Article published online: 2023-03-08

Effect of biopsy protocol adherence vs non-adherence on dysplasia detection rates in Barrett's esophagus surveillance endoscopies: a systematic review and meta-analysis

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submitted 4.7.2022
accepted after revision 13.10.2022

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Endosc Int Open 2023; 11: E221–E229
DOI 10.1055/a-1967-1589
ISSN 2364-3722

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Supplementary material is available under https://doi.org/10.1055/a-1967-1589

ABSTRACT

Background Barrett's esophagus (BE) surveillance endoscopies are advised for early diagnosis of esophageal adenocarcinoma (EAC). Current guidelines recommend obtaining four-quadrant random biopsies every 2 centimeters of BE length alongside with targeted biopsies if visible lesions are present. Low adherence rates for this random biopsy protocol are widely reported. The aim of this systematic review and meta-analysis was to assess the effect of adherence versus non-adherence to the four-quadrant biopsy protocol on detection of dysplasia in BE patients.

Methods We searched for studies that reported effects of adherence and non-adherence to the four-quadrant biopsy protocol on dysplasia detection rates in BE patients. Adherence was defined as taking a minimum of 4 quadrant random biopsies per 2 cm of BE segment. Studies with low risk of bias and without applicability concerns were included in a good quality synthesis. Pooled relative risks (RRs) with 95% confidence interval (CI) of dysplasia detection rates were calculated.

Results A total of 1,570 studies were screened and 8 studies were included. Four studies were included in the good quality synthesis. In the pooled good quality analysis, four-quadrant biopsy protocol adherence significantly increased detection of dysplasia compared to non-adherence (RR 1.90, 95% CI = 1.36–2.64; I2 = 45%). Pooled RRs for LGD and HGD/EAC were 2.00 (95% CI = 1.49–2.69; I2 = 0%) and 2.03 (95% CI = 0.98–4.24; I2 = 28%), respectively.

Conclusion This systematic review and meta-analysis demonstrates that four-quadrant biopsy protocol adherence is associated with increased detection of dysplasia in BE patients. Efforts should be made to increase biopsy protocol adherence rates.

Introduction

Barrett's esophagus (BE) may be defined as the presence of ≥ 1 cm columnar epithelium proximal to the gastroesophageal junction with intestinal metaplasia on biopsy [1]. The clinical importance of BE lies in its premalignant potential, predisposing to esophageal adenocarcinoma (EAC). The risk of progression from non-dysplastic BE to EAC is estimated to be 0.1% to 0.6% per year [2–5]. Despite this low risk, early diagnosis and treatment is of utmost importance since advanced esophageal

adenocarcinoma is characterized by high mortality rates. Therefore, in many countries, BE patients are kept under endoscopic surveillance at regular intervals to detect dysplasia or neoplasia at an early stage [1, 6–9].

After adequate endoscopic inspection of the BE segment and after targeted biopsies of visual abnormalities, if present, current guidelines recommend taking four-quadrant random biopsies of every 2 cm of Barrett's epithelium [1, 6–9]. Obtaining random biopsies is considered indispensable because dysplasia, especially low-grade dysplasia, is often invisible.

Especially in longer Barrett segments, however, taking many biopsies according to this protocol is tedious and time-consuming. In a recent meta-analysis, adherence to the four-quadrant biopsy protocol is reported to be only 49 % (95 % confidence interval [CI] 36–62) [10]. Yet, whether non-adherence to the random biopsy protocol is associated with detection rates of dysplasia and EAC is not fully elucidated. This systematic review and meta-analysis, therefore, aimed to assess the effect of four-quadrant biopsy protocol adherence versus non-adherence on the detection rate of dysplasia in non-dysplastic BE surveillance endoscopies.

Methods

This systematic review and meta-analysis adhered to the Preferred Reporting Items for Systematic review and Meta-Analyses (PRISMA) guidelines (**Supplementary File 1**) [11], and was registered in the international prospective register of systematic reviews (PROSPERO): CRD42021273391.

Search strategy

A literature search was conducted in three online databases on June 24th, 2021: MEDLINE, Embase and Cochrane Library. The search strategy consisted of key terms related to Barrett's esophagus, guideline adherence, and biopsy protocol. No restrictions on publication language or publication date were used. The full search algorithm is provided in **Supplementary File 2**. Reference lists of all included studies were checked manually in order to find additional relevant articles.

