Endoscopic Methods

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Abstract

Endoscopic methods to recognise and treat early gastrointestinal malignancies have increased in recent years. This has resulted in more lesions being diagnosed at an early stage and a shift away from invasive surgery towards endoscopic resection. However, it is necessary for the endoscopist to understand the key principles behind advanced endoscopic diagnosis and the new therapeutic options available. This chapter will review the advances in endoscopic techniques and methods which are changing the way we diagnose and treat these cancers. It will examine the general principles behind advanced endoscopy and then examine their application in Barrett's neoplasia, gastric cancer and the dysplasia associated lesions or masses associated with ulcerative colitis. It will focus on the best techniques for each of the above pathology.

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1 Endoscopic Methods

Gastrointestinal malignancies represent a significant health burden, with the three main malignancies, colon, oesophageal and stomach cancer, representing the 3rd, 9th and 10th most common malignancies in the UK. With the exception of pancreatic cancer, survival has improved significantly over the last three decades, with survival rates doubling for oesophageal and colonic malignancies. This chapter will look at the advancing endoscopic techniques which are contributing to this, both in terms of diagnosis, staging and new novel treatments.

2 Inflammation and Cancer

As most gastrointestinal cancers develop on a background of inflammation it is important to differentiate inflammation from dysplasia. This is not always possible for the endoscopist or for the pathologist and is a common cause for confusion. The best approach is to always ensure that inflammation is completely treated prior to assessment of the mucosa for cancer. The diagnostic value of endoscopy for the detection of early cancer or dysplasia is very low in the presence of oesophagitis, gastritis or colitis. When these conditions are encountered a decision to fully treat inflammation and rescope at a later date should be made to assess for early neoplasia.

3 Fundamental Endoscopic Principles

3.1 Preparation

Good preparation is central to quality endoscopy, and the process starts before performing the endoscopy. In the upper gastrointestinal tract a mucolytic drink is recommended to enable subtle abnormalities to be evaluated. Pronase and Gascon ingested as a drink prior to gastroscopy has been shown to significantly improve mucosal visibility (Bhandari et al. 2010). Improving mucosal visibility should translate into improving early detection of cancers but that remains to be proven. Pronase is not licensed for ingestion, so a 50 ml solution containing 5 ml of 10% *N*-acetyl cysteine (NAC) with 5 ml of infacol can be used as an alternative in Western countries. This should be given as a drink 5 min prior to the procedure. Likewise, in the colon bowel preparation is central to visualising lesions. It is important that patients are informed of the importance of the bowel preparation,

including the timing of the sachets and the importance of consuming a significant volume of water with most of the commonly available preparations. When performing the procedure any residual debris should be washed away and the lens kept clean. Mucous and bubbles hinder the use of advanced techniques like spectral imaging and dye spray. A cap on the end of the endoscope can improve image quality when examining a lesion by stabilising the mucosa.

3.2 Basic Concepts

When visualising the oesophagus, stomach and colon, the mucosa should be inspected after insufflation and then again as the organ is deflated. It is during deflation of the lumen that many abnormalities become visible. Therefore, if inspection is only performed with complete inflation pathology will be missed. All areas should be visualised, with particular care taken to look beneath folds. There are key areas in each organ where pathology is most likely to be found, which will be discussed later. It is becoming recognised that a rapid procedure is not necessarily a good procedure. This has been demonstrated in studies looking at polyp detection in the colon, where a withdrawal time of >6 min is mandatory, and the same principle applies to the upper gastrointestinal tract. Likewise use of hyoscine during gastroscopy and colonoscopy can flatten the folds and help improve the pickup rate of early neoplasia.

3.3 Philosophy of Endoscopy

Most patients have an endoscopy because they are symptomatic and the endoscopist performs the procedure to look for a cause for the patient's symptoms. These causes are likely to be due to findings like peptic ulcer, oesophagitis or cancer in gastroscopy, and colitis or cancer during colonoscopy. However, these are very obvious findings during the procedure so endoscopists should pay special attention when no gross findings are seen. They should spend enough time to look at the fine details of the mucosa to identify subtle mucosal changes suggestive of the presence of early cancerous changes. Endoscopists in Japan have a very good understanding of these changes and also pay special attention looking for the changes. This might explain the higher incidence of early cancers detected in Japan. We believe that the endoscopist should spend more time looking at the mucosa and spend less time taking random untargeted biopsies.

