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Endoscopic Techniques for Colorectal Cancer Surveillance in Inflammatory Bowel Disease

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INTRODUCTION

Inflammatory Bowel Disease **(IBD)** is a chronic and relapsing disorder of the gastrointestinal tract, consisting of two major disorders: Ulcerative Colitis **(UC)** and Crohn's Disease **(CD)**. UC and CD differ in terms of clinical presentation and pathology. UC mostly affects the mucosal layer of colon in an ascending fashion whereas CD causes transmural inflammation in any part of the gastrointestinal tract from oral cavity to the anus. The prevalence of IBD is globally increasing. It is reported that 2.2 million and 1.4 million people are affected in Europe and United States, respectively [1]. It is widely acknowledged that both genetic and environmental factors play a role in pathogenesis of IBD [1]. However, the precise etiology and pathogenesis of IBD is not well understood.

Patients with long standing IBD are at increased risk of developing dysplasia and colorectal cancer as compared to general population. This is due to prolonged and relapsing mucosal and transmural inflammation that puts patients at high risk for dysplasia, especially with colonic involvement, which may lead to Colorectal Cancer **(CRC)** [2-5]. A recent study reported CRC risk of 1.6% in UC patients over 14 years of follow-up and overall risk of developing CRC was 2.4 fold (pooled SIR 2.4, range: 1.05-3.1; 95% CI: 2.1-2.7) [6]. In a meta-analysis of 12 studies in 2006, it was reported that the overall Relative Risk **(RR)** of developing CRC was 4.5 in patients with colonic CD (95% CI 1.3-14.7) [7]. In another study, the cumulative risk of CRC was 2.9% after 10 years, 5.6% after 20 years, and 8.3% after 30 years of disease [8]. Considering this, proper CRC surveillance in patients with IBD is necessary. Hence, endoscopy has an essential role and has evolved not only as a diagnostic but also as a therapeutic tool over past few years.

HIGH DEFINITION WHITE LIGHT VIDEO ENDOSCOPY

Video endoscopy continues to play a crucial role in examining gastrointestinal mucosa and identifying tissue and anatomical pathologies. It allows endoscopists to take sample biopsies and accurately diagnose colonic dysplasia and CRC through histopathologic review. Over past decade the technology surrounding the endoscope has improved significantly. One of the major advancement is the resolution quality, which consists of pixel density. A Standard Definition **(SD)** white light endoscope equipped with a Charge-Coupled Device **(CCD)** can yield a signal of 100,000 to 400,000 pixels, whereas High Definition **(HD)** endoscopes can produce signal images with resolution quality of over 2 million pixels [9,10]. This improvement offers the ability to distinguish and identify minute differences in colonic mucosal tissue. Higher magnification has also improved with high definition endoscopy. A standard endoscope can magnify an image by 30-35 times normal, where as a high definition endoscope can produce images up to 150 times magnification [10,11]. Hence, high definition endoscopy is certainly better than standard definition endoscope. A retrospective study including patients with long-standing (>7 years) colonic IBD showed higher adjusted prevalence ratio of 2.21 (95% CI 1.09-4.45) in detecting any dysplastic lesion and 2.99 (95% CI 1.16-7.79) in detecting dysplastic lesions on targeted biopsy with HD as compared to SD endoscopy [12,13]. Therefore, HD colonoscopy has shown to be an effective surveillance tool for detection of dysplasia in patients with colonic IBD.

CHROMOENDOSCOPY

The conventional method of surveillance in IBD patients involves obtaining random biopsies using SD or HD endoscopy. Chromoendoscopy **(CE)** uses dye based and non-dye based enhancing techniques that allow better visualization of mucosal lining to identify any dysplasia or pathologic changes. Dye-based chromoendoscopy uses stains and pigments, in conjunction with HD endoscopy, to assist in identification of abnormal tissue and flat lesions harboring dysplastic or neoplastic lesions. The number of random biopsies required is also significantly reduced with chromoendoscopy guided target biopsies [14]. There are three types of stains. Absorptive stains

