INTRODUCTION

Gastric cancer continues to be a significant cause of cancer deaths worldwide. Although the age-standardised incidence and mortality rate has been on the decline, an ageing population will continue to sustain the number of new cases of gastric cancer.1

Gastric cancer, if detected and treated early, has an excellent prognosis. Gastric cancer (GC), the intestinal type, occurs through a stepwise progression of premalignant precursors which are endoscopically detectable and whose natural history has been characterised. These precursors, such as intestinal metaplasia, offer an opportunity for targeted endoscopic surveillance and intervention for early gastric cancer. They are also commonly encountered on routine endoscopy and their further management requires clarification.

In this article, we will review the management of Helicobacter pylori (H. pylori) in gastric cancer prevention and developments in the endoscopic surveillance, detection and treatment of early gastric cancer.

H. PYLORI: SCREENING, DIAGNOSIS AND TREATMENT

H. pylori is the most important cause of gastric cancer. An estimated four in five gastric cancers are attributable to H. pylori infection.2 H. pylori is estimated to infect 50 percent of the global population, with the majority of infections acquired in childhood. Those infected have a 1-2 percent likelihood of developing gastric cancer.3 H. pylori infection causes gastritis which, through multiple mechanisms, may lead to a cascade of changes that eventually leads to gastric adenocarcinoma. This cascade, which may be diagnosed histologically, consists of gastric atrophy, intestinal metaplasia, dysplasia and ultimately adenocarcinoma.

Most significantly, H. pylori eradication reduces the risk of gastric cancer. H. pylori eradication is associated with a lower incidence of gastric cancer (pooled incidence rate ratio 0.53, 95% CI: 0.44- 0.64). In patients who have had endoscopic resection of early gastric cancer, H. pylori eradication reduces the risk of metachronous gastric cancer.4

Screening

As H. pylori is the most important preventable risk factor for gastric cancer, the primary physician plays an important role in diagnosing and treating H. pylori infection. While the routine screening of H. pylori at the population level is not recommended, H. pylori should be treated when it is detected in the course of clinical care.

In practice, testing for H. pylori is advised for the following indications. Those with peptic ulcer disease, gastric MALT lymphoma and following endoscopic resection of early gastric cancer.

H. pylori testing may also be considered in young patients with dyspepsia without alarm features, patients with functional dyspepsia, those requiring low-dose aspirin and those commencing on NSAID treatment.5

Diagnosis

Routine endoscopy is not required for the diagnosis of H. pylori infection. H. pylori infection may be diagnosed with H. pylori stool antigen test or urea breath test. In patients who require upper endoscopic examination (OGD) for the evaluation of their symptoms, H. pylori infection may be diagnosed with gastric biopsies taken for histology or the rapid urease test. It is important to bear in mind that antibiotics and anti-secretory medication (e.g. proton pump inhibitors [PPI]) have to be withheld for at least four weeks and two weeks respectively before testing for infection.6 Serological tests for H. pylori are to be avoided as they do not distinguish between active and past infection.

Treatment

Patients with active H. pylori infection should be offered treatment. While no treatment regimen offers 100 percent eradication rates, the initial course of eradication therapy offers the highest likelihood of success. As the likelihood of eradication diminishes with each treatment attempt, a careful attempt must be made to address barriers to adherence. H. pylori treatment regimens may be complex with high pill burden and adverse effects. Adherence may be further influenced by the patient’s lack of understanding of the indication for treatment.

Hence patients should be counselled about the treatment rationale, the importance of completing the full treatment course, dosing instructions and the expected adverse effects.
It may be helpful to highlight the need to ingest multiple pills for an extended period. It’s also important to clarify if the patients had any previous antibiotic exposure, especially to macrolides and fluoroquinolones, as this may predispose to antibiotic resistance and these antibiotics should be avoided in treatment regimens.

Clarithromycin triple therapy that comprise of PPI, clarithromycin and amoxicillin for 14 days is typically used as first-line treatment. In patients with amoxicillin allergy, this may be substituted with metronidazole. Clarithromycin triple therapy should be avoided in those with prior macrolide exposure as this is associated with increased antibiotic resistance. Bismuth quadruple therapy that comprises of PPI, bismuth, metronidazole and tetracycline for 14 days is an alternative regimen. Levofloxacin-based therapies have also been used to treat H. pylori infection.5

Following treatment, H. pylori eradication should be confirmed with a urea breath test. Alternatively, stool H. pylori antigen test or endoscopic biopsy may be used depending on availability, cost and the need for repeat endoscopy. Antibiotics and anti-secretory medication (e.g. PPI) have to be withheld for at least four weeks and two weeks respectively before testing for eradication. The reinfection rate following eradication is low.7

Patients with persistent infection usually have antibiotic resistance and require salvage treatment. This may be a challenge as antibiotics previously used should be avoided, where possible. It’s best that these patients are referred for specialist assessment. Patients with persistent infection despite repeat treatment require gastric biopsies for H. pylori culture to determine antibiotic sensitivities. Patients with amoxicillin allergy that precludes its use may be considered for allergy testing to exclude true allergies. This is because many patients with a history of penicillin allergy do not have true penicillin hypersensitivity and amoxicillin is an important component of first-line and salvage regimens. Removing the allergy label may enable the use of amoxicillin.8 In rare instances of persistent H. pylori infection despite multiple attempts at treatment, the risk benefits of H. pylori eradication are reviewed with the patient, especially if the patient has other serious medical conditions that limit life expectancy.