3.4 Oesophageal Cancer

Oesophageal cancer is the ninth most common cancer in the UK, with 7,800 people diagnosed every year, accounting for 5% of all cancer deaths in the UK. Rates have increased by 50% over the last 30 years. It is more common in men

than women, with an incidence of 8.8–14.1 per 100,000 in men, and 4.8–5.7 per 100,000 in women (Barr 2007). The vague early symptoms have traditionally led to late diagnosis, leading to an overall 5 year survival of 9% (Hellier et al. 2006). However, recent endoscopic advances have made it easier to diagnose the condition at an earlier stage.

A significant risk factor for adenocarcinoma of the oesophagus is Barrett's epithelium, an acquired pre-malignant condition, caused by reflux of gastric contents into the oesophagus. The gastric acid damages the normal squamous epithelium, becoming replaced by a columnar epithelium. The newly updated definition by the British society of Gastroenterology defines Barrett's as 'an endoscopically apparent area above the oesophagogastric junction that is suggestive of Barrett's which is supported by the finding of columnar lined oesophagus on histology' (Playford 2006; Watson et al. 2005).

Barrett's oesophagus effects up to 1.6% of the general population (Ronkainen et al. 2005). It is found in 15–20% of gastrointestinal endoscopies performed for symptoms of reflux. The incidence is increasing in the West (Blot et al. 1991; Pera et al. 1993). It has the potential to progress into adenocarcinoma. Risk factors for this include male gender, age >45, extended segment (>8 cm) disease, duration of reflux history, early age of onset of GORD, duodeno-gastrooesophageal reflux, mucosal damage and family history (Watson et al. 2005).

There is not a national screening policy for the detection of upper gastrointestinal malignancy or for Barrett's. However, once Barrett's is detected patients are entered into a surveillance programme. The benefits of this are controversial, as the absolute risk of malignant transformation is low, 0.8–1.5% per annum. Some studies have concluded that because of this there is no benefit to surveillance (Watson et al. 2005). Computer modelling has been used to predict an effective balance point for surveillance intervals, and a widely used interval for surveillance endoscopy is 2 years (Watson et al. 2005). Quadrantic random biopsies every 2 cm are part of the standard protocol. The cost per life year saved is around £19,000.

Random biopsies are not ideal for identifying neoplasia within Barrett's. There are a range of techniques available for examining the oesophagus in detail, and can help improve neoplasia pickup rate. Chromo endoscopy can be used to identify areas of Barrett's metaplasia and dysplasia. Several dyes have been used, with most of the research examining methylene blue (MB), indigo carmine (IC) and acetic acid (AA).

Methylene blue 0.5% is an absorptive stain which highlights areas of specialised columnar epithelium (Canto et al. 1996, 2001). Dysplasia and cancer are detected more frequently than with random four quadrant biopsies (Canto et al. 2000). Unfortunately MB is inconvenient to use. It must be left in contact with the mucosa for 3 min followed by vigorous washing to clear away excess dye. As a result the endoscopic appearances are unpredictable and subjective (Dacosta et al. 2002). There have been recent concerns about DNA toxicity with MB so it is falling out of favour. IC 0.4% is not absorbed but accumulates in pits and valleys between cells highlighting the architecture (Hetil 2002) and has been shown to help in the detection of dysplasia (Sharma et al. 2003, 2006).

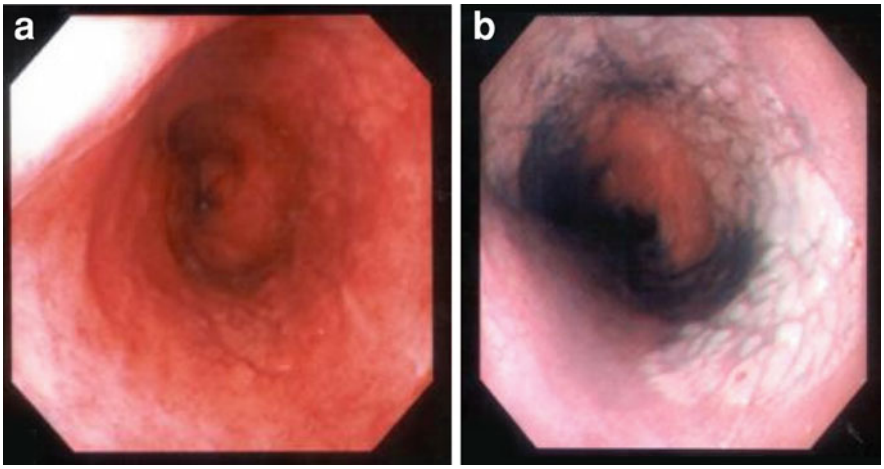

Fig. 1 Oesophagus: **a** routine endoscopic appearances, **b** post acetic acid chromoendoscopy

