Incident colorectal cancer in Lynch syndrome is usually not preceded by compromised quality of colonoscopy

Jutta Lappalainen[1]*, Darja Holmström[2]*, Anna Lepistö[3,4], Juha Saarnio[5], Jukka-Pekka Mecklin[6,7], Toni Seppälä[3,8]

[1]University of Oulu, School of Medicine, Oulu, Finland
[2]University of Helsinki, Medical School, Helsinki, Finland
[3]Department of Abdominal Surgery, Helsinki University Central Hospital, Helsinki, Finland
[4]Research program in applied tumor genomics, University of Helsinki, Helsinki, Finland
[5]Department of Surgery, Oulu University Hospital, Oulu, Finland
[6]Department of Surgery, Central Finland Central Hospital, Jyväskylä, Finland
[7]Faculty of Sports and Health Sciences, University of Jyväskylä, Jyväskylä, Finland
[8]Department of Surgical Oncology, Johns Hopkins Hospital, Baltimore, MD, USA

*Equal contribution as first authors

Corresponding author:
Toni T. Seppälä
Johns Hopkins Hospital
Dept. of Surgical Oncology
600 N Wolfe St
Blalock
21218 Baltimore, MD
USA
toni.seppala@fimnet.fi
+14108149966

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Figures: 1
Tables: 5
Supplementary tables: 1

ABSTRACT

Background

Lifetime incidence of colorectal cancer (CRC) especially in carriers of MLH1 and MSH2 pathogenic germline variants in mismatch repair genes is high despite ongoing colonoscopy surveillance. Lynch syndrome (LS) registries have been criticized for not reporting colonoscopy quality adequately.

Methods

Prospective follow-up data from the national registry were combined with a retrospective assessment of the colonoscopy reports from Helsinki University Hospital electronic patients records in 2004–2019.

Results

Total of 366 MLH1, MSH2 and MSH6 carriers underwent 1564 colorectal endoscopies (mean 4.3 per patient, range 1–10) at a single unit. At least one subsequent examination was performed on 336 patients.

Bowel preparation was suboptimal (Boston Bowel Preparation Scale 0–2) on either right or left side of the colon in 12.9% of planned surveillance examinations. Caecal intubation rate for full-length colonoscopies was 98.9%. Adenoma detection rate (ADR) was 15.8% in 2004–2014 but substantially increased (21.9%) after introduction of high-definition (HD) technology in 2015–2019 (p=0.004; 18.7% across all examinations).

CRCs were detected in 23 cases. Nineteen cancers were detected after 977 optimal quality colonoscopies and 4 after 151 compromised quality (BBPS <3 or non-complete examination; p=0.16). Advanced neoplasias were not more frequently reported after compromised quality examinations.

Conclusion

The majority of LS-associated incident CRCs were detected after colonoscopies with proper bowel preparation and complete examination. There is a considerable time trend towards higher ADR after introducing HD technology of endoscopes. The effect of time trend in ADR to CRC incidence in LS needs to be studied in larger, prospective settings.

KEYWORDS: Lynch Syndrome, hereditary non-polyposis colorectal cancer, surveillance colonoscopy, colonoscopy, colorectal cancer

Introduction

Incident colorectal cancer (CRC) of a pathogenic mismatch repair variant carrier (path_MMR) at a planned surveillance colonoscopy is not a rare event. Recent large prospective studies have shown that up to 50% of path_MLH1 and path_MSH2 carriers develop a CRC during their lifelong 1-3-yearly screening that was previously thought to prevent the Lynch syndrome (LS) associated CRCs by meticulous adenomectomies [1-4]. The findings indicate that the effectiveness of colonoscopy in clinical practice is lower than was interpreted from early clinical intervention studies [5] [6]. The following discussion has raised questions of the historical quality of colonoscopy as a factor contributing to poor preventive performance [7]. On the other hand, alternative hypotheses based on different tumor biology have been proposed: some LS-associated CRCs arise directly from mismatch repair deficient crypt foci and may not be preceded by a macroscopically distinct precursor adenoma [8, 9].

There may be multiple reasons why colonoscopy with polypectomy fails to prevent CRC after certain extent. One possible explanation may be that the quality of colonoscopy measured by the key performance indicators (KPI) of endoscopic quality are compromised, which leads to missed precursor lesions and subsequently to increased incidence of CRC. Since CRC incidence, survival and stage have been consistently shown not to correlate with the interval between surveillance colonoscopies in two large prospective databases [1, 2, 10-12], we sought to investigate whether success in bowel preparation, caecal intubation rate or adenoma detection rate would explain the LS-associated CRC incidence during the past 15 years in the highest volume LS surveillance center in Finland.

