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Endoscopic Surveillance of Gastrointestinal Premalignant Lesions: Current Knowledge and Future Directions

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Abstract

Purpose of the Review—Provide an evidenced-based resource for the surveillance of gastrointestinal premalignant lesions, focusing on the scientific articles reported recently.

Recent Findings—No randomized controlled clinical trials exist to definitively support the efficacy of surveillance programs for Barrett's esophagus and gastric intestinal metaplasia. However, surveillance of these premalignant lesions is recommended by some of the leading organizations. To optimize the usefulness of surveillance programs, targeting high-risk patients might maximize its benefits. A Barrett's esophagus segment of ≥ 3cm and evidence of intestinal metaplasia can help stratify those patients at highest risk for progression to esophageal adenocarcinoma. The location, extent, and severity of intestinal metaplasia are indicators of risk of developing gastric cancer. Patients with extensive intestinal metaplasia should be offered endoscopic surveillance. Quality in the baseline colonoscopy is crucial, in order to decrease the risk of interval colorectal cancers. The importance of serrated polyps is emphasized as well as their surveillance intervals.

Summary—To optimize the usefulness of surveillance programs, targeting high-risk patients might maximize its benefits. Future research is needed to design more effective surveillance strategies. Recently emerging imaging techniques hold promise for improving sensitivity of endoscopic surveillance of premalignant conditions in the gastrointestinal track.

Keywords

Barrett's esophagus; gastric metaplasia; Colon adenomas; gastrointestinal surveillance

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CONFLICTS OF INTEREST

The authors report no conflicts of interest related to the topic of discussion.

Introduction

Endoscopy plays a crucial role in the diagnosis and surveillance of premalignant gastrointestinal lesions. Early recognition of premalignant lesions provides the opportunity to diagnose cancer at an early and curable stage. Our article will review current knowledge of endoscopic surveillance of premalignant lesions as well as emerging concepts that will improve its efficacy and cost effectiveness. The purpose of this article is to provide an evidenced-based resource for the surveillance of premalignant gastrointestinal lesions. The primary conditions addressed will be: Barrett's esophagus, gastric intestinal metaplasia, and colorectal neoplasia. This review will focus on the recent peer-review literature discussing randomized clinical trials, interventional and/or observational studies reported during the last 18-months primarily. Emphasis was placed on scientific articles with sound experimental design and statistical methodology.

I. Barrett's Esophagus

Barrett's esophagus is defined as a metaplastic change from a normal esophageal mucosa to a columnar lined epithelium with goblet cells.[1] It is categorized into non-dysplasia, low-grade dysplasia, and high-grade dysplasia. Their relative proportions are 86%, 10% and 2% respectively.[2] It is found in approximately 6–14% of patients who undergo endoscopy for symptomatic gastro-esophageal reflux disease.[2] The importance of Barrett's esophagus lies in that it is a precursor of esophageal adenocarcinoma, which is an aggressive tumor that has a poor prognosis.[3] Patients with Barrett's esophagus are at least 30 times more likely to develop esophageal adenocarcinoma than patients without Barrett's esophagus.[4] However, endoscopic surveillance for this premalignant condition is controversial because of ongoing debate as to its cost-effectiveness and survival benefit, mainly due to the absence of randomized controlled trials. A recent case-control study, which intended to evaluate whether endoscopic surveillance of Barrett's esophagus was associated with a lower risk of death, revealed that surveillance within 3 years was not associated with a decreased risk of death from esophageal adenocarcinoma (adjusted odds ratio, 0.99; 95% confidence interval, 0.36–2.75), controlling for dysplasia status.[5]

While the incidence of esophageal adenocarcinoma increased in the United States from 1975 to 2001, the risk of cancer in Barrett's esophagus has decreased over time.[6] It is currently estimated at 0.12–0.13% incremental risk for development of esophageal adenocarcinoma per year.[7] This rate is lower than the previously estimated risk of 0.5%. This decrease in progression risk has important implications in the surveillance of Barrett's esophagus since the effectiveness and cost effectiveness of surveillance are dependent on progression rate from Barrett's to esophageal adenocarcinoma.[8]

Risk Stratification—While dysplasia is currently considered the best marker for esophageal cancer risk, other risk factors have been proposed as predictors of cancer risk. There is evidence that the presence of intestinal metaplasia correlates with greater biological instability.[9] A population study on the Northern Irish Cohort showed the cancer risk in patients with intestinal metaplasia was almost three times as high as that in patients without intestinal metaplasia.[7] A recent study reported a positive correlation between the length of

