

**Oesophago-gastric cancer: Factors influencing
presentation and the effect of antisecretory drug
therapy on symptoms and diagnosis**

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Declaration

I declare

(a) that the thesis has been composed by me, and

(b) that the work is my own but with some data collection, statistical analysis and Epi InfoTM database management being carried out by Hilda O'Flanagan (Research Assistant), and

(c) that the work has not been submitted for any other degree or professional qualification except as specified.

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ABSTRACT OF THESIS

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Title of thesis: **Oesophago-gastric cancer: Factors influencing presentation and the effect of antisecretory drug therapy on symptoms and diagnosis.**

Introduction: Upper GI cancer in the UK is associated with a poor prognosis. This thesis was concerned with clarifying the reasons for this, including delays in the diagnosis and the effect of antisecretory drug therapy (AST).

Methods: A retrospective cohort study of 685 patients with oesophago-gastric adenocarcinoma (ACA) diagnosed in South Tees between April 1991-2001 and prospective studies of gastric ulcer disease and chromoendoscopy.

Results: The time course to diagnosis was determined and showed a mean time to diagnosis of 30 weeks. Patients with oesophageal cancer took longer to present to their GP and longer to be seen in secondary care once referred. The part of the diagnostic process in primary care was double that in secondary care.

AST prescribed prior to endoscopy resulted in a delay in diagnosis of 18 weeks (mean) but this had no effect on long-term outcome.

The Urgent Referral Guidelines for upper GI cancer, known as the “two week rule” guidelines showing they fail to identify 29% of patients.

27% of patients have an endoscopy within 3 years of diagnosis where the diagnosis of cancer is not made. Lesions are often seen at the prior endoscopy, and are often ulcerated.

Inadequate biopsying seems responsible, which is influenced by the endoscopist’s perception of whether the lesion is malignant. Only 9.2% of cancers are truly “missed”.

Chromoendoscopy identified benign minor abnormalities in 14%: an aggressive biopsy policy even in patients “at risk” by virtue of age is therefore hard to justify.

Conclusion: There are significant delays in the diagnosis of oesophago-gastric ACA. Treatment with AST delays diagnosis but without affecting outcome. Current endoscopic practice could be improved to reduce the missed cancer rate through the use of a rigorous biopsy protocol especially for ulcerated lesions. As symptoms are used to determine who is endoscoped and are a poor predictor of pathology alternative means of determining “high risk” need to be developed.

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Chapter 1 Introduction

1.1 Background

Cancers of the oesophagus, stomach and pancreas referred to collectively as upper gastro-intestinal (GI) cancers leads to 18,250 deaths in England and Wales per year, or 13.5% of all cancer deaths¹. Currently, gastric cancer alone is the fourth commonest cause of death from cancer in the UK, after cancer of the lung, colon and rectum, and breast². Worldwide it remains the second most common cause of death from malignant disease³.

Over recent years the incidence of oesophageal and gastric cancers has been changing. For more than half a century the overall incidence and mortality rates for gastric cancer has been slowly declining⁴ but recently adenocarcinoma (ACA) of the gastric cardia has become more common⁵⁻⁸. Similarly, adenocarcinoma of the oesophagus is also becoming more prevalent so that it is now the commonest form of oesophageal cancer^{9:9-12}. For these reasons the emphasis for this thesis will be adenocarcinoma of the oesophagus and stomach (figures 1.1-1.4) rather than the less common forms of oesophago-gastric cancer.

Unfortunately, the 5-year survival for patients with oesophageal cancer in England is only around 9% and for those with gastric cancer it is only around 12%. Not surprisingly these patients often consider such a diagnosis as a virtual death sentence. This plight is not universal, indeed within Western Europe and worldwide these patients can have a much better prognosis¹³. We must therefore identify, and understand, why this is the case if we are to improve the outcome for these patients in the UK.

1.2 Epidemiology and aetiology.

Although a disease of the elderly the majority of patients are aged less than 75 years.

These cancers are diagnosed in 1 in 100,000 people under the age of 40, 20 per 100,000 in those aged 45-54 and 155 per 100,000 in those over 55¹.

1.3 Pathogenesis of oesophageal cancer

1.3.1 Environmental and dietary agents in oesophageal cancer.

Both alcohol and tobacco consumption can act independently and synergistically to increase the risk of both squamous and adenocarcinoma of the oesophagus, although the increase is greater for squamous cell carcinomas¹⁴. A French case-control study found a relative risk (RR) of oesophageal cancer among non-smokers in the highest category of alcohol use (>57 u/week) of 5.1, compared with non-smokers who drank least; for those in the highest tobacco use category (20 cigarettes per day) the RR was 18.0; but among those in both highest categories the RR was 44.4¹⁵. This has also been shown in a number of other studies from both Eastern and Western countries¹⁶⁻¹⁹.

Diets lacking in vegetables, fruit and dairy products with low intake of vitamin A, C and riboflavin have been shown to predispose to squamous cell carcinoma of the oesophagus²⁰⁻²².

1.3.2 Gastro-oesophageal and duodeno-gastro-oesophageal reflux.

It is estimated that 4-9% of patients experience daily heartburn and up to 20% experience symptoms on a weekly basis (Gallop organisation), and up to almost 30% experience reflux symptoms at least 6 times during the previous year²³. Case control studies have shown a twofold relative risk of developing adenocarcinoma of the oesophagus as a result of reflux oesophagitis²⁴. Longstanding severe symptoms have been shown to be associated with an increased risk of adenocarcinoma with an odds ratio of 44. The association between reflux and adenocarcinoma of the oesophagus and gastric cardia is becoming more widely accepted^{25:26}. The pathogenesis is also being investigated with an increase in DNA damage seen in patients with reflux disease²⁷.

A number of studies have shown an increase in DNA damage as a result of reflux of duodenal fluid suggesting that this may be important in the progression towards carcinoma. By surgically manipulating the nature of the refluxate in rats, Attwood and others have demonstrated that duodenal refluxate specifically may be important in the development of adenocarcinoma of the oesophagus²⁸⁻³⁰.

1.3.3 Barrett's oesophagus.

Barrett's oesophagus is considered to be a pre-malignant condition with an annual risk of oesophageal adenocarcinoma of around 0.5%³¹. It is probably as a result of chronic reflux that results in the abnormal development of specialised columnar epithelium in the lower oesophagus. Endoscopic studies demonstrate that, although less than 1% of the general population has Barrett's oesophagus³², 5-15% of those with long-term reflux symptoms will have Barrett's oesophagus of some length³³⁻³⁵.

1.3.4 Familial and ethnic risk.

There is little evidence to support a strong genetic component to the development of any type of oesophageal cancer^{36; 37}.

1.4 Pathogenesis and natural history of gastric cancer.

1.4.1 Environmental and dietary agents in gastric cancer.

A number of studies have also shown a role for alcohol and especially tobacco in gastric cancer development^{38;39}. These studies have suggested that the risk with tobacco relates to the chronicity of exposure rather than the amount smoked per day^{40;41}. In a meta analysis of the role of tobacco in the development of gastric cancer, Tredaniel *et al* suggested that worldwide 11% of gastric cancer may be attributable to tobacco smoking, with a relative risk of around 1.6 over non smokers⁴². Heavy alcohol intake has been shown to be correlated with a 6 times increased risk of gastric cancer⁴¹⁻⁴³.

Environmental agents have also been identified as important in both intestinal and diffuse-type gastric cancer development^{44;45}. Important among these are the *N*-nitroso compounds, which are formed in the stomach from nitrites⁴⁶. Protective agents have also been identified, such as vitamin C, which are thought to reduce the *N*-nitroso burden⁴⁷⁻⁴⁹. This protective role is supported by the observation that, as with most cancers, the risk of developing upper GI cancers is lower among those who eat more fruit and vegetables⁵⁰⁻⁵². Dietary cereal has also been shown to be protective against gastric cardia cancer (and probably oesophageal adenocarcinoma)⁵³. Other dietary risk factors include increased salt^{51;52}, starch⁵² and carbohydrate intake⁵⁴. One study

found a reduced incidence of intestinal metaplasia in a population given a diet supplemented with carotene and vitamins A and E^{55;56}.

