GastroIntestinal Endoscopy

newsletter the insider

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Celebrating 30 years

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Our Mission at GastroIntestinal Endoscopy is to deliver experienced and accessible endoscopy services with the highest quality of healthcare standards to improve the health outcomes of patients and the communities we serve.

GIE operates an Open Access Endoscopy Service from four locations:

- **SUNNYBANK** – Brisbane Endoscopy Services
- **CHERMSIDE** – Chermside Day Hospital
- **EVERTON PARK** – North West Private Hospital
- **AUCHENFLOWER** – The Wesley Hospital

Dr Hugh Spalding

Gastric intestinal metaplasia: what is the risk and what to do?

Gastric intestinal metaplasia (GIM) is the replacement of normal gastric epithelium with intestinal-type epithelium and is a result of chronic injury. It is well recognised as a premalignant lesion in much the same way as Barrett's oesophagus, although management is much less clearly defined for GIM.

Gastric adenocarcinoma is the second leading cause of cancer death worldwide and the majority of gastric adenocarcinomas are thought to arise from IM (so-called intestinal type) whilst the less common diffuse type adenocarcinoma appears to be largely independent of IM and probably has a primary hereditary aetiology. There is likely to be a stepwise progression from chronic gastritis (often associated with *H. pylori*) to atrophic gastritis (AG) and IM, to dysplasia, then adenocarcinoma. It follows that AG and IM are often found together.

Gastric IM can be identified endoscopically with high definition narrow band imaging with a sensitivity of around 70-80%, but is often found incidentally on histology. The true prevalence of GIM in the general population is difficult to assess. Prevalence data varies considerably with the indication for endoscopy. Risk factors include *H. pylori* status (up to 30% or more with *H. pylori* have IM), older age, male gender, smoking and to a minor extent heavy alcohol intake. Ethnicity is important; in a Korean cohort the incidence was 12.5% and it was 3% in a large cohort of male U.S. veterans. First degree relatives of patients with gastric cancer are about twice as likely to have IM.

What is the risk from IM?

Intestinal metaplasia imparts perhaps a 10 fold increased risk for gastric cancer, but only a small proportion of patients with IM get it and the difficulty is in knowing who is at greatest risk. In the presence of IM the most important risk factor for cancer is dysplasia. In a large Dutch cohort the progression to cancer was of the order of 0.1% per year with atrophic gastritis 0.25% with IM, rising to 0.6% with "mild-to-moderate dysplasia" and 6% with "severe dysplasia"*. Others have estimated a 25% risk of a diagnosis of gastric cancer within 1 year of diagnosis of high grade dysplasia.

The extent, location and severity of AG/IM also influence risk. Compared with focal or antrum-predominant IM the extension through the entire lesser curve may increase cancer risk > 5x, whilst diffuse distribution (antrum + body) may increase this risk 12x. Atrophic gastritis and IM are often patchy, so multiple biopsies are required for staging. The Operative Link on Gastrointestinal Metaplasia (OLGIM) and Operative Link on Gastritis Assessment (OLGA) are staging systems based on the extent and severity of AG or IM with stages I and II considered to carry minimal risk of progression to cancer, probably not requiring surveillance, at least in the absence of other significant

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risk factors. These systems require more work for full validation.

Intestinal metaplasia can be either complete (type1 with goblet cells interspersed with columnar absorptive cells, resembling small intestinal epithelium) or less commonly incomplete (types II and III with goblet cells and interspersed mucin secreting columnar cells, resembling colonic epithelium). The risk of cancer appears to be much higher with incomplete IM (up to 18x in one study).

Who should get endoscopic surveillance?

Advances in endoscopic detection using high definition endoscopy and mucosal resection of dysplastic lesions and early gastric cancers have increased the potential benefits of surveillance. Endoscopic surveillance is associated with earlier stage of cancer detection and better survival.

However, there are no significant randomised controlled trials to guide surveillance of GIM. Endoscopic screening and surveillance varies widely even amongst countries with a high incidence of gastric cancer.

European guidelines of 2012 are perhaps the most relevant available for Australia and are partly incorporated into American Society for Gastrointestinal Endoscopy guidelines (2015). It is recommended that extensive AG and or extensive IM should prompt endoscopy at three yearly intervals and no surveillance should be given for mild to moderate AG or IM limited to the antrum. Family history, but not age or gender, should be taken into account in the follow up of precancerous lesions.

Asian heritage may also influence screening and surveillance although this is not clearly addressed in the European guidelines. For example, the Korean National Cancer Screening Program provides universal two yearly screening for citizens 40 years and older and is not further stratified on the presence or absence of IM, although yearly surveillance for IM has been advocated.

What to do with dysplasia?

If a dysplastic lesion is endoscopically visible, endoscopic or surgical resection is generally recommended. Low grade dysplasia on histology in the absence of a visible lesion should be followed up within a year. High grade dysplasia requires immediate reassessment, extensive biopsies and resection of visible lesions; close surveillance at 6–12 monthly intervals is required in the absence of a visible lesion.

