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Screening and surveillance methods for dysplasia in inflammatory bowel disease patients: Where do we stand?

Michail Galanopoulos, Emmanouela Tsoukali, Filippos Gkeros, Marina Vraka, Georgios Karampekios, Gerassimos J Matzaris

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Abstract

Patients with long-standing ulcerative colitis (UC) and extensive Crohn's colitis (CC) are at increased risk for dysplasia and colorectal cancer (CRC). Several studies have shown that UC extending proximal to the rectum, CC involving at least 1/3 of the colon, co-existence of primary sclerosing cholangitis, undetermined or unclassified colitis, family history of CRC and young age at diagnosis appear to be independent risk factors for inflammatory bowel disease (IBD) - related CRC. Therefore, screening and surveillance for CRC in IBD patients is highly recommended by international and national guidelines, whilst colonoscopy remains the unequivocal tool in order to detect potentially resectable dysplastic lesions or CRC at an early stage. Although the importance of screening and surveillance is widely proven, there is a controversy regarding the time of the first colonoscopy and the criteria of who should undergo surveillance. In addition, there are different recommendations among scientific societies concerning which endoscopic method is more efficient to detect dysplasia early, as well as the terminology for reporting visible lesions and the management of those lesions. This article concisely presents the main endoscopic methods and techniques performed for detecting dysplasia and CRC surveillance in patients with IBD focusing on their evidence-based accuracy and efficiency, as well as their cost-effectiveness. Finally, newer methods are mentioned, highlighting their applicability in daily endoscopic practice.

Key words: Inflammatory bowel disease; Ulcerative colitis; Crohn's disease; Dysplasia; Colorectal cancer;

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Core tip: There is an established association between inflammatory bowel disease (IBD) and colorectal cancer (CRC). Therefore, surveillance of these patients for CRC is crucial and recommended by international guidelines. In this review we present the main endoscopic methods and techniques performed for detecting dysplasia and CRC surveillance in patients with IBD, highlighting chromoendoscopy with targeted biopsies as the gold standard method. Finally, newer methods are mentioned, examining their applicability in daily endoscopic practice.

Galanopoulos M, Tsoukali E, Gkeros F, Vraga M, Karampekios G, Matzaris GJ. Screening and surveillance methods for dysplasia in inflammatory bowel disease patients: Where do we stand? *World J Gastrointest Endosc* 2018; 10(10): 250-258 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v10/i10/250.htm> DOI: <http://dx.doi.org/10.4253/wjge.v10.i10.250>

INTRODUCTION

Patients with inflammatory bowel disease (IBD) have a higher incidence of colorectal cancer (CRC) compared to the general population, even though only 1% of all CRC cases are attributed to IBD^[1]. The incidence rates reported by Eaden *et al*^[2,3], as well as the St. Mark's group in the United Kingdom, showed comparable cumulative probabilities of CRC and dysplasia, approximately 8% and 18% by 20 and 30 years of ongoing disease, respectively. According to Bernstein *et al*^[4], both Crohn's disease (CD) and ulcerative colitis (UC) patients face an increased risk for colon cancer [relative risk (RR) 2.64 and 2.75, respectively]. Factors linked to an increased incidence of CRC include: prolonged duration of colitis, extensive colonic involvement, presence of primary sclerosing cholangitis (PSC), positive family history for CRC and, according to some studies, earlier onset and severity of inflammation^[1,5-9] (Table 1). Oncogenesis in IBD has been well described as a result of chronic inflammation, leading *via* low- and high-grade dysplasia, finally, to CRC^[1,10-24] (Figure 1). Dysplasia is divided into two categories: (1) Endoscopically visible dysplastic lesion, *e.g.*, polyps, which are detected by targeted biopsies or resection of endoluminal masses; and (2) Endoscopically invisible dysplasia which is detected by blinded random biopsies on endoscopically normal lumen and is characterized as the most dependable marker for increased CRC risk in IBD patients^[1,25,26]. The resection of visible dysplasia, in combination with a rigorous follow-up program has been shown to be a safe alternative to colectomy for select patients^[27,28]. On the other hand, a study by Picco *et al*^[29] showed that the detection rate for dysplasia with the use of white light

endoscopy (WLE) was 9.3%, compared to 21.3% when using both WLE and dye-spray chromoendoscopy (DCE). This demonstrates the need for the implementation of a surveillance strategy in IBD patients based on better techniques and technologies, aiming at reducing the prevalence of metachronous lesions during follow-up. However, uncertainties exist regarding the soundness of this approach on preventing CRC. In a recent systematic review, people undergoing periodic surveillance for CRC were not found to have lower mortality when compared to those under no surveillance (RR 0.81, 95%CI: 0.17 to 3.83)^[30,31].