1.4.2 Familial and ethnic risk in gastric cancer.

In comparison to oesophageal cancer a familial tendency to gastric cancer has been suggested³⁷. Zanglieri *et al* studied the familial occurrence of tumours in 154 individuals with gastric cancer. Among first-degree relatives of the registered patients there were 30 cases of gastric carcinoma versus 15 cases in a control group matched for age and sex (Mantel-Haenszel odds ratio [M-H OR] 3.14, $p < 0.01$). This excess of gastric neoplasms was observed in siblings (17 versus 7, M-H OR 4.33, $p < 0.02$) but not in parents (13 versus 8, not significant). Overall the risk to first degree relatives is thought to be in the order of 2 to 3 fold⁵⁷.

There is also variation in the incidence of gastric cancer among certain ethnic groups^{58;59}. Migrant studies show that individuals acquire a higher risk of gastric cancer at an early age⁶⁰.

1.4.3 The role of *H. pylori*- the link with gastric cancer

H. pylori has been implicated in the development of gastric cancer, distal to the cardia; the role of *H. pylori* in the development of cardia cancer is unclear.

It is thought that *H. pylori* infection occurs at an early age⁶¹ and is life-long.

Combining the results of serological studies from 11 developed countries reveals that between 15 and 54% of the population are infected with *H. pylori*⁶². The link between *H. pylori* infection and gastric cancer was recognised following several serological studies which compared stored sera, tested for IgG antibodies to *H.*

pylori, from large cohorts of patients developing gastric cancer and control subjects. Bacterial seropositivity was significantly more common in those with gastric adenocarcinoma, with an odds ratio of 2.8 –6.0, suggesting a strong association between *H. pylori* exposure and gastric malignancy^{63 64 65;66} although only for non-cardia and non-junctional tumours⁶⁵. Further research has shown that differences in gastric cancer rates are directly related to *H. pylori* prevalence⁶⁷ and studies in the West and developing countries have shown that prevalence is inversely proportional to socio-economic status^{62;68;69}.

Although *H. pylori* infection is prevalent, in up to 50% as stated earlier, less than 1% of those infected will develop cancer⁵⁹. This may, in part, be related to the pathogenicity of the infecting *H. pylori* with respect to its Cag A expression and also a feature of the site of infection within the stomach.

Parsonnet *et al* found that subjects infected with *H. pylori* who had Cag A antibodies were 5.8-fold more likely than uninfected subjects to develop gastric cancer. This was true for both intestinal and diffuse type cancers. By contrast, *H. pylori* infected subjects without Cag A antibodies were only slightly, and not significantly, at increased risk of gastric cancer⁷⁰.

H. pylori infection causes a chronic active gastritis in virtually all infected individual^{71;71-74}. Atrophic gastritis is found in around 80-90% of patients with gastric cancer and is therefore believed to be aetiologically related to the tumour development⁷⁵. Severe atrophic gastritis accompanying intestinal metaplasia caused by persistent *H. pylori* infection is closely related to the development of intestinal type gastric cancer^{76;77}. *H. pylori* may also be involved in the development of diffuse

type gastric cancer as shown by epidemiological and histological studies^{78;79}.

Chronic atrophic gastritis is nearly universal in populations at high risk of gastric cancer⁸⁰. Approximately 10% of patients with chronic atrophic gastritis will develop gastric cancer during a 15 year period^{75;81}.

H. pylori is also linked with the development of intestinal metaplasia^{82;83}. As mentioned earlier, it is known that the intestinal type of gastric cancer is strongly associated with the presence of intestinal metaplasia and frequently arises within it. However, only 10% of these patients with this precancerous condition will develop cancer⁸⁴. Despite this, Whiting *et al* advocate considering the follow up of patients with intestinal metaplasia (of any type) by annual endoscopy suggesting such a strategy may improve the detection of earlier lesions⁸⁵.

1.4.4 The progression from premalignant to malignant change.

It has been proposed by Correa that gastric cancer (intestinal-type) develops through a sequence of these histological events: normal to diffuse chronic gastritis, often with mucosal atrophy, to intestinal metaplasia, to dysplasia and finally to invasive carcinoma⁸⁶. The relationship between the three types of intestinal metaplasia and gastric cancer (intestinal type) is at present unclear. It is thought that type III (or incomplete intestinal metaplasia) has a greater chance of progression to dysplasia⁸⁷. As the progression to tumour evolves a dysplastic change occurs. The grading system of gastric dysplasia is subjective and open to significant interobserver variation therefore this system is simplified into low and high grade stratification⁸⁸. Clearly follow up of those patients with significant histology should be considered. Whiting *et al* go further and suggest a possible advantage to surveillance of those with

atrophic gastritis or intestinal metaplasia and that a multi-centre randomised controlled trial is warranted⁸⁵.

1.4.5 Early gastric cancer progression.

A study recently published by Tsukuma *et al* supports their previous work showing that the natural history of Early Gastric Cancer (EGC), certainly in the majority of cases (36/56), is for it to progress to advanced disease; with the median duration of EGC (before it became advanced) being 37 months^{89;90}. It would seem that early detection of gastric cancer and early treatment is related to improved outcome^{91;92}. Many early cancers are believed to go through a life cycle consisting of ulceration, followed by healing, then re-ulceration. The doubling time for early gastric cancer is slow^{1;93}, 1.6-9.5 years (577-3462 days) compared with 0.2-0.84 years (69-305 days) for advanced cancer⁹⁴.

1.4.6 Genetic markers associated with gastric malignancy.

Genetic factors have been suspected of playing a pivotal role in the etiology of gastric cancer but no clear inheritance pattern has emerged and environmental influences remain the focus of many current theories of pathogenesis. Current evidence implicates the non-random involvement of certain chromosomes and related oncogenes especially Ras and p53. Genes that may predispose to gastric cancer have not been clearly implicated but some studies indicate a familial aggregation of gastric cancer⁹⁵.

Gastric cancer is relatively common worldwide, mainly in its sporadic form, but familial aggregation of the disease may be seen in approximately 10% of the cases. This suggests a genetic cause for the cancer in those families that has not been

identified in most cases. Despite all efforts to determine its genetic basis, a single syndrome has been characterised, the hereditary diffuse gastric cancer (HDGC), which is specifically associated with CDH1 (E-cadherin) germline mutations in one third of the families. The other two thirds and all the gastric cancer families not fulfilling the HDGC criteria remain without molecular diagnosis⁹⁶.

1.5 Clinical impact of oesophago-gastric cancer.

1.5.1 Morbidity and mortality

The overall mortality associated with oesophago-gastric cancer in the UK is substantial, as mentioned earlier (see Table 1.1). However for early gastric cancer (EGC), defined in 1962 by the Japanese Society of Gastroenterological Endoscopy as adenocarcinoma confined to the mucosa or submucosa irrespective of lymph node involvement⁹⁷ (which may be present in 10-20%³)(figure 1.4), the 5 year survival is in excess of 90%^{98;99}. Clearly the emphasis should be to identify these patients in whom a more positive outcome can be expected.

EGC was known to have a favourable outcome as early as 1938 when Saeki reported patients who had gastric cancer confined to the submucosa had a five year survival in excess of 90%¹⁰⁰. However the reported incidence of EGC in the UK is low. When UK pathological records were examined the incidence was reported at 3.9%¹⁰¹.

Among resected cases, in Western series, the incidence of EGC was found to be around 10-20% of the resected cancers¹⁰², whereas the Japanese national records show that the percentage of early cancers among their resected cases was 40% in 1985 with a gradual increase in detection rates of EGC throughout the country over the preceding 20 years¹⁰³. The detection of EGC is increasing in many centres in

Europe, reflecting the increased use of gastroscopy^{98;104}, it is, however, still significantly less than in Japan^{103;105}. At the Cancer Institute of Tokyo the percentage of EGC overtook advanced cancers in 1990¹⁰⁶.

