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Dye-Based Chromoendoscopy in Patients With Lynch Syndrome: An Individual Patient Data Meta-Analysis of Randomized Trials

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INTRODUCTION: **The additional diagnostic value of dye-based chromoendosocpy (CE) for surveillance of patients with Lynch syndrome is subject of debate.**

METHODS: **To clarify this debate, we performed an individual patient data meta-analysis of randomized studies that compared CE with WLE for the detection of adenomas in patients with Lynch syndrome.**

RESULTS: **Three randomized studies comprising 533 patients were included. The adenoma detection rate was 74/265 (28%) in patients randomized to WLE compared with 83/266 (31%) in patients randomized to CE (odds ratio 1.17; 95% confidence interval 0.81–1.70).**

DISCUSSION: **Based on low-quality evidence, CE showed no apparent increase in adenoma detection compared to WLE during surveillance of patients with Lynch syndrome.**

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/AJG/B865, http://links.lww.com/AJG/B866, http://links.lww.com/AJG/B867, http://links.lww.com/AJG/B868, http://links.lww.com/AJG/B869, http://links.lww.com/AJG/B870, http://links.lww.com/AJG/B871.

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INTRODUCTION

Studies have shown inconsistent results regarding the additional diagnostic value of dye-based chromoendoscopy (CE) for polyp detection in patients with Lynch syndrome. Based on these inconsistent results, advanced imaging recommendations and guidelines differ between countries (1–4). The present study aimed to address this controversy regarding the use of dye-based CE.

METHODS

An individual patient data (IPD) meta-analysis was performed according to the PRISMA-IPD guidelines (PROSPERO CRD42018095692) (5). Randomized trials comparing the efficacy of dye-based CE with white-light endoscopy (WLE) (standard definition [StD] and high definition [HD]) for the detection of adenomas in patients with Lynch syndrome were included. Only individuals with a proven Lynch syndrome–associated gene mutation (*MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EpCAM*) were included in the analysis. The primary outcome measure was the adenoma detection rate (ADR) (i.e. proportion of patients with at least one adenoma detected during colonoscopy). Patients were subdivided in 2 groups—(1) StD equipment and (2) HD equipment. Mixed-effect models were used to estimate detection rates across studies. Complete methods can be found in Supplemental Digital Content 1 (see Supplementary A, http://links.lww.com/AJG/B865).

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Table 1. Study and baseline characteristics of included patients with Lynch syndrome

	Haanstra (Netherlands)	Sanchez (Spain)	Stoffel (United States)	Total
Study				
Year published	2018	2019	2008	
Enrolment period	2008–2014	2016–2018	NA	
Design	RCT	RCT	Tandem RCTb	
Anatomical region CE	Proximal[a]	Total	Total	
Indigo carmine solution	0.4%	0.4–2%	0.2%	
No. of centers	6	14	4	
No. of endoscopists	NA	26	7	
Patients				
No. of patients	231	256	46	533
Age, mean (SD)	46 ± 12	47 ± 14	42 ± 14	46 ± 13
Male, N (%)	95 (43)	103 (36)	20 (43)	218 (44)
Mutation, N (%)				
MLH1	59 (26)	74 (29)	15 (33)	148 (28)
MSH2	75 (32)	106 (41)	29 (63)	210 (39)
MSH6	92 (40)	57 (22)	2 (4)	151 (28)
EpCAM	5 (2)	2 (1)	0 (0)	7 (1)
PMS2	0 (0)	17 (7)	0 (0)	17 (3)
History of CRC surgery, N (%)	0 (0)	54 (21)	10 (22)	64 (12)
Procedure				
Total # detected carcinomas	1	0	0	1
Total # detected adenomas	103	142	17	262
Total # detected proximal adenomas[c]	70	90	4	164
Total # detected polyps	190	275	33	498
Total # detected proximal polyps[c]	60	164	6	237
High definition, N %	107 (46)	256 (100)	0 (0)	363 (68)
Excellent bowel preparation, N %	174 (75)	96 (38)	46 (100)	316 (59)

[a]The colon of patients in the CE allocation arm was inspected with CE in the proximal colon and with WLE in the distal colon.
[b]The colon of patients in the study of Stoffel was inspected twice. Study patients were randomized after a first exam with white light to an immediate second examination with either dye-based CE or WLE.
[c]Lesions located proximal to the splenic flexure were defined as proximal lesions.
CE, chromoendoscopy; CRC, colorectal cancer; RCT, randomized controlled trial; WLE, white-light endoscopy SD, standard deviation.

RESULTS

After assessing all studies, 2 randomized controlled trials and one randomized tandem colonoscopy study were included, comprising 533 patients with Lynch syndrome with a proven gene mutation (see Supplementary B, Supplemental Digital Content 2, http://links.lww.com/AJG/B866) (6–8). The mean age of the included patients was 46 years (standard deviation 13) and 218 (44%) were men (Table 1). Baseline characteristics of the included patients did not differ between CE and WLE. HD equipment was used in 363/533 (68%) of the colonoscopy procedures.

The ADR was 74/265 (27.9%; 95% confidence interval [CI] 22.6–33.7%) in patients randomized to WLE compared with 83/266 (31.2%; 95% CI 25.7–37.1%) patients randomized to CE (odds ratio [OR] 1.17; 95% CI 0.81–1.70, $P = 0.41$) (Table 2). No difference in the ADR was observed for either imaging modality within the HD equipment group (OR 1.20, 95% CI 0.77–1.90, $P = 0.42$) or the StD equipment group (OR 1.17; 95% CI 0.60–2.32, $P = 0.65$). The mean number of adenomas per patient detected with CE was 0.52 compared with 0.47 with WLE (incidence rate ratio 1.09; 95% CI 0.78–1.52, $P = 0.60$) (Table 3). Subgroup analyses showed no significant differences between CE and WLE for proximal adenomas (OR 1.40, 95% CI 0.92–2.14, $P = 0.11$), flat adenomas (OR 1.34; 95% CI 0.80–2.24, $P = 0.26$), or diminutive adenomas (OR 1.21, 95% CI 0.81–1.81, $P = 0.34$) (see Supplementary C, Supplemental Digital Content 3, http://links.lww.com/AJG/B867). CE took significantly more time than WLE (median procedure time 29 vs 21 minutes, $P < 0.01$; extubation time: 19 vs 12 minutes, $P < 0.01$).

