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Screening and surveillance for Barrett's esophagus: current issues and future directions

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Abstract

Purpose of review—Our article discusses the current understanding of screening and surveillance options for Barrett's esophagus and emerging concepts that have the potential to improve the effectiveness and cost-effectiveness of surveillance.

Recent findings—Although endoscopic surveillance of patients with Barrett's esophagus is commonly practiced in order to detect high-grade dysplasia and early esophageal adenocarcinoma (EAC), the reported incidence of EAC in Barrett's esophagus patients varies widely. Recent studies found the risk of progression from Barrett's esophagus to EAC to be significantly lower than previously reported, raising concerns regarding the limitations of current surveillance strategies. Advances in imaging techniques and their enhanced diagnostic accuracy may improve the value of endoscopic surveillance. Additionally, various efforts are ongoing to identify biomarkers that identify individuals at higher risk of cancer, possibly allowing for individual risk stratification.

Summary—These new data highlight some of the opportunities to revise and improve surveillance in patients with Barrett's esophagus. The incorporation of new advances such as imaging techniques and biomarkers has the potential to improve the effectiveness and cost-effectiveness of new surveillance regimens.

Keywords

Barrett's esophagus; cost-effectiveness; esophageal adenocarcinoma; surveillance

INTRODUCTION

The incidence of esophageal adenocarcinoma (EAC) has been drastically increasing over the past 40 years, particularly in Western populations [1]. Efforts to curb this rise in EAC incidence have focused on screening for Barrett's esophagus, a precursor to EAC. Current practice has been to selectively screen individuals over the age of 50 with a history of chronic gastroesophageal reflux disease (GERD) symptoms to identify patients with Barrett's esophagus. For the patients diagnosed with Barrett's esophagus, older guidelines recommended endoscopic surveillance in an effort to reduce morbidity and mortality

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Conflicts of interest

There are no conflicts of interest.

through early detection of high-grade dysplasia (HGD) and noninvasive EAC. Although there is no convincing clinical data or conclusive evidence to support this strategy [2], the practice continues.

CURRENT STRATEGIES

GERD is a known risk factor for EAC along with advanced age (older than 50 years), male sex, white race, and elevated BMI. A previously published cost-effectiveness analysis found that screening 50-year-old white men with GERD symptoms for the presence of Barrett's esophagus, followed by subsequent surveillance of Barrett's esophagus patients with dysplasia is probably cost effective, however, surveillance of nondysplastic patients is an expensive practice, even at 5-year intervals.

Current guidelines for Barrett's esophagus patients recommend endoscopic surveillance intervals of 3–5 years for patients without dysplasia, 6–12 months for those with low-grade dysplasia (LGD), and every 3 months for HGD patients [3, 4]. Barrett's esophagus may ultimately lead to EAC following a proposed dysplasia–carcinoma sequence: intestinal metaplasia to LGD to HGD to adenocarcinoma. Because there are no controlled trials that examine the efficacy of surveillance, the question of whether the current strategies to detect and diagnose Barrett's esophagus are optimal or justified still remains unanswered. In addition to the lack of data to support current practice, there is a wide variation in the reported progression rate to EAC in Barrett's esophagus patients [5, 6]. Consequently, both the effectiveness and cost-effectiveness of current surveillance strategies are dependent on the progression rate from Barrett's esophagus to EAC, with lower progression rates negatively impacting surveillance, as a larger percentage of individuals will never develop cancer [7, 8].

UPDATES ON THE RISK OF ESOPHAGEAL ADENOCARCINOMA

Although the cost-effectiveness of screening and surveillance is highly dependent on the risk of progression from Barrett's esophagus to EAC, the reported incidence of EAC in patients with Barrett's esophagus varies widely, ranging from 0 to 3.5% per year [9, 10]. Accurate estimates of EAC incidence are pivotal to investigating both the necessity and frequency of endoscopic surveillance for Barrett's esophagus patients. The current endoscopic surveillance guidelines are largely based on the assumed risk of approximately 0.5% per year [5]. This estimate dates back to a meta-analysis in 2000, with recognition that publication bias had resulted in a systematic overestimation of the risk. In order to obtain a current and better estimate of the risk of EAC in Barrett's esophagus patients without dysplasia at baseline, Desai *et al.* [11] performed a meta-analysis of observational studies with some improvements over earlier meta-analyses, such as exclusion of prevalent cancers and patients with dysplasia. In this recently published meta-analysis, the reported incidence of EAC in nondysplastic patients was 0.33% per year, lower than the previously assumed 0.5% annual risk, emphasizing the need for re-evaluation of the utility and cost-effectiveness of current surveillance strategy among Barrett's esophagus patients.