There are clearly reasons why the detection of EGC is higher in Japan such as the use of mass screening^{92;107}. Other issues include the endoscopic techniques used in Japan and the differences in the use of acid suppressing medication prior to endoscopy, that may delay diagnosis, which is not a factor in Japan

In the UK, once cancers have been detected, the results of treatment of oesophago-gastric cancer are also poor when compared to other parts of Europe. The 5 year survival rate for gastric cancer in Europe is 21% compared with 12% in England^{13;108}. When compared to Japan the poor outcome for gastric cancer is particularly apparent where the 5 year survival is reported as over 60% after curative resection^{109;110}, compared with the UK 5 year survival of 20-24%^{6;111} after curative resection. Overall the 5-year survival in Japan is around 24%.

1.6 Reasons for discrepancies in outcome

Clearly the discrepancy in outcome is multi-factorial and includes issues regarding:-

1.6.1 Clinical suspicion in primary care and referral for investigation

Recently, this area has been addressed for many cancers including upper GI cancers (oesophageal, gastric and pancreatic) by the Department of Health with the development of guidelines to help identify patients who should be referred for urgent assessment (Referral Guidelines for Suspected Cancer, available from

<http://www.doh.gov.uk/cancer>). These guidelines identify the following symptoms as justification for urgent referral:-

Dysphagia – food sticking on swallowing (any age).

Dyspepsia combined with one or more of the following 'alarm' symptoms:

- weight loss;
- proven anaemia;
- vomiting.

Dyspepsia in a patient aged 55 years or more with at least one of the following 'high-risk' features:

- onset of dyspepsia less than one year ago;
- continuous symptoms since onset.

Dyspepsia combined with at least one of the following known risk factors:

- family history of UGI cancer in more than two first-degree relatives;
- Barrett's oesophagus;
- pernicious anaemia;
- peptic ulcer surgery over 20 years ago;
- known dysplasia, atrophic gastritis, intestinal metaplasia.

Jaundice.

Upper abdominal mass.

Although the majority of these patients will not have “early” disease, it is hoped that these guidelines will highlight the cases in primary care that should be referred urgently, thus reducing the delays observed within primary care.

The NICE dyspepsia guideline document has also been released to help GPs manage dyspepsia including advice as to who should be referred for endoscopy. These are not designed to improve the outcome of upper GI cancer and increase the threshold for endoscopy. It is to be seen if these guidelines have a detrimental effect on the diagnosis of upper GI cancer.

As things stand a number of studies have shown that there are delays in the diagnosis of oesophago-gastric cancer in the UK^{112;113}. Delays were identified before the patient saw their general practitioner (GP) (29-80%) and also before referral was made (23%) and delay in establishing the diagnosis (20-40%). These delays were attributed to patient's ignorance, general practitioners' reluctance to refer patients and logistical problems inherent in referral. The median GP stage times were longer than median hospital stage times for both oesophageal and gastric cancer¹¹⁴. Overall there is a delay in the diagnosis of around 15% of patients with oesophago-gastric cancer, with the median delay being around 17 weeks^{113;115}. These studies also indicated that many patients, up to 50% of those with gastric cancer, were taking some form of acid-suppressing medication at the time of diagnosis but the effect of this treatment was unknown.

1.6.2 Patient factors

Clearly the patient's perception of the importance of the dyspeptic symptoms has an influence on consultation behaviour and management.

For GORD symptoms socio- economic variables do not affect consultation behaviour, but the patient's age and the burden (number and type) of associated symptoms do²³. However for dyspepsia it seems that socio-economic status does

affect consultation behaviour; the consultation rate rising from 17% in social class 1 to 29% in social class 4¹¹⁶.

It also appears that consulting behaviour amongst patients with dyspepsia is driven in part by psychological factors and, in particular, by symptom-related anxiety as well as by the frequency of dyspepsia, but not primarily by fear of serious disease^{117;118}.

Anxiety may help sustain health care utilisation once the behaviour has been established¹¹⁷.

Health promotion initiatives have been looked at to improve the awareness of dyspepsia amongst the general population in an attempt to mitigate against some of these traits. One such initiative involved sending letters to patients asking them to report new dyspeptic symptoms – this strategy increased gastroscopy uptake by 85%¹¹⁹.

1.6.3 Detection at endoscopy

In order to detect a lesion at endoscopy and perform an adequate upper GI examination, the operator must not only be sufficiently skilled technically to carry out the procedure but also sufficiently experienced to recognise an abnormality.

1.6.4 Competence

A study of gastroenterology fellows and fourth year surgical residents in the USA concluded that experience of over 100 procedures was necessary before success was achieved in 90% of attempts to pass an endoscope through the oesophagus. In this series the abnormality pick up rate was <85%¹²⁰. Gjorup *et al* showed that the ability to detect a duodenal ulcer known to be present is only 91%¹²¹. Clearly this has

implications when trying to detect the relatively subtle mucosal abnormalities of an EGC.

1.6.5 Chromoendoscopy

In Japan chromoendoscopy (also known as dye-scattering, chromoscopy, dye staining, vital staining), is widely used to improve the detection of subtle mucosal changes in both the upper and lower GI tract, such as those of EGC, early oesophageal carcinoma and those within Barrett's oesophagus, thus allowing targeted biopsy (see Figure 1.4). This technique is not routinely utilised in the UK and thus there is little published UK data regarding its efficacy in improving the endoscopic detection of suspicious lesions. What is published relates to the use of chromoendoscopy in the colon for detecting flat adenomas and dysplasia in patients with colitis^{122;123}.

The technique utilises the coloured dyes to delineate the surface under scrutiny - be that oesophageal, gastric or indeed colonic mucosa. Many different stains have been described for use, singly or in combination, prior to or during endoscopy. These dyes are classified also by the way that they work. Contrast staining (with indigo carmine, methylene blue) highlights tissue topography by entering mucosal depressions and crevices and encircling elevations. Increasingly small or minute (< 5mm) tumours are being detected and flat "gastritis-like" EGCs are being identified in Japan by the recognition at endoscopy of mucosal discolouration or unevenness¹²⁴. This method of dye staining is less susceptible to disruption by surface mucus. Absorptive or vital stains (Lugol's iodine, methylene blue, toluidine blue, cresyl violet) identify specific epithelial types or cellular constituents by preferential staining. Lugol's solution reacts with glycogen in the non-keratinised squamous mucosa and produces a dark

greenish brown colour. Abnormal mucosa, such as that resulting from inflammation, dysplasia or carcinoma has a less, if any, glycogen and so is not stained (figure 1.4). Screening tests in patients with a high risk of oesophageal carcinoma (heavy smokers and drinkers) have shown a higher diagnostic yield than "routine" endoscopy¹²⁵. In Linxian, China, an area with a high rate of oesophageal carcinoma, Dawsey *et al* showed that using Lugol's solution improved the sensitivity of detecting high-grade dysplasia or invasive carcinoma from 62 to 96%. Also, 23% of the cases of severe dysplasia and 55% of the cases of mild dysplasia were found after the use of the dye¹²⁶. Similar improvement has been demonstrated using methylene blue as a vital stain. Canto *et al* demonstrated an improvement in the detection of dysplasia within Barrett's oesophagus using methylene blue, which stains the abnormal area less vividly¹²⁷. Reactive (non-absorbed) stains (Congo red) identify cellular products, for example by the colour change of a pH indicator (see Tables 1.2, 1.3).

By utilising these dyes in combination a significant improvement can be made in the detection of gastric cancer. Tatsuta *et al* reported the endoscopic diagnosis of EGC by means of an endoscopic Congo red-methylene blue test^{128;129}. With routine examination a correct diagnosis of minute and flat cancers in the upper stomach was made in only 27.3% and 25.0% of cases, respectively. However, using the Congo red-methylene blue test the rates of correct diagnosis were raised significantly to 75.0% and 83.3%, respectively. The test has also been used in the diagnosis of co-existing EGC. Using the Congo red-methylene blue method the detection of simultaneous gastric cancers was increased from 28.3% to 88.9%¹³⁰. In this test the Congo red and methylene blue are sprayed onto the surface and after 2-5 minutes

areas of abnormality are highlighted as "bleached" areas. The mechanism of this "bleaching" is unknown.