What about *H. pylori*, chemoprevention and lifestyle

H. pylori is a recognised carcinogen and eradication of *H. pylori* appears to improve atrophic gastritis, but has much less impact on established IM. Eradication is still recommended to reduce progression of IM. There is insufficient evidence to promote the use of COX-2 inhibitors or antioxidants such as vitamin C or beta carotene. It would seem sensible to promote a healthy diet with plenty of fruit and vegetables, moderation of alcohol and dietary salt and to stop smoking.

(*) The classification of dysplasia is now divided into low or high grade.

The sessile

Sporadic colorectal carcinomas fall into two broad groups; namely conventional and serrated. The precursors of conventional colorectal carcinomas include tubular, tubulovillous and villous adenomas that have been recognised for decades. The precursors of serrated carcinomas are more controversial and have only been broadly accepted in the last ten years.

The major subtypes of serrated colorectal polyps are hyperplastic polyps, sessile serrated adenomas and traditional serrated adenomas. Hyperplastic polyps are the most prevalent, followed by sessile serrated adenomas and then the rare traditional serrated adenomas; with each group accounting for 34%, 15% and <1% respectively of all polyps received at our practice. Hyperplastic polyps are benign without any significant risk of malignant transformation. On their own, hyperplastic polyps do not necessitate any specific follow-up. In contrast sessile serrated adenomas and traditional serrated adenomas are premalignant polyps that require surveillance colonoscopy at similar intervals to conventional adenomas.

Sessile serrated adenomas tend to occur in the seventh decade and are more common in women. They have a definite predilection for the proximal colon. Like most polyps, they are asymptomatic. Because of their sessile nature they are less likely to bleed than conventional adenomas and thus are less likely to be detected by faecal occult blood tests such as those used in the national bowel cancer-screening program. Also because of their subtle nature they can be very difficult to detect at colonoscopy. Hyperplastic polyps and sessile serrated adenomas both have *BRAF* mutations and show methylation of gene promoter regions that can result in gene silencing.

serrated adenoma

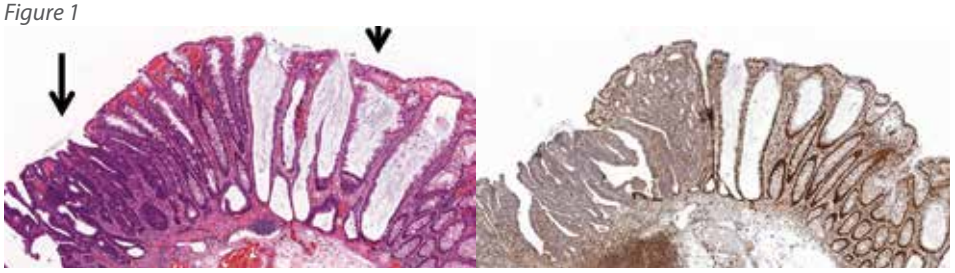
Dr Mark Bettington *MBBS FRCPA*

They are histologically similar but sessile serrated adenomas have altered cell proliferation resulting in abnormal crypt architecture, their defining feature. Unlike conventional adenomas they lack cytological dysplasia.

An ordinary sessile serrated adenoma is in some ways the counterpart of a tubular adenoma of the conventional pathway. Roughly one in 20 of both types would become cancer if left in situ and, in average risk individuals, mandate a five-year surveillance interval. Just as a conventional adenoma can develop high-grade dysplasia, an advanced form of the sessile serrated adenoma also exists and is referred to as the sessile serrated adenoma with dysplasia. In this lesion an area of the polyp does become overtly cytologically dysplastic (see figure 1A). These polyps harbour a range of molecular abnormalities, the most frequent of which is a sporadic loss of DNA mismatch repair enzyme function (see figure 1B). This allows for a rapid accumulation of mutations and thus these polyps can rapidly transform into colorectal cancer. Worryingly, these advanced sessile serrated adenomas are mostly small polyps. In a study from our practice the median size is only 9.5mm. Because of their subtle endoscopic appearance, potential for rapid malignant transformation and frequent small size, cancers arising from sessile serrated adenomas are over-represented amongst colorectal carcinoma occurring between scheduled colonoscopies.

Many clinicians have noted the dramatic rise in sessile serrated adenoma diagnoses over the last ten years. There are several reasons for this. The most important is that sessile serrated adenomas have only been recognised by pathologists since 2003. Prior to that they were called hyperplastic polyps, or giant hyperplastic polyps

Figure 1



(A) *(B)*

if they were very large. Furthermore, gastroenterologists are becoming more adept at identifying and removing these subtle polyps. Finally, over the last decade the pathological diagnostic requirements have been relaxed, meaning more polyps are now diagnosed as sessile serrated adenomas with a commensurate decline in hyperplastic polyps. Research from Envoi pathology in collaboration with QIMR has provided some of the first experimental evidence to support these relaxed criteria.