(Lugol's solution and methylene blue) are absorbed by specific epithelial cell membranes and can help identifying flat adenomas and carcinomas [15]. Contrast agents (indigo carmine and acetic acid) do not get absorbed or stain tissue. These agents are actually used to highlight small creases and flat lesions, which can help distinguishing between hyperplastic and adenomatous polyps [16]. Reactive staining agents (phenol red and congo red) are used to identify specific cell types as they react with specific cellular components and change color. In one meta-analysis of 665 patients from 6 studies demonstrated that chromoendoscopy with targeted biopsy was 9 times more likely to detect dysplasia than white light endoscopy with random biopsies (8.9 OR; 95% CI 3.4-23.0). Furthermore, the overall procedure time was reduced by 10.9 minutes with chromoendoscopy as compared to white light endoscopy [17]. In a more recent 28-month prospective study of 68 patients with IBD, CE (OR 5.4; 95% CI 2.9–9.9) was found to be superior to white light endoscopy with random biopsies in detecting dysplasia [18].

While dye based chromoendoscopy uses stains to identify dysplasia, dye-less chromoendoscopy uses high-contrast imaging of the mucosal surface without any stains or dye. There are two types of dye-less chromoendoscopy. One uses a high quality optical filter system called Narrow Band Imaging **(NBI)** (Olympus, Tokyo, Japan). These techniques use specialized optical lens filters integrated within the white light source of the endoscope that narrow the bandwidth in the blue and green regions of the spectrum [19,20]. Another technique uses virtual chromoendoscopy, which digitally processes the endoscopic images produced by the video processor in real-time. These digital processing systems include i-Scan (Pentax, Tokyo, Japan) and Fujinon Intelligent Color Enhancement **(FICE)** by (Fujinon Inc., Saitama, Japan) [12-22]. In recent studies, these techniques were shown to be useful for differentiating adenomatous versus hyperplastic colonic polyps, as compared to white light endoscopy with random biopsies, with good histologic correlation [23,24].

NBI enhances the visualization of the superficial mucosal layer using optical lenses that narrow the bandwidth of visible light spectrum. It is a user-friendly tool because no dyes, stains or other specialized equipment are required, and the learning curve is relatively short. NBI has been subject of multiple clinical trials to assess for diagnostic accuracy in IBD as compared to other modalities, and so far the results have been inconclusive [25-29]. In the study by Danese et al [25], conventional and NBI colonoscopy on 14 patients with colonic inflammation demonstrated NBI superiority in detecting angiogenesis and vessel density ($P<0.05$ and $P<0.01$, respectively) in areas of mucosal inflammation. In a prospective randomized study of 80 patient's with IBD, Pellise' et al [26] showed that CE was slower than NBI endoscopy (26.87 ± 9.89 minutes vs. 15.74 ± 5.62 minutes, $P<0.01$). Furthermore, NBI resulted in a significantly inferior false-positive biopsy rate ($P=0.001$) and a similar true-positive rate. However, the percentage of missed intraepithelial neoplastic lesions and patients was higher with NBI, although the result did not reach statistical significance. In another prospective study of 44 patients with colonic IBD, Efthymiou et al [27] demonstrated that CE detected more lesions than NBI (131 vs. 102, $P<0.001$); however, most

were nondysplastic. CE detected 23 neoplastic (dysplastic or indefinite for dysplasia) lesions in 11 patients and NBI detected 20 lesions in 10 patients albeit, this finding was not statistically significant (P=0.180). Hence, Efthymiou et al [27] did not recommend NBI as a standard for dysplasia surveillance in colitis. Leung et al [28] performed a randomized controlled trial in 360 patients who underwent CRC surveillance with HD White Light **(HD-WL)** colonoscopy and NBI. Their study showed that NBI had significantly higher adenoma detection rate than HD-WL (48.3% vs. 34.4%, P=0.01) and there was no significant difference in adenoma miss rate between the two groups (21.8% vs. 21.2%). Hence, in their study NBI was superior to HD-WL colonoscopy for CRC surveillance. In one of the most recent studies, Leifeld et al [29] showed that the combination of targeted and segmental biopsy specimens in the NBI technique is as sensitive as stepwise biopsy specimens in WL colonoscopy, but requires fewer biopsy specimens (11.9 vs. 38.6, P<0.001) and less withdrawal time (23 vs. 13 min, P<0.001). They suggest that the highest sensitivity should be achieved by combining the WL and NBI techniques by switching between the modes. Thus, there is no conclusive evidence for or against narrow band imaging being superior to white light and chromoendoscopy; further studies are required. That said, a combination of these techniques could theoretically yield the highest sensitivity in detecting CRC or other pathologic abnormalities in patients with inflammatory bowel disease.