Generally these dyes are considered non-toxic¹³¹ but care should be taken especially as the maximum doses are not known, and any excess dye should be aspirated.

Specifically methylene blue used for chromoendoscopy has virtually no side effects¹³² although it may cause discolouration of the urine and stool, about which the patient should be warned¹³³. Certain dyes must be used with caution - Lugol's solution can cause nausea and heartburn in higher concentrations and due to its iodine content should not be used in those with a known iodine allergy or in those with hyperthyroidism; toluidine blue can cause nausea, vomiting and restlessness, agranulocytosis and methaemoglobinaemia, at higher concentrations, and in the clinical setting has been surpassed by Lugol's solution¹³³. Occasionally (intravenous) indigocarmine has given rise to cardiovascular instability, probably related to stimulation of alpha receptors¹³⁴ and (intravenous) methylene blue has been associated with haemolytic anaemia in infants¹³⁵.

There is little data on the effect of chromoendoscopy on the subsequent diagnosis of *H. pylori* using a rapid urease test (Clo™) although methylene blue is thought not to affect this test or histopathological examination for the diagnosis of *H. pylori*¹³⁶.

1.6.6 Biopsy techniques

Once a lesion has been detected, endoscopy allows samples of the suspect lesions to be collected for pathological examination, which is a distinct advantage over other methods of diagnosis, in particular, radiological methods such as the barium meal.

When considering the detection of EGC, endoscopy has a clear advantage over barium studies^{101;137}.

It has been shown that the accuracy of sampling, by biopsy or fine needle aspiration *and* brushing, for the diagnosis of oesophageal cancer can approach 100%¹³⁸.

Endoscopic diagnosis of gastric cancer appears to offer similar levels of accuracy, around 98%¹³⁹. It is known, however, that several biopsies are often needed to confirm the diagnosis of cancer. The more biopsies that are taken increases the diagnostic yield, such that 100% positive yield was achieved with 6 oesophageal biopsies¹⁴⁰. Graham *et al* showed that 1 biopsy was sufficient to make the diagnosis in 70% of gastric cancers and 93% of oesophageal cancers but 7 biopsies was the optimum to ensure diagnoses were not missed¹⁴¹.

1.6.7 Antisecretory drug therapy

A further factor, which may influence the detection of cancers at endoscopy, is the use of antisecretory drug therapy.

H₂ receptor antagonists (H₂RA) and proton pump inhibitors (PPI) account for approximately 15% of primary care prescribing costs in the UK and in the period 1991-95 the number of new prescriptions rose by 174.5%. It would appear that there was also an increase in prescribing for unlicensed indications such as non-ulcer dyspepsia and non-specific abdominal pain^{142;143}.

There are two issues relevant to antisecretory drug use and the delay in the diagnosis of cancer. Firstly, rapid control of dyspepsia may lead patients and/or their GP to underestimate the importance or significance of the symptoms so referral for

investigation is delayed. Secondly, these treatments may result in lesions healing such that they are missed completely or mis-diagnosed as benign at endoscopy.

Antisecretory drugs have certainly been shown to reduce the occurrence of mucosal inflammation at endoscopy. The odds ratio of not having mucosal inflammation when ulcer healing drugs were taken within 2 weeks of gastroscopy was 3.1 (95% CI 1.3-7.1 $p < 0.01$) and the odds ratio when these drugs were taken 2-4 weeks before was 2.0 (95% CI 1.0-3.9 $p < 0.04$). Clearly the use of these medications reduces diagnostic yield¹⁴⁴. Antisecretory medication has also been implicated in the mis-diagnosis of lesions at endoscopy. In a retrospective study looking at the effect of antisecretory medication on the diagnosis, and earlier mis-diagnosis, of oesophago-gastric cancer, 133 patients were identified over a 3-year period. Only one of the 54 patients (1.9%) on no treatment, or antacid alone, was erroneously diagnosed with benign disease at an earlier endoscopy whereas 22 of 62 (35.5%) of those treated were mis-diagnosed¹¹⁵. Thus acid-suppressing medication is implicated in the mis-diagnosis of the malignancy at the first endoscopy: the diagnosis may have been masked in some patients whose lesions appeared benign (particularly ulcers, with confirmatory biopsy results), and who continued on acid suppression after the endoscopy. Only when the malignancy became manifest were some patients discovered to have had an earlier endoscopy which demonstrated minor abnormalities or normal results. There are other reports of H₂RA and PPI "masking" gastric cancers at endoscopy^{145;146}. Presumably these powerful acid-suppressing medication allowed healing to occur with re-epithelialisation providing a covering of normal mucosa over the underlying malignancy, or there is sufficient healing to make a lesion appear less "suspicious" to the endoscopist (see figure 1.5). Associated

with this is a resulting delay in the diagnosis of patients with oesophago-gastric cancer if they have been taking treatment^{115;147}. Clearly associated with the healing of the lesions may well be a resolution or at least a modification of the symptom complex as a result of treatment. Certainly there are reports of such, with cimetidine resulting in healing of ulcers and resolution of symptoms¹⁴⁵ and similar with PPIs apparently causing resolution of the symptoms associated with malignancy¹⁴⁷.

1.6.8 Availability of and access to endoscopy

Current estimates suggest that the provision of open access in Britain has risen from about 50% in 1990 to around 75% in 1994, with two thirds of those not offering open access then hoping to do so in the near future^{148;149}. GPs appear to use open-access endoscopy services effectively and this can avoid a large number of unnecessary outpatient clinic visits¹⁵⁰⁻¹⁵². A Danish randomised study which compared prompt endoscopy for patients with dyspepsia (average age 44 years) with attempted symptom control with an H₂ receptor antagonist found that prompt endoscopy was associated with reduced prescribing, further consultation and days lost from work in patients with dyspepsia¹⁵³. The proportion of patients with malignancies is generally as high among patients referred by GPs as among patients referred by specialists. Overall 1–2% of patients referred for endoscopy were likely to have cancer^{151;154;155}. Although several studies suggest that rapid access to endoscopy could be associated with improved survival, there is as yet no evidence that demonstrates this unequivocally. Prompt access to endoscopy tends to yield a higher proportion of early (treatable) cancers, but there has been no comparative study demonstrating that this affects long-term survival rates^{151;154;156;157}.

Although diagnostic endoscopy is not risk-free, most adverse effects are mild and transient, such as sore throat and a feeling of bloatedness. A 36 hospital audit demonstrated that the morbidity rate associated with gastroscopy is around 1 in 200, the perforation rate is around 1 in 2,000, and the overall death-rate around 1 in 10,000¹⁵⁸.

1.6.9 Treatment

Essential to successful treatment of oesophago-gastric cancer is accurate staging. This is multi-modality but involves at least spiral CT scanning and often endoscopic ultrasound; in selected cases ultrasound, MRI or laparoscopy may be essential to stage accurately. Following staging all cases should be discussed in a multi-disciplinary meeting to formulate the best management plan which is often multi-modal. In depth discussion of the treatment of oesophago-gastric cancer is beyond the scope of this thesis.

Suffice to say, it would appear that the crucial factor, if the results of treatment in Britain and the West are to improve, is earlier diagnosis.

Improving endoscopic practice is one way to improve the detection of early disease but other areas that contribute to delayed or late diagnosis also need to be identified and addressed.

Aims

This thesis aims to clarify and resolve these issues of late diagnosis of oesophago-gastric adenocarcinoma in the UK. It has the following parts: -

- To quantify the delays in diagnosis of oesophago-gastric adenocarcinoma and evaluate the effect of antisecretory drug therapy on the delays and outcome
- To identify the effect of strategies to facilitate referral.
- To identify how many cancers are missed at endoscopy.
- To investigate the use of chromoendoscopy.
- To investigate the endoscopist's evaluation of histopathology from the appearance of ulcer disease.