Subsequent to the meta-analysis, Bhat *et al.* [12] reported their cancer risk estimates from a population-based study from Northern Ireland. The risk estimates derived from previous studies were likely overestimated because of small study size, short duration of follow-up, variable definitions of Barrett's esophagus, inclusion of patients with prevalent cancers, and inclusion of Barrett's esophagus patients with HGD [5, 6]. In efforts to overcome these limitations, this study captured the entire population of Northern Ireland (1.7 million), an unselected nonreferral-based cohort, with a mean follow-up of 7 years, employing rigid exclusion of baseline HGD and early incident cancer. Bhat *et al.* [12] reported the risk estimate of EAC to be 0.13% per year [95% confidence interval (CI), 0.10–0.16], which was

significantly lower than previously reported rates. They included Barrett's esophagus patients with or without intestinal metaplasia and reported combined rates of EAC, HGD, and cancer of the gastric cardia. When the analysis was limited to 'well defined Barrett's esophagus', both presence of specialized intestinal metaplasia at index biopsy and a visible segment seen, the annual incidence of EAC was 0.18% and the combined annual incidence of HGD, EAC and gastric cardia cancer was 0.33%, which is similar to the estimate from the meta-analysis by Desai *et al.* [11■].

The risk estimate of EAC incidence among Barrett's esophagus patients in the largest population-based studies to date was even lower than the 0.13% that Bhat *et al.* [12■] reported. Hvid-Jensen *et al.* [13■] conducted a nationwide cohort study in Denmark, involving all Barrett's esophagus patients of all ages and both sexes with little loss to follow-up. By using data from the Danish Pathology Registry and the Danish Cancer Registry encompassing the entire population of Denmark (5.4 million), this study was largely able to eliminate referral and diagnostic bias. This nationwide study found the absolute risk of EAC after a diagnosis of Barrett's esophagus to be significantly lower than previous studies, with an estimated annual risk of EAC of 0.12% per year (95% CI, 0.09–0.15). The calculated relative risk of EAC among Barrett's esophagus patients compared with the risk in the general population was 11.3. These findings raise further questions regarding current screening and surveillance regimens.

IMPROVEMENTS IN ENDOSCOPIC IMAGING TECHNIQUES

Although there have been a number of studies evaluating the cost-effectiveness of surveillance for Barrett's esophagus, the majority of studies used the EAC incidence rate of 0.5% that is now suspected to be an overestimate [14–17]. Along with the progression rate from Barrett's esophagus to EAC, the diagnostic accuracy of endoscopy needs to be updated when re-evaluating the cost-effectiveness of the current surveillance program. A systematic review by Hirst *et al.* [18] concluded that the current endoscopic surveillance strategy for nondysplastic Barrett's esophagus patients is unlikely to be cost-effective, unless new technologies improve the quality-adjusted survival benefit from the surveillance. Because the majority of the cost-effectiveness analyses used the rates of misdiagnosis from a personal communication with one pathologist in 1994 [19], the rates used in prior studies may not be representative of the current endoscopic technology which has improved since then (see following paragraphs). These technological advances may improve the predictive value of endoscopic surveillance and consequently, the cost-effectiveness of the Barrett's esophagus surveillance program.

Surveillance utilizing white light endoscopy (WLE) has been critical in recognition of lesions, but when viewed by WLE, dysplastic lesions are still difficult to distinguish from nondysplastic mucosa. Because only a small fraction of the Barrett's esophagus mucosa is randomly biopsied, it is difficult to obtain an accurate assessment regarding the presence of cancer or dysplasia due to sampling error and poor sensitivity [20]. Advanced endoscopic imaging technologies, such as narrow band imaging (NBI), autofluorescence imaging (AFI), and confocal laser endomicroscopy (CLE), may improve the accuracy in the detection of dysplasia and early cancer, increasing the effectiveness of endoscopic surveillance.

NBI allows for better detection of early neoplastic lesions by visualizing the patterns produced by subsurface vascular changes. It has been demonstrated that NBI can detect significantly more patients with dysplasia and higher grades of dysplasia with fewer biopsy samples compared with standard resolution WLE [21]. A meta-analysis on the performance and clinical utility of NBI in upper endoscopy found a sensitivity of 97% (95% CI, 0.89–

0.99), a specificity of 94% (95% CI, 0.60–0.99), and an overall accuracy of 96% (95% CI, 0.72–0.99) of NBI in differentiating dysplasia from nondysplastic Barrett's esophagus [22].

Recent studies have evaluated the efficiency of using NBI in conjunction with other advanced imaging technologies. Curvers *et al.* [23] performed a multicenter randomized study that evaluated endoscopic trimodal imaging (ETMI), NBI used in combination with high-resolution endoscopy and AFI, and found that it improved the detection of HGD and early cancer in Barrett's esophagus. ETMI significantly improved the targeted detection of HGD and EAC compared with standard video endoscopy. In another multicenter randomized controlled trial, Sharma *et al.* [24] examined the diagnostic characteristics of probe-based CLE (pCLE), high-definition white-light endoscopy (HD-WLE), NBI, HD-WLE/NBI, or HD-WLE/pCLE in detecting HGD and early cancer [25]. They found that pCLE combined with HD-WLE significantly improved the ability to detect HGD and early cancer in Barrett's esophagus patients compared with HD-WLE alone. The sensitivity and specificity for HD-WLE were 34.2% and 92.7%, respectively, compared with 68.3% and 87.8%, respectively, for HD-WLE or pCLE ($P=0.002$ and $P<0.001$, respectively).