Study selection

After removal of duplicates, all titles and abstracts retrieved from the search were screened and assessed for eligibility by two independent members of the research team (I.B. and E.A.). Any discrepancies between the reviewers' findings were discussed and resolved. Full-text articles were retrieved for all studies that were possibly eligible. The following pre-defined selection criteria were used for the inclusion of studies:

1. Studies including patients with an established diagnosis of BE, i. e. ≥ 1 cm endoscopically visible BE with a histologic diagnosis of intestinal metaplasia
2. Studies reporting on adherence versus non-adherence to the four-quadrant random biopsy protocol. Adherence was defined as taking a minimum of four quadrant random biopsies per 2-cm BE segment. Any less than the minimum number of biopsies was defined as non-adherence.
3. Studies reporting on detection of dysplasia, defined as presence of low-grade dysplasia (LGD), high-grade dysplasia (HGD), and/or EAC.
4. Primary studies with the following study designs: randomized controlled trials, prospective intervention studies, or retrospective observational studies.

Studies were excluded in case of:

1. Survey outcomes
2. Comparisons between the four-quadrant biopsy protocol and (virtual) chromoendoscopy with targeted biopsies.
3. Review articles, case reports, case series or studies reported as abstracts only.

Studies that partly met the definitions in our inclusion criteria were discussed and were considered individually on a case- by base basis. A third assessor (B.W) was available to resolve any conflict on which studies were to be included.

Data extraction

Data from all included studies were extracted independently by the two investigators. All relevant parameters were entered in a standardized data collection form designed previous to data extraction. Any differences in the data extracted by the two members were resolved by discussion.

For each study, the following variables were extracted: first author, year and country of publication, study design (i. e. randomized or observational, prospective or retrospective), study setting, number of patients included, mean age and gender of patients included, mean BE segment length, mean number of biopsies obtained, the average number of biopsies per 2 cm of BE length, patient history with dysplasia, and detected percentage of LGD, HGD and EAC. Relative risks (RRs) for dysplasia detection for adherence versus non-adherence to the four-quadrant biopsy protocol, including 95 % confidence intervals, were extracted or calculated for each study.

Risk of bias assessment

All included studies were subjected to a risk of bias analysis via a modified version of the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) bias tool. The QUADAS-2 tool was originally created for assessment of diagnostic accuracy studies [12]. Therefore, the tool was adapted to fit our diagnostic research question, comparing two diagnostic strategies for diagnosis of dysplasia or early EAC. Additional questions derived from the preliminary version of the QUADAS-C tool were added to the modified QUADAS-2 tool, to allow for a risk of bias assessment in comparative diagnostic test studies. Also, because we expected to include mainly non-randomized studies, we included an additional question to evaluate the risk of confounding bias in the individual studies. We considered BE length as the most important confounding factor. The final version of our modified assessment tool can be found in **Supplementary File 3**.

Two independent members of the research team (I.B. and E.A.) individually assessed each study for risk of bias in the domains included in the modified QUADAS-2: patient selection,

index tests, reference standard and flow and timing. With the exception of the flow and timing, each domain was also assessed for concerns regarding applicability for the review question. For each domain, signaling questions and risk of bias was assigned a response of "yes" if concerns or bias were present, "no" if absent or "unclear" if information was inconclusive or incomplete in the articles. In case of inconsistencies between the individual assessments, a consensus was reached by discussion.

