

Quality of colonoscopy in Lynch syndrome

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Lynch syndrome (LS) accounts for 2–4% of all colorectal cancers. Affected family members have a germline mutation in one of the DNA mismatch repair genes MLH1, PMS2, MSH2, or MSH6, and a lifetime risk for development of colorectal cancer of 25–75%. Current guidelines recommend annual to biannual surveillance colonoscopy in mutation carriers. Several factors may predict failure to prevent interval cancer in LS: more lesions in the right colon; more flat (“non polypoid”) and lateral growing polyps; small adenomas may already harbor high grade dysplasia or a high percentage of villous component and become advanced adenomas; there is a short duration of the adenoma–carcinoma sequence; synchronous lesions have high prevalence; patients are younger and less tolerant to colonoscopy (need more sedation); and repeated colonoscopies are needed for lifelong surveillance (patient experience is

important for compliance). In order to prevent cancer in LS patients, surveillance colonoscopy should be performed in an endoscopic unit experienced with LS, every 1–2 years, starting at age 20–25 years, or 10 years younger than the age of first diagnosis in the family (whichever is first), and yearly after the age of 40 years. Colonoscopy in LS patients should be a very meticulous and precise procedure (i.e. taking sufficient withdrawal time, documentation of such warranted), with removal of all of the polyps, special attention to the right colon and alertness to flat lesions. Following quality indicators such as successful cleansing of the colon and removal of every polyp will probably improve prevention of interval cancers. At this moment, none of the new endoscopic techniques have shown convincing superiority over conventional high resolution white light colonoscopy.

Introduction

Lynch syndrome (LS), formerly referred to as hereditary nonpolyposis colorectal cancer (HNPCC) accounts for 2–4% of all colorectal cancers (CRCs) [1]. Affected family members have a germline mutation in one of the DNA mismatch repair genes MLH1, PMS2, MSH2, or MSH6, and a lifetime risk for development of CRC of 25–75% [2]. Centralized organizations of surveillance for Lynch syndrome families have been established in Finland, Netherlands, Germany, and Canada, and follow-up results have been published since 1995, with essential information on the efficiency of prevention of CRC incidence and mortality [3–6]. Colonoscopy has been shown to decrease both by 63% [7,8]. In spite of colonoscopic surveillance, interval cancers (defined as CRC found within 2 years after a negative colonoscopy or leaving a colon “clear” of polyps) have been described [4, 9–11]. Vasen et al. described interval CRC in 29 out of 2200 mutation carriers [4]. These 29 cases,

with a median age of 52 years, and a median time since previous colonoscopy of 17 months to the diagnosis of interval cancer, were MLH1 and MSH2 mutation carriers. Of these, 39% had previous CRC, and those who had never undergone colonic resection developed proximal lesions in 84% of cases; 77% were stage T1–3, N0M0. In 9%, an incomplete previous colonoscopy was reported, and the tumor was located in the unexamined colon. In six cases, the cancer was at the site of a removed adenoma. The authors concluded that MLH1 and MSH2 mutation carriers, previous CRC, incomplete colonoscopy, and incomplete polypectomy were risk factors for diagnosis of interval cancer in LS [9]. Several factors may predict failure to prevent interval cancer in LS: more lesions in the right colon; more flat (“nonpolypoid”) and lateral growing polyps; small adenomas may already harbor high grade dysplasia or a high percentage of villous components and become advanced adenomas. Overall, there is an acceleration of the adenoma–carcinoma sequence,

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synchronous lesions have a high prevalence and, importantly, patients with LS are younger and less tolerant to colonoscopy (need more sedation); and repeated colonoscopies are needed for life-long surveillance (patient experience is important for compliance) [12]. Thus, a very meticulous and precise procedure is required with removal of all of the polyps. Nonpolypoid lesions, defined as a lesion with height less than half the diameter, is a characteristic of LS [13]. Rondagh et al. studied 59 LS patients in comparison with 590 controls, and found that 43.3% and 58.1% of adenomas and serrated adenomas were nonpolypoid, in comparison with 16.9% and 20.4% in controls, respectively ($P<0.001$) [13].

When, where, and how to perform colonoscopy in Lynch syndrome patients

Regular colonoscopy should be performed repeatedly and at short intervals when LS is suspected according to Amsterdam II criteria, or when a mutation in one of the DNA mismatch repair genes (MMR) is found. The procedure should be performed in an endoscopic unit experienced with LS, to minimize the potential for missing polyps and thus exposing patients to interval cancer. Four endoscopic methods have been tested in order to improve the diagnostic yield of colonoscopy and the polyp/adenoma detection rate: high resolution white light endoscopy (HR), chromoendoscopy, narrow band imaging (NBI) and autofluorescence endoscopy (AFE) (Table 1). Four prospective trials have compared chromoendoscopy to HR and NBI in “back-to-back” studies [14–17]. Lecomte et al. examined 33 patients with LS and found an additional 45 lesions (11 adenomas) with chromoendoscopy performed after HR colonoscopy [14]. Similar findings have been described by Hurlstone and colleagues who found an additional 52 lesions (32 adenomas) in 25 patients [15]. Huneburg et al. performed colonoscopy in 109 patients in two investigational arms: chromoendoscopy was found to be better than HR colonoscopy in 47 patients, with 1.5 and 0.5 lesions per patient, respectively ($P<0.01$), and also better than NBI, with 1.8 and 0.7 lesions per patient, respectively ($P=0.032$). Comparing NBI with HR colonoscopy in 62 patients with LS according to Amsterdam II criteria, NBI added 21 polyps (6 flat adenomas) ($P<0.001$) [17]. The method of “back-to-back” endoscopy has a methodological bias, since additional lesions can be found in the second procedure. Stoffel et al. performed conventional colonoscopy in 54 patients with LS (46 with MMR gene mutation) [18]. Then patients were randomized into one of two arms: chromoendoscopy or “intensive” inspection. Chromoendoscopy detected more polyps