Many of the cancers that arise from sessile serrated adenomas lose DNA mismatch repair enzyme function, causing specific mutations leading to 'microsatellite instability', a feature shared with cancers in Lynch syndrome. However, there are several important differences. First Lynch syndrome cancers arise in conventional adenomas rather than serrated polyps. Next, the loss of DNA mismatch repair enzyme function in serrated cancers is limited to methylation induced silencing of *MLH1*. In Lynch syndrome, loss of mismatch repair enzyme function occurs via mutation (one germ-line (inherited) and one sporadic) and can affect any of the DNA mismatch repair enzymes (*MLH1, PMS2, MSH2, MSH6*), although *MLH1* and *MSH2* account for over ninety percent. Finally the majority of serrated cancers harbour a *BRAF* mutation, whereas the cancers of Lynch syndrome do not.

Some individuals develop large numbers of serrated polyps. These patients may have serrated polyposis syndrome, particularly if the polyps are >10mm and proximal. The genetic basis for serrated polyposis remains unknown; however there is a significantly increased risk of colorectal carcinoma. Close colonoscopic surveillance is required and in some patients prophylactic colectomy may be recommended.

Figure legend:

(A) H&E of a sessile serrated adenoma with dysplasia. Note the abrupt transition from the ordinary (arrowhead) to dysplastic (arrow) component.
(B) Immunohistochemical stain for the mismatch repair enzyme MLH1 showing loss of staining in the dysplastic component, indicative of methylation induced silencing of the gene.

Further reading:

1. Bettington M, Walker N, Clouston A, Brown I, Leggett B, Whitehall V. *The serrated pathway to colorectal carcinoma: current concepts and challenges.* Histopathology. 2013;62(3):367–86.

Dr Mark Bettington is a pathologist with Envoi Specialists Pathologists. Dr Bettington is completing his PhD at the QIMR Berghofer Medical Research Institute in the Conjoint Gastroenterology Laboratory. His research is focused on the pathology and genetics of colorectal neoplasia.

Frequently Asked Questions Dr Neville Sandford

Q For a patient with a clear colon and no risk factors; what do you recommend for their review and how does FOBT fit in here?

A Current evidence suggests that patients with no risk factors for Colorectal cancer and who have no polyps on a screening colonoscopy, have a low risk of developing advanced polyps or colorectal cancer and can safely wait 10 years before having a repeat colonoscopy. This does not exclude the investigation of new symptoms (change in bowel habit or rectal bleeding) if this occurs during this time. It is now not recommended for patients who are already in a colonoscopy screening programme to have regular FOBTs done in the intervening time between colonoscopies. The reason for this is twofold: firstly a normal test may lull the patient into a false sense of security that they do not need a colonoscopy if their FOBT is negative, and secondly patients with a polyp-free colon at colonoscopy have a low yield for polyps if they have a repeat colonoscopy before their scheduled follow-up even in the presence of a positive FOBT. Annual screening FOBTs is recommended in patients who decline the offer of screening colonoscopy, but a positive FOBT should be followed with a colonoscopy.

Q What is the frequency of post-polypectomy bleeding?

A Post-polypectomy bleeding is the most common serious complication of colonoscopy. It either occurs immediately following polypectomy (reported in up to 1.5% cases) and can be controlled by the endoscopist, or at a later stage usually at 5-7days but occasionally up to one month post polypectomy. Delayed bleeding occurs in up to 2.5% cases and the frequency is determined by the size of the polyp (<1% incidence if polyps are <1cm but up to 6% for polyps >2cm), the location of the polyp (more likely in right colon), the number of polyps, the age of the patient, the presence of medical comorbidities (cardiovascular disease, chronic renal failure, haematological disorders), and the use of anticoagulants or antiplatelet agents. Aspirin and NSAIDs do not significantly increase the risk of bleeding, but thienopyridines (eg clopidogrel) (RR 4.66) and warfarin (RR 10) are associated with a higher risk of bleeding. Almost all delayed bleeds can be managed endoscopically (95% cases) but occasionally radiologic embolization or surgery is required. The more ready availability of haemoclips which can be applied prophylactically in high-risk situations may have reduced the incidence of bleeding, as a recent personal audit of my patients resulted in a post-polypectomy bleeding rate of 0.4%.

If you require A5 referral pads, please contact one of our four locations below. Electronic referral templates can be downloaded from our website www.gastros.com.au

GIE practice locations and contact details For all appointments, call 1300 4 GASTRO (1300 442 787)

Brisbane Endoscopy Services

Suites 16–18
McCullough Centre
259 McCullough Street
Sunnybank QLD 4109

Phone: 07 3344 1844
Fax: 07 3344 2739

Chermside Day Hospital

Level 1
Chermside Medical Complex
956 Gympie Road
Chermside QLD 4032

Phone: 07 3120 3407
Fax: 07 3120 3443

The Wesley Hospital

3rd Floor, East Wing
451 Coronation Drive
Auchenflower
QLD 4066

Phone: 07 3870 3799
Fax: 07 3870 5069

North West Private Hospital

Endoscopy Unit
137 Flockton Street
Everton Park
QLD 4053

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