Colorectal cancer is the third most commonly diagnosed cancer in the United States and the second most common cause of death from cancer in men and women. Around 6% of all colon cancer arises from hereditary causes. These conditions have an increased risk for development of colorectal cancer and guidelines exist for earlier and more frequent screening and surveillance colonoscopies. Many hereditary conditions present with moderate to heavy colon polyposis. Patients with Lynch syndrome (LS) and serrated polyposis syndrome (SPS), however, may have fewer, sessile polyps and advanced colonoscopy imaging may be of value in these syndromes. There is debate regarding the ideal advanced imaging technique to supplant with colonoscopy in detecting lesions that otherwise could be missed in these patient populations. This review summarizes the current literature available in advanced imaging techniques including the role of narrow band imaging and chromoendoscopy in LS and SPS.

INTRODUCTION

Colorectal cancer is the third most commonly diagnosed cancer as well as the second leading cause of cancer deaths in both men and women in the United States. Hereditary etiologies of colorectal cancer comprise upwards of 5-6% of all colorectal cancers diagnosed. These commonly include hereditary nonpolyposis colorectal cancer (HNPCC), also known as Lynch Syndrome (LS), familial adenomatous polyposis syndrome (FAP), and serrated polyposis syndrome (SPS), among others. Due to the high risk for development of colorectal cancer, guidelines exist for earlier screening and frequent surveillance colonoscopy in these high-risk populations. What is less clear, however, is the optimal advanced imaging technique to be utilized or supplemented along with conventional colonoscopy to detect lesions amongst patients with known hereditary gastrointestinal disorders.

Advanced imaging may have a useful role in LS and SPS as they do not clinically present with heavy colon polyp burden as noted in typical polyposis conditions like FAP or hamartomatous polyposis syndromes. Patients with Lynch and serrated polyposis syndromes may also present with sessile, flat polyps with indistinct margins which are hard to detect and can be potentially missed on traditional colonoscopy. (Figure 1)
In 2014, the European Society of Gastrointestinal Endoscopy (ESGE) published recommendations regarding the use of advanced imaging in both average risk and high-risk populations, including hereditary polyposis syndromes such as LS and SPS. In the United States, however, there are currently no guidelines available outlining the use of advanced imaging for surveillance in hereditary polyposis syndromes. The goal of this review is to summarize the available literature in advanced imaging of hereditary gastrointestinal syndromes with special focus on Lynch Syndrome (LS) and Serrated Polyposis Syndrome (SPS).

**Endoscopic Imaging**

The standard of care for routine colon cancer screening has been through the use of traditional white light colonoscopy, however the main drawback to this procedure lies in its potential for missing polyps, otherwise known as the miss rate. Recent advancements have been made in endoscopic imaging in order to better detect polyps and decrease overall miss rates. High-definition white light (HDWL) endoscopy involves the use of a high definition monitor to enhance the resolution of images in order to increase the visibility of potential polyps. Since the advent of HDWL, additional imaging modalities have been invented and tested against standard white light colonoscopy (SWLC). In 2011, Gross et al. conducted a randomized controlled trial evaluating SWLC versus image enhanced colonoscopy. Results from this study demonstrated that use of an image enhanced method for screening led to decreased polyp misses as compared to conventional colonoscopy. A limitation of this study is the elucidation of which enhanced imaging modality, such as narrow band imaging, chromoendoscopy, or confocal microscopy would be the superior imaging technique of choice.