Data analysis

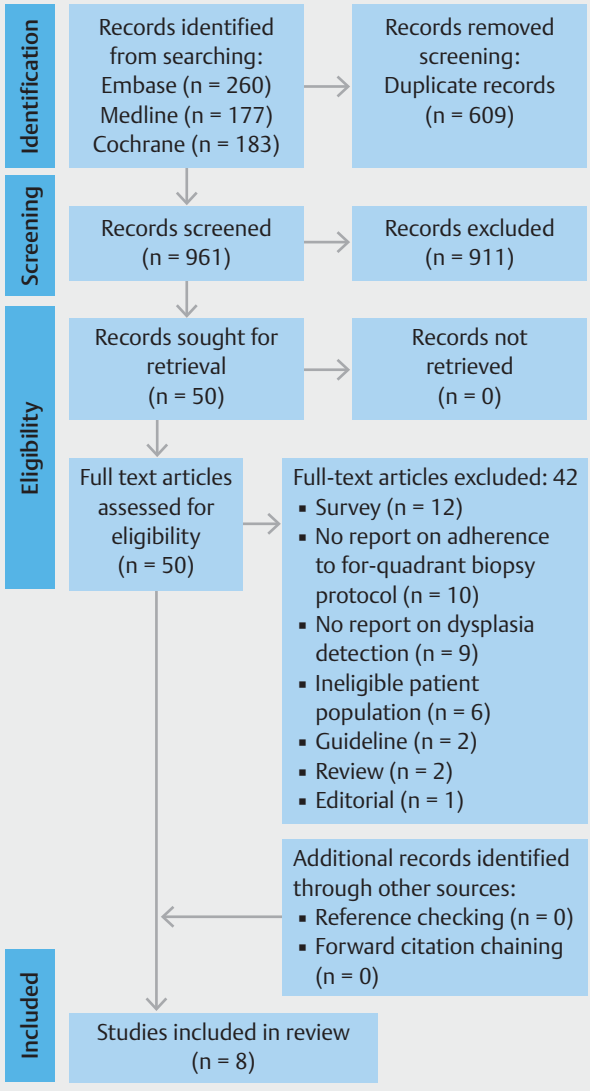
The primary outcome was the dysplasia detection rate, defined as a finding of LGD, HGD or worse during the endoscopy of interest. RRs with 95 % confidence intervals were extracted as summary statistic of each individual study. If not reported, these estimates were calculated based on reported data in each study. The Mantel-Haenszel method was used to calculate a weighted summary statistic and 95 % confidence interval for studies that provided stratified data [13].

To compare dysplasia detection rates for adherence versus non-adherence to the four-quadrant biopsy protocol, pooled RRs including 95 % CIs were generated by random effects meta-analyses. Generic inverse variance meta-analysis was used in case of pre-calculated effect sizes, where the Mantel-Haenszel approach was used when raw effect size data were available [14]. The Paule and Mendel estimator was used to calculate the heterogeneity variance tau^2 [15]. A constant continuity correction was applied in case the dysplasia detection rate was zero. Adjusted estimates (adjusted for BE length) were used for meta-analysis were possible. However, since most of the included studies did not adjust for possible confounding factors, mostly crude estimates were used. Subgroup analysis was done by stratification for degree of dysplasia (i. e. HGD/EAC versus non-dysplastic BE/LGD and LGD versus non-dysplastic BE) and BE length for studies that provided these data.

A good-quality synthesis was conducted for studies with low risk of bias and low concern regarding applicability, as judged by the modified QUADAS-2 tool. If a study scored "high risk" or "unclear risk" in one or more domains regarding risk of bias or applicability, the study was excluded from good-quality synthesis. The first domain "patient selection" was not taken into account, because of the lack of paired or randomized studies.

Heterogeneity among studies was assessed by visual inspection of the forest plots, the use of I^2 statistics and by 95 % prediction intervals (PIs) for analyses with ≥ 3 included studies [16]. The I^2 statistic represents the percentage of variation between individual study estimates that is attributable to heterogeneity rather than chance. The I^2 statistic was interpreted as per the Cochrane Handbook recommendations (0 %–40 % unimportant heterogeneity; 30 %–60 % moderate; 50 %–90 % substantial; 75%-100 % considerable heterogeneity) [14]. The 95 % prediction interval is also a useful measure to determine the amount of heterogeneity and reflects (with 95 % confidence) the expected interval of true effects in future studies. Publication bias assessment was done examining funnel plot asymmetry by visual inspection. Statistical tests for funnel plot asymmetry were not performed because of the relatively low number of included studies and subsequent low power of the tests.

Risk of bias summary plots were made in Review Manager 5.3. Meta-analyses, forest plots and funnel plots were derived using R (version 3.5.1 "meta" package; functions "metagen" and "metabin").



▶ **Fig. 1** The PRISMA flow chart depicting study selection process.

Results

Search results

The initial search yielded 1,570 records. Duplicate studies were removed after which 961 records were screened based on title and abstract. A total of 50 potentially relevant studies were retrieved for full-text analysis. After assessment for eligibility, 42 studies were excluded based on the inclusion and exclusion criteria. Therefore, eight studies were included in this systematic review and meta-analysis (▶ **Fig. 1**) [17–24]. Reference lists

of all included studies were manually checked, but did not yield additional eligible articles.

