Digestive and Liver Disease 51 (2019) 1515–1521

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Meta-Analysis

Chromoendoscopy or white light endoscopy for neoplasia detection in Lynch syndrome, a meta-analysis

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ARTICLE INFO

Article history:
Received 12 December 2018
Accepted 25 July 2019
Available online 13 September 2019

Keywords:
Chromoendoscopy
Colonoscopy
Hereditary non-polyposis colorectal cancer
Lynch syndrome
Meta-Analyses
Surveillance

ABSTRACT

Background: Lynch syndrome carries an increased risk of colorectal neoplasia, hence annual surveillance colonoscopy is recommended. This study aimed to compare the diagnostic yields of image enhancement modalities for colorectal neoplasia in patients with Lynch syndrome.
Methods: Meta-analysis of pooled ratios of lesion detection rates (RRs) and odds ratios (ORs) with 95% confidence intervals (CIS), comparing white light endoscopy (WLE) and chromoendoscopy (ChE).
Results: Four studies comparing WLE to ChE were analyzed. ChE fared better than WLE in overall lesion detection (RR 1.97, 95% CI 1.63–2.38) and detection of adenomas (RR 1.53, 95% CI 1.07–2.17), flat lesions (RR 3.4, 95% CI 2.47–4.67) and proximally-located lesions (RR 2.93, 95% CI 1.91–4.5). The odds of a patient having any lesion found were higher in ChE compared to WLE (OR 2.42, 95% CI 1.56–3.75). The odds of a patient having adenoma(s) found on endoscopy were not significantly higher in chromoendoscopy compared to white light endoscopy (OR 1.81, 95% CI 0.65–5.01).
Conclusion: Using standard definition technology, ChE allows detection of more lesions, especially adenomas, flat lesions and proximal lesions in Lynch syndrome patients, compared to WLE. The results show that surveillance colonoscopy of Lynch syndrome patients should be performed using ChE.

1. Introduction & background

Lynch syndrome (LS) is an autosomal-dominant hereditary colorectal neoplasia (CRN) syndrome. Compared to sporadic CRN, the precursor lesions in LS patients tend to be more proximally located, with flat morphology [1,2]. A characteristic feature of LS lesions is a rapid adenoma-carcinoma sequence, faster than that of sporadic CRN [3]. Therefore, several professional societies [4–8] recommend surveillance colonoscopy every 1–2 years, starting at 20–25 years of age in LS patients. However, despite frequent screening, the miss rate for significant lesions is not negligible. While a CRN screening miss rate of 20% has been reported for the general population [9], a 55% miss rate has been described in LS patients [10]. In this patient population, the ability to improve lesion detection by using advanced-imaging techniques such as chromoendoscopy (ChE) is appealing. Based on four rather small studies, current ESGE guidelines [10] are the only ones which recommend ChE in LS surveillance. In patients with long-standing ulcerative colitis, representing yet another high-risk population, ChE has been shown to improve significant lesion detection in meta-analyses [11,12], but this comparison modality has never been used to address the question in LS patients.

The aim of this study was to compare the diagnostic yield (DY) of conventional white light endoscopy (WLE) to that of advanced-imaging colonoscopy for the detection of colorectal neoplasia in patients with LS by undertaking a meta-analysis of the existing literature.

2. Methods

2.1. Search strategy

A MEDLINE search was performed on January 8th, 2017 using the search terms “Lynch”, “hereditary non-polyposis colorectal cancer”, “imaging”, “chromoendoscopy”, “narrow band imaging”,

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https://doi.org/10.1016/j.dld.2019.07.018
1590-8658/

"cap-assisted", "virtual", "i-scan", "autofluorescence", "endoscopy" and "colonoscopy". A repeat search was performed on May 20th, 2018 to capture any relevant new publications. Only studies published as full articles were included. Duplicate entries were removed. Reference lists of the relevant publications were screened to retrieve additional articles.

2.2. Study eligibility criteria

Studies were eligible for analysis if they met the following criteria: (1) prospective with parallel or crossover design; (2) the outcome measures compared neoplastic lesion detection using at least 2 endoscopic imaging methods; (3) including patients with LS.