**Narrow Band Imaging**

Narrow band imaging (NBI) is an endoscopic technique which involves light manipulation to enhance visualization of the overall colonic structure. The principle behind NBI lies in its ability to utilize blue and green wavelengths to be absorbed by vessels in the colon while simultaneously being reflected by the mucosa; red wavelengths are canceled out altogether. In this way, the colon’s architecture is maximally highlighted, providing stark contrast of the overall colonic vasculature for the endoscopist to better detect suspicious lesions. The advantage of this particular type of imaging is in its ability to illuminate the superficial vasculature...
of the colon, with the potential to differentiate pre-malignant versus malignant lesions at time of actual endoscopic visualization prior to any histopathological manipulation and analysis.9

Leung and researchers conducted a randomized controlled trial in 2014 comparing NBI to traditional white light endoscopy in terms of adenoma detection rates.10 In this study, the newer NBI equipment—toted to provide double the brightness as the original scope—was utilized and 360 patients were randomized to the NBI or white light endoscopy arm as part of the research design. Their findings revealed NBI to have better adenoma detection rates, however no significant differences were attributed to adenoma miss rates between NBI and conventional colonoscopy.10

In the spring of 2019, a meta-analysis reviewing eleven randomized controlled trials was conducted comparing white light endoscopy to NBI with regards to adenoma detection rate (ADR) on routine colonoscopy.11 This review found NBI to have improved ADR, especially with adequate bowel preparation. While this meta-analysis points to the potential role advanced imaging like NBI may have in the near future as an additional endoscopic tool for routine colon screening, it did not take into account hereditary gastrointestinal syndromes as a separate entity from the general population.11

Chromoendoscopy
Chromoendoscopy involves the application of various dyes to the colonic mucosa in real time in order to better visualize lesions that may be missed on routine white light colonoscopy.12 The utility of these pigments is in their ability to enhance the subtle contours of the colon, thereby improving the endoscopist’s likelihood of detecting polyps that may otherwise go unnoticed until they are more advanced in appearance.13 There are several types of pigmented dyes available for use in chromoendoscopy, with indigo carmine or methylene blue being the most commonly used when evaluating for colorectal lesions.5 The blue pigment is able to collect within the mucosal folds and provide a stark contrast to the normal pink mucosa of the colon wall itself. The dyes utilized in surveillance chromoendoscopy are self-limiting as opposed to the permanent dyes employed for tattooing locations of the colon for surgical evaluation at a later date.

Chromoendoscopy has been studied against conventional white light colonoscopy as a screening technique for colorectal cancer in average risk populations. Kahi and colleagues conducted a study comparing chromoendoscopy to traditional white light endoscopy in 660 average risk patients presenting for routing colorectal cancer screening.14 The results from this randomized study showed that chromoendoscopy did increase the overall adenoma detection rate, including flat and small adenomas, however the results were similar for advanced neoplasm detection in both the chromoendoscopy and white light colonoscopy groups. Authors concluded that the study could not advocate the use of chromoendoscopy in screening for the average risk population14.

Though not currently recommended for the average risk population, chromoendoscopy has been largely studied in inflammatory bowel disease (IBD) as a potential primary surveillance modality given the higher risk for colorectal cancer development in this patient population.15 In a 2007 study involving 161 patients with ulcerative colitis, Kiesslich et al. revealed that the number of neoplastic lesions identified via chromoendoscopy was higher by 4.75-fold than the amount exposed by traditional colonoscopy alone, demonstrating chromoendoscopy’s strength as an advanced imaging technique in IBD.16 Marion and researchers conducted a prospective trial in 2008 which included 115 patients with IBD, 79 with ulcerative colitis, and 23 with Crohn’s disease, and they concluded that biopsies utilizing chromoendoscopy yielded superior results as compared to traditional biopsy methods.15 There is a wealth of literature available demonstrating chromoendoscopy’s benefit as an adjunct imaging modality in the IBD population for surveillance; less research has been done, however, as to its role in alternative high-risk populations, such as the hereditary gastrointestinal syndromes discussed in this review.

Virtual Chromoendoscopy (ISCAN)
While dye chromoendoscopy is more often employed as an advanced imaging modality, the virtual technique is an alternative method of chromoendoscopy that does not involve the
application of dyes in real time. Instead, virtual chromoendoscopy utilizes software enhancements to better visualize potential alterations in the colonic mucosa. Amplifications to the images include the surface, contrast, and tone in order to create the highest quality image. Narrow band imaging is a type of virtual chromoendoscopy utilized to identify difficult to detect colonic lesions, however it utilizes light augmentation in real time whereas other virtual chromoendoscopy techniques modify images utilizing advancements in computer software imaging to detect subtle colonic lesions. More research and technological advancements need to be undertaken for virtual chromoendoscopy to be used as an advanced imaging option. We discuss the utility of this technique in high risk populations.