Study characteristics and risk of bias

The characteristics of included studies are summarized in ▶ **Table 1**. Of the eight included studies, five were retrospective observational studies evaluating the effect of four-quadrant biopsy protocol adherence on dysplasia detection [17–20, 24]. Two prospective studies by Ooi et al. and Britton et al. primarily evaluated the effect of dedicated BE surveillance lists (i. e. clustered BE surveillance endoscopies on the same endoscopy program, performed by an endoscopist who is trained in BE surveillance) on dysplasia detection rates [21, 23]. Fitzgerald et al. assessed the dysplasia detection rate in a prospective cohort with four-quadrant biopsy protocol adherence versus a historical cohort without adherence to a systematic biopsy protocol [22]. The studies included a total sum of 58,016 participants. Individual sample sizes varied between 144 and 53,541 patients.

All studies had been found to be at risk of bias regarding patient selection, since none had fully paired or randomized study designs (▶ **Fig. 2**). The study of Britton et al. scored high risk of bias in domain "flow and timing," because not all patients that were recruited into the study were included in the analysis [21]. The same domain was scored "unclear" for the studies of Bampton et al. and Wani et al. due to incomplete reporting of patient inclusion and exclusion for final analysis [20, 24].

Three of the included studies were scored as high risk for applicability concerns of the index tests [21, 23, 24]. Wani et al. reported an alternative definition of four-quadrant biopsy protocol adherence, i. e. BE length divided by the number of pathology jars submitted to the pathology department (a ratio of ≤ 2.0 was defined as non-adherence) [24]. Ooi et al. and Britton et al. evaluated dedicated Barrett surveillance lists instead of four-quadrant biopsy protocol adherence versus non-adherence [21, 23]. A summary of outcomes of the risk of bias and applicability assessment for the included studies are presented in ▶ **Fig. 2**.

Dysplasia detection rate

Adherence to the four-quadrant biopsy protocol was associated with increased dysplasia detection in seven of the eight included studies. This difference was statistically significant in three of eight studies. The individual RRs of these seven studies varied between 1.30 and 2.81 (▶ **Table 2**). In a single study, adherence was associated with lower dysplasia detection, with a relative risk of 0.82.

In the pooled analysis of all eight studies, four-quadrant biopsy protocol adherence significantly increased detection of dysplasia compared to non-adherence (RR 1.59, 95 % CI 1.17–2.16) (▶ **Fig. 3**). There was a considerable amount of heterogeneity among studies in this meta-analysis (I^2 = 90 %; 95 % PI 0.62–4.11).

Good-quality synthesis

Based on the risk of bias and applicability assessment using the modified QUADAS-2 tool, four studies were included in the good-quality synthesis (▶ **Fig. 4**). Similarly, to the full analysis, the pooled results from the good-quality synthesis were in favor of adherence to the four-quadrant biopsy protocol, yet with only moderate heterogeneity (RR 1.90, 95 % CI 1.36–2.64; I^2 = 45 %; 95 % PI 0.58–6.23).

Subgroup analysis

Five studies reported on dysplasia detection rate stratified by degree of dysplasia. Meta-analysis by degree of dysplasia is depicted in **Supplementary Figure 1**. Pooled RRs for LGD and for HGD/EAC were 2.00 (95 % CI 1.49–2.69; I^2 = 0 %; 95 % PI 1.24–3.23) and 2.03 (95 % CI 0.98–4.24; I^2 = 28 %; 95 % PI 0.29–14.18) respectively.

Two studies described dysplasia detection rates stratified by BE length (**Supplementary Figure 2**). A favorable effect of four-quadrant biopsy protocol adherence was seen in subgroups with a BE length > 4 cm (RR 1.11–1.56), though this effect was not statistically significant.

Publication bias

Supplementary Figure 3 displays a funnel plot including confidence intervals. Visual inspection of the funnel plot indicates asymmetry and may, therefore, suggest the possibility of publication bias. However, this should be interpreted cautiously because the presence of considerable heterogeneity between included studies.

Discussion

The aim of this systematic review and meta-analysis was to evaluate the effect of four-quadrant biopsy protocol adherence on dysplasia detection rates in BE surveillance endoscopies. Our meta-analysis demonstrated that adherence to the four-quadrant biopsy protocol is associated with significantly increased dysplasia detection in BE patients (RR 1.59, 95 % CI 1.17–2.16). Based on the good-quality synthesis, the association between biopsy protocol adherence and a finding of dysplasia was even higher (RR 1.90, 95 % CI 1.36–2.64).

