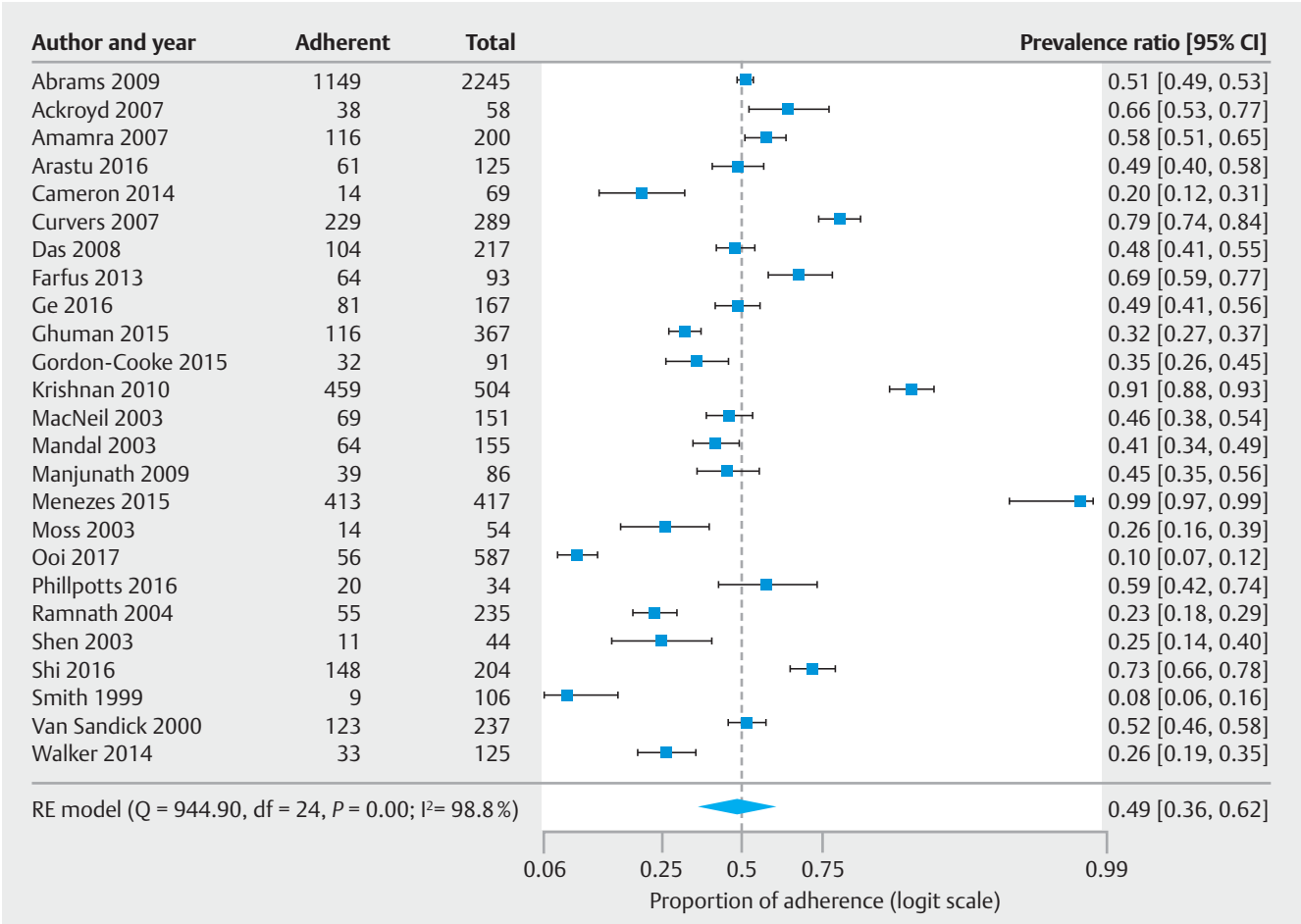

▶ **Fig. 3** Forest plot of pooled proportion of adherence to guideline recommendation "Seattle protocol." CI, confidence interval; RE, random effect.