Confocal Laser Microendoscopy
Confocal laser microendoscopy utilizes laser technology to obtain high resolution imaging of the gastrointestinal mucosa. The laser light is directed towards the tissue in question, and the light reflected back onto the lens is refocused through a pinhole which allows for enhanced magnification of the tissue layer itself. This concept of light being directed towards the tissue surface via the laser with subsequent reflection back into the same plane through the pinhole lends the confocal portion of the technique’s name. In this way, confocal microendoscopy can be utilized in conjunction with traditional white light endoscopy to enhance features of the colonic wall to better detect subtle changes in the mucosa. Given its relatively new status in the advanced imaging world, confocal laser microendoscopy has not been widely studied in high risk populations such as hereditary gastrointestinal syndromes. This fact limits its use as an advanced endoscopic imaging tool currently. Additionally, the novelty of this modality restricts its utility given costs accrued with it as compared to alternative imaging modalities more readily accessible. In the end, further research should be completed to evaluate confocal laser microendoscopy’s potential role as an imaging tool in high risk populations including those discussed in this review.

HEREDITARY GASTROINTESTINAL SYNDROMES

Lynch Syndrome
Lynch Syndrome (LS), an autosomal dominant disorder due to DNA mismatch repair dysfunction, is the most common cause of an underlying hereditary etiology for colorectal cancer. In normal DNA synthesis, routine errors can occur

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during DNA replication. These errors are accounted for via mismatch repair (MMR) genes, which serve to identify and remove any abnormalities encountered in the newly synthesized DNA strand. In LS, there is a mutation in one of the vital MMR genes, which allows for unchecked DNA strands to be replicated despite possible errors within the strand. These errors lend themselves to increased risk of cancer development.

LS comprises roughly 3-5% of all colon cancers, and individuals with this disorder have an overall 50 to 80% increased risk of developing colon cancer as compared to the average population. Overall prevalence of LS is estimated 1 in 440. Current surveillance guidelines for LS include screening colonoscopy beginning at 20 to 25-years old with follow-up every 1 to 2 years thereafter. Biopsies obtained during colonoscopic surveillance can be further studied with genetic testing for microsatellite instability and immunohistochemical staining for additional analysis.

**Serrated Polyposis Syndrome**

Formerly called hyperplastic polyposis syndrome, serrated polyposis syndrome (SPS) is an underdiagnosed disorder in which patients are at increased risk of developing colonic neoplasia. The lifetime risk of colon cancer ranges from 16-42%. Due to the rarity of the disease, the overall prevalence is difficult to ascertain. In 2017, a prospective multi-center cross-sectional study analyzed the prevalence of SPS in four European countries. Those results revealed SPS prevalence of 0-0.5% at first screening colonoscopy, increasing to 0.4-0.8% prevalence on subsequent endoscopic evaluations. The prevalence of SPS in the fecal occult blood test-based Spanish screening cohort was noted to be 1 in 127 subjects and in the Netherlands colonoscopy cohort to be 1 in 238 subjects, suggesting SPS likely is a more prevalent condition than previously thought.

SPS is diagnosed clinically with one or more of the following criteria set forth by the World Health Organization (WHO): at least five serrated polyps located proximal to the sigmoid colon (of which at least two are ten millimeters or more in size); more than twenty serrated polyps located throughout the colon; and/or any serrated polyps found proximal to the sigmoid colon in a patient with a known first degree relative with SPS. In contrast to Lynch Syndrome and Familial Adenomatous Polyposis Syndrome, SPS is not diagnosed through genetic testing, and further research is needed to understand the underlying genetic etiology of SPS.

**ADVANCED IMAGING IN LYNCH SYNDROME**

Lynch syndrome patients require frequent colonoscopy to surveil for polyps and colorectal cancer. However, less is known and controversy exists regarding use of advanced imaging in the detection of adenomas in patients with LS.