Each of these topics is dealt with in a separate chapter. Where necessary ethics committee approval was obtained.

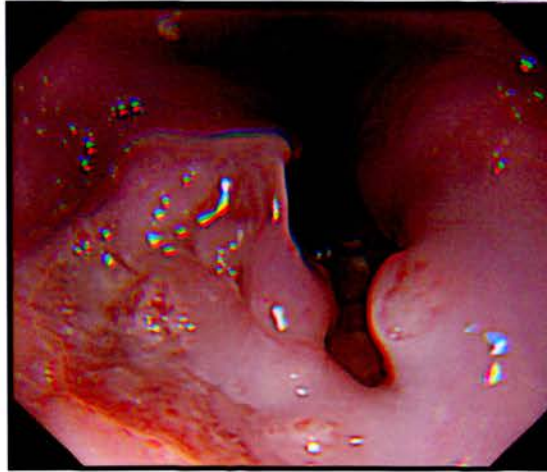


Figure 1.1 Oesophageal adenocarcinoma

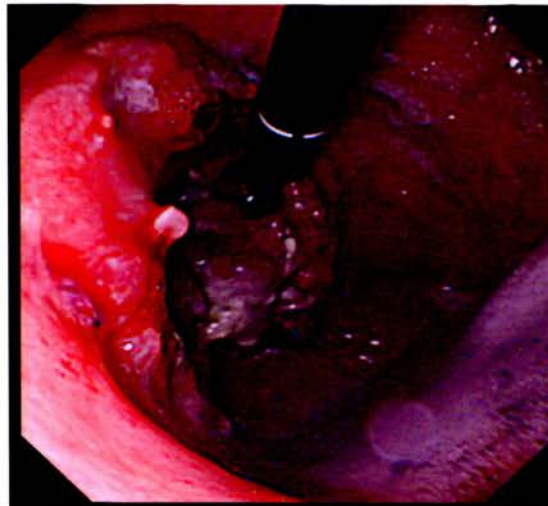


Figure 1.2 (a) Gastric cardia adenocarcinoma



Figure 1.2 (b) Distal gastric adenocarcinoma

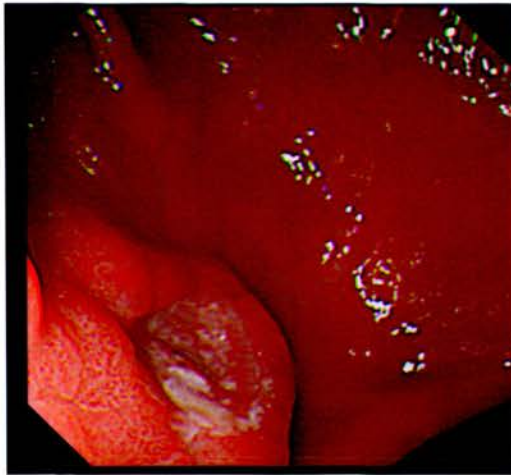


Figure 1.3 (a) Ulcerated gastric adenocarcinoma

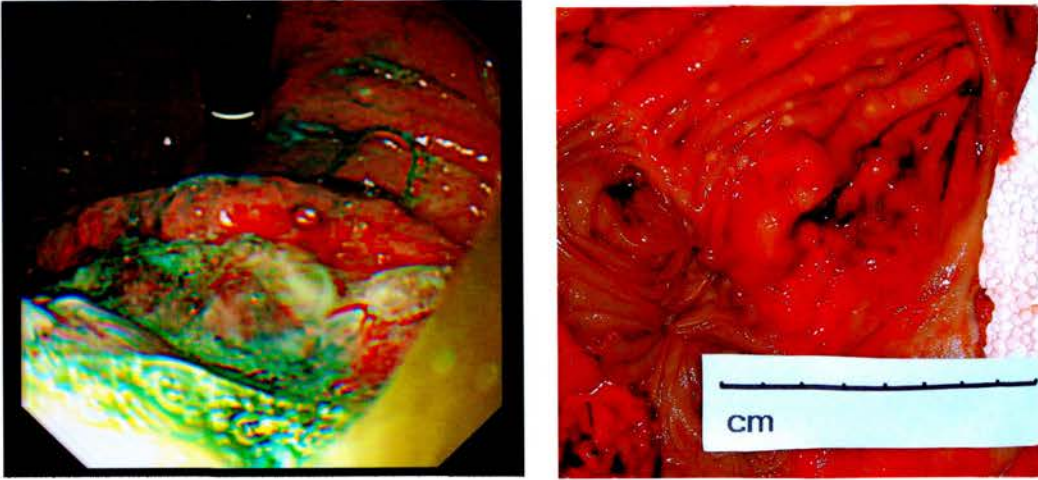


Figure 1.3 (b) Ulcerated gastric adenocarcinoma showing endoscopic view and resected specimen.

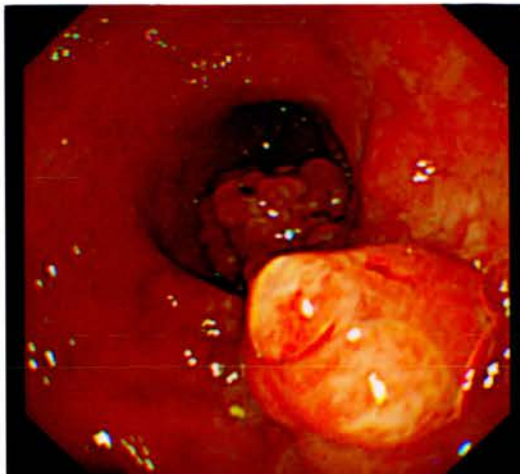


Figure 1.3 (c) "Mass-like" gastric adenocarcinoma

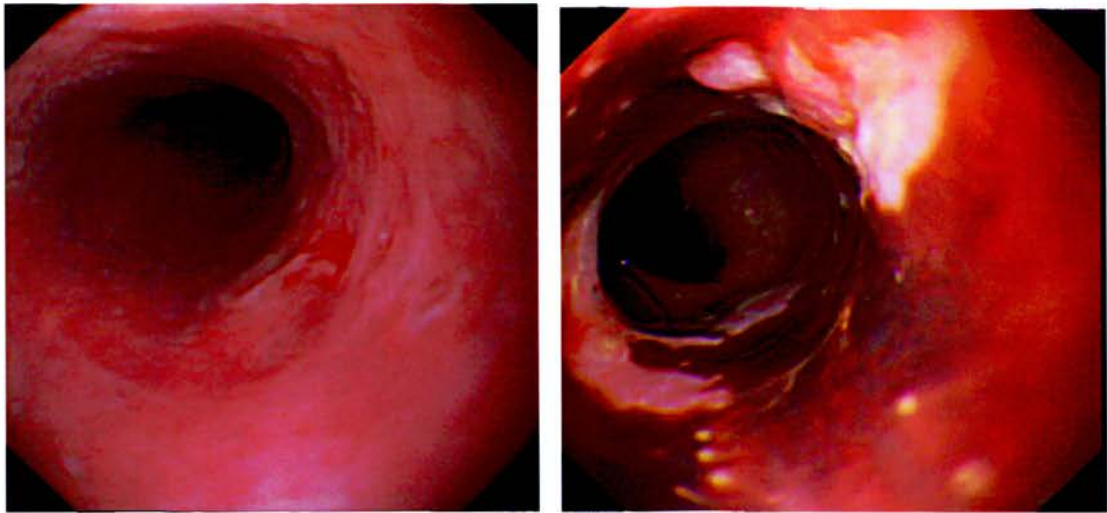


Figure 1.4 (a). Early oesophageal cancer (a) without dye (b) with iodine.