Discussion

In this systematic review and meta-analysis, we pooled the overall worldwide rates of adherence to guideline recommendations as researched in the literature, which showed a large variance between studies. Difference in country and type of practice were the main contributing factors for the large heterogeneity in pooled estimates. Although many studies aimed to identify explanatory parameters for nonadherence, most of them were observed in univariate analysis in a retrospective cohort design. The graphical representation of this study shows that factors most frequently reported to be associated with better adherence were shorter BE length, salaried employment, surveillance in university hospitals, and dedicated surveillance programs. We performed our research according to established guidelines for systematic reviews and did a thorough meta-analysis. Because results from multiple studies were combined, this study provides insight into the variability between studies, rather than adherence rates of single studies.

In line with the subgroup analysis, surveillance was reported to be more often in line with guideline recommendations in university hospitals than in general hospitals. In addition, better adherence was observed in dedicated programs. This indicates that persistent alertness of guidelines is important. We found that interventions such as a dedicated nurse and other formalized surveillance programs improved adherence, and that the effect of only implementing a guideline is limited. It is known that more than 1 year after a guideline has been implemented, clinicians' adherence to it declines [32]. Simply being aware of the guideline was not often contributing to adherence in our review; however, younger gastroenterologists, who had been trained more recently, were more adherent to the use of the Prague criteria. University hospitals, with their emphasis on teaching and research, were also associated with better adherence.

Remarkably, we found that more intensive surveillance was recommended if there was more belief in the efficacy of surveillance, and that more agreement with the guideline was related to better adherence to the surveillance interval. Similar findings have been reported for adherence to guidelines in other specialties [33]. Furthermore, the evidence behind the Barrett's surveillance guideline recommendations is moderate at best. Therefore, to improve adherence, the evidence underpinning

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▶ **Table 2** Subgroup analysis of adherence to the guideline of primary recommendations. R^2 indicates the proportion of heterogeneity among studies that is explained by the difference between subgroups.

Subgroup analysis based on	Groups	OR[1] (95 %CI) per subgroup (n = number of studies) of adherence to primary recommendations									
		Surveillance interval general	n	Surveillance interval NDBE	n	Surveillance interval LGD	n	Seattle protocol	n	Prague classification[2]	n
Country	Argentina	ref.	1	n.a.		n.a.		n.a.		n.a.	
	Australia	n.a.		ref.	1	ref.	1	ref.	4	ref.	2
	Canada	n.a.		0.51 (0.06 – 4.29)	1	0.11 (0.01 – 2.01)	1	1.52 (0.09 – 24.7)	1	1.08 (0.08 – 14.1)	1
	Scotland (& England)	n.a.		4.33 (0.34 – 55.4)	1	0.09 (0.01 – 1.46)	2	0.60 (0.03 – 10.4)	1	n.a.	
	France	6.04 (0.19 – 190)	1	1.10 (0.13 – 9.18)	1	0.34 (0.02 – 6.12)	1	2.49 (0.15 – 40.4)	1	n.a.	
	Ireland	20.9 (1.00 – 437)	2	0.23 (0.03 – 2.00)	1	0.03 (0.00 – 0.50)	1	0.63 (0.04 – 10.8)	1	n.a.	
	The Netherlands	2.94 (0.09 – 92.6)	1	0.20 (0.03 – 1.28)	2	0.06 (0.00 – 0.75)	2	3.66 (0.42 – 31.7)	2	n.a.	
	United Kingdom	6.03 (0.19 – 189)	1	0.14 (0.03 – 0.74)	5	0.08 (0.01 – 0.79)	6	0.92 (0.20 – 4.16)	9	0.60 (0.11 – 3.24)	7
	United States	10.4 (0.51 – 210)	2	0.54 (0.11 – 2.74)	8	0.08 (0.01 – 0.74)	6	6.24 (1.23 – 31.6)	6	0.49 (0.08 – 2.98)	4
	Missing	–	0	–	0	–	0	–	0	–	1
R^2		0.00 %		43.0 %		8.03 %		13.6 %		0.00 %	
Data collection	Reports	ref.	5	ref.	3	ref.	4	ref.	12	ref.	11
	Questionnaire	0.41 (0.07 – 2.22)	3	1.72 (0.51 – 5.86)	17	2.01 (0.51 – 7.92)	16	2.41 (0.85 – 6.81)	13	2.49 (0.86 – 7.22)	4
	Missing	–	0	–	0	–	0	–	0	–	0
R^2		0.00 %		0.00 %		0.00 %		7.21 %		11.5 %	
Year of publication	≤ 1998	n.a.		ref.	1	ref.	1	ref.	1	ref.	7
	≥ 1999 and ≤ 2007	ref.	3	3.87 (0.47 – 31.6)	11	0.22 (0.02 – 1.98)	10	0.32 (0.02 – 6.14)	9	n.a.	
	≥ 2008 and ≤ 2015	1.77 (0.33 – 9.48)	4	6.22 (0.72 – 53.45)	7	0.40 (0.04 – 3.79)	8	0.74 (0.04 – 13.8)	10	n.a.	
	≥ 2016	8.79 (0.68 – 112)	1	2.12 (0.13 – 35.16)	1	0.58 (0.03 – 10.9)	1	0.43 (0.02 – 9.03)	5	0.96 (0.34 – 2.75)	8
	Missing	–	0	–	0	–	0	–	0	–	0
R^2		11.0 %		0.23 %		1.83 %		0.00 %		0.00 %	