Digital chromoendoscopy is the other non-dye chromoendoscopy technique. Unlike NBI, no lens filters are required. Instead, a digital contrast method with integrated software is used to enhance endoscopic images in real time. The mucosal surface is digitally enhanced using surface, tone and contrast enhancement techniques. Fujinon Intelligent Color Enhancement **(FICE)** and i-scan are two methods currently available. In recent years, i-scan has been the focus of multiple comparative studies for CRC surveillance in IBD patients. A randomized controlled study of 78 patients with IBD compared i-scan and HD-WL endoscopy to detect mucosal vascular pattern and other abnormalities. The average procedure time for i-scan and HD-WL were similar: 18 and 20.5 minutes, respectively. When comparing the endoscopic prediction of inflammatory extent and activity with the histological results, an overall agreement of 48.71% and 53.85% in HD-WL endoscopy and 92.31% and 89.74% in i-scan were reported (P<0.001 and P=0.066) [30]. In another prospective randomized trial, i-scan with tone enhancement and HD-WL endoscopy were compared for colorectal adenoma detection in 80 patients. The study was designed so each patient first underwent HD-WL colonoscopy. Then the second colonoscopy using either i-scan or HD-WL endoscopy was done to detect any missed adenomas. Sixty-seven lesions (n=34 and n=33 for HD-WL and i-scan, respectively) were detected in first colonoscopy. The second colonoscopy detected 78 additional lesions: n=60 with tone enhancement vs. n=18 with white light endoscopy (P<0.001). Tone enhancement found more additional adenomas, n=20 vs. HD-WL n=6 (P<0.05) and identified significantly more missed adenomas per subject (0.5 vs. 0.15, P=0.006) [31].

AUTOFLUORESCENCE IMAGING

Autofluorescence Imaging **(AFI)** is an imaging technique that relies on tissues to emit fluorescent light when excited by ultraviolet (>400 nm) or short visible light (400-550 nm). All cells have molecules called fluorophores such as collagen, flavin, and elastin. These fluorophores become excited when exposed to UV or short visible light and emit fluorescent light of longer wavelength [32,33]. This emission of fluorescent light with longer wavelength is picked up by video endoscopy and real-time colored images are projected on the screen depending on the light color emitted by the tissue fluorophores. The principle behind this technique is that inflamed tissues will exhibit different autofluorescence than non-inflamed tissues due to changes in amount and distribution of endogenous fluorophores. Therefore, AFI can be a novel tool for detecting inflammation and neoplastic lesions in IBD. In a randomized comparative study in 50 patients with ulcerative colitis, neoplasia miss-rates for AFI and WL endoscopy were 0% and 50%, respectively (p=0.036). However, AFI had 100% of sensitivity since all neoplasia was colored purple on AFI, while NBI had a 75% of sensitivity according to the Kudo classification [34]. This study demonstrates the potential capability of AFI for detection of dysplasia and CRC in patients with IBD; however further studies with higher power are needed for more conclusive data and before changes are made to the guidelines for CRC surveillance in patients with IBD.

SUMMARY

In conclusion, CRC surveillance is essential for patients with IBD as they are at higher risk of developing dysplasia and CRC compared to general population. Surveillance endoscopy is an important tool for preventing and reducing mortality from CRC. While HD-WL endoscopy with biopsies is the standard technique for CRC surveillance, new techniques are being developed for more precise and accurate diagnosis of IBD and neoplasia. Chromoendoscopy with methylene blue and indigo carmine dyes have improved detection of dysplasia and reduced the overall time of endoscopy, but this technique requires specialized training. Optical filter technology such as NBI and advanced imaging software such as i-scan continue to be of interest. Further studies are needed to establish their superiority compared to conventional high definition and chromoendoscopy. As we move forward, additional techniques and tools will be introduced. Therefore, it is a tedious but essential that gastroenterologists keep up with the new technology and analyzes it in well-designed clinical investigations.

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