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Risk stratification and surveillance in Barrett oesophagus

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Abstract

Advances are being made in understanding the pathogenesis, treatment outcomes and surveillance of Barrett oesophagus. Central obesity and age at onset of gastro-oesophageal reflux are being recognized as risk factors that have implications for screening. The persistent finding of nondysplastic Barrett oesophagus during surveillance is associated with low risk of malignant progression, whereas dysplastic Barrett oesophagus requires continued surveillance.

In 2013, several studies continued to contribute to our evolving understanding of the pathogenesis, treatment outcomes, and yield of surveillance for Barrett oesophagus. These research endeavours have been propelled by the current understanding that Barrett oesophagus is the strongest risk factor in the development of oesophageal adenocarcinoma (EAC). EAC has been the fastest rising malignancy in Western countries over the past four decades.¹ In spite of the fact that GERD and Barrett oesophagus are established risk factors for EAC, approximately half of patients with EAC do not present with chronic GERD or a prior diagnosis of Barrett oesophagus.

Given the ongoing interest in linking central obesity with the risk of EAC, Robertson *et al.*² compared the length of cardiac mucosa, gastric acid exposure in the lower oesophageal sphincter (LES) and LES pressure between healthy volunteers with small waist circumference and volunteers with large waist circumference, matched by age and gender. Small waist circumference was defined as <94 cm in males and <80 cm in females. The length of the cardiac mucosa was reliably evaluated using jumbo forceps biopsies across the squamocolumnar junction. Intrasphincteric acid reflux and pressure were assessed using standard pH and manometric studies. The study demonstrated an association between central obesity and increased cardiac mucosa length (2.5 mm versus 1.7 mm in volunteers with large and small waist circumference, respectively; $P = 0.008$) and more proximal gastric acid exposure in the LES (2.6 cm versus 4.1 cm, respectively; $P = 0.027$).

Robertson *et al.*² make an important contribution to our understanding of squamocolumnar junction injury in the setting of central obesity. On the basis of their findings, obesity and increased intra-abdominal pressure might contribute to increased acid reflux within the LES,

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Competing interests

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leading to the proximal extension of the cardiac mucosa. This development might be similar to the progression of columnar-like epithelium found in EAC.³ This process might also represent an underlying mechanism for the rise of EAC and other gastro-oesophageal junctional malignancies in parallel with the increasing prevalence of obesity. Future studies are needed to elucidate the mechanistic pathways behind these changes in the gastro-oesophageal junction in patients with central obesity. Understanding these factors could lead to strategies for effective screening of high-risk patients for EAC rather than relying on the presence of symptomatic GERD or a prior diagnosis of Barrett oesophagus.

Thrift *et al.*⁴ presented a cross-sectional analysis of 683 patients who underwent upper gastrointestinal endoscopy to assess the significance of age at the onset of reflux symptoms. 236 patients with histologically-confirmed Barrett oesophagus and 447 patients without Barrett oesophagus were included in the study. All study participants completed a validated survey on reflux. Cumulative reflux duration in years was defined as the number of years in which the patient had frequent reflux symptoms, beginning at 10 years of age. Frequent reflux was defined as having weekly symptoms at a minimum. The age of onset was divided between ages 10–19, 20–29, 30–49, and 50–70 years. Their results show that patients whose onset of frequent reflux started when they were <30 years old were at higher risk of developing Barrett oesophagus (OR 15.1, 95% CI 7.9–28.8). This association was independent of the duration of cumulative reflux symptoms. Among patients with early onset reflux, those who reported a history of being treated with PPIs were at even higher risk of developing Barrett oesophagus than those who had not been treated with PPIs. These conclusions will require supporting evidence from other studies before they can be accepted as established risk factors.⁵ In addition, the underlying mechanism for the apparent risk of Barrett oesophagus associated with a younger age of onset is still unclear. These factors could include complicated life-course events—such as development of obesity and exposure to tobacco and alcohol—whose actual risk contributions might be difficult to individually evaluate. For now, this cross-sectional study provides another layer of risk stratification in identifying patients who need to be screened for Barrett oesophagus in addition to our current approach of identifying patients with symptomatic reflux and metabolic syndrome.