A systematic review by van de Wetering et al. suggested that chromoendoscopy in LS did not add significant benefit to detection rate in the high-risk LS population as compared to conventional white light endoscopy alone. This 2018 review echoed Haanstra and colleague’s 2013 review of advanced imaging in LS patients. At that time...
though, only six studies had been published outlining advanced imaging in LS surveillance, none of which demonstrated superiority to white light colonoscopy.\textsuperscript{29} Chromoendoscopy, narrow-band imaging, and autofluorescence endoscopy were the advanced techniques under scrutiny back then, and of these it was determined that chromoendoscopy could be the emerging leader in the field of advanced imaging.\textsuperscript{29} The limiting factor for those in favor of advanced imaging, though, was the paucity of studies available utilizing advanced imaging in LS patients to determine their efficacy as a surveillance modality compared to conventional white light endoscopy.\textsuperscript{29}

Despite some of the literature suggesting advanced imaging may not have a role in LS surveillance, other studies pointed towards its utility. Stoffel and colleagues conducted a small study in 2008 in which 54 patients with LS received routine colonoscopic surveillance.\textsuperscript{3} Roughly half of these individuals underwent conventional colonoscopy alone, whilst the other half went on to receive an additional chromoendoscopic exam.\textsuperscript{3} Those who received chromoendoscopy had more polyps detected, though the findings were not statistically significant.\textsuperscript{3}

Stoffel’s study highlighted the importance of the role chromoendoscopy could play in high-risk populations such as LS and the need for larger study populations to further investigate the role of advanced imaging in these patients.\textsuperscript{3} Additional studies since then have demonstrated the potential for advanced imaging as primary surveillance modalities in patients with LS. Several years after Stoffel’s initial study, a larger study completed by Rahmi et al revealed that chromoendoscopy in conjunction with colonoscopy improved adenoma detection rates in LS patients as compared to conventional colonoscopy alone.\textsuperscript{30} Similarly, Lecomte and researchers conducted a prospective study following 36 patients with LS comparing standard endoscopy to chromoendoscopy; their findings demonstrated improved adenoma detection rates with chromoendoscopy as compared to regular colonoscopy.\textsuperscript{31}

While much of the current literature juxtaposes conventional colonoscopy with chromoendoscopy, other advanced imaging techniques have been investigated recently as possible alternatives to white light endoscopy. In 2017, Bisschops and researchers illuminated virtual chromoendoscopy’s role as a potential surveillance agent in patients with LS with their randomized controlled crossover trial.\textsuperscript{32} This prospective trial with 61 subjects showed that those who received virtual chromoendoscopic surveillance in addition to white light endoscopy had higher adenoma detection rates as compared to those who received surveillance with white light endoscopy alone.\textsuperscript{32} East and colleagues followed 62 patients with family histories significant for LS and found that narrow band imaging improved adenoma detection rates, especially those of flat morphology, as compared to conventional white light endoscopy as well as narrow band imaging.\textsuperscript{33} These studies suggest that chromoendoscopy may be at the forefront of advanced modalities available for surveillance imaging when compared to narrow band imaging, however more studies need to be commenced in the future for further clarity as to the advanced imaging test of choice. Figures 2, 3, and 4 show endoscopy images of an 8 mm polyp using HDWL, NBI, and chromoendoscopy in a 69-year old patient with Lynch syndrome. Figure 5 shows a sessile polyp highlighted by using chromoendoscopy in a patient with LS.