Studies were excluded if: (1) published in an abstract form only; (2) if they were non-comparative publications such as: (a) reviews (b) opinion pieces (c) previous meta-analyses.

2.3. Study selection and data extraction

Studies retrieved were screened by title and abstract. Abstracts of eligible studies were then retrieved and screened independently by two authors (O.H, L.H.K). Any disagreement was resolved by discussion and consensus agreement. The full texts of potential studies were reviewed, and the list of eligible studies was finalized. Data extraction was independently performed by three authors (O.H, L.H.K, B.A).

In this work, "lesions" refers to all lesions that were found (adenoma, hyperplastic, normal colonic tissue) and ädenomas̈includes all adenomatous lesions (low/ high grade dysplasia, cancer, serrated). For each included study, data were extracted for the numbers of patients undergoing endoscopy with WLE and those who underwent ChE, and the numbers of patients with lesions detected using each endoscopic modality. Data were extracted for the following lesion types: adenomatous lesions, proximal lesions, flat lesions, lesions with high-grade dysplasia histology and cancers. Only dysplastic lesions were included in the analysis while hyperplastic lesions, inflammatory lesions or those indefinites for dysplasia were excluded.

2.4. Statistical analyses

Meta-analysis was performed if data were available for more than 3 studies comparing each outcome measure.

Three types of analyses were conducted:

1) Pooled rate ratios (RRs) with 95% confidence intervals (CI) were used to compare the rate of detected lesions or adenomas per patient in those undergoing colonoscopies with ChE vs WLE.
2) Pooled odds ratios (ORs) with 95% CI were used to compare the odds of detecting lesions or adenomas in individual patients undergoing ChE vs WLE.
3) Pooled proportions with 95% CI were used to compare proportions of lesions which were detected using ChE vs WLE, based on the total number of each type of lesion detected.

For each analysis, the I^2 statistic [13] was used to report the percentage of heterogeneity across the included studies. High heterogeneity was taken to be $I^2 > 50\%$, and low heterogeneity was indicated by $I^2 \leq 25\%$. Initial summary measures were obtained using the DerSimonian-Laird (random effects) model as a default, following which heterogeneity was assessed. The Mantel–Haenszel (fixed effects) method was applied instead if heterogeneity was found to be low.

Heterogeneity was examined using forest plots to visually assess the effects of individual studies on the pooled results, in addition to further subgroup analyses where appropriate, e.g. examining various, more specific, types of lesions.

Funnel plots were not obtained to assess study bias due to the small number of studies, see Section 3.

The risk of bias in each included study was assessed using the quality assessment of diagnostic accuracy studies (QUADAS)-2 scale [14]. Statistical analyses were carried out using the meta package [15] in R version 3.4.2 [16] and Review Manager 5.3 software [17].

3. Results

3.1. Study retrieval

The initial database search yielded 132 potential citations. 36 duplicates were removed and 79 were excluded based on title. 17 abstracts were screened; 9 were excluded and 8 full-text articles [18–25] were retrieved for review. After full-text review, 3 studies comparing WLE to autofluorescence, NBI and i-scan were excluded as their data could not support meta-analysis. 5 studies [19–22,24], comparing WLE to traditional ChE, were deemed eligible for final analysis. One of these studies [19] used a different methodology by which lesions were not removed during the first WLE, hence this study could not be compared to the other studies and therefore was excluded from statistical analysis (see Characteristics of included studies). Four studies [20,20,21,22,24] were finally analyzed, Fig. 1.

3.2. Characteristics of the included studies

Study characteristics are summarized in Table 1. Three studies [20–22] used a cross-over "back-to-back" design, in which WLE examination was performed first, and the ChE examination was performed immediately after. In these studies, lesions that were identified during WLE were resected (or biopsied, according to their size). The remaining study by Stoffel et al. [24] used a different design where WLE was performed first with resection/biopsy of identified lesions and then randomization in the second phase to either ChE or ïntensive WLE.̈ For the purpose of this meta-analysis we extracted data only from the first WLE examination and compared them to the ChE group in the second phase.