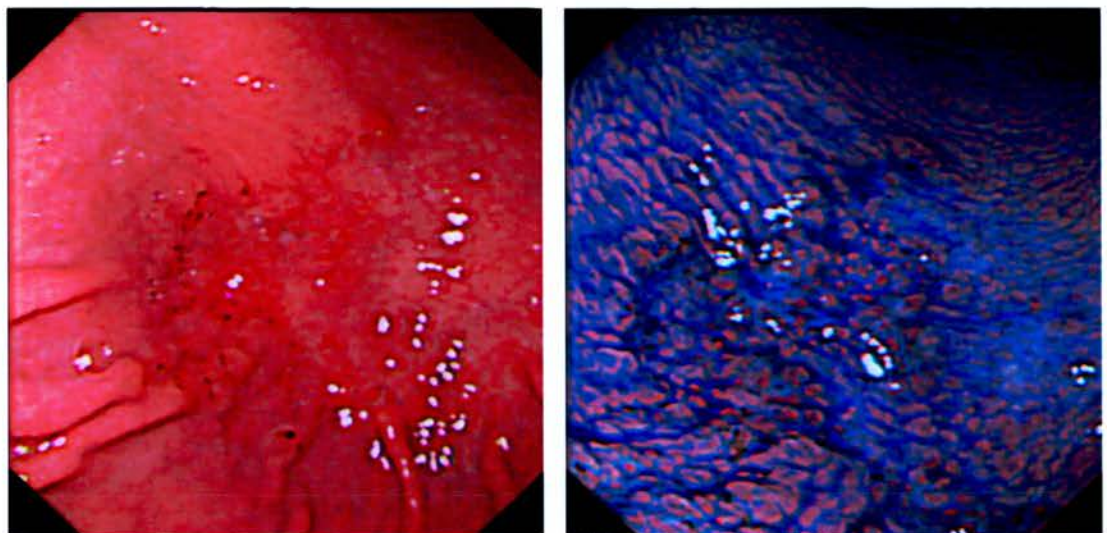


Figure 1.4 (b). Early gastric cancer (a) before dye spray (b) after dye spray.

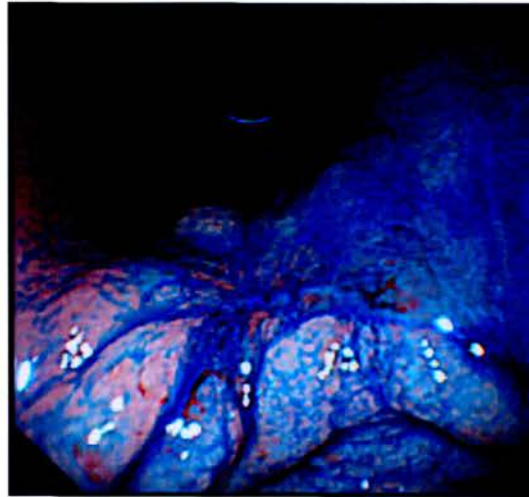
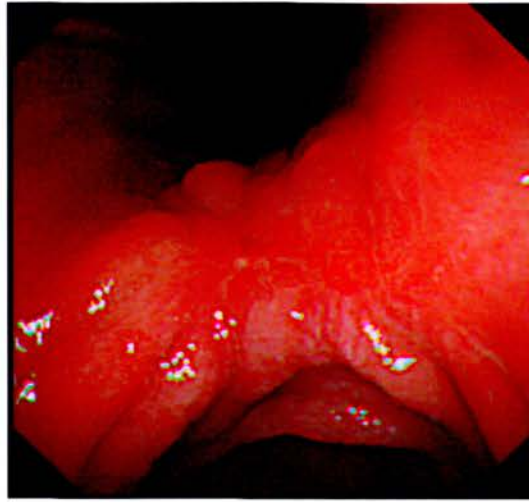


Figure 1.5. Healed gastric adenocarcinoma (a) without dye (b) with methylene blue.

Cancer site	Incidence: rate per 100,000		One-year survival rate, England	Five-year survival rate, England	Deaths, England & Wales, 1997	Death rate per 100,000, England and Wales	
	Men	Women				Men	Women
Oesophagus	14.0	9.2	27%	9%	5,855	13.6	8.4
Stomach	24.3	13.8	28%	12%	6,613	15.1	9.5

Table 1.1. Oesophageal and gastric cancer: incidence, survival and death rates^{1;13;159}.

Contrast staining	Emphasises depressions and protuberances of uneven mucosal surfaces by making use of dye solution pooling. Useful for morphological diagnosis. Dyes: indigo carmine, Evan's blue, brilliant blue, methylene blue
Vital staining	For observing stain in biological tissues caused by infiltration, absorption and direct staining by dye solution. Dyes: methylene blue, toluidine blue, azure A
Reaction staining	Utilises the specific reaction of the dye solution under specific circumstances. Dyes: Congo red, crystal violet, Lugol's iodine, phenol red
Fluorescent staining	Utilises fluorescence of orally or intravenously prescribed dye solution. Dyes: fluorescein, acridine orange
Intravascular staining	Use of intravascular dye to delineate vasculature Dyes: indigocyanine green
Combined method	Combination of above methods.

Table 1.2. Classification of endoscopic dye methods (Japanese Gastroenterological Endoscopy Society)

Method	Dye	Colour	Concentration
Contrast staining	Indigo carmine	Blue	0.1-0.5%
	Evan's blue	Greenish blue	0.1-0.2%
	Brilliant blue	Blue	0.5-1.0%
Vital staining	Methylene blue	Blue	0.2-1.0%
	Toluidine blue	Purplish blue	0.2-1.0%
	Azure A	Purplish blue	0.2
Reaction staining	Congo red	pH 3 purplish blue pH5 red	0.3-0.5%
	Crystal violet	pH dependent	0.05%
	Lugol's iodine	Reddish brown	1-3%
	Phenol red	From yellow to red	0.5% (use with urea)

Table 1.3. Concentration of dye solutions. ^{133;160;161}

Chapter 2 Delays in the diagnosis of oesophago-gastric cancer

2.1 Introduction

As stated earlier, for more than half a century the overall incidence and mortality rates of gastric cancer have been slowly declining⁴ although adenocarcinoma of the gastric cardia is becoming more common⁵⁻⁷. The incidence of adenocarcinoma of the oesophagus is also increasing; this has been attributed to the increasing prevalence of gastro-oesophageal reflux⁹. Adenocarcinoma of the oesophagus is now the commonest form of oesophageal cancer⁹⁻¹¹.

In the United Kingdom there are often delays in the diagnosis of oesophago-gastric cancer^{112;113} for reasons that are unclear but that are likely to be multifactorial.

Patients may delay seeing a doctor and referral to hospital may be deferred by a previous history of dyspepsia¹⁶² or absence of alarm symptoms¹⁶³. Many other factors are likely to influence the process leading to delays in obtaining endoscopy and thus establishing a diagnosis but where possible these should be addressed through health promotion and GP education. As mentioned one health promotion initiative looked at improving the awareness of dyspepsia amongst the general population by sending letters to patients asking them to report new dyspeptic symptoms – this strategy increased gastroscopy uptake by 85%¹¹⁹. Quality improvement initiatives in health services rely upon the effective introduction of clinical practice guidelines. However, even well constructed guidelines have little effect unless supported by dissemination and implementation strategies. One study looking at the effectiveness of supporting guidelines with seminars suggested that

educational outreach may be more effective than passive guideline dissemination in changing clinical behaviour¹⁶⁴.

In addition, and more specifically, the empirical use of antisecretory drugs prior to diagnosis, particularly proton pump inhibitors (PPIs) can contribute to the delay through the modification of symptoms and the potential healing of early malignant ulcers¹⁴⁷. Also, dyspepsia management guidelines increasingly advocate empirical therapy for *H. pylori* negative patients under 55 years without alarm symptoms¹⁶³; thus people who have previously received antisecretory drug therapy are likely to receive further prescriptions when symptoms recur.

Despite this trend towards empirical therapy there is no data available with regards the effect antisecretory therapy prescribed before investigation has on patient's outcome.