Thieme

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Table 2 (Continuation)

Subgroup analysis based on	Groups	OR[1] (95 %CI) per subgroup (n = number of studies) of adherence to primary recommendations: Surveillance interval general	n	Surveillance interval NDBE	n	Surveillance interval LGD	n	Seattle protocol	n	Prague classification[2]	n
Type of practice	Community	ref.	1	ref.	1	ref.	1	ref.	6	ref.	5
	Mixed	4.51 (1.39 – 14.7)	2	2.69 (0.30 – 24.2)	9	0.94 (0.03 – 31.3)	9	2.59 (0.39 – 17.4)	7	0.88 (0.25 – 3.10)	4
	University	23.0 (7.16 – 73.6)	3	2.76 (0.24 – 31.5)	3	0.81 (0.02 – 30.9)	3	1.18 (0.11 – 13.1)	3	0.35 (0.09 – 1.38)	3
	Missing	–	2	–	7	–	7	–	9	–	3
R^2		89.6 %		0.00 %		0.00 %		0.00 %		4.76 %	

OR, odds ratio; CI, confidence interval; NDBE, nondysplastic Barrett's esophagus; LGD, low grade dysplasia; n.a, not applicable.
[1] OR > 1 indicates adherence is more likely for the mentioned characteristic. Bold ORs represent a significant difference between subgroups.
[2] In subgroup analysis of Prague classification for year of publication, only 2 categories were used (≤ 2015 and ≥ 2016) because the issue of the American College of Gastroenterology guidelines on quality indicators for endoscopic procedures was published as a recommendation in 2015.

the guidelines should be strengthened, for example by improvement of risk stratification.

In this systematic review, pooled estimates showed large heterogeneity, as expected. To evaluate the influence of methodological differences of studies, rather than, for example, type of practice, we also estimated whether the data could be influenced by self-reported data collection [34]. This explained only a small proportion of the heterogeneity in the subgroup analysis. However, as the heterogeneity between studies addressing adherence to Prague classification could be explained by > 10 % by differences in data collection, results should be interpreted with caution. We also estimated the influence of the year of publication. In other words, we evaluated whether the year of publication could explain heterogeneity, and if adherence improves or declines over time. For surveillance interval in general, > 10 % of heterogeneity could be explained by the year of publication. Although the results per year category are not statistically significant, increasing ORs for categories of more recent publications may indicate improving adherence over the years.