AA 2.5% when sprayed onto Barrett's mucosa causes a reversible acetylation of nuclear proteins to occur. This leads to an acetowhitening reaction, with increased opacity of the mucosal surface (Lambert et al. 2003). The associated vascular congestion improves visualisation of the surface vasculature (Lambert et al. 2003). It also enhances the surface pattern assessment allowing early recognition of neoplasia (see Fig. 1).

AA has been successfully used in the detection of neoplasia of the cervix during colposcopy (Guelrud and Herrera 1998; Van Le et al. 1993). While no randomised controlled trials for its use in the oesophagus exist, cohort studies have demonstrated effectiveness in the identification of dysplasia. The sensitivity for the identification of neoplasia has been suggested to be 71–100%, with a specificity between 80 and 99% (Vázquez-Iglesias et al. 2007; Gossner et al. 2005; Fortun et al. 2006; Longcroft-Wheaton et al. 2010). We believe that this is the dye of the future in the evaluation of Barrett's. It is cheap, effective and universally available.

Narrow band imaging (NBI) is a form of 'digital virtual chromo endoscopy'. It carries the potential advantage that it can be activated at the press of a button on the endoscope. It highlights mucosal vascular patterns to enhance abnormal dysplastic areas. A prospective cohort study has demonstrated that a sensitivity of 100%, specificity of 98.7% and positive predictive value of 95.3% for HGD could be achieved. Another tandem endoscopy study involving 65 patients compared standard resolution endoscopy to NBI. It found that NBI directed biopsies detected dysplasia in more patients (57%) compared to biopsies taken using standard resolution endoscopy (43%) (Wolfsen et al. 2008). Auto-fluorescence imaging (AFI) is another novel technique which is based on the principle of variable fluorescence between tissues. Normal mucosa when exposed to light emits a green fluorescence as compared to magneta/pink fluorescence in neoplastic areas within the mucosa. This principle is exploited by the technique of AFI to detect early

neoplasia. Early studies without NBI suggested that while detection rates were very good (91%) a 51% false positive rate limited its use without NBI (Kara et al. 2005). AFI is now being used as a 'red flag' technique to highlight points of concern in wide areas followed by detailed scrutinising using NBI (Curvers et al. 2008).

Fujinon has developed a technology for vascular enhancement, known as FICE. Rather than using filters it utilises a post processor technology to digitally reconstruct spectral data to enhance particular wavelengths. When compared with random biopsy in patients with suspected high grade intraepithelial neoplasia or early cancer, a sensitivity of 83% for FICE was achieved (Pohl et al. 2007). There was high grade dysplasia or early cancer in 24/57 patients. Due to its nature as a post processor technology, FICE can utilise a wide range of different frequencies for lesion enhancement. Therefore it has the potential to develop into a very powerful tool for examining Barrett's for neoplasia, perhaps with specific settings for the purpose. This is an area for future research.

All of the 'virtual chromo endoscopy' techniques (NBI, FICE and i-scan) produce different appearances. Although some of the skills are transferrable additional training is normally required to transfer between systems.

Confocal endomicroscopy is a new technology for obtaining true in vivo histology. Studies in Barrett's surveillance have suggested that Barrett's oesophagus with associated neoplasia could be predicted with a sensitivity of 96.4% (Trovato et al. 2008). It has been shown that confocal endomicroscopy improves the yield of neoplasia in apparent Barrett's oesophagus compared to a four quadrant random biopsy protocol (Dunbar et al. 2009). There is limited evidence that it is also effective in the identification of gastric cancers (Yeoh et al. 2005). This technique only works once neoplasia has been identified by the endoscopist using other endoscopic techniques, so it does not help improve detection but can improve the confidence for diagnosis. We believe that this is an excellent experimental technique which has yet to find a major clinical role.