Methods

Patients

Lynch Syndrome Registry of Finland (LSRFi) prospectively records the cancer diagnoses, planned and performed endoscopic procedures and their histological findings. Surveillance colonoscopies of about 1500 identified path_MMR carriers are provided in public healthcare mostly by 5 university hospitals and 7 other major hospitals. The Helsinki University Central Hospital (HUCH) is the largest single center performing surveillance colonoscopies of high-risk individuals. Confirmed path_MMR carriers under surveillance in HUCH were listed from LSRFi and the quality indicators of their colonoscopy surveillance were reviewed from the HUCH electronic patient records in 2004–2019. Only colonoscopies during this study period were assessed for quality, without selection. Patients deceased during study period were included. Colonoscopy findings were reviewed against LSRFi data to confirm that no CRC diagnoses were missed. LSRFi data is in turn periodically compared to data of the Finnish Cancer Registry to confirm that inadequate recording or reporting does not lead to loss of follow-up.

Surveillance colonoscopies

Endoscopic surveillance by rectosigmoideoscopies and colonoscopies (later referred to as colonoscopies or endoscopies) were performed solely by experienced specialists working as attendings/consultants of the colorectal surgery unit of the HUCH. The mean number of full-length surveillance colonoscopies per observer per year was 122. Altogether, the observers performed 250-300 lower gastrointestinal endoscopies yearly per person.

In 2004-2007, endoscopy equipment contained Olympus CF Q 145 L, 160 DL and 165 L. From 2008 to 2014, the Pentax EC 3890 Li and Olympus CF Q 160 DL, CF H 180 DL and H 180 AL were primarily used. From January 1st, 2015 onwards, the colonoscopes have been Olympus CF H 180 AL, HQ 190, HQ 190 L, and HQ 190 DL series white light endoscope with high definition (HD) image and narrow band imaging (NBI) option (supplementary table 1). Either CO^2 or room air insufflator were used. Magnetic 3D endoscope location device (ScopeGuide UPD, Olympus) was used when available (2014 onwards) and compatible with the endoscope model in use. Chromoendoscopy was not routinely performed during the study period.

Bowel preparation was advised by written instructions that were sent to patients with their appointment confirmation. Either Phosphoral (until 2014; sodiumdihydrophosphate, di-sodiumphosphate-decahydrate; CCS Healthcare, Zaragoza, Spain), MoviPrep (PEG-3350, sodium sulfate, sodium chloride, potassium chloride, sodium ascorbate and ascorbic acid for oral solution; Salix Pharmaceuticals, USA) or ColonSteril (macrogol 4000, sodium chloride, potassium chloride, sodium sulfate, sodiumbicarbonate; Orion Ltd, Finland) were recommended, in written form and again orally at the pharmacy, to use according the manufacturer's protocol for bowel preparation before endoscopy.

Colonoscopies were scheduled mainly three-yearly for path_MMR carriers without previous CRC and 2-yearly for those with a previous CRC. Shorter colonoscopy intervals (6 to 12 months) were scheduled for postoperative surveillance after surgically treated CRC, or verifying the result of an endoscopic removal of a neoplastic lesion.

Review of colonoscopy quality

Endoscopy reports were reviewed for colonoscopy quality using a Boston Bowel Preparation Scale (BBPS) simplified for this study as follows. The modification included that only right (proximal or oral from ceacum to splenic flexure) and left (from splenic flexure to anus) side were assessed separately and the quality of the final visibility to bowel mucosa after endoscopic rinsing was graded by a numerical value 0, 1, 2 or 3. The quality of the bowel preparation was assessed verbally and images by the physician performing the procedure and translated into modified BBPS by the reviewers (DH and JL) gathering the data. For adenoma detection rate (ADR), determined as a finding containing either adenoma, serrated adenoma or colorectal cancer as verified by a report from histopathological examination, number of endoscopies with an event was divided by number of examinations excluding postoperative controls (when entire large bowel length was not necessarily assessed).

Statistics

Retrospective evaluation data were collected in Excel (Microsoft, USA) together with prospective LSRFi data and analysed in SPSS 25.0 (IBM, USA). Chi-square test was used for determining statistical difference between variables.

Ethical considerations

Institutional research permission was obtained from the Helsinki University Hospital. As this was a study based on patient records, separate ethical board review was not required.

RESULTS

During the 15-year study period in 2004–2019, 366 path_MMR carriers underwent 1564 (mean 4.3 per patient, range 1–10) colorectal endoscopy examinations at the HUCH endoscopy unit. For 30 carriers (8.2%), the colonoscopy was their only one during the study period, mainly due to recent onset of the surveillance program. Inclusion criteria for the study to assess the effect of the quality of the previous colonoscopy to the finding at the subsequent colonoscopy was therefore fulfilled for 336 carriers that underwent 1534 examinations. Mean follow-up was 9.1 years. Table 1 presents the demographic information of the 336 carriers fulfilling the inclusion criteria.