Barrett's segment, ulceration within the Barrett's segment and the risk for adenocarcinoma. This study showed that the presence of a long segment carried a seven fold increased risk of progression.[3] It also showed that ulceration within the Barrett's segment was associated with an increased risk of progression (Hazard Ratio 1.72; 95% confidence interval: 1.08–2.76).[3]

Chromosomal instability is also associated with progression from Barrett's esophagus to esophageal adenocarcinoma.[10] A biomarker panel which detects 9p LOH (inactivation p16), 17p LOH (inactivation of p53), and DNA aneuploidy and tetraploidy has shown to be superior to histology alone for risk stratification.[11] Studies have also shown that p53 is another molecular marker for predicting disease progression. P53 immunostaining can improve interobserver agreement for reporting dysplasia and was recently recommended in 2014 guidelines of the British Society of Gastroenterology as an adjunct to routine clinical diagnosis.[9] Another possible emerging risk factor is the transcriptionally active Human Papilloma Virus. A recent study revealed that transcriptionally active high risk Human Papilloma Virus (genotypes 16 and 18) was strongly associated with Barrett's dysplasia.[12]

Surveillance Guidelines—The survival benefit conferred by surveillance in Barrett's esophagus is unclear and their cost-effectiveness is still debatable. No randomized controlled trials exist to definitively support the efficacy of surveillance programs. However, surveillance of Barrett's esophagus is recommended by some of the leading organizations. Current 2012 guidelines for Barrett's esophagus from the American Society for Gastrointestinal Endoscopy (ASGE) recommend endoscopic surveillance intervals of 3 to 5 years for patients without dysplasia. They also recommend 6–12 month intervals for those with low-grade dysplasia, and every 3 months for high-grade dysplasia.[4] Given the emergence of effective endoscopic treatments for high-grade dysplasia and early esophageal adenocarcinoma, surveillance of Barrett's esophagus with high-grade dysplasia should be offered to patients who are not suited or unwilling to undergo these therapies.[4]

Current 2014 guidelines from the British Society of Gastroenterology recommend for patients with Barrett's segment <3cm without intestinal metaplasia (IM) or dysplasia, a repeat endoscopy to confirm diagnosis. If there is absence of IM, surveillance is not encouraged. Patients with Barrett's segment <3cm with IM should receive surveillance every 3–5 years. For patients with Barrett's segment ≥3 cm should receive surveillance every 2–3 years. Patients with confirmed low-grade dysplasia should receive surveillance at 6-months intervals. For patients with high-grade dysplasia, endoscopic therapy is preferred over surveillance.[9]

Other technologies including the use of chromoendoscopy with either digital (ie. narrow band imaging) or applied stains (methylene blue (MB), lugol stain, etc.) have been advocated for increasing diagnostic yield of surveillance for BE. The value of acetic acid (AA) to improve the diagnostic yield of surveillance has also been studied. A randomized crossover study which aimed to evaluate the diagnostic yield of magnifying endoscopy with AA-targeted biopsies compared to random 4-quadrant biopsies, showed that AA guided biopsies had a sensitivity of 100% and a specificity of 66% for the diagnosis of Barrett's epithelium. AA guided biopsies had a significantly higher percentage of tissues containing

specialized columnar epithelium (78%), compared to 4-quadrant biopsies (57%) (p=0.01).[13] A recently published prospective randomized trial, where detection rates of intestinal metaplasia and neoplasia in Barrett's esophagus were assessed with narrow band imaging (NBI) and high definition white light endoscopy (HD-WLE), showed that NBI detected a larger number of high grade dysplastic areas compared with HD-WLE (30% vs 21%, p<0.001)[14] More data are needed to decide the usefulness of these emerging techniques. The 2014 British Society of Gastroenterology recommendations regarding the advanced imaging modalities, is that they are not superior to standard white light endoscopy in Barrett's esophagus surveillance and therefore are not recommended for routine use.[9]

Due to the fact that there are no randomized controlled trials that assess the efficacy of surveillance, the question remains of whether current strategies are optimal and cost-effective. To optimize the usefulness of surveillance programs, targeting surveillance to high-risk patients might maximize its benefits.