3.5 Treatment

Traditionally the only treatment for high grade dysplasia and intramucosal adenocarcinoma was an oesophagectomy. This is a highly invasive intervention, associated with significant mortality and morbidity, variable according to centre, with high volume units producing better results (Birkmeyer et al. 2002). Postoperative morbidity is accepted to be significant, with rates between 30 and 50%, with a mortality of 2–10% (Chang et al. 2008).

Endoscopic resection and ablation techniques are becoming increasingly popular due to low morbidity and mortality. Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) involve removing the mucosal and submucosal layers of the oesophagus. EMR uses either a cap and snare kit from Olympus or Duette banding ligator from Cook to remove the abnormal tissue. This can be taken in one piece (May et al. 2002a, b; Pech et al. 2008) or, for larger areas,

piecemeal excision can be performed. EMR gives a better histological diagnosis as compared to biopsy. However, if a lesion is >1.5 cm then piecemeal resection can make it hard to determine completeness of the lateral resection margins. ESD uses a specialised endoscopic knife to dissect out neoplastic areas of any size in an en-block fashion. It can provide a clear resection margin but carries increased risks, including that of perforation. This can be combined with Argon plasma coagulation (APC), multipolar electrocautery (MPEC), which all aim to destroy any residual abnormal tissue through either ionised argon gas or an electric current.

Ablative photodynamic therapy (PDT) involves the use of a photosensitizing agent which is preferentially taken up by tumour tissue (Panjehpour et al. 2008). After a suitable time period an endoscopy is performed where the abnormal area is exposed to light at an appropriate wavelength. The neoplasia which has preferentially taken up the drug then undergoes cell death. Using this technique a randomised controlled trial has shown 98% efficacy at eliminating low grade dysplasia (Ackroyd et al. 2000). Success has also been demonstrated with HGD and superficial T1 cancers, with successful ablation of HGD as high as 93% in one prospective series (Overholt et al. 1999), although a more recent RCT by the same author has suggested that complete HGD ablation is achieved in 77% of cases over a mean follow up period of 24 months (Overholt et al. 2005). It can cause stricture formation and photosensitivity reactions. Radiofrequency ablation (RFA) is similar in concept. Radiofrequency electrodes deliver thermal energy through a focal device or balloon inflated to make contact with the oesophageal wall. This induces mucosal destruction. The depth of burn is less than with PDT which improves the safety profile of RFA over that of PDT, with a low oesophageal stricture rate of 6%, no deaths and no perforations seen in a large sham-controlled trial (Shaheen et al. 2008). RFA is a useful technique for multifocal dysplasia (Shaheen et al. 2009). It is not suitable for raised nodular areas which should first be removed by EMR. There have been no trials conducted to date which show whether RFA combined with EMR is any better than EMR alone.

4 The Stomach

The incidence of gastric cancer is falling in the west. This is attributed to the declining incidence of *Helicobacter pylori* (*H. pylori*) colonisation. Gastric cancer is therefore considered to develop on a background of inflammation (McNamara and El-Omar 2008; Ernst 1999). Eradication of *H. pylori* is probably effective in reducing risk and possibly cost effective (Parsonnett et al. 1996; Roderick et al. 2003). In practical terms in the west the incidence is falling anyway, so the gain from actively seeking to eradicate in an asymptomatic population may be small.

The most common areas for gastric cancer associated with *H. Pylori* is in the antrum or insura. In helicobacter negative patients it is more prevalent along the greater curve or in the body. It is very important therefore when examining patients to look closely in these areas.

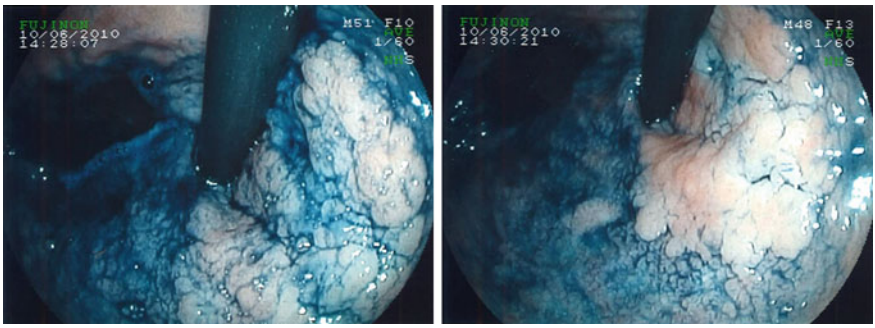

Fig. 2 High grade dysplasia in the gastric cardia after indigo carmine dye spray

Screening for gastric cancer is controversial. A screening programme place is in Japan, which has been successful in reducing mortality. This has not been adopted in the west, where the lower prevalence of the condition makes the usefulness questionable. However, patients with atrophic gastritis are at increased risk, and yearly endoscopic screening has been suggested in this group of patients (Whiting et al. 2002).