Nevertheless, the current recommendations favor DCE with targeted biopsies of any identified lesions^[1,26,32,33] (Figure 2). Whenever DCE is not available, WLE with random, four quadrant biopsies every 10 cm should be performed with additional targeted biopsies from visible lesions. Other endoscopic modalities, like narrow band imaging (NBI), i-SCAN and autofluorescence imaging, did not achieve superior dysplasia detection rates when compared to standard (SD)- or high-definition (HD) WLE in randomized controlled trials^[34-39].

Taking all these into consideration, the aim of our review is the brief and up-to-date description of the basic screening endoscopic modalities, as well as their efficacy and accuracy for CRC surveillance in IBD patients.

STANDARD-DEFINITION AND HIGH-DEFINITION WHITE LIGHT ENDOSCOPY

The standard method in CRC surveillance has until recently been SD colonoscopy, with the use of targeted as well as random quadrant biopsies every 10 cm, which amounts to at least 33 biopsies to achieve 90% confidence of detecting dysplasia. However, this technique ultimately inspects less than 1% of the mucosal surface of the colon^[40]. According to a Dutch study examining long-standing UC, the overall rate of dysplasia detection with SD colonoscopy was 0.19^[36]. With the advent of HD endoscopes and monitors, the endoscopist is able to better identify dysplastic lesions. A study by Subramanian *et al*^[41] comparing SD to HD colonoscopy for dysplasia screening in UC, reported a three-fold increase in the yield of the HD endoscope combined with targeted, as well as random biopsies, especially in the right colon. Based on the aforementioned study, the SCENIC consensus statement by American Society for Gastrointestinal Endoscopy (ASGE) favors HD- over SD-WLE when implementing a surveillance program, even though the HD cost remains a limitation^[33]. This improvement in detection of dysplastic lesions by HD-WLE and targeted-biopsy sampling changed the therapeutic considerations regarding colectomy, favoring more conservative approaches^[41]. Furthermore, it was pointed out that the increased turnout with HD colonoscopy is probably a true reflection of the increased yield of this technique^[41]. Nevertheless, based on the same study, neither

Table 1 Colorectal cancer risk factors and surveillance

High risk factors
Annual surveillance
Extensive colonic involvement (pancolitis, CD with > 50% colonic involvement)
Moderate-severe endoscopic or histological active inflammation sustained over time
PSC
Disease commencing at age < 15 yr
Family history of sporadic CRC in a first-degree relative < 50 yr
Presence of a stricture or dysplasia detected during the previous 5 yr
High risk factors in case of pouch existence
Dysplasia
Previous CRC
Type C mucosa
Intermediate risk
Every three years surveillance
Mild or moderate endoscopic/histological inflammation sustained over time
Family history of sporadic CRC in a first-degree relative older than 50 yr
Presence of inflammatory polyps
Low risk factors
Every five years surveillance
Pancolitis without inflammation
Left-sided UC or CD with < 50% colonic involvement

CRC: Colorectal cancer; CD: Crohn's disease; PSC: Primary sclerosing cholangitis; UC: Ulcerative colitis.