Lecomte et al. [21] performed ChE from the cecum to the splenic flexure, while all other studies applied pan-colonic ChE. The meta-analysis dataset is summarized in Table 2.

3.3. Quality analysis of included studies

The QUADAS analysis of the included studies is outlined in Table 3. The main risk of bias resulted from the back-to-back study designs, which were sometimes carried out by the same endoscopist.

4. Comparison of chromoendoscopy vs white light endoscopy

4.1. Lesions per patient analysis

In total, 164 patients underwent ChE while 190 underwent WLE. 311 lesions were detected by ChE and 169 by WLE. Patients undergoing ChE had a lesion detection rate almost twice that of those undergoing WLE (RR 1.97, 95% CI 1.63–2.38, $I^2 = 0\%$), Fig. 2a. Of all lesions detected in the included studies, an overall proportion of 0.65 (i.e. 65%) of lesions were detected by chromoendoscopy. 81 adenomas were detected by ChE and 56 by WLE. The adenoma detection rate was 1.5 times using ChE compared to WLE (RR 1.53, 95% CI 1.07–2.17, $I^2 = 45\%$), Fig. 2b. 57% of all adenomas detected

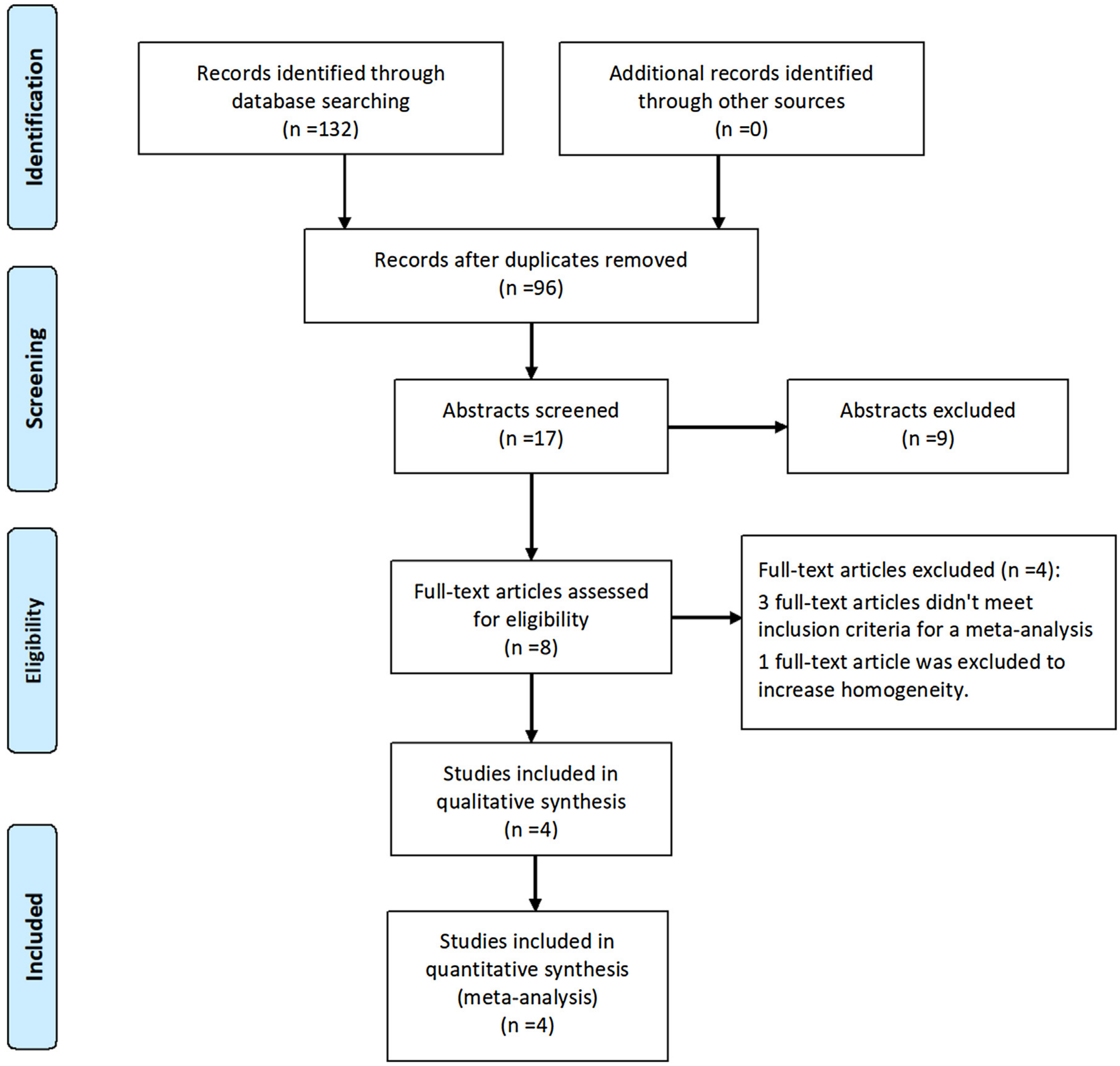

Fig. 1. Flow chart of the studies selection process.

in all studies were detected by ChE. 173 flat lesions were detected by ChE and 52 by WLE. The flat lesion detection rate was 3.4 times using ChE compared to WLE (RR 3.4 95% CI 2.47–4.67, $I^2 = 44\%$), Fig. 2c. 77% of all flat lesions detected in all studies were detected by ChE. 86 proximal lesions were detected by ChE and only 30 by WLE; using ChE, proximal lesions were detected at a rate almost 3 times that of WLE (RR 2.93, 95% CI 1.91–4.50), $I^2 = 18\%$), Fig. 2d. 72% of all proximal lesions were picked up by ChE. Since cancer was found only in one study, and HGD in two, meta-analyses were not valid for these parameters.

4.2. *Affected patient identification analysis*