To our knowledge, this is the first study to provide the pooled estimates of adherence to guideline recommendations of BE surveillance. The findings of this study stress the relevance of improving the adherence of BE surveillance for two reasons. First, poor adherence to the Seattle protocol could increase the health care burden. Although there is no conclusive evidence available, the Seattle protocol has been shown to reduce sampling error with improved detection of dysplasia, compared with random biopsies [35]. Alternatively, nonadherence reduces the likelihood of detecting dysplasia. In a previous study with a cohort of 2245 BE patients under surveillance, the detection was reduced by almost half in cases of nonadherence to the biopsy protocol [7]. Consequently, because of nonadherence, EAC may be detected at a later stage, with a negative influence on the outcome for BE patients. However, missed dysplasia in a repeat endoscopy within 24 months was not associated with adherence to the Seattle protocol [36]. The detection of dysplasia was influenced not only by adherence to the biopsy protocol, but adherence to reporting the length of the BE segment using the Prague classification was also associated with better detection of dysplasia [37].

Second, performing surveillance endoscopies at an earlier time point than that recommended in the guideline increases the total number of surveillance endoscopies performed. The cost-effectiveness of the current surveillance strategies, as recommended by guidelines, is under discussion; there is disagreement about the optimal surveillance interval. However, three studies suggested this interval should not be less than 3 years for NDBE and not less than 1 year for LGD [9, 38]. The results of these studies indicate that a shorter interval than recommended by the current guidelines would increase the health care costs even more. Only one study reported cost-effectiveness with shorter intervals [39].

Consequently, if impaired cost-effectiveness of surveillance due to shorter surveillance intervals is accompanied by lower detection of dysplasia because of nonadherence to the Seattle protocol and the Prague classification, the health care burden