The diagnosis of gastric cancer is predominately by endoscopy. A non-healing gastric ulcer is the classical appearance of gastric cancer. This however, typically represents advanced disease. The key problem is in detecting early, potentially treatable lesions. However, the Japanese have demonstrated that not only it is possible to find early gastric cancer, but that it is even possible to accurately stage the depth of lesion invasion in 95% early cancer and 86% for advanced cancer (Yin et al. 2009). This assessment is best made by indigocarmine assisted chromo endoscopy techniques (see Fig. 2). NBI has been utilised with some success. There is very limited evidence available regarding whether FICE is beneficial.

4.1 Treatment

Early gastric cancer in the west has traditionally been treated by gastrectomy. However, in Japan endoscopic resection is the standard treatment. The Japanese gastric cancer association (JGCA) released a series of recommendations for the management of gastric cancer in 2001, (Nakajima 2002) updated in 2008 to reflect the rapid advances in management options available. Endoscopic resection is indicated for lesions <2 cm in size with a differentiated histological type where there is no ulceration present (Tsujitani et al. 1999). Recently the indications have been expanded further to include all intramucosal cancer regardless of size without ulceration, or intramucosal cancer <30 mm with ulceration.

EMR of mucosal cancer is indicated for lesions under 2 cm, where the risk of lymph node metastasis is very low. An enbloc resection should be performed whenever possible, and is important in reducing the risk of recurrence (Eguchi et al. 2003). A problem with both cap and snare and duette cap ligation devices is that the

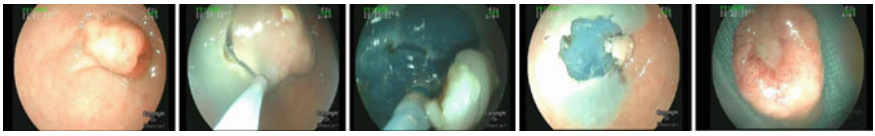

Fig. 3 Dual and IT-2 knives being used to resect a gastric lesion. Note how a circumferential incision is made and the final specimen removed enbloc

maximum size lesion which can be resected in one piece is 15 mm (Ell et al. 2000; Tanabe et al. 2002). Using these techniques recurrence free survival can be achieved in up to 92% of cases (Oda et al. 2006), with the recurrence rate most often quoted in the literature as being between 2 and 32% (Gotoda 2007).

Because of the importance of enbloc resection on recurrence free survival and the inherent limitations imposed by EMR techniques. ESD has become increasingly popular in Japan. This enables a true R0 resection to be achieved in a greater proportion of cases, and allows larger lesions to be removed. It is used for all lesions over 2 cm in diameter or where there is ulceration seen. There are now a wide range of endoscopic knives available for performing ESD, and it is accepted that these techniques are technically challenging (Choi et al. 2005). The risk of serious complications, including bleeding and perforation, is higher than that with EMR, with a risk of delayed bleeding of 6% and perforation around 4% (Oda et al. 2005). It is generally accepted that it is necessary to perform between 30 and 40 resections in a closely supervised environment before becoming competent. However, the potential gain in disease free survival is clear, with a comparative multicentre study demonstrating a significant difference in the disease free survival rates between ESD and EMR (97.6 vs. 92.5%) (Oda et al. 2006). We believe that ESD is an excellent technique for lesions over 2 cm, but is very challenging and expertise outside of Japan in this technique remains limited (see Fig. 3).

5 The Colon

A major risk factor for inflammatory neoplasia in the colon is ulcerative colitis. This is an idiopathic inflammatory condition which affects the large bowel. It has a prevalence of 3–12 per 100,000 in Northern Europe and America, but is much less common in Asia and the Far East, with a prevalence between 1 and 6 per 100,000 (Loftus 2004).