2.2 Aims

The aim of this study was to identify the delays in diagnosis of oesophago-gastric adenocarcinoma by focusing on the patterns of presentation. The effect of prior antisecretory drug therapy on the time to a definitive diagnosis and the effect on symptoms, tumour stage and outcome were also studied.

2.3 Patients and Methods

The study design was a survey of the records of all patients with an established diagnosis of primary oesophageal or gastric adenocarcinoma over the ten-year period April 1991-April 2001, in a fixed population base.

The study was based in the South Tees health district of Teesside, a mixed industrial and rural area with a catchment population of approximately 300,000. Due to the centralisation of gastroenterology services it is estimated that over 95% of all patients referred with gastrointestinal problems are seen at one hospital, the James Cook University Hospital (formerly South Cleveland). This enabled central access to patient records, and endoscopy and pathology reports. Both primary and secondary care records were accessed.

To meet the inclusion criteria patients had to have a definitive cancer diagnosis established within the population area, for the first time, in the ten years to April 2001.

Patients were initially identified from the computerised pathology database. The list obtained was cross-referenced with the regional cancer registry (Northern and Yorkshire Cancer Registry and Information Service) and the hospital's own cancer records to ensure completeness and accuracy of the patient cohort. The identified patients' primary care records were reviewed at their general practices or, where the patients were dead, retrieved from the central registry of Tees and North Yorkshire Health Authorities. These were reviewed to record demographic characteristics and to detail the diagnostic pathway leading to the definitive diagnosis and eventual outcomes. These details included the timings of the onset of symptoms, first GP

consultation with new onset symptoms and the timings of referral and investigations. Details about the prescribing of antisecretory drugs prior to investigation were also recorded and the hospital records reviewed for endoscopy findings, including the endoscopist, number of biopsies taken, tumour stage at diagnosis and long-term outcome.

2.3.1 Statistics

Data handling and analysis was performed using the Epi Info™ epidemiological database and statistical analysis package (US Department of Health and Human Services Centre for Disease Control, Atlanta, Georgia). The accuracy of data entry was optimised by using double data entry and cross checking. Data were analysed using parametric methods for normally distributed continuous data (*t* test, ANOVA) and non-parametric methods (χ^2 , Kruskal Wallis) for categorical data and non-normally distributed continuous data. Results were considered to be statistically significant with p values <0.05 (95% confidence limits).

2.4 Results

A total of 747 patients with adenocarcinoma (ACA) (squamous carcinomas excluded) were identified of whom 685 (92%) were included in the study. Medical records for 15 patients (2%) were missing and 47 patients (6%) were excluded because they were found not to have had a primary gastric or oesophageal adenocarcinoma or had the diagnosis made prior to the study period. Two patients had all investigations and the diagnosis made outside of the population area and four had incidental post mortem findings of oesophago-gastric ACA (not the cause of death).

Table 2.1 and Figure 2.1 detail patient numbers.

Table 2.1. Demographics for all upper GI adenocarcinomas with oesophageal and gastric subsets.

Figure 2.2. Details of study cohort.

Figure 2.3 Age and sex distribution at diagnosis.

2.4.1 Referral patterns

The mean time from first symptoms, as recorded in the notes from the patients' history, to diagnosis, was 30 weeks (range 1-428) (table 2.1). Compared to patients with gastric adenocarcinoma those with oesophageal adenocarcinoma took longer to present to their GP (mean 16.4 weeks v 12.2) ($p=0.003$) and longer to be seen in secondary care once referred ($p=0.03$). All the other time periods (time to be

referred, time to definitive diagnosis) showed no statistically significant differences. The mean and median time durations during which the patient remained under primary care management only was double the hospital phase times, for both oesophageal and gastric cancer (22.0 (8) and 19.4 (6) v 10.0 (3) and 9.4 (3) weeks respectively) ($p < 0.0001$). There were no significant differences between the time periods the patient remained in primary care alone or in hospital management for either oesophageal or gastric cancer.

Details are shown in table 2.1.

2.4.2 Symptoms

Figure 2.3 shows the symptoms as recorded in the GP and hospital notes at the various stages in the diagnostic process. Initially only 50% of patients had alarm symptoms (i.e. anaemia/dysphagia/weight loss/vomiting). By the time of referral this had risen to 71% and at diagnosis to 78%.

2.4.3 Empirical Treatment

Overall, of the 685 patients with adenocarcinoma 47.7% had antiseecretory drugs treatment between the onset of symptoms and diagnosis. In 66.8% this was initiated at the first GP visit. Patients with oesophageal adenocarcinoma were more likely than patients with gastric adenocarcinoma to be taking antiseecretory drugs prior to their first GP consultation with new onset symptoms (13.6% v 6.2%) ($p = 0.002$). Patients were predominantly prescribed PPIs although 33.9% were on a H₂RA beforehand. There was no significant difference between males and females in relation to rates of antiseecretory drugs prescribing at any stage. Details are shown in Table 2.1.

2.4.3.1 Antisecretory drug prescribing and time to diagnosis of cancer

An increase in the time to diagnosis was associated with the use of antisecretory drugs at all stages (Table 2.1). The time interval before referral from primary care to hospital was significantly longer in those prescribed antisecretory drugs compared with those who were not prescribed these. This was irrespective of the presenting symptoms except for those presenting with haematemesis/ melaena. For those treated with antisecretory drugs prior to gastroscopy the mean time from their first GP visit with new onset symptoms to diagnosis was increased by 17.6 weeks ($p<0.001$).

2.4.3.2 Effect of AST on symptoms

The number of patients with alarm symptoms at each stage of the diagnostic pathway, in relation to whether or not they were prescribed antisecretory drugs is shown in Figure 2.3. In total 339 (49.5%) of patients had benign symptoms at their first GP consultation; of these 175 (51.6%) were given antisecretory drugs. For patients with alarm symptoms 20.2% were prescribed antisecretory drugs. Thus patients with more benign sounding symptoms were more likely to have been prescribed antisecretory drugs ($p<0.0001$).

Patients with benign symptoms prescribed antisecretory drugs ($n=175$) were referred later than patients with benign symptoms not given antisecretory drugs ($n=164$) (mean 16.4 v 5.54 weeks, median 8 v 1 weeks, $p<0.0001$). Similarly, patients with alarm symptoms were referred later if antisecretory drugs had been prescribed (5.6 v 1.8 weeks, median 1 v 0, $p=0.0008$). Thus the use of antisecretory drugs was

associated with a longer time to referral. During this period more patients developed alarm symptoms. However, 98.6% of patients with alarm symptoms at the first GP consultation and who were prescribed antiseecretory drugs still had alarm symptoms by the time of hospital consultation. This suggests that the use of antiseecretory drugs did not change alarm symptoms to benign sounding symptoms.

2.4.3.3 Effect of antiseecretory drug therapy on tumour stage at diagnosis

Staging data using the TNM classification ¹⁶⁵ (appendix II) was available for 477 patients (70% of total). Of these 287 underwent surgery. Treatment with antiseecretory drugs was not associated with the tumour stage at diagnosis for either oesophageal or gastric adenocarcinoma ($p=0.49$ and $p=0.31$ respectively) as shown in Table 2.1.

2.4.3.4 Effect of antiseecretory drug therapy on survival

The effects of empirical antiseecretory drugs on survival (Kaplan-Meier) following diagnosis are shown for both oesophageal adenocarcinoma and gastric adenocarcinoma in Figure 2.3 (a)-(d). No significant differences were observed between the two groups except for gastric adenocarcinoma where patients with stage IIIa disease had a worse prognosis with prior empirical antiseecretory drugs.

2.5 Discussion

PPIs are now the drugs of choice for treating symptomatic reflux and their efficacy means that increased prescribing of these powerful acid suppressants is a modern phenomenon seen in many western countries^{143;166}. Concern about these drugs masking cancer or delaying diagnosis^{115;147;162;162} is therefore important if the net effect is to worsen prognosis.