**ADVANCED IMAGING IN SERRATED POLYPOSIS SYNDROME**

Serrated polyposis syndrome, one of the uncommon hereditary gastrointestinal disorders, conveys a higher risk for colorectal cancer development than the average risk individual. Earlier screening is recommended in SPS patients, however there is debate in the current literature regarding surveillance frequency and even less is known about the role advanced imaging plays in this high-risk population.\textsuperscript{35}

In 2015, Hazelwinkel et al. examined the use of narrow band imaging (NBI) in patients with known serrated polyposis syndrome as compared to high resolution white light endoscopy (HR-WLE) in terms of polyp miss rate.\textsuperscript{36} In this multicenter randomized crossover study with a sample size of 52 patients, an initial surveillance colonoscopy was
completed to detect polyps; during the subsequent encounter, the same endoscopist then utilized either HR-WLE or NBI to further detect any potential missed polyps. Hazelwinkel and colleagues ultimately did not find a significant difference in polyp miss rates when comparing the two imaging techniques, however this study was largely limited by the small sample size and use of the same endoscopist for all second pass colonoscopies.36

Hazelwinkel’s results conflict with Boparai and researchers’ 2011 randomized crossover study comparing high resolution endoscopy (HRE) to NBI polyp miss rates in patients with known SPS.37 In this single center study comprised of just 22 patients, Boparai et al revealed that the polyp miss rate was significantly reduced when utilizing the advanced technique of NBI in addition to conventional colonoscopy as compared to HRE.37 Their study demonstrates that not only could advanced imaging play a role in SPS polyp detection, but also NBI could be one of the future favorites in the advanced imaging world for SPS. Of note, Boparai’s study found that flat polyp morphology was independently associated with a higher polyp miss rate.37 As a result of their research, Boparai and colleagues recommend incorporating NBI or chromoendoscopy into routine polyp surveillance in patients with SPS.37 Similar to Hazelwinkel’s study design,36 Boparai’s study was limited by small sample size and further studies should be conducted to ensure reproducibility of their initial results.37

In 2018, a group of Spanish researchers conducted a multicenter, randomized control trial comparing the efficacy of HD-WLE colonoscopy exams to panchromoendoscopy with indigo carmine dye for polyp detection.38 Panchromoendoscopy, a type of chromoendoscopy, involves the application of dye throughout the entirety of the colon for maximal contour enhancement. Eighty-six patients with SPS from seven centers in Spain were randomized to undergo either tandem HD-WLE or panchromoendoscopy; results revealed significantly increased polyp detection rates in those who received panchromoendoscopy as compared to HD-WLE alone. Researchers also noted that panchromoendoscopy yielded a higher rate of serrated lesion identification proximal to the sigmoid colon, though there was no significant difference between the two imaging techniques when detecting lesions larger than ten millimeters. As a result of this study, researchers recommended the use of panchromoendoscopy in surveillance for patients with SPS, along with the suggestion that further studies be completed to evaluate the overall long-term efficacy of this imaging method as a surveillance technique in SPS patients.38 Figure 6 and 7 shows serrated polyps using NBI and Figure 8 shows a serrated polyp highlighted using chromoendoscopy in patients with serrated polyposis syndrome.

While the ESGE recommends the use of high definition endoscopy or virtual narrow band imaging chromoendoscopy as advanced imaging techniques in SPS,5 no guidelines have been put forth in the United States currently. NBI and chromoendoscopy may be top contenders for the advanced imaging test of choice according to the current literature,5,37,38 however the scarcity of studies available to review point to the need for larger prospective trials looking at these advanced techniques and their associated long-term outcomes in order to determine the best imaging modality to be utilized in SPS.

SUMMARY

Patients with hereditary gastrointestinal syndromes such as Lynch syndrome and serrated polyposis syndrome are at an intrinsically higher risk of colon cancer development requiring early scrutinized surveillance at more frequent intervals than the average risk population. This review offers a comprehensive analysis of the available literature surrounding current colonoscopy surveillance techniques utilized in LS and SPS, including the introduction of advanced imaging as a possible surveillance modality in these syndromes. Currently, the ESGE recommends NBI or virtual chromoendoscopy advanced imaging modalities for both LS and SPS,5 however to date there are no formal recommendations or guidelines published in the United States. Thus, more research should be devoted to advanced imaging techniques including chromoendoscopy, narrow-band imaging, and virtual chromoendoscopy to better elucidate their role as surveillance tools in these high-risk populations.
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