Lesions of any type were found in 105/164 (64.02%) patients undergoing ChE compared to 78/190 (41.05%) patients undergoing WLE (OR 2.42, 95% CI 1.56–3.75, $I^2 = 0\%$), Fig. 3a. 44/131 (33.58%) of patients who underwent ChE harbored at least one adenoma, compared to 33/157 (21.01%) detected by WLE. The OR of a patient having adenoma(s) on ChE vs in WLE was 1.81 (95% CI 0.65–5.01, $I^2 = 62\%$); however, this result did not reach statistical significance, Fig. 3b.

5. Discussion

The importance of early detection of colorectal dysplasia in patients with LS cannot be overemphasized. Numerous guidelines recommend surveillance colonoscopy every 1–2 years, but the exact endoscopic method for performing these examinations has yet to be determined. Currently, only the ESGE [10] guidelines recommend the usage of ChE in LS, albeit based on limited, low quality evidence. Our meta-analysis, which is – to the best of our knowledge – the first on this topic, shows that ChE is superior to WLE for CRC surveillance in patients with LS, and provide evidence for the usage of ChE in this group. Especially important is the advantage of ChE over WLE in proximal lesion detection, as proximal lesions are particularly prevalent in LS [26].

Our dataset comprises four studies [20–22,24] in which the first colonoscopy was done using WLE, followed by ChE examination. In the study by Stoffel [24], after WLE, patients were randomized to either ChE or intensive WLE. For the purposes of the meta-analysis, we used only the data from the ChE arm. The cross-over design posed an inherent disadvantage for the ChE arm. Lesions were detected and resected under WLE and were therefore not available for the ChE analysis. In addition, in the study by Lecomte et al. [21] the ChE was performed only to the splenic flexure. In spite these

Table 1
Characteristics of the included studies.