All included studies were judged to have a high risk of bias in blinding of participants and personal (see Supplementary D, Supplemental Digital Content 4, http://links.lww.com/AJG/B868). All

Table 2. Adenoma detection rate

Equipment	No. studies	CE % (n/N)	WLE % (n/N)	Odds ratio[a] (95% CI)	*P*-value
All	3	31.2% (83/266)	27.9% (74/265)	1.17 (0.81–1.70)	0.41
High-definition	2	30.8% (57/185)	27.0% (74/178)	1.21 (0.77–1.90)	0.42
Standard-definition	2	32.9% (25/76)	29.5% (23/78)	1.17 (0.59–2.32)	0.65

[a]Calculated as odds of adenoma detection in the CE group relative to odds in the WLE group.
CE, chromoendoscopy; WLE, white-light endoscopy.

other domains were judged as low or unclear bias. There was little evidence of publication bias for the ADR (see Supplementary E–G, Supplemental Digital Content 5, http://links.lww.com/AJG/B869). Because of imprecision (i.e. too wide 95% CIs) and lack of blinding, the quality of evidence was considered low when applying the GRADE approach (9).

DISCUSSION

In this meta-analysis that has included IPD from randomized trials in patients with Lynch syndrome, dye-based CE showed no apparent increase in ADR or total numbers of detected adenomas per patient compared to WLE. CE seemed to be associated with a prolonged extubation time. However, given the wide confidence intervals, differences in study design, and lack of blinding, all evidence was classified as low quality.

Four previously published nonrandomized small tandem studies that were not included in this meta-analysis compared CE with WLE (StD or HD) for the colonoscopic surveillance of patients with Lynch syndrome (8,10–12). These studies that were summarized in a recent meta-analysis suggested a benefit of CE over WLE and revealed that the average number of additional adenomas detected with CE after a first inspection with WLE ranged from 0.13 to 0.37 per patient (13). Although patients in these tandem studies underwent a back-to-back colonoscopy, no randomization was performed between the 2 image modalities—e.g., the first colonoscopy was always performed with WLE (StD or HD) and the second with CE. Because CE was always performed as second imaging modality, it remains unknown whether the detection of additional adenomas with CE after the first inspection with WLE because the use of the dye itself or just because of a careful second examination. The latter is a well-known phenomenon demonstrated by a recent meta-analysis of tandem colonoscopy studies (14). Therefore, we believe that excluding these tandem colonoscopy studies in our meta-analysis contributed to a homogeneous study population and minimized the risk of bias.

The present meta-analysis has several strengths. We adopted a strict methodology of selecting studies and excluded patients without a proven Lynch syndrome–associated gene variant or poor bowel preparation. Furthermore, because we had access to the data of individual patients, we had the ability to perform subgroup analyses on the use of StD and/or HD equipment, polyp size, location, and morphology. This is countered by limitations that could affect the generalizability of the results, including a small number of studies and patients, and subtle variations in study design. For example, in the study of Stoffel et al., the colon was examined twice, and in the study of Haanstra et al., CE was only applied in the proximal colon. In addition, because of the heterogeneity in study designs and because most studies were performed by dedicated endoscopists, the calculated ADRs in this meta-analysis are not one-to-one comparable with an ADR of a single colonoscopy in a patient with Lynch syndrome. However, because the aim of this study was to compare the ADR between 2 imaging modalities, this does not influence the primary aim or outcome of the study. Last, 2 studies were started before the appreciation of the importance of sessile serrated lesions, and therefore, no appropriate data were available to perform a subanalysis for these type of lesions (15).

Based on low-quality evidence, this meta-analysis demonstrated no difference between dye-based CE and WLE for detection of adenomas. Therefore, a possible benefit of dye-based CE for surveillance of patients with Lynch syndrome remains unresolved.

NOTES

Note that the study of Hurlstone DP, Karajeh M, Cross SS, et al. (The role of high magnification-chromoscopic colonoscopy in hereditary nonpolyposis colorectal cancer screening: a prospective "back-to-back" endoscopic study. *The American Journal of Gastroenterology*. 2005;100(10):2167-73), was not taken into account due to potential irregularities in data sets.

Table 3. Mean number of adenomas per patient

		CE		WLE			
Equipment	No. studies	N	Mean (SD)	N	Mean (SD)	Incidence risk ratio[a] (95% CI)	*P*-value
All	3	266	0.52 (0.91)	265	0.47 (0.95)	1.09 (0.78–1.52)	0.60
High-definition	2	185	0.51 (0.89)	178	0.49 (1.02)	1.04 (0.69–1.57)	0.85
Standard-definition	2	76	0.55 (0.97)	78	0.45 (0.80)	1.23 (0.69–2.20)	0.48

[a]Incidence rate ratio (IRR), calculated as number of adenoma detection in the CE group relative to number of adenomas in the WLE group.
CE, chromoendoscopy; SD, standard deviation; WLE, white-light endoscopy.

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CONFLICTS OF INTEREST

Guarantor of the article: Evelien Dekker, MD, PhD.

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