Gaddam *et al.*⁶ conducted a multicentre, retrospective cohort analysis of 1,401 patients with nondysplastic Barrett oesophagus who underwent endoscopic surveillance to assess risk stratification in surveillance endoscopy. Study participants were stratified according to the number of surveillance biopsies that did not detect dysplasia or EAC. After adjusting for age, gender and length of the Barrett mucosa, the persistence of nondysplastic Barrett oesophagus was associated with low risk of progression to EAC. There was a progressive decline in the incidence of EAC between each surveillance endoscopy of 0.32%, 0.27%, 0.16%, 0.20%, and 0.11% from the annual risk of EAC. This study provides a new understanding of the clinical implication of multiple negative surveillance biopsies. These results might also support the need to re-evaluate our current surveillance guidelines, which are mostly arbitrary and have not been subjected to rigorous prospective trials.⁷ The results are important given population-based estimates of the absolute annual risk of EAC in Barrett oesophagus to be about 0.12%.⁸ Although the conclusions of Gaddam *et al.*⁶ are derived from retrospective data, varied surveillance intervals and lack of central pathology

interpretation, their findings contribute to the growing evidence that there might be an end point for surveillance in patients with persistent nondysplastic Barrett oesophagus.

The topic of surveillance remains an important issue when dealing with patients who have undergone radiofrequency ablation for Barrett-associated dysplasia. Gupta *et al.*⁹ performed a retrospective analysis of 592 patients from one of the largest US multicentre Barrett oesophagus treatment and surveillance programs. The goal was to estimate the incidence and risk factors for recurrence after inducing remission of intestinal metaplasia using radio-frequency ablation. In their study, complete remission from intestinal metaplasia had stringent criteria that included lack of visible or histologic evidence of intestinal metaplasia on two consecutive biopsies using the Seattle protocol (which required obtaining four quadrant biopsy samples every 1–2 cm along the length of the Barrett oesophagus segment). In 24 months, 56% of patients achieved complete remission of intestinal metaplasia. However, 20% developed recurrent metaplasia within 12 months and 33% had evidence of metaplasia after 24 months. Increased length of Barrett oesophagus segment and older age were associated with longer treatment time interval before achieving complete remission of intestinal metaplasia. However, no clinical or other endoscopic factors were found to be associated with recurrence. Unlike patients with nondysplastic Barrett oesophagus, patients with Barrett-associated dysplasia seem to have a low but persistent risk of developing recurrence even after treatment. Future studies are needed to find better predictors for assessing the risks of recurrence after endoscopic treatment. Improved ways of performing surveillance aside from our current endoscopic examination and biopsy protocol are also needed.

The current surveillance strategy using upper endoscopy with biopsies was examined in a case–control study by Corley *et al.*¹⁰ They compared the odds of having undergone endoscopic surveillance in patients diagnosed with Barrett oesophagus who died of EAC with those for matched controls who had Barrett oesophagus but had not died of EAC. Patients with Barrett oesophagus who died of EAC were likely to have undergone a similar frequency of endoscopic surveillance to the controls (55.3% versus 60.4% of patients had endoscopic surveillance, respectively). Their conclusion showed no association between surveillance and decline in EAC-related deaths (OR 0.99, 95% CI 0.36–2.75) in spite of adjusting for multiple confounders. This study compels us to again re-examine our current endoscopic surveillance strategies for Barrett oesophagus.

For surveillance in Barrett oesophagus to be effective, we must find innovative ways to identify patients who would greatly benefit from it. Otherwise, surveillance will be a futile exercise for those who might not benefit from it or it might be poorly utilized for those patients who need it the most. Novel endoscopic technologies, predictive biomarkers, and innovative sampling techniques—such as transnasal endoscopy and cytosponge—might provide the answers to this ongoing dilemma. In the coming years, we can expect more studies attempting to refine the current methods for risk stratification and surveillance in Barrett oesophagus.

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Key advances

- Central obesity was associated with increased gastric acid exposure in the lower oesophageal sphincter and expansion of the cardiac mucosa, which might lead to asymptomatic injury to the squamocolumnar junction²
- Younger age at onset of frequent gastro-oesophageal reflux was associated with risk of Barrett oesophagus development, independent of the cumulative duration of reflux symptoms⁴
- In a multicentre retrospective analysis, the persistent finding of nondysplastic Barrett oesophagus in surveillance biopsies was associated with decreased risk of malignant progression⁶
- Patients treated for dysplastic Barrett oesophagus with radiofrequency ablation required continued surveillance owing to substantial risk of recurrence within 2 years of achieving remission from intestinal metaplasia⁹
- Current endoscopic surveillance strategies performed in a community-based setting did not demonstrate decreased mortality from oesophageal adenocarcinoma; novel approaches and effective modalities are still needed to improve outcomes in Barrett oesophagus surveillance¹⁰