Emerging Technologies and Future Directions—Endoscopic surveillance includes an established biopsy protocol, which consists of 4 quadrant biopsies every 1–2cm of Barrett's length as well as targeted biopsies of mucosal lesions.[4] A large number of biopsies may be needed which typically result in a low (1–10%) diagnostic yield.[15] Confocal laser endomicroscopy combines endoscopy and microscopic imaging of the mucosa, enables real-time diagnosis of Barrett's esophagus neoplasia and targeted biopsies of abnormal mucosa.[15] A recently published randomized controlled trial which compared high- definition white-light endoscopy (HDWLE) alone with random biopsies and HDWLE followed by endoscope based confocal laser endomicroscopy (eCLE) with targeted biopsies, showed that HDWLE followed by eCLE with targeted biopsies resulted in a higher diagnostic yield of neoplasia (34% vs. 7%; p<0.0001), compared with HDWLE with random biopsies.[15] These results cannot be extrapolated to community centers where this technology is not available. These approaches need prospective studies for validation.

We focused our review of Barrett's esophagus on recently published studies from 2013 and 2014. We included the most recent guidelines of the role of endoscopy in Barrett's esophagus from the ASGE, which were updated in 2012 and we also included the recently published British Society of Gastroenterology 2014 Guidelines.

Only two of the studies presented were from 2011, one of them being the American Society for Gastrointestinal Endoscopy (ASGE) medical position for the management of Barrett's Esophagus. An important randomized controlled trial 2006 on the use of chromoendoscopy was also included in our review.

II. Gastric Intestinal Metaplasia

Gastric cancer remains the second leading cause of cancer related mortality worldwide.[16] The pathogenesis of gastric cancer is thought to be a sequential pathway starting with inflammation, metaplasia and progressing to dysplasia and gastric carcinoma.[17] Although it is a worldwide problem, its incidence varies across countries, where the incidence is high in Japan, Korea, China, Taiwan, Honduras, Salvador, and is low in India, Australia, Thailand, and New Zealand.[16, 18] Differences in incidence have led to a wide disparity in

the management of patients with this premalignant condition. In Japan there is universal screening of the population, while in countries with a low incidence rate, screening is not considered cost effective.[19] The prevalence of intestinal metaplasia varies depending on the rate of Helicobacter pylori infection of a population.[20] It has been estimated that annually, 0–10% of patients with intestinal metaplasia progress to gastric cancer.[16] It is important to recognize that most patients with intestinal metaplasia do not progress to gastric cancer. Therefore, additional risk factors for progression to gastric cancer need to be identified that will justify endoscopic surveillance.

Risk Stratification—The location, extent, and severity of intestinal metaplasia are indicators of the risk of developing gastric cancer. Premalignant lesions found in the gastric body, may be more likely to progress to gastric cancer.[21] In addition, the risk of gastric cancer is higher in patients with widespread intestinal metaplasia in the antrum or lesser curvature, and is highest for patients with diffuse intestinal metaplasia.[21] However, most published studies use different biopsy protocols that are not comparable.[22] A recent published study, which aimed to identify the role of the distribution and severity of premalignant lesions in risk categorization, showed that intestinal metaplasia in the gastric body was more likely to progress to more than one location (57%; 95% CI 36–76%). It also showed that the proportion of patients with multifocal premalignant lesions increased from 24% at baseline endoscopy to 31% at surveillance (p=0.014).[22] If severity, location and extent are going to be used for risk stratification, a uniform and widely applied biopsy protocol needs to be applied.

Surveillance Guidelines—Even though intestinal metaplasia is commonly found in practice, there is no clear consensus on the need of surveillance to guide physicians. Guidelines for the surveillance of gastric intestinal metaplasia have been published by several international societies. Guidelines from the European Society for Gastrointestinal Endoscopy (ESGE) recommend that patients with extensive intestinal metaplasia (in both antrum and corpus) should be offered endoscopic surveillance every 3 years.[23] Furthermore, patients with antral intestinal metaplasia should not be followed.[23] *The recommended biopsy protocol is that at least four biopsies of the proximal and distal stomach, and of the lesser curvature and greater curvature are needed for adequate assessment of premalignant gastric conditions*. Patients with low-grade dysplasia in the absence of an endoscopically defined lesion should receive follow up within a year after diagnosis. In the presence of an endoscopically defined lesion, endoscopic resection should be considered to obtain a more accurate diagnosis. For patients with high-grade dysplasia, in the absence of endoscopically defined lesions, reassessment with extensive biopsy sampling and surveillance at 6 months to 1-year intervals is indicated. Resection needs to be considered in the case of endoscopically defined lesions.[23]