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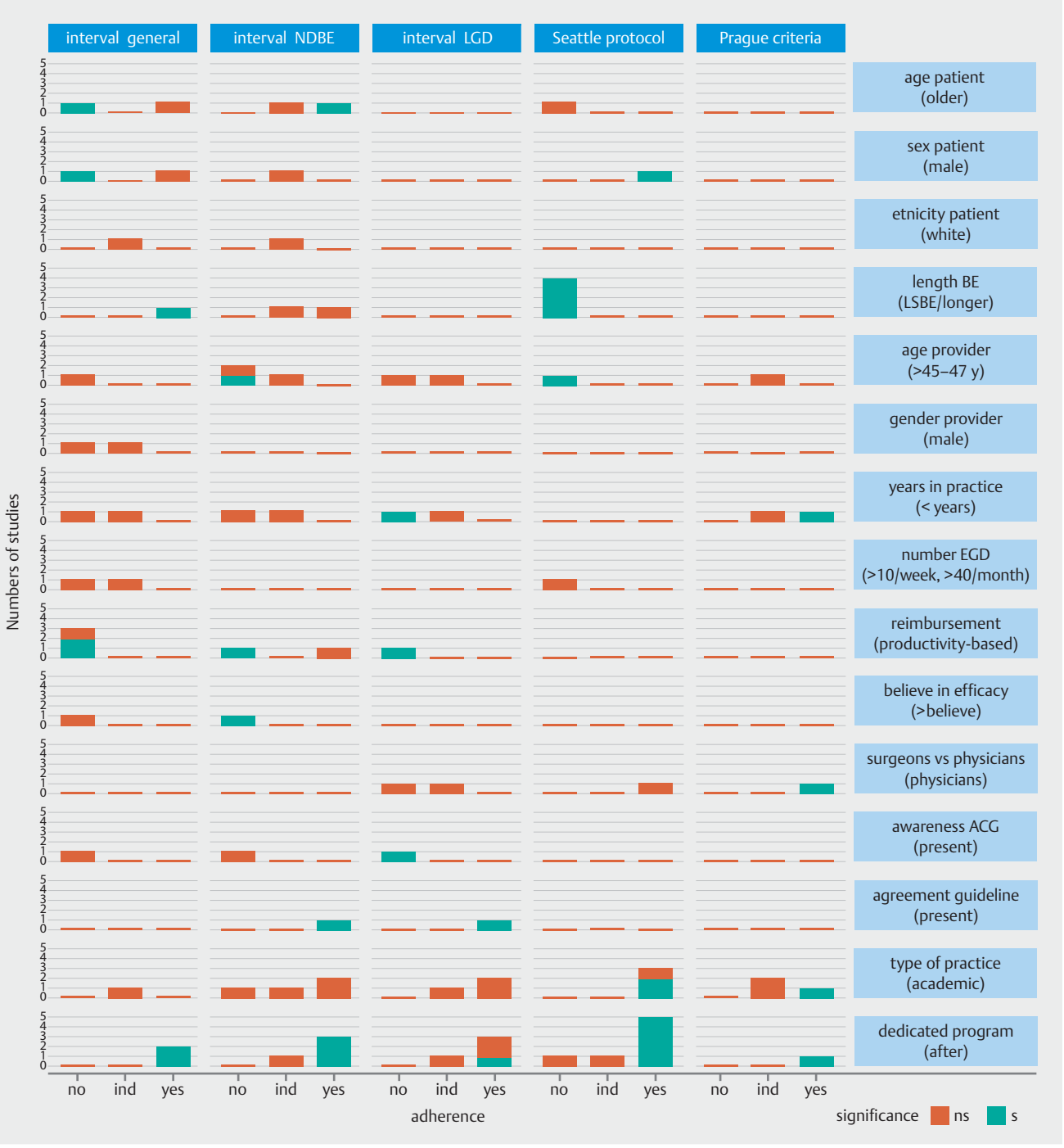

▶ **Fig. 4** Overview of association between primary recommendations of adherence to the guideline (top horizontal pane) and explanatory parameters (right vertical pane). The *x*-axis (adherence) represents whether studies were associated with adherence ("yes"), not associated with adherence ("no"), no difference between groups ("ind", if the absolute proportions of each group were not mentioned in the study, only that there was no difference). These results could be significant (black, "s"), or nonsignificant (grey, "ns"). The *y*-axis represents number of studies that reported the associations as mentioned in the graph. Results of multivariate analysis were used if available. ACG, American College of Gastroenterology; BE, Barrett's esophagus; EGD, esophagogastroduodenoscopy; LGD, low grade dysplasia; LSBE, long-segment Barrett's esophagus; NDBE, nondysplastic Barrett's esophagus.

of surveillance of BE patients is disproportionate. This results in exorbitant costs for society and poorer detection of early neoplastic progression in BE patients.

This study has several strengths and limitations. We conducted this systematic review and meta-analysis according to standardized protocols. Additional analysis for between-study variation provided insight into data and heterogeneity of re-

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sults. The methodological quality of some included studies was limited, with data collection based on self-report as a contributing factor in over one-third of articles. As all studies on adherence have been conducted in highly developed countries, caution should be exercised with regard to the generalizability of the results. An important limitation with a potentially large contribution to the results is that parameters associated with adherence were identified in most studies in univariate analysis, whereas other confounders could be important as well.

In conclusion, adherence to BE surveillance guidelines is suboptimal, thereby adversely affecting health care burden (e. g. impaired detection of dysplasia and superfluous costs). Opportunities for improving adherence should be further investigated, preferably without self-reported surveys and with adjustment for confounding factors. Attention should be paid to increase the evidence for guideline recommendations. Short-term meaningful consequences include optimal introduction and monitoring of formalized surveillance programs.

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Competing interests

None

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