Overall quality of colonoscopies

Table 2 presents the basic characteristics of the 1534 endoscopies during surveillance with their indications and main findings. Out of 1534 examinations, 1383 endoscopies (90.2%) were planned primary surveillance examinations with an intention to view the entire large bowel length, while the rest were either postoperative control examinations that were based on symptoms, or early repeat procedures due to failure of previous attempt. Out of 1383, the entire large bowel length was examined successfully in 1361 cases (98.4%). Out of 1383, 1046 were planned and scheduled full-length colonoscopies for patients with no prior colorectal surgery, in 1035 of which caecum was reached (caecal intubation rate 98.9%).

ADR over 1464 examinations (excluding only postoperative controls) was 18.7%. Advanced (including serrated) adenomas were found in 5.1% across all (n=1464) examinations. There was a considerable time trend for better ADR per examination from 2004–2014 towards 2015–2019 after HD-able colonoscopes were introduced: 15.8% versus 21.9 %, (p=0.004, Pearson's chi-square). Unsuccessful colonoscopies were rare, but reported slightly more frequently during 2015–2019 compared to 2004–2014.

Examinations were performed within 37 months from previous colonoscopy in 89.7% of the times. At the inclusion round (first colonoscopy during study period 2004-2019), 10 CRCs were detected. Since these ten were not preceded by an examination during the study period, the quality of the previous colonoscopies were not evaluated.

Quality of previous colonoscopies related to subsequent cancer finding

At their second colonoscopy recorded to the LSRFi during 2004-2019, 250 carriers (74.4%) had not undergone colorectal surgery and 86 (25.6%) had had previous large bowel resections. During subsequent surveillance colonoscopies after the inclusion round, 24 CRCs in 23 patients were diagnosed (one patient with two synchronous cancers; table 3). Nineteen patients were diagnosed with CRC after 977 optimal quality colonoscopies and four after 151 compromised quality colonoscopies (BBPS < 3 or non-complete examination; p=0.16). Adenoma was removed from the same bowel segment in 2/23 at the previous colonoscopy. Two follow-up colonoscopies with a cancer finding clearly exceeded their scheduled interval (41 and 48

months). One cancer in the transverse colon was diagnosed due to symptoms 7 months after previous examination, where no signs of compromised quality were recorded. In examinations that were preceded by a (quality-assessed) previous endoscopy, 42 advanced neoplasias were detected in 2015–2019 in 470 colonoscopies and 37 advanced neoplasias in 2004–2014 in 658 colonoscopies (p=0.032).

Other findings at the subsequent colonoscopy were not significantly associated with previous colonoscopy quality. With intention to examine the entire remaining large bowel, 1128 surveillance colonoscopies showed no difference in the frequency of advanced or non-advanced lesions between those with previously well-performed colonoscopy and those preceding a compromised quality procedure (table 4). In a sensitivity analysis, those with only full-length colonoscopies in the absence of previous colorectal surgery showed no difference, either (table 5).

DISCUSSION

The current report indicates that the vast majority of incident colorectal cancers that occur during surveillance for pathogenic mismatch repair variants causing Lynch syndrome are not preceded by poor colonoscopy quality that would result from incomplete examination or inadequate bowel cleansing. There was a considerable time trend towards better ADR at the end of the study period, likely reflecting the technological evolution of endoscopes.

It has been generally accepted for over 20 years that the core of the CRC prevention and early diagnosis in LS is formed by the regular endoscopic surveillance by colonoscopies that decrease the mortality and the incidence of CRC compared to no surveillance [5] [6]. However, 15% of path_MMR still continued to develop CRC within 10 years during surveillance [6, 13] [14], that has been confirmed by large registry studies [1, 2]. Colonoscopy was widely adopted in clinical guidelines and even very short (annual) intervals between examinations are still being recommended [15-17]. However, it has been recently shown in large prospective datasets that the shorter intervals between colonoscopies do not benefit the patients compared to 3-yearly intervals in terms of decreased CRC incidence, better overall survival or lower AJCC stage of the CRC [1, 2, 10, 12]. On the other hand, the excellent survival after CRC reported in the same studies proves that the role of colonoscopy is justified and can be considered as success in terms of preventing cancer deaths compared to no surveillance [12]. The lack of benefit from very frequent colonoscopy compared to less frequent has raised questions and directed the research towards finding the differences between genes and carcinogenetic pathways. The

quality of colonoscopy surveillance has been questioned as one reason for incident and interval cancers since it has not been widely reported to prospective international databases.