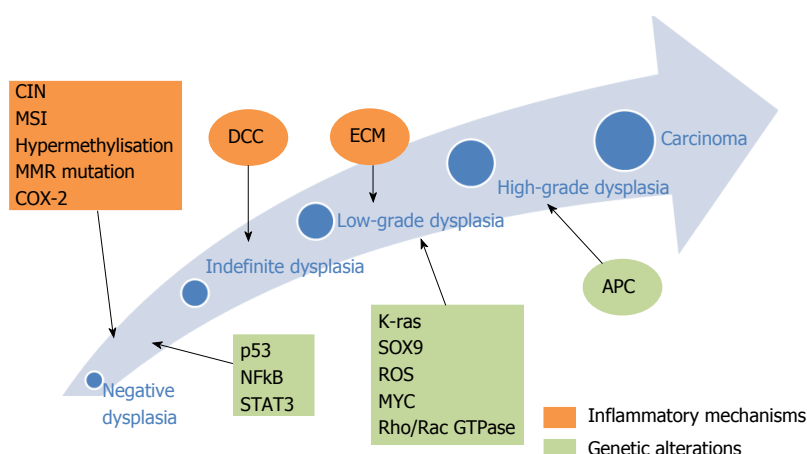


Figure 1 Colitis-associated colon cancer sequelae. COX-2: Cyclooxygenase-2; ECM: Extra-cellular matrix; MMR: Mismatch repair mutation; DCC: Deleted in colorectal carcinoma; APC: Adenomatous polyposis coli; MSI: Microsatellite instability; CIN: Chromosomal instability; ROS: Reactive oxygen species; K-ras: Kirsten rat sarcoma 2 viral oncogene homolog; p53: Tumor protein p53; NF-kB: Nuclear factor kappa-light-chain-enhancer of activated B cells; STAT3: Signal transducer and activator of transcription 3; SOX9: SRY-box 9 gene.

significant change in the detection of lesions with high grade dysplasia nor early carcinoma or flat lesions were observed.

On the contrary, the study by van den Broek *et al.*^[36] showed no substantial difference in clinical outcomes for patients, in whom low grade dysplasia was revealed using random biopsies, thus advocating the use of improved visualization through advanced techniques^[36,41].

Concluding, even though the most widespread technique for dysplasia surveillance in IBD until recently has been the WLE with random biopsies, it is arduous and protracted^[40]. Furthermore, the diagnostic reliability of WLE is challenged in a recent review, which found a sensitivity of 76%^[42]. Therefore, this method's practicability has been clearly questioned and the research for the development of diagnostic modalities is supported^[43].

RANDOM BIOPSIES

Four quadrant biopsies every 10 cm throughout the colon has been the gold standard of IBD surveillance for more than 30 years. This approach originates from the theory of "flat dysplasia", which suggests that dysplasia is difficult to visualize in colitis-affected mucosa^[40,44]. Random biopsy only samples less than 1% of the luminal mucosa; has a subpar detection rate (< 2 per 1000 biopsies taken) and when used in conjunction with advanced endoscopic techniques, it does not affect clinical decisions^[44]. A large retrospective analysis by van den Broek *et al.*^[36] reviewing 1010 colonoscopies during 10 years of surveillance stated that the result of random biopsy surveillance was poor, and neoplasia was detected only in four patients with random biopsies.

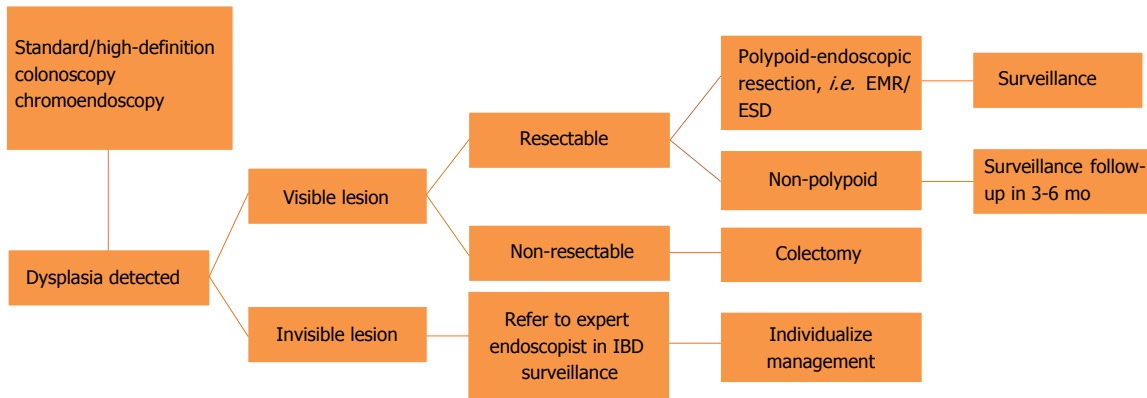


Figure 2 Algorithm for colorectal cancer surveillance in inflammatory bowel disease patients. IBD: Inflammatory bowel disease; EMR:

Additionally, neoplasia was macroscopically visible in 94% of colonoscopies^[43,44]. Current guidelines by British Society of Gastroenterology (BSG) and ASGE advocate the use of DCE without the need for random biopsies; however, it is suggested that random biopsies be acquired during HD colonoscopy, if DCE is not available or technically feasible^[26]. Random biopsies remain a reasonable alternative if there are conditions that lower the diagnostic yield, such as inflammation, pseudo-polyposis, poor preparation or a poorly visualised mucosa^[26,45].

DYE-SPRAY CHROMOENDOSCOPY

Several studies have proven the efficacy of DCE in the detection of dysplasia in patients with IBD. DCE may reduce the need for random biopsies and may allow prolonged surveillance-interval, leading to cost reduction, as well as an increase the detection sensitivity of dysplastic lesions per examination^[46].

This technique helps to augment dysplasia detection by topical application of dye on the colonic mucosa during colonoscopy. Areas that are macroscopically elevated or depressed, friable, obscure in vasculature, and with a villous or nodular pattern, can be detected more easily and biopsies can be taken. The most common dyes that in use are methylene blue and indigo carmine^[47]. Dye solution can be sprayed by catheter, or flushing pumps, or administered as controlled release tablets, taken with bowel preparation^[48]. When performing DCE, it is important to avoid active disease and to have adequate bowel preparation. Paris classification seems to be the standard method to describe any visible lesion, and targeted biopsies should be taken from any suspected area. If the lesion is well-defined, *en-bloc* endoscopic resection should be performed and biopsies should be taken from the adjacent mucosa. In case the lesion is unresectable, the endoscopist should take biopsies and tattoo the area.

Kiesslich *et al*^[49] were the pioneers conducting a large randomized study with 263 individuals with long-standing UC. In the DCE-group, there was a statistically important correlation between the endoscopic estimation of the

level and extent of inflammation of the colon ($P = 0.0002$) and the histology report, when compared to WLE ($P = 0.0002$) (89% vs 52% $P < 0.0001$). Additionally, more targeted biopsies were possible and these biopsies detected significantly more intraepithelial neoplasia (INs) when performing DCE (32 vs 10 $P = 0.003$). In a well-designed prospective study, Hurlstone *et al*^[50] examined 350 patients with long-standing UC undergoing colonoscopy surveillance with high-magnification chromoscopic colonoscopy (HMCC) comparing the data with matched controls who had undergone WLE. The HMCC-group found significantly more intraepithelial neoplasias compared to controls (69 vs 24 $P < 0.0001$), and only 0.16% of the random biopsies have shown INs vs 8% from the targeted biopsies. Furthermore, Marion *et al*^[51] studied 102 patients with IBD who underwent in a single examination, initially a WLE with random biopsies, then a targeted biopsy protocol and finally, DCE with targeted biopsies. They reported that biopsies obtained by the latter method detected significantly more dysplastic lesions than random biopsies with WLE ($P = 0.001$), as well as more than WLE with targeted biopsies ($P = 0.057$).

According to Subramanian *et al*^[52] meta-analysis study including a large number of patients, the overall difference between the DCE and WLE in the detection of dysplasia was approximately 7% (95%CI: 3.2-11.3), with the former showing a better rate of dysplastic lesions detected by targeted biopsies, as well as a higher rate of detection for flat lesions at 27% (95%CI: 11.2-41.9). On the other hand, the omission of random biopsies during chromoendoscopy will result in missing endoscopically invisible dysplasia. According to another meta-analysis, Wu *et al*^[47] reported that DCE offers median to good sensitivity and a very good accuracy for revealing lesions with dysplasia in UC after analyzing six randomized controlled trials with 1,528 patients. The pooled sensitivity and specificity for DCE with targeted biopsies were 83.3% (95%CI: 35.9%-99.6%) and 91.3% (95%CI: 43.8%-100%) respectively, with conventional colonoscopy demonstrating lower rates. Soetikno *et al*^[53] in a well-designed meta-analysis with 665 patients with IBD, demonstrated that the pooled positive percentage of DCE over WLE for the