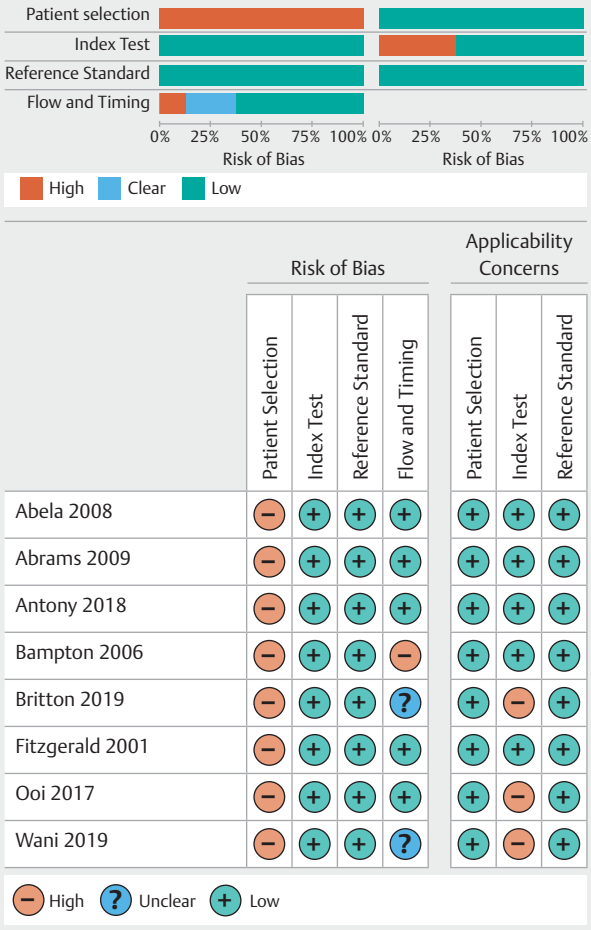
Our results strengthen the advice to obtain an adequate number of random biopsies in BE surveillance endoscopies. This finding is in line with previous research showing that in daily practice, BE patients are still diagnosed with dysplasia by only random biopsies, even after the emergence of high-resolution endoscopes and advanced imaging modalities [25, 26]. Non-adherence to the four-quadrant biopsy protocol could subsequently lead to missed diagnosis of dysplasia.

In our stratified analysis, we found that the association between four-quadrant biopsy protocol adherence and dysplasia detection was mainly based on an increased detection of LGD. This may be explained by the fact that HGD and EAC are mostly diagnosed through targeted biopsies from a visible lesion, rather than random biopsies from flat BE. In a recent study, van Munster et al. found that the yield of random biopsy differed along with the worst histological diagnosis: LGD was detected on random biopsy in 83 % of patients, HGD in 47 % of patients, and EAC in only 1 % [27]. Adherence to the four-quadrant biopsy protocol would, therefore, particularly increase the yield of

▶ **Table 1** Study characteristics.

First author (year)	Country	Study design	Setting	n	Primary study comparison	Definition adherence biopsy protocol	Adherence (n)	Non-adherence (n)
Abela (2008) [17]	UK	Retrospective observational	Tertiary care	362	Adherence four-quadrant biopsy protocol vs non-systematic biopsy protocol	Four-quadrant biopsies every 2 cm of BE length. Number of biopsies received in specimen containers were used to confirm that sufficient biopsies were taken	180	182
Abrams (2009) [18]	USA	Retrospective observational	Secondary care	2,245[1]	Adherence for-quadrant biopsy protocol vs non-adherence four-quadrant biopsy protocol	Number of esophageal biopsies divided by BE length in cm A ratio of ≥ 2.0 was defined as adherent.	1,149	1,096
Antony (2018) [19]	USA	Retrospective observational	Tertiary care	174[2]	Adherence four-quadrant biopsy protocol vs non-adherence four-quadrant biopsy protocol	Four-quadrant biopsies every 2 cm of BE length, as stated in endoscopy reports. Pathology reports were used to confirm that sufficient biopsies were taken	71	103
Bampton (2006)[20]	Australia	Retrospective observational	Secondary care	466	Surveillance program with high (83 %) adherence to four-quadrant biopsy protocol vs surveillance program with low (26 %) adherence to four-quadrant biopsy protocol.	Four-quadrant biopsies every 2 cm of BE length[3]	213	253
Britton (2019) [21]	UK	Prospective intervention, non-randomized	Secondary care	295	Dedicated BE endoscopy programs with high (72 %) adherence to four-quadrant biopsy protocol vs non-dedicated BE endoscopy programs with low (42 %) adherence to four-quadrant biopsy protocol.	Expected number of biopsies (BE length/ 2 × 4) versus the actual number of biopsies taken.	188	71
Fitzgerald (2001)[22]	UK	Prospective intervention vs historical cohort	NR	204	Adherence four-quadrant biopsy protocol vs non-systematic biopsy protocol	Four-quadrant biopsies every 2 cm of BE length[3]	108	96
Ooi (2017) [23]	UK	Prospective intervention vs historical cohort	Secondary care Tertiary care	729	Dedicated BE endoscopy programs with high (77 %) adherence to four-quadrant biopsy protocol vs non-dedicated BE endoscopy programs with low (10 %) adherence to four-quadrant biopsy protocol.	Four or more biopsies per 2 cm of BE sent to pathology department	142	587
Wani 2019[24]	USA	Retrospective observational	Secondary care	53,541	Adherence four-quadrant biopsy protocol vs non-adherence four-quadrant biopsy protocol	BE length divided by number of pathology jars submitted to pathology department. A ratio of ≤ 2.0 with rounding up was defined as adherent	21,013	7,280