Chronic ulcerative colitis increases the risk of colonic cancer. The cancer risk in patients with ulcerative colitis is dependent on the extent of disease and the frequency of attacks. It is generally accepted that the cumulative risk for patients with extensive disease between 7 and 15% at 20 years. Up to 15 years the risk is very low. Carcinoma is usually preceded by dysplasia. Because of this there is a national screening policy for patients with Ulcerative colitis. It is the general consensus that colonoscopic screening should start at 8–10 years for patients with a pan-colitis or after 15 years for disease restricted to the left side (Riddell 1990), with regular

follow up thereafter. The standard approach has been to take quadrantic biopsies every 10 cm. This is unfortunately time consuming and expensive. There is evidence that more dysplastic lesions are picked up using methylene blue or indigo carmine than with white light alone (Marion et al. 2008; Rutter et al. 2004). The most recent guidelines from the British Society of Gastroenterology are recommending the use of chromo endoscopy where there is appropriate expertise available. Unfortunately to date colonoscopy with NBI has not been shown to be effective (Dekker et al. 2007). Caution needs to be taken when interpreting these findings; however, as the amount of evidence available is very limited.

The aim of chromoendoscopy in ulcerative colitis is to pick up areas of dysplasia associated lesions or mass (DALMS) which could turn into cancer. These abnormalities can be very subtle. As a result it is not possible where pseudo-polyps predominate or there is significant active inflammation. Dye can be applied by a spray catheter or flushed directly down the endoscope, depending on the preferences of the endoscopist. It is important to note that at present the evidence is not there for abandoning random biopsies in these patients. Therefore if dye spray is used and no abnormalities are seen biopsies still need to be taken. This may change with time.

Confocal endomicroscopy has been used in the examination of patients with ulcerative colitis. Early studies have shown some promise, with yields for intraepithelial neoplasia greater in the chromo endoscopically guided biopsies than those targeted by chromo endoscopy alone (Hurlstone et al. 2008; Kiesslich et al. 2007). This suggests that if a targeted area is examined by the confocal endomicroscope it has the potential to prove or disprove whether it needs to be biopsied, in doing so reducing the number of unnecessary biopsies taken.

6 Endoscopic Resection of DALMS

The traditional treatment of high grade dysplasia on a background of ulcerative colitis has been colectomy. However, this strategy was developed on the hypothesis that dysplasia could not be visualised. The traditional view was that colon cancers originating on a background of dysplasia associated lesion or mass (DALMS) do not follow the traditional adenoma-carcinoma sequence, with rapid progression being seen (Blackstone et al. 1981). This view is now being challenged. There have been two studies which have investigated the endoscopic resection of polyp like DALMS (Rubin et al. 1999; Engelsgjerd et al. 1999). The principle behind removal is to distinguish between lesions which are close to turning into cancer from those which are likely to behave more like adenomatous polyps.

An adenomatous DALM is defined as a well-circumscribed, smooth or papillary, non-necrotic sessile or pedunculated lesion (Odze and Robert 2008). Non-adenoma like lesions appear as velvety patches, plaques, irregular bumps, stricturing lesions and broad based masses. A small long term outcome study has investigated the outcome of 34 patients who had DALMs, 28 resected

endoscopically and six by colonic resection. These were compared to 49 non-colitic patients treated for sporadic adenomas. It showed that one patient developed adenocarcinoma 7.5 years after resection. However, she was a high risk patient with sclerosing cholangitis. Twenty patients developed further DALMS. This was no different to the rate of sporadic adenomas in the control group (Hornick et al. 2004).

The current American Gastroenterology Association guidelines are that adenomatous like DALMS can be removed provided they can be completely excised, with an absence of dysplasia at the resection margins, and that there is no flat dysplasia anywhere else in the colon. All patients with flat non-adenoma like dysplasia should be treated with total colectomy (Itzkowitz et al. 2010).

7 Conclusions

Neoplasia in the gastrointestinal tract can develop on a background of chronic inflammation or via a non-inflammatory pathway. These neoplasias can be recognised by an endoscopist at a very early stage. The prerequisites for early diagnosis are adequate luminal preparation, a high resolution endoscope and an endoscopist with an ability to recognise subtle mucosal changes indicative of neoplasia.

Endoscopic resection and ablation techniques can now cure patients with dysplasia or early cancerous lesions without the need for radical resectional surgery and its associated morbidity and mortality. However, the success of these techniques depends on the skills and experience of the endoscopist and we believe that these procedures should only be performed at high volume early cancer centres.

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