We hypothesized that if the quality of colonoscopy was the reason for high incidence during colonoscopy surveillance, it should be clearly evident in the setting where the longest intervals between colonoscopies are being recommended, such as Finland with a 2–3-yearly recommendation. As in some Nordic countries, the colonoscopies in the current study were performed by dedicated colorectal surgeons. KPIs did not seem to be substantially compromised, and the few shortcomings in the measured quality did not seem to cause the majority of the cancers that were detected. The unlikeliness of compromised quality as a causative factor in a setting with highest vulnerability of the surveillance program (longest interval) makes it even less probable for the high (or even higher) CRC incidence to be caused by poor quality in the short interval programs. In fact, the point estimates for CRC incidence have historically been lower in the 3-year interval groups than in 1–2 yearly interval groups [2, 10].

The optimal adenoma detection rate during colonoscopy surveillance of path_MMR carriers is not known, and may be largely dependent on age, the genetic distribution of the pathogenic variants in the study cohort, the extent of previous large bowel resections, as well as geographical and ethnic variability in the adenoma risk. In the current study, the 22% ADR of a single center is higher than previously reported mean 16% in the database study of Finland, Germany and Netherlands [2], but lower than 23-30% reported by recent trial series in

specialized centers in Europe [18-22]. The differences are unlikely to be caused by inter-observer differences only, although the technology may play a role. It is possible that the endoscopies performed with more advanced technology, such as HD video quality, have increased the ADR in the more recent studies, in addition to trial setting where colonoscopy is performed twice in back-to-back manner. The unique cascade testing performance and inclusion to surveillance in Finnish LS registry during the past 35 years separates Finland from more recently established registries. Since the high-risk families are carefully scrutinized and the uptake to genetic testing is high, many more young individuals are under surveillance than in settings where surveillance is performed to mostly older probands. This decreases the ADR since adenoma incidence is heavily dependent on age.

We also report a time trend towards higher ADR in 2015–2019 when HD-level colonoscopes became widely in use in our institution. In addition to HD techniques, at least chromoendoscopy (CE) may be more efficient in detecting lesions on the ascending side of the colon based on recent meta-analysis [23], although CE did not overall result in higher ADR in high-volume LS surveillance centers compared to HD WLE [20]. Furthermore, a recent back-to-back trial demonstrated that indigo carmine CE outperforms third generation NBI colonoscopy in ADR (20% versus 30%) and that the rate of missed adenomas is high even with modern NBI [21].

Especially for proximal colon adenomas and flat lesions, the miss rates in studies carried out by tandem colonoscopies have been high. Based on a recent meta-analysis, up to 26% of

adenomas in general, 9% of advanced adenomas, 14% of right-sided adenomas, 27% of serrated polyps and 34% of flat adenomas are missed during colonoscopies [24]. Adenoma miss rate was especially high (33%) in patients with high risk of CRC [24]. On the other hand, as many of these studies reporting high ADRs have been tandem studies, CE with substantially longer withdrawal times being the latter and preceded by WLE of the two, which may have accounted for the higher detection rate [7].

ADR is a widely used endpoint in the endoscopic literature, as it has been assumed that all adenocarcinomas have always been preceded by an endoscopically removable precursor. On the other hand, it still remains to been proven if more advanced technologies or the recent high ADR performance as a result of HD image, NBI and CE – possibly outperforming the conventional WLE techniques – would actually convert to decreased CRC incidence in the LS setting.

Furthermore, recent advances in the study of carcinogenetic pathways in LS suggest that all adenocarcinomas are not developing through traditional adenoma-carcinoma sequence but may start directly from the MMR-deficient crypt foci, without preceding adenoma phase [8, 9]. Therefore, until further studies show CRC incidence, survival or cost benefit from high ADR using the latest endoscopic techniques, adequate ADR remains an open question. In fact, the high numbers of CRCs found during surveillance and lack of association between the colonoscopy interval and stage, survival and incidence may be accounted for by over-diagnosis [11]. The current finding that more advanced lesions were found in conjunction with increasing

ADR after moving to era of HD image would support this idea. The increasing number of findings could alternatively be interpreted as an example of lead-time bias associated with improved performance of a diagnostic modality.

The strengths of this study are the population-based patient material, prospective registry data verifying the findings and robust inclusion criteria that enabled assessing only colonoscopies that were preceded by at least one other colonoscopy during the study period. The weaknesses of the study were the retrospective nature of the bowel preparation quality assessment and unavailability of the colonoscopy withdrawal time. As in all studies other than tandem colonoscopy studies, the miss rates of adenomas could not be assessed in the current analysis. It is possible that the somewhat limited ADR compared to recently reported very high ADRs may be resulting from missed small or flat adenomas, especially due to delay in the widespread use of HD technology.