Author	Definition of LS - genetic/clinical	Type of study	Crossover design?	WL-scope definition	Preparation method	Type of spray	High definition Y/N	Mean withdrawal time-WLE	Mean withdrawal time-CE	Funding
Lecomte et al. [21]	18 genetic + 18 clinical (LS family members)	Prospective, non randomized	Yes	EC485ZW, Fujinon	PEG 4-6 L + 3 days diet	Indigo carmine 0.4%	High-resolution	N/A (41+/−11 for WLE + CE)	17+/−6	Fuji donated the endoscope
Hurlstone et al. [20]	19 genetic + 18 clinical (LS family members)	Prospective, non randomized	Yes	Olympus CF240Z	PEG 2-4 L	Indigo carmine 0.5%	No	Median 13, 8–36	median 14, range 9–38	Fuji donated the endoscope
Stoffel et al. [24]	46 genetic 8 clinic	Prospective non randomized/ prospective randomized	Yes	Olympus 160/ pentax 160	magnesium citrate + 4 L PEG or magnesium citrate + phosphosoda or magnesium citrate + visicol	Indigo carmine 0.2%	No	N/A (only total time was provided)	N/A (only total time was provided)	None
Rahmi et al. [22]	78 genetic (all)	Prospective non randomized	Yes	Olympus CF-H 180; Fujufilm EC530 Wm	PEG 4 L or sodium phophate	Indigo carmine 0.4% - spray catheter	No	Median 10, 7–14	21.5 17–30	A research grant

Table 2
The meta-analysis extraction dataset.

Author	# of total WLE patients	# of patients with any lesion in WLE	# of patients with adenomas in WLE	# of total ChE patients	# of patients with any lesion in ChE	# of patients with adenomas in ChE
Lecomte et al. [21]	33	13	NA	33	20	NA
Hurlstone et al. [20]	25	10	7[a]	25	15	17[a]
Stoffel et al. [24]	54	15	8	28	15	3
Rahmi et al. [22]	78	40	18	78	55	24

Author	# of lesions detected in WLE	# of lesions detected in ChE	# of adenomas detected in WLE	# of adenomas detected in ChE	# of proximal lesions detected in WLE	# of proximal lesions detected in ChE	# of flat lesions detected in WLE	# of flat lesions detected in ChE	HGD- WLE	HGD- ChE	cancer detected-WL	cancer detected-ChE
Lecomte et al. [21]	25	45	7	11	8	35	5	39	0	0	None	None
Hurlstone et al. [20]	24	52	13[b]	36[c]	8	28	7	35	3	7	1	0
Stoffel et al. [24]	22	26	10	5	4	2[d]	9	11	0	0	0	0
Rahmi et al. [22]	98	188	26	29	10	21	31	88	1	0	0	0

[a] It is unclear if the serrated/adenocarcinoma lesions were diagnosed in the same patients that are included in the database or in additional patients.
[b] Including one cancer and one serrated lesion.
[c] Including 4 serrated lesions.
[d] One lesion was normal colonic mucosa.