discernment of dysplasia of any grade per patient was 7% (95%CI: 3.3%-10.3%), as well as the possibility to miss dysplasia was 93% lower by performing chromoendoscopy with targeted biopsies (the pooled OR was 0.07; 95%CI: 0.03-0.21). Interestingly, according to a prospective study, Marion *et al*^[54] showed that apart from the superiority of DCE when compared to WLE, a DCE examination without any findings was considered as the most probable indicator for a patient without any level of dysplasia, whereas an exam with any sort of findings was positively correlated with earlier referral for colectomy (hazard ratio, 12.1; 95%CI: 3.2-46.2).

Nevertheless, lately, the advantages of DCE over WLE have come into question, as well as the practicability of applying DCE in a real world setting of hectic endoscopy units. Trying to highlight this problem, a large retrospective non-randomized trial with different types of endoscopes used over time showed that the performance of DCE for IBD surveillance did not increase detection of dysplasia compared with WLE with targeted and random biopsies (11% vs 10%, $P = 0.80$)^[55]. The number of lesions with neoplasia was also comparable between the DCE and WLE groups ($P = 0.30$).

As a final point, an interesting cohort analysis regarding cost-effectiveness was conducted by Konijeti *et al*^[56], that compared DCE with targeted biopsies to WLE with random biopsies at various surveillance intervals and no surveillance at all. Chromoendoscopy was more efficient in the detection of dysplasia and cost more effective when compared with WLE. DCE exhibited cost-effectiveness relative to patients not undergoing any surveillance when performed at intervals bigger than 7 years.

VIRTUAL CHROMOENDOSCOPY SYSTEMS

Technological progression has enabled newer modalities based on older technologies for mucosal assessment. Given the success rate of chromoendoscopy in assessing colonic mucosa, the newest endoscopic devices have filters and algorithms that enable the mimicry of chromoendoscopy by filtering some light wavelengths to better underline abnormal tissues, while foregoing the limiting factors of chromoendoscopy. Dye-less or virtual chromoendoscopy has been developed by three major manufacturers for their respective endoscopic platforms. NBI filters out red and green light bands while contributing more to blue light bands at the 415 nm wavelength. This modality allows for visualization of the vasculature of the upper mucosa and different patterns correlating to different degrees of mucosal inflammation and predicts disease relapse. In the same vein, the i-Scan system provides detailed analysis, which is based on principles similar to NBI, with parameters allowing the processing of light through specific algorithms. This

process provides detailed analysis based on vessel, mucosal pattern or surface architecture (i-Scan v, i-Scan p and i-Scan SE, respectively), with each analysis being readily available during endoscopy^[57].

It has been reported that the yield of surveillance can be improved by the use of autofluorescence with NBI^[36]. According to a study by Dekker *et al*^[34], 52 suspicious lesions were detected in 17 patients using NBI, in comparison to 28 lesions in 13 patients detected with WLE. The pathology of the targeted biopsies revealed neoplasia in 11 patients; neoplasia was detected in 4 patients with both those modalities, in another 4 neoplasia was detected only by use of NBI, and in 3 patients neoplasia was discovered only by WLE, demonstrating non-statistical significance ($P = 0.705$) for those three modalities. In addition to targeted biopsies, 1522 random biopsies were taken in the context of surveillance. The pathology of these biopsies added only 1 patient with dysplasia that remained undetected by both NBI and WLE^[34]. A prospective multicenter study by Leifeld *et al*^[35] concluded that the two techniques did not differ in the statistical probability of lesion detection, but NBI required less withdrawal time (23 min vs 13 min, respectively $P < 0.001$) and biopsy samples (11.9 vs 38.6 biopsy specimens, respectively $P < 0.001$), when compared to WLE. These results are backed by a randomized study by Ignjatovic *et al*^[38], which revealed no difference between the two modalities, regarding the detection of dysplasia. Overall, NBI does not seem to achieve a significantly higher probability of dysplasia detection, compared to conventional HD colonoscopy.