Standardization of surveillance should be performed focusing on the patients at greatest risk. In low incidence countries, an approach to identify high–risk individuals should be considered. This approach should start with an initial screening that will focus on epidemiological factors, genetic risks and status of Helicobacter pylori infection.[16] After an

initial screening, high-risk patients with intestinal metaplasia should then enter surveillance protocols.[16]

Emerging Technologies and Future Directions—The current standard of practice consists of random biopsies under white light endoscopy. This approach may not be practical because it is time consuming and has low specificity. Therefore, other strategies that can detect precancerous lesions are emerging. Confocal laser endoscopy technique provides a higher magnification (×1000) of the gastrointestinal tract epithelium and has been used for evaluation for real-time gastric intestinal metaplasia confirmation.[24] A recent study, which evaluated the role of digital chromoendoscopy and confocal laser endomicroscopy for gastric intestinal metaplasia and cancer surveillance, recommend using a high definition white light endoscopy to identify abnormal gastric epithelium, and then using digital chromoendoscopy to further characterize lesions and possibly identifying more lesions. They recommend further study of suspicious lesions with confocal laser endomicroscopy, taking a biopsy if gastric intestinal metaplasia (GIM) with high-grade dysplasia or early gastric cancer is suspected. Taking a biopsy from a lesion confirmed as complete (GIM) is not recommended due to low risk of progression to gastric cancer.[17]

Standardization of surveillance practices will benefit patients and may be cost-effective by concentrating resources on patients identified to have the highest risk of progression to gastric cancer. Large prospective randomized trials are needed which compare different follow up strategies.

We focused our review of gastric intestinal metaplasia on key studies from 2013 and 2014. We included the 2012 guidelines from the European Society of Gastrointestinal Endoscopy, European Helicobacter Study, European Society of Pathology and the *Sociedad Portuguesa de Endoscopia Digestiva*. We also included a study from 2012 on the role of digital chromoendoscopy and confocal laser endomicroscopy.

III. Colorectal Neoplasia

Colorectal cancer is the second leading cause of cancer related mortality in the United States. Until recently, adenomatous polyps were thought to be the precursors of sporadic colorectal cancer. Recent studies have shown that the previously known hyperplastic polyps are now recognized as serrated polyps. Serrated polyps are characterized by their saw tooth appearance of the colonic crypts. The serrated lesions are classified by the WHO into three general categories: hyperplastic polyp, sessile serrated adenoma, and the traditional serrated adenoma.[25] Serrated lesions have been established as the precursor of colorectal cancers that exhibit methylation of CpG islands, *BRAF* mutations, with inactivation of *MLH1*, resulting in tumor microsatellite instability.[25] Serrated lesions are thought to be the precursors for 20–35% of colorectal cancer cases.[26] In average risk patients undergoing screening, the prevalence of sessile serrated adenomas ranges from 2–7%.[26]

Adenomatous polyps are the precursor lesions of over 70% of the cases of colorectal cancer. They are subdivided according to “the extent of villous architecture on the polyp surface as tubular, tubulovillous, and villous”.[27] The risk of developing colorectal cancer is predicted by the number, histology, and size of the lesions at baseline colonoscopy. Low-risk

adenomas refer to patients with 1–2 tubular adenomas, < 10mm, high risk adenomas refers to patients with tubular adenomas ≥ 10mm, 3 or more adenomas, and adenomas with a villous pathology.[28]

Surveillance Guidelines—Colorectal cancer colonoscopy surveillance intervals are based on evidence supporting decrease in cancer related mortality and in interval cancers.[27] The American Gastroenterological Association updated their colonoscopy surveillance guidelines in 2012. Some issues updated since 2006 include surveillance guidelines for serrated polyps and the risk of interval cancer. For sessile serrated polyps <10 mm without evidence of dysplasia, the recommended surveillance interval is 5 years. For sessile serrated polyps ≥ 10 mm, sessile serrated polyp with dysplasia or traditional serrated adenoma, the recommended surveillance interval is 3 years. For serrated polyposis syndrome, which includes: at least 5 serrated polyps proximal to sigmoid with 2 or more ≥ 10 mm, any serrated polyp proximal to the sigmoid with family history of serrated polyposis syndrome, > 20 serrated polyps of any size throughout the colon, the recommended surveillance interval is 1 year.