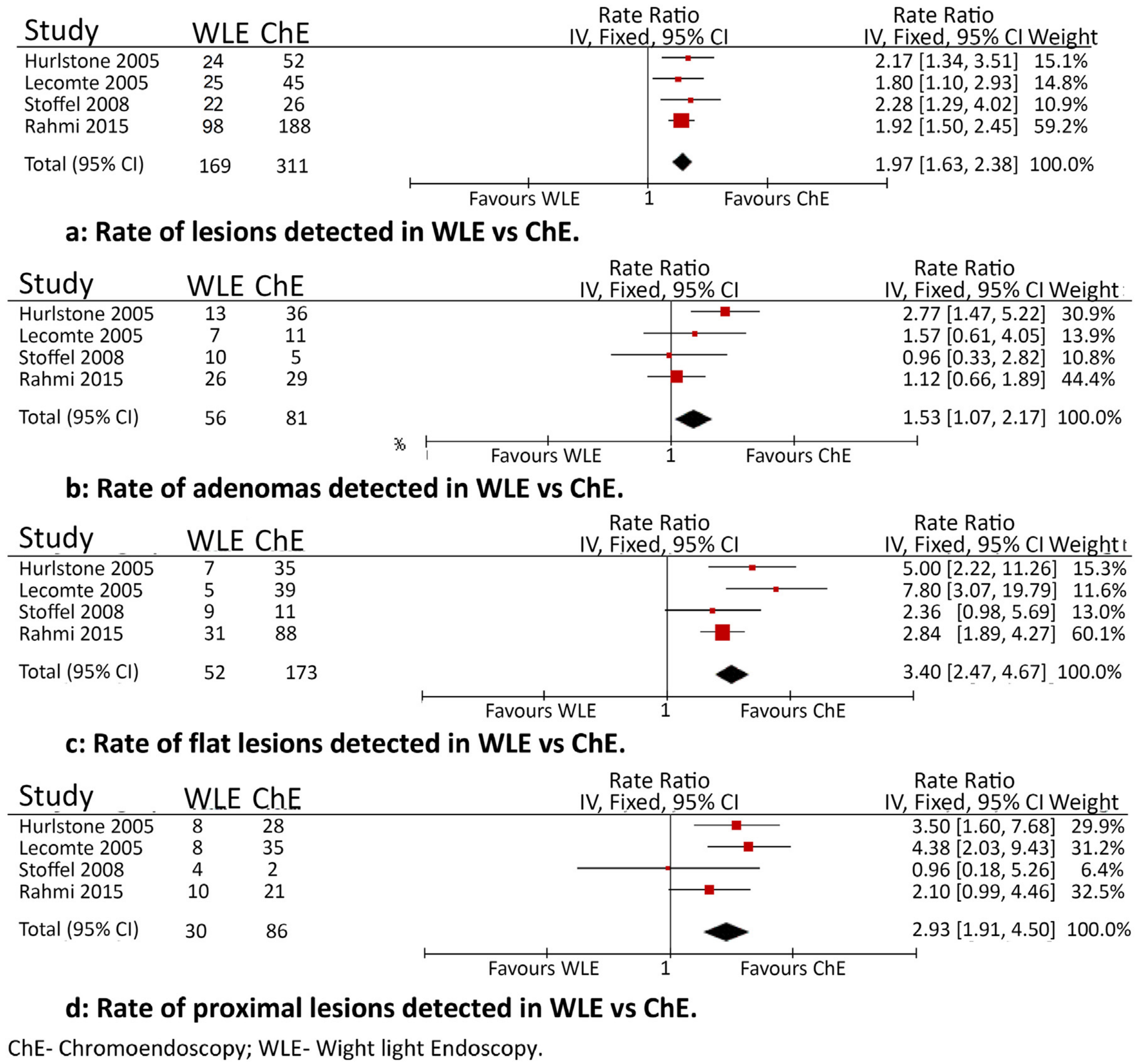

Fig. 2. (a) Rate of lesions detected in WLE vs ChE. (b) Rate of adenomas detected in WLE vs ChE. (c) Rate of flat lesions detected in WLE vs ChE. (d) Rate of proximal lesions detected in WLE vs ChE.