The high quality colonoscopy surveillance remains the cornerstone of the risk-reducing surveillance in LS. Compromised colonoscopy quality seems infrequent and the results of the current study do not support the hypothesis that colonoscopy quality is the only major cause of the incident/interval colorectal cancers during LS endoscopic surveillance in this population. For patients and healthcare, it is pivotal to understand that incident colorectal cancers during planned endoscopy surveillance program do not reflect solely unsuccessful performance or malpractice, but may rather be a hallmark of the underlying variation of the cancer biology that so far has not been solved by current endoscopic techniques. Population-specific ADRs should

be studied systematically and the target thresholds for detection to be set for centers performing surveillance for high-risk individuals. The time trends in colonoscopy should be studied in larger prospective setting in order to prove the possible CRC incidence benefit of higher ADR.

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DISCLOSURE STATEMENT

The authors report no conflicts of interest.

References

1. Dominguez-Valentin M, Sampson JR, Seppälä TT, et al (2019) Cancer risks by gene, age, and gender in 6350 carriers of pathogenic mismatch repair variants: findings from the Prospective Lynch Syndrome Database. Genet Med 1–11. doi: 10.1038/s41436-019-0596-9

2. Engel C, Vasen HF, Seppälä T, et al (2018) No Difference in Colorectal Cancer Incidence or Stage at Detection by Colonoscopy Among 3 Countries With Different Lynch Syndrome Surveillance Policies. Gastroenterology 155:1400–1409.e2. doi: 10.1053/j.gastro.2018.07.030

3. Møller P, Seppälä T, Bernstein I, et al (2017) Cancer incidence and survival in Lynch syndrome patients receiving colonoscopic and gynaecological surveillance: first report from the prospective Lynch syndrome database. Gut 66:464–472. doi: 10.1136/gutjnl-2015-309675

4. Møller P, Seppälä TT, Bernstein I, et al (2018) Cancer risk and survival in path_MMR carriers by gene and gender up to 75 years of age: a report from the Prospective Lynch Syndrome Database. Gut 67:1306–1316. doi: 10.1136/gutjnl-2017-314057

5. Järvinen HJ, Mecklin JP, Sistonen P (1995) Screening reduces colorectal cancer rate in families with hereditary nonpolyposis colorectal cancer. Gastroenterology 108:1405–1411.

6. Järvinen HJ, Aarnio M, Mustonen H, et al (2000) Controlled 15-year trial on screening for colorectal cancer in families with hereditary nonpolyposis colorectal cancer. Gastroenterology 118:829–834.

7. Mankaney G, Burke CA (2019) Enhancing the efficacy of colonoscopy in Lynch syndrome: the search for the holy grail continues. Gastrointest Endosc 90:633–635. doi: 10.1016/j.gie.2019.06.006

8. Ahadova A, Knebel-Doeberitz von M, Bläker H, Kloor M (2016) CTNNB1-mutant colorectal carcinomas with immediate invasive growth: a model of interval cancers in Lynch syndrome. Familial Cancer 15:579–586. doi: 10.1007/s10689-016-9899-z

9. Ahadova A, Gallon R, Gebert J, et al (2018) Three molecular pathways model colorectal carcinogenesis in Lynch syndrome. Int J Cancer 143:139–150. doi: 10.1002/ijc.31300

10. Seppälä T, Pylvanainen K, Evans DG, et al (2017) Colorectal cancer incidence in path_MLH1 carriers subjected to different follow-up protocols: a Prospective Lynch Syndrome Database report. Hered Cancer Clin Pract 15:18. doi: 10.1186/s13053-017-0078-5

11. Seppälä TT, Ahadova A, Dominguez-Valentin M, et al (2019) Lack of association between

screening interval and cancer stage in Lynch syndrome may be accounted for by over-diagnosis; a prospective Lynch syndrome database report. Hered Cancer Clin Pract 17:1–8. doi: 10.1186/s13053-019-0106-8

12. Dominguez-Valentin M, Seppälä TT, Sampson JR, et al (2019) Survival by colon cancer stage and screening interval in Lynch syndrome: a prospective Lynch syndrome database report. Hered Cancer Clin Pract 1–6. doi: 10.1186/s13053-019-0127-3

13. de Vos Tot Nederveen Cappel WH, Nagengast FM, Griffioen G, et al (2002) Surveillance for hereditary nonpolyposis colorectal cancer: a long-term study on 114 families. Dis Colon Rectum 45:1588–1594. doi: 10.1097/01.DCR.0000034502.64985.3F

14. Mecklin J-P, Aarnio M, Läärä E, et al (2007) Development of colorectal tumors in colonoscopic surveillance in Lynch syndrome. Gastroenterology 133:1093–1098. doi: 10.1053/j.gastro.2007.08.019