BE, Barrett's esophagus; NR, not reported.
[1] Twenty-nine patients (1.3 %) had a documented history of dysplasia.
[2] Forty-six patients (26 %) received prior endoscopic therapy.
[3] No information on how adherence was confirmed.



▶ **Fig. 2** Application of the modified QUADAS-2 tool to the eight included studies.

LGD, which is currently the most important risk factor for progression to HGD or cancer.

Previous studies have reported malignant progression in BE to be more prevalent in the longer BE segments [28–31]. Adherence to the four-quadrant biopsy protocol tends to decrease with increasing BE lengths. Abrams et al. and Wani et al. showed adherence to four-quadrant biopsy protocol of 76 % and 79 % respectively, in patients with short BE segment (< 4 cm) compared to 11 % and 38 % in patients with BE segment > 8 cm [18, 24]. In a subanalysis, we aimed to evaluate whether BE length impacted the association between adherence and dysplasia detection. However, only two studies included in our meta-analysis, stratified their analysis for Barrett length [18, 24]. In the pooled analysis, there appeared to be a trend toward an increased risk ratio for dysplasia detection in longer BE segments. One potential explanation could be that non-adherence in a short-segment BE may indicate that only one or two biopsies are not obtained. However, in a 10-cm-long BE, for example, non-adherence may imply that instead of the 20 required biopsies, only 14 biopsies would have been obtained. This finding suggests that patients with higher progression risks are mostly disadvantaged by non-adherence.

Whereas seven of the eight included studies in our meta-analysis showed increased detection of dysplasia when adhering to the random biopsy protocol, the study of Wani et al. found that non-adherence to the four-quadrant biopsy protocol was significantly associated with an increase in dysplasia detection [24]. The authors emphasized that the database they conducted their retrospective study with did not contain information on the presence of visible lesions within the BE segment. Therefore, discrimination between dysplasia detected by random biopsies from dysplasia obtained from targeted biopsies of visible lesions was not possible. This is of particular importance since endoscopists detecting visible lesions might well take only targeted biopsies and omit the random biopsies thereafter because of the limited clinical relevance of those additional random biopsies, hence reducing the adherence to the random biopsy protocol in these patients. Moreover, in this study, adherence to the four-quadrant biopsy protocol was defined as the number of pathology jars divided by Barrett length. The use of pathology jars instead of the number of biopsies could have led to misclassification of non-adherent cases to adherent cases.