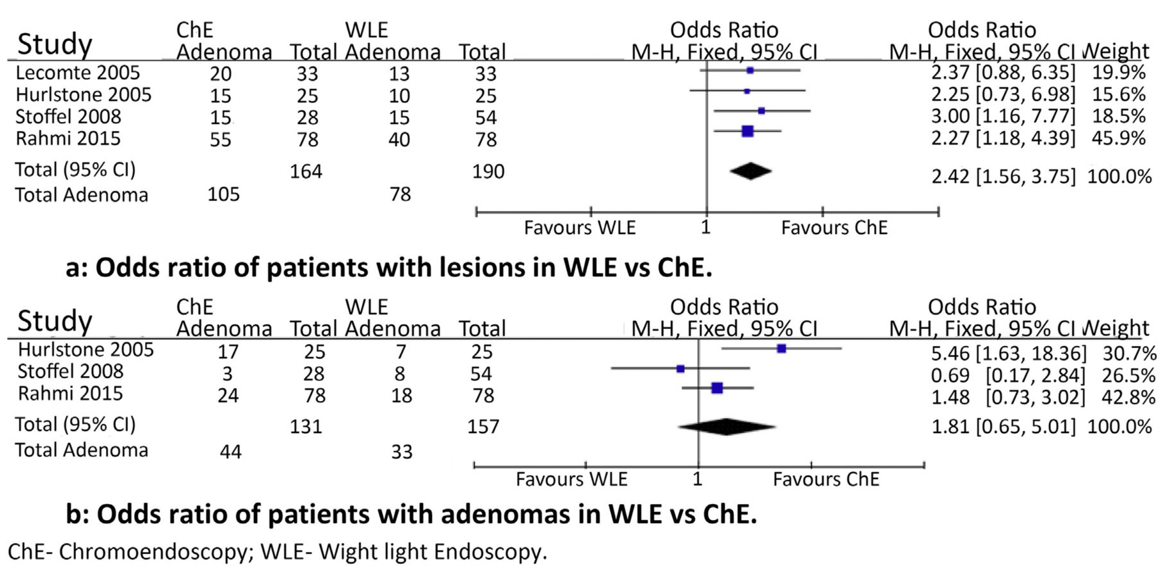

Fig. 3. (a) Odds ratio of patients with lesions in WLE vs ChE. (b) Odds ratio of patients with adenomas in WLE vs ChE.

Table 3
Quality assessment of included studies using QUADAS-2 framework.

First author, year [ref]	Item 1: risk of bias in patient selection	Item 2: representative patient spectrum?	Item 3: risk of bias in conduct or interpretation of index test (CE)	Item 4: applicability of index test (CE) to review question	Item 5: risk of bias from conduct or interpretation of reference standard (WLE)	Item 6: risk of bias from applicability of reference standard (WLE)	Item 7: risk of bias from timing/patient flow
Lecomte, 2005 [21]	Low	Low	High	Unclear	Low	Low	High
Hurlstone, 2005 [20]	Low	Low	High	Low	Low	Low	High
Stoffel, 2008 [24]	Low	Low	Unclear	Low	Low	Low	Unclear
Rahmi, 2015 [22]	Low	Low	Unclear	Low	Low	Low	Unclear

Abbreviations: CE, chromoendoscopy; WLE, white light endoscopy.

Che fared better. A fifth study by Huneburg et al. [19] which compared two independent examinations was excluded from analysis because of different methodology from the four analyzed studies, although it otherwise met inclusion criteria. However, this study [19] also found more adenomatous lesions in the ChE arm compared to the WLE arm. The different methodology used by this, as well as by the Stoffel's study [24] emphasize the superiority of ChE over WLE even more.

Implementing ChE in routine practice does not come smoothly [27,28]. It is perceived as time and resource consuming, with a strong requirement for high-quality training and equipment. However, in patients with longstanding ulcerative colitis, another high-risk population, it has already been demonstrated [29,30] that ChE can be implemented into ř̌eal-lifep̌ractice without a significant learning curve and with only a modest increase in examination time. Such data is currently missing for patients with LS, but extrapolating from this, ChE may have an advantage over WLE.

There are some limitations to this work. None of the primary studies was randomized-controlled and the sample size was small. This is likely due to the relatively limited population of patients with LS, as well as ethical and administrative difficulties in running studies where patients are required to undergo two colonoscopies back to back. Furthermore, the limited amount of data has restricted the sensitivity analyses which we have been able to carry out. However, for most outcomes tested, the heterogeneity between studies was minimal and most of the comparisons reached statistical significance.

Another potential limitation stems from the use of standard definition (SD) endoscopy in most of the included studies. Only one study [21] used a high-resolution endoscope, while the other three studies [20,22,24], published earlier, employed SD technology. SD technology has now been replaced in many endoscopy suits by modern high-definition (HD) technology and the impact of HD on CRC surveillance in LS patients is still unknown. The use of modern image-enhanced technologies (NBI, i-scan, autofluorescence etc.) is another conundrum. Overall, these limitations serve to reflect the paucity of data available for patients with LS and show that much further work is needed to optimize care for this patient group.

6. Conclusion

This meta-analysis implies an advantage of ChE over WLE in LS surveillance colonoscopies. More studies are needed comparing HD technology and advanced imaging methods with ChE for adenoma detection as well as and to assess the impact of ChE on advanced polyps and cancer detection.

Conflict of interest

None declared.

Disclosures

UK-research grants – Takeda, Medtronic, Janssen; Consultancy – Jannsen, CTS; Lecture fees – Abbvie, Jannsen, Takeda, CTS; All other authors – none relevant to this article.

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