15. Singh S, Falck-Ytter YT, AGA Institute Clinical Guidelines Committee, et al (2017) American Gastroenterological Association Institute Guidelines for the Diagnosis and Management of Acute Liver Failure. Gastroenterology 152:644–647. doi: 10.1053/j.gastro.2016.12.026

16. Herzig DO, Buie WD, Weiser MR, et al (2017) Clinical Practice Guidelines for the Surgical Treatment of Patients With Lynch Syndrome. Dis Colon Rectum 60:137–143. doi: 10.1097/DCR.0000000000000785

17. Stoffel EM, Mangu PB, Gruber SB, et al (2014) Hereditary Colorectal Cancer Syndromes: American Society of Clinical Oncology Clinical Practice Guideline Endorsement of the Familial Risk-Colorectal Cancer: European Society for Medical Oncology Clinical Practice Guidelines. Journal of Clinical Oncology JCO.2014.58.1322. doi: 10.1200/JCO.2014.58.1322

18. Rahmi G, Lecomte T, Malka D, et al (2015) Impact of chromoscopy on adenoma detection in patients with Lynch syndrome: a prospective, multicenter, blinded, tandem colonoscopy study. Am J Gastroenterol 110:288–298. doi: 10.1038/ajg.2014.423

19. Perrod G, Samaha E, Rahmi G, et al (2018) Impact of an optimized colonoscopic screening program for patients with Lynch syndrome: 6-year results of a specialized French network. Therap Adv Gastroenterol 11:1756284818775058. doi: 10.1177/1756284818775058

20. MD JFH, PhD EDM, PhD ACM, et al (2019) Effect of chromoendoscopy in the proximal colon on colorectal neoplasia detection in Lynch syndrome: a multicenter randomized controlled trial. Gastrointest Endosc 1–9. doi: 10.1016/j.gie.2019.04.227

21. Cellier C, Perrod G, Colas C, et al (2019) Back-to-Back Comparison of Colonoscopy With Virtual Chromoendoscopy Using a Third-Generation Narrow-Band Imaging System to

Chromoendoscopy With Indigo Carmine in Patients With Lynch Syndrome. Am J Gastroenterol. doi: 10.14309/ajg.0000000000000386

22. Vleugels JLA, Sahin H, Hazewinkel Y, et al (2018) Endoscopic detection rate of sessile serrated lesions in Lynch syndrome patients is comparable with an age- and gender-matched control population: case-control study with expert pathology review. Gastrointest Endosc 87:1289–1296. doi: 10.1016/j.gie.2017.11.034

23. Har-Noy O, Yung DE, Koulaouzidis A, et al (2019) Chromoendoscopy or white light endoscopy for neoplasia detection in Lynch syndrome, a meta-analysis. Dig Liver Dis. doi: 10.1016/j.dld.2019.07.018

24. Zhao S, Wang S, Pan P, et al (2019) Magnitude, Risk Factors, and Factors Associated With Adenoma Miss Rate of Tandem Colonoscopy: A Systematic Review and Meta-analysis. Gastroenterology 156:1661–1674.e11. doi: 10.1053/j.gastro.2019.01.260

Figure legends

Figure 1. Formation of the study cohort.

Table legends

Table 1. Demographic characteristics of the study population and surveillance examinations

Table 2. Indications, findings and performance during colonoscopy surveillance, presented by previous colorectal surgery status and era of colonoscopies

Table 3. Colorectal cancers found at the second and following surveillance colonoscopies during the study period (2004-2019). Quality and the findings of the previous colonoscopies are presented for each cancer.

Table 4. Findings at the next examination after surveillance colonoscopies with optimal and compromised bowel preparation and/or completion

Table 5. Colorectal cancer and advanced adenoma findings at the next examination after optimal or compromised quality of colonoscopy presented by previous colorectal surgery status at the time of the diagnosis

Table 1

		Previous colon surgery	No previous surgery	Total
N		76 (22.6%)	260 (73.4)	336 (100%)
Age at baseline (mean)		54	40	43
Sex	Male	39 (51.3%)	136 (52.3%)	175 (52.1%)
	Female	37 (48.7%)	124 (47.7%)	161 (47.9%)
Gene	*MLH1*	56 (73.7%)	184 (70.8%)	240 (71.4%)
	MSH2	13 (17.1%)	49 (18.8%)	62 (18.5%)
	MSH6	7 (9.2%)	27 (10.4%)	34 (10.1%)
Previous cancer	Yes	72 (94.7%)	1 (0.4%)	73 (21.7%)
	No	4 (5.3%)	259 (99.6%)	263 (78.3%)
Mean number of colonoscopies		4.9	4.5	4.6
Mean follow-up time		8.1	9.1	8.9
Total number of colonoscopies		407 (26.5%)	1127 (73.5%)	1534 (100%)
Total number of follow-up years		617 (20.6%)	2372 (79.4%)	2989 (100%)