**PREMALIGNANT PRECURSORS OF GASTRIC CANCER AND THE IMPLICATIONS FOR MANAGEMENT**

Beyond H. pylori eradication, we now have the means of translating our understanding of gastric carcinogenesis into interventions for the prevention and endoscopic treatment of early gastric cancer.

Gastric adenocarcinoma has two distinct subtypes - intestinal and diffuse. The former is associated with H. pylori infection and develops through a cascade of stages from gastritis, atrophic gastritis, intestinal metaplasia, dysplasia (low grade and high-grade dysplasia) to ultimately, adenocarcinoma. This cascade is initiated by H. pylori infection. While progression to carcinoma is not invariable, the risk of progression is associated with the extent and severity of histological changes.

This cascade is clinically relevant for the following reasons. The stepwise progression of premalignant change provides an opportunity for early detection, surveillance and endoscopic intervention. This is analogous to the adenoma-carcinoma sequence in colorectal cancer that has led to colonoscopy and polypectomy becoming an effective tool in colorectal cancer prevention by detecting adenomatous polyps. Also, while H. pylori eradication reduces the risk of gastric cancer, this may be less effective in patients who have already developed precancerous change9 and continue to be at risk of gastric cancer. Furthermore, intestinal metaplasia (IM), which is a step in the carcinogenesis cascade, is a common finding on routine endoscopy. IM is a clinical problem increasingly encountered by clinicians whose optimal management needs to be clarified. Hence the detection of precancerous change, often as an incidental endoscopic finding, provides us with an opportunity for intervention against GC.

**Intestinal metaplasia: surveillance for a minority**

Intestinal metaplasia refers to a change in the gastric mucosa where the gastric epithelium is replaced by the intestinal epithelium. This is a common finding on routine endoscopy. While it is associated with an increased risk of gastric cancer, the absolute risk is low. Studies have reported that the risk of progression to adenocarcinoma in patients with atrophic gastritis and intestinal metaplasia (IM) is <1 percent a year.10

In a cohort study of Singaporean Chinese patients, the age-adjusted incidence of early gastric neoplasia in patients with IM was 133.5 per 100 000 person-years (GCEP study).11 Hence, the absolute risk of GC is too low to justify routine surveillance in patients with IM.

However, the risk of progression to GC is associated with the extent and severity of IM. The Operative Link of Gastric Intestinal Metaplasia (OLGIM) is a staging tool that characterises the extent of IM based on mapping biopsies of the stomach.12 The risk of GC increases with the OLGIM stage. In the GCEP study, the majority of patients were OLGIM I. In these patients the age-adjusted incidence of early gastric neoplasia was 21.5 per 100 000 person-years. In contrast, patients with OLGIM III-IV, the most severe cases of IM, had the highest risk of early gastric neoplasia (adjusted HR 20.7; 95% CI 5.04 - 85.6, p< 0.01). Hence OLGIM staging improves risk stratification and identifies a subset of patients who may be at higher risk of GC.13

Patients with OLGIM I, who constitute the majority of patients, generally do not require endoscopic surveillance. Patients with higher OLGIM stages may benefit from endoscopic surveillance every 3-5 years with the specific interval being guided by the OLGIM stage. Patients with additional risk factors such as smoking, persistent H. pylori infection and a first-degree family history of GC may benefit...
from closer surveillance intervals. In addition, patients should undergo H. pylori eradication and be counselled on smoking cessation. Local guidelines on surveillance are in the process of being formulated by a workgroup and are expected to be published in due course.

**Dysplasia: close surveillance and treatment**

The presence of dysplasia on biopsies is a clinically significant finding for the following reasons. Gastric dysplasia is associated with a risk of synchronous GC, an increased risk of progression to GC and in some patients, the dysplastic lesion may already harbour cancer.

The presence of dysplasia is associated with a synchronous GC in up to 30 percent of cases. Furthermore, 65-80 percent of patients with high-grade dysplasia (HGD) progress to adenocarcinoma over a median interval of 4-48 months. It is also challenging to differentiate HGD from adenocarcinoma on biopsy specimens. Hence patients with HGD may be harbouring cancer that may not be seen on biopsies due to sampling.