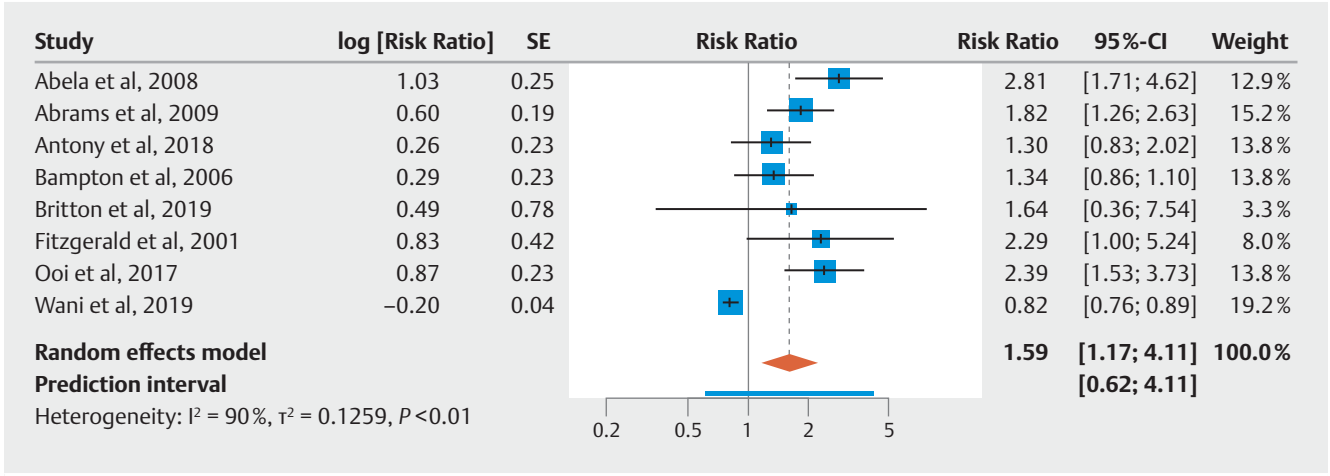
To the best of our knowledge, this is the first systematic review and meta-analysis to assess the effect of four-quadrant biopsy protocol non-adherence on dysplasia detection rates. To ensure methodological quality, we did a thorough systematic search and analysis according to current guideline recommendations for systematic review and meta-analyses [14]. Ultimately, we aimed to translate previous research on four-quadrant biopsy protocol adherence rates into concrete, clinically relevant results, i. e. dysplasia detection.

This study has also limitations that need to be mentioned. First and foremost, the review included non-randomized, mainly retrospective studies only, and few included studies used methods to adjust for confounding such as BE length, visible lesions, endoscopy time, and the use of advanced imaging techniques. We performed a good-quality synthesis to partly address this limitation and reduce the influence of possible bias. Although randomized trials on this topic are impossible to conduct, the flaws in non-randomized study design are the reason the risk of selection bias and presence of confounding cannot be ruled out. Second, there was considerable heterogeneity between studies, as reflected by high values of the I^2-statistic and predominantly wide prediction intervals. The between-study heterogeneity could potentially be a result of differences in the definition of four-quadrant random biopsy adherence, study population and outcome measures. By performing a good-quality synthesis, we aimed to diminish the level of methodological heterogeneity. Although prediction intervals in this review are based on few studies and should be interpreted with caution, intervals containing the null effect indicate that there could be settings where adherence to the four-quadrant random biopsy protocol will not result in increased dysplasia detection rates. Yet, meta-regression analyses for thorough exploration of sources of heterogeneity were not considered feasible considering the limited number of included studies. Third,

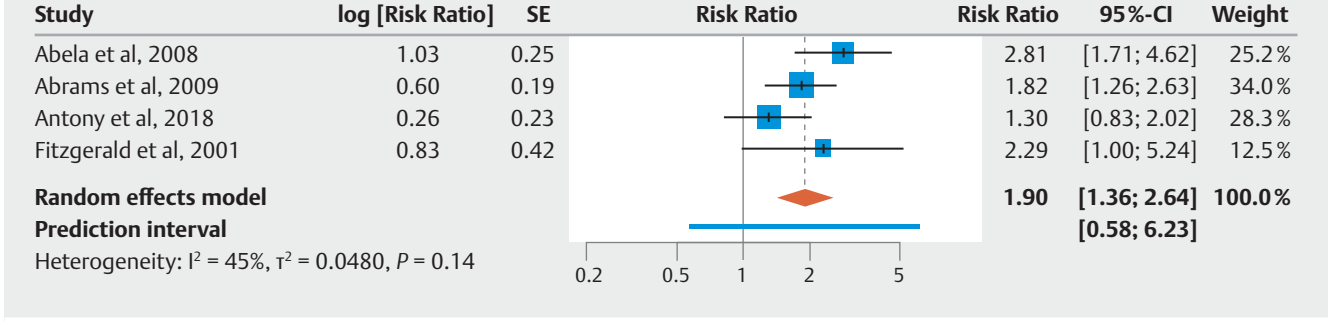
▶ **Table 2** Patient and disease characteristics.