than “intensive” inspection ($P=0.04$), but adenoma detection was not significantly different ($P=0.27$). However, the second colonoscopy (chromoendoscopy or “intensive”) doubled the diagnostic yield for adenoma. The only procedure that demonstrated a higher diagnostic yield for adenoma than HD colonoscopy, without the methodological bias of back-to-back colonoscopy, was autofluorescence endoscopy (AFE) [19], but this observation has not yet been confirmed in other studies. Seventy-five LS or familial CRC patients were examined with either white light colonoscopy (WLE) followed by AFE, or with AFE followed by WLE, by two blinded endoscopists. All lesions were removed on the 2nd endoscopy (or the 3rd if missed). At least one adenoma was found in 41 (55%) patients. White light endoscopy identified 65 adenomas in 28/41 patients with adenomas, less than AFE which identified 87 adenomas in 37/41 patients, an increase of 32%. Sensitivities of AFE and WLE were 92% and 68%, respectively ($P=0.001$). The adenomas additionally detected with AFE were smaller than those detected with WLE, with means of 3 mm versus 4.9 mm, respectively ($P<0.01$).

Quality indicators for colonoscopy

Quality indicators for colonoscopy are constantly published and are all directed towards complete examination and removal of all polyps. A correlation is suspected between the incidence of interval cancer and the quality of colonoscopy in screening average-risk as well as high risk populations [20]. Validated quality indicators are even more important to follow in LS, since the adenoma–carcinoma sequence is shorter than in sporadic cancer patients [21]. Fifty-four patients with a known pathogenic mutation in MLH1 or MSH2 underwent colonoscopy every 1–2 years, with a mean follow-up period of 9.3 years. The diagnostic yield for colonic lesions was 112 adenomas and 31 CRCs. The polyp dwell time was 35.2 ± 22.3 months, and shorter for the right than the left colon, 28.7 vs. 43.6 months, respectively. Thus, a withdrawal time of more than 6 minutes, an excellent preparation, complete examination (photographic evidence showing the ileocecal valve and appendix orifice), U-turn in the rectum, adequate adenoma detection rate (ADR) and polyp detection rate (PDR), and complete polypectomy by experienced endoscopists are cornerstones for surveillance endoscopy in LS.

Series	Number of patients	Methods compared ¹	Additionally detected adenomas
Lecomte et al. [14]	33	Chromo vs. HRC	11
Hurlstone et al. [15]	25	Chromo vs. HRC	32
Huneburg et al. [16]	109	Chromo vs. WLE Chromo vs. NBI	1.5 vs. 0.5 lesion/patient 1.8 vs. 0.7 lesion/patient
East et al. [17]	62	NBI vs. HDWL	21
Stoffel et al. [18]	54	Chromo vs. WLE “Intensive” WLE (>20 min) vs. WLE	5 7
Ramsoekh et al. [19]	75	AFE vs. WLE	22

Chromo, chromoendoscopy; HRC, high resolution colonoscopy; WLE, white light endoscopy; NBI, narrow band imaging; HDWL, high definition white light endoscopy; AFE, autofluorescence endoscopy.

¹ The first method listed is the better method.

Table 1 Comparison of different methods for surveillance in Lynch syndrome (LS).

How often to perform colonoscopy in Lynch syndrome

Guidelines recommend colonoscopy every 1–2 years, starting at age 20–25 years, or 10 years younger than the age of first diagnosis in the family (whichever is first), and yearly after the age of 40 years [4,22–26]. In four US cancer genetics clinics, 181 patients with LS (according to Amsterdam criteria or with a proven mutation) were screened. Only 132 (73%) had appropriate surveillance according to the guidelines [27]. Personal history (OR 2.81), first degree relative with CRC (OR 2.61), and genetic evaluation (OR 4.62) were associated with appropriate surveillance. Stuckless and co-investigators looked at the impact of colonoscopic screening in male and female LS carriers with the MSH2 mutation [28]. They compared 54 male and 98 female LS mutation carriers who had been surveyed (screened carriers) with 94 male and 76 female carriers (unscreened carriers). In men, the median age to develop CRC was 58 years versus 47 years in screened and unscreened patients, respectively ($P<0.0001$), and the median survival was 66 years versus 62 years, respectively ($P=0.034$). In women, the median age to develop CRC was 79 years versus 57 years in screened and unscreened patients, respectively ($P<0.0001$), and the median survival was 80 years versus 63 years, respectively ($P=0.001$). Twenty percent of men and 7% of women developed CRC within 2 years of previous colonoscopy. The authors concluded that “CRC development may be further reduced by decreasing the screening interval to 1 year and improving the quality of colonoscopy”. The risk factors for adenoma or cancer in LS patients, on top of genetic propensity, are male gender, MLH1 and MSH2 mutations, cigarette smoking, not participating in colonoscopic surveillance, previous CRC, incomplete colonoscopy, and residual adenomatous tissue after polypectomy [7,8,29–32].

Conclusion

In LS patients and individuals fulfilling the Amsterdam II criteria, surveillance colonoscopy should be performed using modern high resolution technology by experienced endoscopists every 1–2 years, starting at age 20–25 years, or 10 years younger than the age of first diagnosis in the family (whichever is first), and annually after the age of 40 years. Colonoscopy in LS patients should include meticulous inspection and precise removal of all polyps, with special attention to the right colon and alertness to flat lesions. At the moment, none of the new endoscopic techniques have shown convincing superiority over high resolution white light colonoscopy in LS patients.

Competing interests: None

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