The risk of progression to cancer in low-grade dysplasia (LGD) is less well defined. LGD may regress in 38-75 percent and persist in 19-50 percent. In those with persistent LGD, 23 percent progress to carcinoma over 10-48 months. In lesions with a biopsy finding of LGD, the final histology of the resected specimen may reveal the presence of adenocarcinoma in 6.9 percent. The diagnosis of LGD may also be subject to inter-observer variation, even amongst expert pathologists. The diagnosis of dysplasia often requires corroboration from more than one pathologist.

While dysplasia may indicate a focal area of neoplastic progression within the gastric mucosa, it may be challenging to identify dysplasia as an actual discrete lesion on endoscopy. Unlike precancerous colorectal polyps which are easily identifiable on endoscopy by their mushroom-like shape, gastric dysplasia often manifest as a subtle change in the gastric mucosal contour (i.e., flat polyp) which may be easily missed, even by experienced endoscopists. This accounts for the clinical scenario where random ("blind") gastric biopsies taken from a seemingly normal gastric mucosa, often with the aim of diagnosing H. pylori, demonstrates dysplasia. The clinician is left with the dilemma of repeating the procedure to detect any lesion that may have not been evident on the initial OGD. Sometimes, even the repeat OGD may not reveal the site of the dysplastic lesion.

In these instances, advanced endoscopic imaging techniques such as chromoendoscopy are employed to improve the detection of subtle lesions. These imaging techniques broadly comprise two groups, dye-based chromoendoscopy and electronic chromoendoscopy. Dye-based chromoendoscopy involves the administration of colour dyes into the stomach during OGD. The dyes differentially stain normal and abnormal mucosa to better highlight neoplastic lesions in the stomach. Electronic chromoendoscopy uses optical filters within the endoscope system to alter the properties of light used to illuminate the stomach. As normal and neoplastic mucosa have different optical signatures, they can be more readily differentiated and characterised. An example of electronic chromoendoscopy is narrow band imaging (NBI) which is operated by pressing a button on the endoscope. In patients with incidental HGD or cancer on random biopsies, 80 percent will have a detectable lesion by chromoendoscopy. Hence these imaging techniques are useful tools to detect and characterise gastric premalignant lesions.

The detection of a precancerous dysplastic lesion allows for it to be resected endoscopically thus arresting its progression to cancer. The resected lesion also provides a more definitive histological diagnosis compared to biopsies and in some instances, this may upstage or downstage the initial diagnosis. However, these gastric premalignant lesions are technically challenging to resect compared to colonic polyps. Conventional polypectomy techniques that are commonly used by the endoscopist in colonic polyps are not feasible in gastric premalignant lesions because the latter are not shaped like a polyp. Gastric dysplastic lesions usually require more advanced resection techniques such as endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD).

Hence the finding of dysplasia on gastric biopsies identifies a patient who may either already have an early gastric cancer or is at risk of developing one in the near future. These patients will require a repeat careful endoscopic examination to characterise the dysplastic lesion and also look for concurrent cancer. Any endoscopically visible lesion that corresponds to the biopsy finding of dysplasia requires endoscopic resection and definitive histological assessment. In the absence of any visible lesion, continued endoscopic surveillance is required to detect subsequent malignancy.

**Endoscopic treatment of early gastric neoplasia**

The detection of precancerous lesions and early gastric cancer provides an opportunity for treatment with endoscopic resection. Whereas gastric cancers are often detected at a more advanced stage that requires gastrectomy, early gastric cancers and dysplastic lesions may be treated with organ-sparing endoscopic resection techniques like EMR and ESD.

Studies have shown that patients undergoing endoscopic resection of early gastric cancers had comparable long-term survival, shorter hospitalisation and fewer complications compared to those undergoing surgery. While endoscopic treatment was associated with higher rates of recurrence, these are usually amenable to repeat endoscopic resection. Hence these patients will retire continued endoscopic surveillance following endoscopic resection.

While endoscopic surveillance lends itself to early intervention for GC, we need to keep in mind the following considerations. For the majority of patients with IM, the absolute risk of GC is very low and does
not require any surveillance. Also, there are presently no randomised controlled trials that demonstrate a survival benefit with endoscopic surveillance. Endoscopy is invasive and premalignant lesions are subtle and can be missed on endoscopy. Hence the decision to survey should be individualised taking into account the patient's wishes as well as any other medical conditions that may limit the patient's life expectancy.

H. pylori eradication remains the cornerstone of GC prevention and the primary care physician plays a crucial role in detecting and treating H. pylori. Gastric premalignant lesions will be increasingly encountered by the primary physician and this review attempts to provide a framework to better understand the issues that influence management.

REFERENCES


LEARNING POINTS

- H. pylori eradication reduces the risk of gastric cancer.
- As the initial course of H. pylori eradication therapy is most likely to succeed, barriers to adherence should be identified and addressed.
- The intestinal type of gastric carcinoma develops through a cascade of premalignant stages which provides an opportunity for early detection, surveillance and endoscopic intervention.
- The detection of precancerous lesions and early gastric cancer provides an opportunity for treatment with organ-sparing endoscopic resection techniques.