The aforementioned studies that have evaluated advances in imaging techniques provide promising results, which may be applied to Barrett's esophagus endoscopic surveillance. With the ability to improve the detection of HGD and early cancer, these enhanced diagnostic techniques have the potential to make the current Barrett's esophagus/EAC surveillance strategies more cost-effective. Additionally, the ability to more reliably detect HGD during Barrett's esophagus surveillance may provide opportunities for patients to choose nonsurgical therapeutic options, such as radiofrequency ablation, which would also affect the cost-effectiveness of a Barrett's esophagus surveillance regimen [26]. The enhanced diagnostic accuracy obtained from advanced imaging techniques needs to be considered when re-evaluating the current surveillance Barrett's esophagus/EAC surveillance strategies, particularly as they become standard of care.

FURTHER DEVELOPMENTS IN RISK STRATIFICATION: BIOMARKERS

Lower risk estimates for progression to EAC and advanced imaging techniques underscore the potential benefits from developing a risk stratification method for Barrett's esophagus patients. With the help of improved technology, conducting intensive surveillance at an appropriate interval for a high-risk group of patients would make endoscopic surveillance more practical and cost-effective. Many genetic and molecular biomarkers are currently under investigation because of their great potential to aid in cancer prevention and surveillance of high-risk individuals. Using biomarkers to stratify patients according to their risk of progression would allow us to decrease the pool of patients who undergo intensive surveillance, ultimately improving the cost-effectiveness of a surveillance strategy. Additionally, biomarkers have the potential to decrease the high interobserver variability in pathologists' interpretation of dysplasia.

Most Barrett's esophagus segments have two normal p53 alleles [27]. The overexpression of p53 protein has been associated with Barrett's esophagus progression to EAC, with a report that the presence of p53 antibodies in plasma predates the diagnosis of both Barrett's esophagus and EAC in some patients [28]. However, during progression to EAC, one allele of p53 may be inactivated by mutation and the second frequently is lost by a mechanism termed loss of heterozygosity (LOH). P53 LOH is the most common genetic lesion in EAC [27, 29–32]. In efforts to overcome some limitations around p53, Reid *et al.* [33] conducted a LOH analysis in 325 Barrett's esophagus patients, using baseline p53 as a predictor and aneuploidy, HGD, and EAC as outcomes. The study found that patients with p53 LOH were at increased risk for progression to EAC as well as HGD and aneuploidy. The prevalence of

p53 LOH increased from 6% in non-dysplastic Barrett's esophagus to 57% in HGD, and was an independent predictor of progression to EAC. Thirty-seven percent of patients with baseline p53 LOH progressed to EAC, whereas 3% without baseline p53 LOH developed cancer. P53 LOH may be a predictor of progression to EAC that can potentially be combined with a panel of other validated biomarkers for risk stratification.

Aberrant DNA methylation of certain tumor suppressor genes has been studied as a potential predictor of progression from Barrett's esophagus to EAC [34]. Recently, a multicenter study [35] supported by the Early Detection Research Network analyzed a panel of eight methylation biomarkers in approximately 200 patients for their accuracy in predicting progression in Barrett's esophagus. Jin *et al.* [35] found that a methylation biomarker-based panel has the potential to predict neoplastic progression in Barrett's esophagus, and used receiver operating characteristic curve-based thresholds to risk-stratify patients. At high specificity levels, their risk stratification strategy accurately predicted approximately half of HGDs and EACs. Although these results are encouraging, there are some limitations and technical challenges to validating biomarkers as a predictor of EAC risk, such as variation in methodology and lack of prospective trials. Once a panel of strong candidate biomarkers can be identified and tested in large-scale multicenter trials, utilizing biomarkers in risk stratification would certainly have added value in optimizing endoscopic surveillance strategies.

CONCLUSION

Although endoscopic surveillance of Barrett's esophagus is commonly practiced to detect dysplasia and malignancy in an early and curable stage, the effectiveness and cost-effectiveness of current endoscopic surveillance strategies remain controversial. Newly published data on the risk of progression to EAC highlight the need for better risk stratification. Ongoing trials investigating the benefit of advances in imaging technologies and biomarkers underscore potential improvements to a refined surveillance regimen, which could improve the effectiveness and cost-effectiveness of Barrett's esophagus surveillance.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- ■ of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

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KEY POINTS

- Newer and lower estimates of the risk of cancer in Barrett's esophagus patients impact surveillance strategies.
- Improvements in endoscopic imaging techniques could improve surveillance.
- Biomarkers could allow for better risk stratification.
- These new data could substantially affect the optimal surveillance strategy for Barrett's esophagus.