In the same vein Pellisé *et al*^[58] conducted a prospective, randomized, controlled trial comparing NBI to DCE in 60 patients with long-standing inactive colonic IBD. The authors reported that NBI was less time-consuming ($P < 0.01$), equally effective in detecting dysplastic lesions and had a lower rate of false-positive biopsies ($P = 0.001$). However, NBI missed suspicious lesions with a non-significant miss rate difference of 30.7% (95%CI: -64.2% to 2.8%). As a result, the study surmised that NBI should not be standard modality for surveillance.

In general, NBI did not substantially differ from DCE, a claim that needs to be verified by more robust data pooling. A possible explanation is that NBI can more readily identify non-neoplastic inflammatory lesions than WLE, which were not pooled in the meta-analysis comparing those techniques^[37]. Furthermore, the iterations of NBI are different in those studies, with older generation systems producing suboptimal, darker images^[37,42]. Based on the current level of evidence, DCE remains the standard technique for the surveillance in IBD patients.

A large randomized prospective study comparing HD-iScan and HD-WLE to standard DCE did not prove inferiority for those two techniques, with the question of whether i-Scan and HD-WLE will benefit an expert endoscopist remaining unanswered^[39]. The authors conclude that they need more multiple-operator studies

to assess the helpful potential of these new techniques.

CONFOCAL LASER ENDOMICROSCOPY

One of the newest tools in the arsenal of mucosal assessment for dysplasia is the confocal laser endomicroscopy (CLE) that allows *in vivo* microscopic inspection and evaluations of a targeted lesion in the gastrointestinal tract. This new and evolving method is used in conjunction with HD-WLE and DCE to further define suspicious lesions and assess their histology, by performing real time analysis of the cellular and subcellular characteristics at high resolution. The technique is based on fluorescence, which requires the addition of fluorescein intravenously or topically, but results in high quality images, comparable to traditional histology.

Kiesslich *et al.*^[59] first used the endoscope-based integrated system in 2007 to demonstrate that neoplastic changes in patients with UC can be identified with very good accuracy (94.7% sensitivity, 98.3% specificity, 97.8% accuracy), compared with standard surveillance endoscopy. Overall, 4.75-fold more neoplastic areas could be identified than with a WLE ($P = 0.005$), while requiring only half the number of biopsy samples (median 21.2 in the CLE group vs 42.2 undergoing surveillance endoscopy), despite the fact that CLE prolonged colonoscopy by an additional 10 min on average ($P > 0.05$). A recent study by Wanders *et al.*^[60], on the application of integrated CLE for surveillance in CD, which was terminated early due to critical equipment failure at 4 of the 5 participating centers, came up with a much lower diagnostic yield, with sensitivity of 42.9%, specificity of 92.4% and accuracy of 86.7%. The authors concluded that the technique probably will not be used in the daily practice of screening for CRC in patients with colitis.

A recent study of the probe-based CLE (pCLE) comes from Sweden where it was used for the surveillance of dysplasia in patients with PSC-IBD, a population with 6-fold increase in the incidence of CRC compared with the average risk for CRC population^[61]. The study showed good diagnostic accuracy, with the estimated accuracy at 96%, sensitivity at 89% and specificity at 96%, with a low PPV at 41%, but with a very high NPV at 99% for the pCLE. The authors noted that the yield for accuracy fell when assessing areas with mucosal inflammation being misinterpreted as dysplasia. This study challenges the earliest attempts at pCLE systems for CRC surveillance in IBD patients by van den Broek *et al.*^[62], where the authors reported much lower diagnostic yield.

CONCLUSION

Despite the fact that DCE with targeted biopsies is the gold standard technique for IBD surveillance, it has some limitations. The need for adequate bowel preparation, the long procedure time, and its operator

dependence are some of them. Moreover, the presence of active mucosal inflammation or post-inflammatory polyps may affect the images of chromoendoscopy and, in these cases random biopsies are still justified. There are no sufficient data about the effectiveness of the different dyes in detecting dysplasia and there are some concerns about methylene blue inducing DNA damage but have not yet been validated. Two recent editorials have questioned the SCENIC consensus, because chromoendoscopy and targeted biopsies have not been shown to improve CRC mortality^[63,64]. Even when accounting for those limitations, chromoendoscopy remains a validated technique that becomes more and more recommended for CRC surveillance in IBD patients, whilst white light endoscopy with random biopsies should only be performed when the skill or the equipment for chromoendoscopy is unavailable.

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