Table 2

		Whole bowel left	Partial colectomy before baseline	p	2004–2014	2015–2019	p	Total cohort
N of patients		260	76		NA	NA		336
Number of examinations		1127 (73.5%)	407 (26.5%)		1109 (65.8%)	525 (34.2%)		1534
Mean time interval, years (SD)		2.78 (0.85)	1.91 (1.01)	< 0.001	NA	NA		2.54
Era	Examination 2004-2014	754 (74.7%)	255 (25.3%)	0.121	1109 (100%)	0 (0%)	NA	1009
	Examination 2015-2019	373 (71.0%)	152 (29.0%)		0 (0%)	525 (100%)		525
Reason	Planned surveillance examination	1046 (92.8%)	337 (82.8%)	< 0.001	930 (83.9%)	453 (86.3%)	0.003	1383
	Unplanned due to symptoms	45 (4.0%)	21 (5.2%)		33 (29.8%)	33 (6.3%)		66
	Early repeat due to previous quality issues	7 (0.6%)	8 (2.0%)		7 (0.6%)	8 (1.5%)		15
	Post-procedure control	29 (2.6%)	41 (10.1%)		39 (3.5%)	31 (5.9%)		70
Primary finding	Colorectal cancer*	23 (2.0%)	10 (2.5%)	0.067	20 (1.8%)	13 (2.5%)	0.002	33
	Colorectal cancer at first colonoscopy during study period**	9	1		8	2		10
	Adenoma (tubular or tubulovillous) with high grade dysplasia or size > 1 cm	34 (3.0%)	23 (5.7%)		29 (2.6%)	28 (5.3%)		47
	Serrated adenoma	16 (1.4%)	2 (0.5%)		9 (0.8%)	9 (1.7%)		18
	Tubular adenoma with low grade dysplasia	120 (10.6%)	46 (11.3%)		100 (9.0%)	66 (12.6%)		166
	Hyperplastic polyp(s)	178 (15.8%)	47 (11.5%)		170 (15.3%)	55 (10.5%)		225
	Other polyp(s)	6 (0.5%)	2 (0.5%)		8 (0.7%)	0 (0%)		8
	Other finding	44 (3.9%)	20 (4.9%)		39 (3.5%)	25 (4.8%)		64
	No biopsies or no diagnostic findings	706 (62.6%)	257 (22.8%)		634 (57.2%)	329 (62.7%)		963
Adenoma detection rate (%)		17.0	20.2	0.168	15.8	21.9	0.004	18.7
Bowel preparation quality	mBBPS 3 (optimal)	904 (86.4%)	300 (89.0%)	0.217	831 (89.4%)	373 (82.3%)	< 0.001	1204 (87.1%)
	mBBPS < 3 (compromised)	142 (13.6%)	37 (11.0%)		99 (10.6%)	80 (17.7%)		179 (12.9%)
Completeness of	Complete	1035 (98.9%)	326 (96.7%)	0.005	920 (98.9%)	441 (97.4%)	0.028	1361

examination								(98.4%)
	Incomplete	11 (1.1%)	11 (3.2%)		10 (1.1%)	12 (2.6%)		22 (1.6%)

Table 3

Patient #	Age at baseline colonoscopy	Age cancer	Cancer site	Cancer stage and procedure	Sex	Gene	Previous surgery	Reason for colonoscopy	Interval since previous colonoscopy months	Previous colonoscopy bowel prep quality right	Previous colonoscopy bowel prep quality left	Previous colonoscopy complete	Previous colonoscopy finding	Location of previous finding
1	57.9	60.9	Rectum	Adenoca in adenoma	F	*MLH1*		Planned	36	3	3	Complete	Tubular adenoma with LG dysplasia	Rectum
2	40.4	43.4	Right hemicolon	Adenoca T2N0M0	M	*MLH1*		Planned	36	3	3	Complete	Biopsied normal mucosa	Right hemicolon
3	71.3	74.2	Transverse colon	Adenoca T3N0M0	F	*MSH2*		Planned	35	2	2	Complete	No findings	
4	79.4	82.4	Left hemicolon	Adenoca T2N0M0	M	*MLH1*	age 53, hemicol. l.dx	Planned	37	N/A	3	Complete	Hyperplastic polyp	Rectum
5	61.1	64.1	Right hemicolon	Adenoca T2N0M0 & T2	M	*MLH1*	age 57, anterior resection	Planned	37	3	3	Complete	No findings	
6	51.7	56.4	Left hemicolon	Adenoca T1N0M0	M	*MLH1*	age 22, hemicol. l. dx.	Planned	20	N/A	3	Non-complete	Hyperplastic polyp	Left hemicolon
7	54.3	55.6	Transverse colon	Stage IV carcinoma mucocellulare	F	*MLH1*	age 32, hemicol. l.dx.	Symptomatic	7	N/A	3	Complete	Hyperplastic polyp	Transverse colon
8	35.9	38.2	Right hemicolon	Adenoca T1N0M0	M	*MSH2*	age 34, anterior resection	Planned	26	2	2	Complete	Hyperplastic polyp	Right hemicolon
9	27.0	36.5	Right hemicolon	Adenoca T1N0M0	M	*MLH1*		Planned	36	2	2	Complete	No findings	
10	43.6	50.5	Right hemicolon	Adenoca T1N0M0	M	*MLH1*		Planned	36	3	3	Complete	Inflammatory polyp	Left hemicolon
11	34.4	43.5	Left hemicolon	Adenoca T1N0M0	F	*MLH1*		Planned	37	3	3	Complete	Hyperplastic polyps (2)	Right hemicolon
12	57.5	66.6	Right hemicolon	Adenoca T2N0M0	F	*MSH2*		Planned	37	3	3	Complete	Hyperplastic polyp	Transverse colon