Author (year)	Mean age, years	Gender, M:F	Mean BE segment length, cm (sd)	Mean no. biopsies per 2 cm	Definition dysplasia	Detection rate adherence, % (n)	Detection rate non-adherence, % (n)	Relative risk (95 % CI)
Abela et al (2008) [17]	65	1.6:1	6.0 (4–9)	Adherence: 4.6[1] Non-adherence: 1.6[1]	LGD HGD EAC	27.8 (50/180)	9.9 (18/182)	2.81 (1.71–4.62)
Abrams et al (2009) [18]	63	2.2:1	3.0 (2–5)[1]	3.3[1]	IND LGD HGD EAC	< 3 cm: 2.9 (24/826) 3–5cm: 10.4 (27/259) 6–8 cm: 19.1 (8/42) ≥ 9 cm: 18.2 (4/22)	< 3 cm: 2.2 (5/223) 3–5 cm: 4.0 (20/497) 6–8 cm: 11.4 (22/193) ≥ 9 cm: 17.5 (32/183)	1.82 (1.26–2.63)[2]
Antony et al (2018) [19]	67	3.0:1	3.0[1]	NR	NR	35.0 (25/71)	27.2 (28/103)	1.30 (0.83–2.02)
Bampton et al (2006) [20]	NR	NR	NR	NR	LGD HGD EAC	16.4 (35/213)	12.3 (31/253)	1.34 (0.86–2.10)
Britton et al (2019) [21]	NR	NR	Adherence: 3.6 Non-adherence: 4.1	Adherence: 4.2 Non-adherence: 2.9	IND LGD HGD EAC	4.3 (9/209)	2.6 (2.76)	1.64 (0.36–7.40)
Fitzgerald et al (2001) [22]	64	Adherence: 3.5:1 Non-adherence: 2.8:1	Adherence: 6.0 (1–15)[3] Non-adherence: 5.0 (1–15)[3]	Adherence: 4.0 Non-adherence: 1.6	LGD HGD EAC	16.7 (18/108)	7.3 (7/96)	2.29 (1.00–5.23)
Ooi et al (2017) [23]	62	Adherence: 1.6:1 Non-adherence: 2.0:1	Adherence: 3.7 (0.25) Non-adherence: 4.1 (0.14)	Adherence: 4.0 Non-adherence: 2.0	IND LGD HGD EAC	18.3 (26/142)	7.7 (45/587)	2.39 (1.53–3.73)
Wani et al (2019) [24]	61	1.5:1	2.3 (2.3)	NR	IND LGD HGD	≤ 4 cm: 6.6 (1313/20,034) 4–6 cm: 14.1 (203/1,442) 6–8 cm: 17.9 (108/602) > 8 cm: 20.0 % (124/620)	≤ 4 cm: 9.3 (347/3,718) 4–6 cm: 13.9 (108/777) 6–8 cm: 16.6 (74/445) > 8 cm: 18.0 (118/655)	0.82 (0.76–0.89)[2]

BE, Barrett's esophagus; NR, not reported; LGD, low-grade dysplasia; HGD, high-grade dysplasia; EAC, esohageal adenocarcinoma; IND, indeterminate.
[1] Median, (IQR).
[2] Weighted relative risk over strata of BE length.
[3] Mean (range).



▶ **Fig. 3** Forest plot depicting the relative risks of dysplasia detection for adherence to the four-quadrant biopsy protocol versus non-adherence, using a random effects model.



▶ **Fig. 4** Good-quality synthesis: random effects meta-analysis of relative risks of dysplasia detection for adherence versus non-adherence to the four-quadrant biopsy protocol.

although this systematic search was conducted extensively and aimed to include all eligible and available studies, the asymmetry in the funnel plot may suggest a risk of publication bias. The high level of heterogeneity between studies could also contribute to funnel plot asymmetry, and should therefore be interpreted with caution. Finally, this review solely focused on differences in dysplasia detection rates. Therefore, it does not provide direct evidence for the effect of four-quadrant biopsy protocol adherence on patient outcomes, such as neoplastic BE treatment success or patient survival.

This systematic review and meta-analysis focused only on four-quadrant biopsy adherence to improve detection of dysplastic BE. The use of advanced imaging techniques, such as acetic acid chromoendoscopy, have been shown to increase dysplasia detection rates in BE surveillance endoscopies compared to white-light endoscopy [32–34]. Furthermore, computer-aided detection systems using artificial intelligence have emerged as a promising tool and may help endoscopists in detecting dysplastic lesions [35]. The additional diagnostic value of four-quadrant biopsies in the presence of these advanced imaging modalities is yet to be studied.

Conclusions

In conclusion, this systematic review and meta-analysis provides evidence for the importance of random biopsy protocol adherence in BE surveillance endoscopies. In an effort to optimize the quality of BE surveillance, an increase in biopsy protocol adherence rates is a goal that clinicians should strive to achieve.

Competing interests

The authors declare that they have no conflict of interest.

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