Interval cancers are cancers that develop after a colonoscopy and before the next surveillance colonoscopy. Some possible explanations for the development of interval cancer include: missed lesions at index colonoscopy, incomplete polypectomy and rapidly progressive new lesions.[29] Published studies reveal that up to 17% of lesions are missed in colonoscopy and that 19–27% of interval cancers occur in the same portion of the colon as the site of polypectomy.[27] The molecular biology of interval colorectal cancers appears to be different from non-interval cancers. They are more likely to have microsatellite instability, CpG island methylation, and low rates of KRAS, all characteristic of the serrated pathways.[29] These guidelines reinforce the importance of quality in the baseline colonoscopy in order to decrease the risk of interval colorectal cancers. A published study revealed that an adenoma detection rate of <20% was associated with a higher risk of developing interval colorectal cancer in the next 5 years.[27] Guidelines from leading organizations recommend an adenoma detection rate of at least 15% in women and at least 25% in men.[30] A recently published study, which evaluated the relationship between the adenoma detection rate and the risk of developing interval CRC (diagnosed between 6 months to 10 years after colonoscopy), showed an inverse association between the adenoma detection rate and the risk of interval cancer. Among patients of physicians with adenoma detection rates in the highest quintile, as compared with patients of physicians with adenoma detection rates in the lowest quintile, the adjusted hazard ratio for interval cancer was 0.52% (95% CI: 0.39–0.69).[31]

Emerging Technologies and Future Directions—In order to maximize the detection of colorectal neoplasia, emerging technologies have been developed. The European Society of Gastrointestinal Endoscopy (ESGE)[32] has recently published in 2014 their guidelines for advanced imaging for the detection of colorectal neoplasia. Their main recommendations include: the routine use of high definition white light endoscopy in average risk populations, the use of narrow band imaging (NBI) and chromoendoscopy for known or suspected Lynch Syndrome and serrated polyposis syndrome, the use of 0.1% methylene blue or 0.1%–0.5%

indigo carmine chromoendoscopy with targeted biopsies for surveillance in patients with long standing colitis, the use conventional or virtual (NBI) chromoendoscopy to predict the risk of invasive cancer and deep submucosal invasion in lesions with a depressed component or nongranular or mixed-type laterally spreading tumors, the use of conventional or virtual (NBI) chromoendoscopy for real-time optical diagnosis of diminutive ≤5 mm colorectal polyps to replace histopathological diagnosis.[32]

Other emerging image enhanced techniques are confocal laser endomicroscopy (CLE) and autofluorescence. A recently published meta-analysis, which aimed to evaluate the sensitivity, specificity, and real-time negative predictive value (NPV) of these image-enhanced techniques, showed that for autofluorescence imaging, the overall sensitivity was 86.7 (CI 79.5–91.6), a specificity 65.9% (CI 50.9–78.2), and a real time NPV 81.5% (54.0–94.3). For CLE, overall sensitivity was 93.4 (CI 88.4–96.2), specificity 89.9% (81.8–94.6), and a real time NPV 94.8% (86.6–98.1) [33] Further studies should focus in evaluating if these advances could eventually be translated into the clinical practice.

We focused our review of colorectal neoplasia on key recent studies from 2013 and 2014. We also included the recently published 2014 European Society of Endoscopy Guidelines for advanced imaging for the detection of colorectal neoplasia. The American Gastroenterological Association colonoscopy surveillance guidelines from 2012 were included to emphasize the surveillance recommendations for serrated polyps and briefly discuss the importance quality in index colonoscopy for decreasing the risk of interval cancers.

Conclusion

Surveillance of premalignant lesions of the gastrointestinal tract is essential for diagnosing cancers at an early and curable stage. This translates in a decrease in cancer incidence and mortality. Emerging technologies are currently being studied that will aid in the recognition of premalignant lesions. Training future generations in these advanced imaging techniques will be needed in order to integrate these techniques in clinical practice. Further studies will be needed to validate these new techniques and assess their cost effectiveness, which will hopefully translate into better patient care.

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Key Points

- To optimize the usefulness of surveillance programs, targeting high-risk patients might maximize its benefits.
- Future research is needed to design more effective gastrointestinal cancer surveillance strategies.
- Recently emerging imaging techniques hold promise for improving sensitivity of endoscopic surveillance.