13	44.4	52.9	Right hemicolon	Adenoca T2N0M0	F	*MLH1*		Symptomatic	32	3	3	Complete	Hyperplastic polyp	Transverse colon
14	48.1	57.1	Right hemicolon	Adenoca T1N0M0	M	*MLH1*	age 45, anterior resection	Planned	25	3	3	Complete	Tubular adenoma with LG dysplasia	Right hemicolon
15	48.9	54.6	Left hemicolon	Adenoca T2N0M0	M	*MLH1*		Symptomatic	20	3	3	Complete	Tubular adenoma with LG dysplasia	Right hemicolon
16	37.3	46.4	Transverse colon	Adenoca T1N0M0,	M	*MLH1*		Planned	36	3	3	Complete	Tubular adenoma with LG dysplasia	Right hemicolon
17	70.8	81.9	Right hemicolon	Adenoca in adenoma	F	*MLH1*		Symptomatic	26	3	3	Complete	Tubular adenoma with LG dysplasia	Transverse colon
18	61.4	70.6	Transverse colon	Adenoca T4N1M0	F	*MLH1*		Planned	36	3	3	Complete	Hyperplastic polyps (2)	Transverse colon
19	40.8	53.9	Left hemicolon	Adenoca T1N0M0	F	*MLH1*		Planned	41	3	3	Complete	Hyperplastic polyp	Right hemicolon
20	37.6	54.9	Right hemicolon	Adenoca T1N0M0	M	*MLH1*		Planned	37	3	3	Complete	Tubular adenoma with LG dysplasia	Left hemicolon
21	57.1	65.5	Rectum	Adenoca T1N0M0	F	*MSH2*	age 55, STC+ISA	Planned	48	N/A	3	Complete	Biopsied normal mucosa	Rectum
22	61.0	70.4	Left hemicolon	Adenoca T1N0M0	M	*MLH1*	age 43, STC+ISA	Symptomatic	17	N/A	3	Complete	No findings	
23	68.6	70.7	Left hemicolon	Adenoca in adenoma	M	*MLH1*	age 49, hemicol. l.dx	Planned	26	N/A	3	Complete	Biopsied normal mucosa	Left hemicolon

Table 4

Following colonoscopy finding	Previous colonoscopy quality		
	BBPS 3 and all large bowel examined	BBPS < 3 or all large bowel not examined	
N	977	151	p
Colorectal cancer	19 (1.9%)	4 (2.6%)	0.163
Adenoma (tubular or tubulovillous) with high grade dysplasia or size > 1 cm	34 (3.5%)	6 (4.0%)	
Serrated adenoma	14 (1.4%)	2 (1.3%)	
Tubular adenoma with low grade dysplasia	109 (11.2%)	29 (19.2%)	
Hyperplastic polyp(s)	153 (15.7%)	20 (13.2%)	
Other finding	56 (5.7%)	3 (2.0%)	
No biopsies or no diagnostic findings	592 (60.6%)	87 (57.6%)	

Table 5

	All patients			Patients with no prior colorectal surgery before second colonoscopy during the study period		
	n=336			n=250		
	BBPS 3 and all large bowel examined in previous colonoscopy	BBPS < 3 or all large bowel not examined in previous colonoscopy	p	BBPS 3 and all large bowel examined in previous colonoscopy	BBPS < 3 or all large bowel not examined in previous colonoscopy	p
Adenocarcinoma or advanced adenoma in current colonoscopy	67 (6.9%)	12 (7.9%)	0.625	47 (6.4%)	5 (4.6%)	0.455
No finding or low risk finding in current colonoscopy	910 (93.1%)	139 (92.1%)		683 (93.6%)	104 (95.4%)	