Symptoms are the major influence on the timing and presentation of patients to their General Practitioner and subsequent referral for investigation. The vast majority of dyspeptic patients in the 'at risk' age group will have benign disease, even if some of their symptoms are 'worrying', as symptoms are a poor predictor of pathology^{167;168}. Some patients are also very elderly and would potentially not be suitable for surgery even if diagnosed early. However the mean age was 70.3 years at diagnosis and we can find no evidence that age per se delayed referral.

A limitation of this study is its retrospective nature and that only those with cancer were studied rather than the dyspeptic population as a whole. However, the fact that patients with oesophageal adenocarcinoma took longer to present to their GP suggested that they were not concerned by their symptoms until relatively later. These patients were also more likely to have been on antisecretory drugs previously, compared to those with gastric adenocarcinoma.

This study confirms previous work showing that patients given antisecretory drugs endure a delay to a definitive morphological diagnosis. Patients given antisecretory

drugs on their first visit to the GP had a longer time to diagnosis at all stages of the process but the longest delay occurred because patients previously prescribed antisecretory drugs did not seek a further medical opinion and when they did, the GP was likely to restart the antisecretory drugs rather than refer for investigation. Patients with worrying symptoms received antisecretory drugs less frequently and were referred quickly compared to those with more dyspeptic symptoms. In many cases the delay was many months during which time it might be assumed that the tumour would progress significantly and worsen both the stage of the disease at diagnosis and long-term survival. The results indicate this did not happen. Those patients with early stage disease (early gastric cancer or stage I disease) had the longest period on treatment but were still 'early' when eventually diagnosed.

The reasons for this are probably explained by the natural history of upper gastrointestinal adenocarcinoma. In the oesophagus the disease spreads relatively early⁹³ and even those patients referred quickly are likely to have disease that has infiltrated the lymphatics, making curative resection less likely. Thus delays resulting from prior antisecretory drugs are unlikely to affect prognosis. In relation to stomach cancer, patients with early disease were more likely to have benign symptoms and more likely to have been prescribed antisecretory drugs. Tumour-doubling time is long in early stage disease^{93;94;169} making a delay less critical in terms of tumour stage at diagnosis. Patients with alarm symptoms have more advanced disease⁶ associated with a rapid tumour doubling time⁹⁴. In this study patients with alarm symptoms were less likely to receive antisecretory drugs and were referred more quickly. Thus those patients presenting with mucosal disease and benign sounding

symptoms in primary care still had mucosal disease when diagnosed at gastroscopy despite many months' delay.

In conclusion, this study confirmed that empirical antisecretory drug therapy was associated with a significant delay in arriving at the definitive diagnosis of cancer but revealed the new information that this did not affect the tumour stage at diagnosis. Also the long-term outcomes were identical in those who had been prescribed antisecretory drugs prior to diagnosis and those who had not. Withholding antisecretory drugs prior to investigation may accelerate a definitive diagnosis but is not likely to affect the eventual outcome. We cannot recommend routinely treating 'at risk' patients with antisecretory drugs prior to gastroscopy, as patients will still perceive this as a delay. However this data does support the concept that such a delay has little significance, as outcome is poor in both groups.

	All	Oesophageal	Gastric
Total number	685	198	487
Male	451	143	308
Female	234	55	179
Mean age at diagnosis (range) in years	70.3 (28-94)	69.4 (41-94)	70.7 (28-92)
% under 45 years at diagnosis	2.6 (n=18)	1.5 (n=3)	3.1 (n=15)
% under 55 years at diagnosis	8.9 (n=61)	10.1 (n=20)	8.4 (n=41)
Mean time to diagnosis in weeks (median, range)	29.7 (14, 1-428)	32.0 (15, 1-428)	28.8 (13, 1-415)
Mean primary care stage time in weeks (median, range)	20.2 (7, 1-423)	22.0 (8, 1-423)	19.4 (6, 1-408)
Mean hospital stage time in weeks (median, range)	9.6 (3, 1-165)	10.0 (3, 1-164)	9.4 (3, 1-165)
% patients prescribed AST at any time	47.7	48.5	47.4
% PPI	57.8	65.6	54.5
% H₂RA	42.2	34.4	45.5
% on PPI at diagnosis previously treated with H₂RA	33.9	34.9	33.3
Mean time to diagnosis in weeks (median, range) + AST	44.3 (21, 1-428)	48.0 (27, 2-428)	42.7 (21, 1-415)
- AST	16.5 (10, 1-294)	17.0 (12, 1-294)	16.3 (9, 1-260)
	p <0.0001	p <0.0001	p <0.0001

Mean stage times in weeks (median)	+AST, -AST		+AST, -AST		+AST, -AST	
1 st symptom to 1 st GP visit	13.4(4)	58.6(6), 9.3(4) p<0.0001	16.4(4)	59.4(4), 9.6(4) p=0.04	12.1(3)	57.8(12), 9.1(2) p<0.0001
1 st GP visit to referral	6.8(1)	13.3(5), 3.2(0) p<0.0001	5.6(1)	9.7(3), 3.2(0) p<0.0001	7.3 (1)	14.9 (6), 3.2 (0) p<0.0001
Referral to 1 st hospital contact	2.7(2)	3.0(2), 2.5(1) p=0.003	2.8(2)	2.9(2), 2.8(2) p=0.6	2.6 (2)	3.1 (2), 2.3 (1) p=0.002
1 st hospital contact to diagnosis	6.9(0)	12.7(1), 2.5(0) p<0.0001	7.2(0)	14.2 (½), 1.5(0) p=0.0005	6.8 (0)	12.1 (1), 2.9 (0) p<0.0001
TMN stage at diagnosis			+AST, -AST		+AST, -AST	
0 (Tis)	-		2	1, 1	3	3, 0
I	-		10	7, 3	45	20, 25
II	-		19	11, 8	43	23, 20
III	-		37	15, 22	107	51, 56
IV	-		39	19, 20	172	76, 96
Stage unknown	-		91	42, 49	117	58, 59

Table 2.1. Demographics for all upper GI adenocarcinomas with oesophageal and gastric subsets.

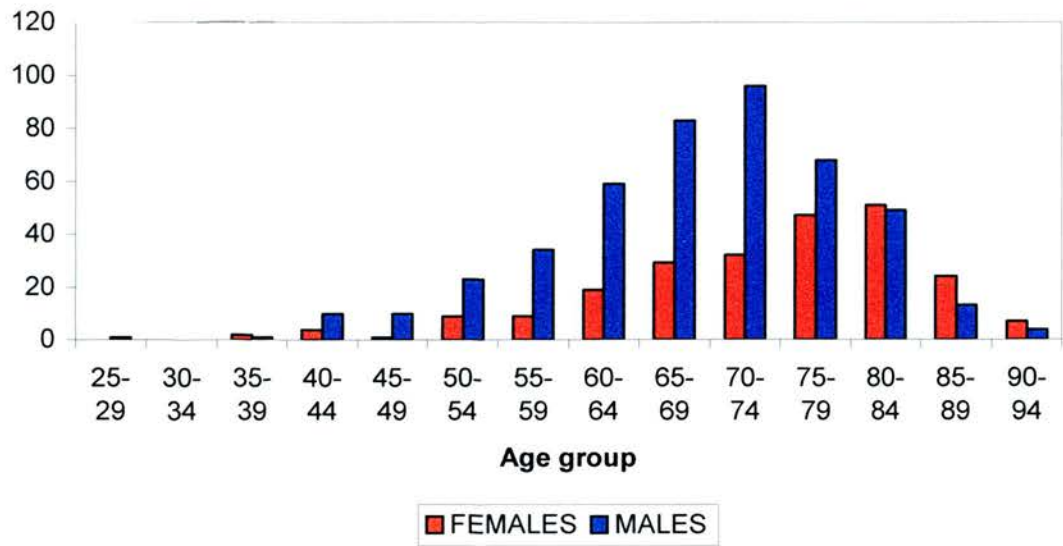


Figure 2.1 Age distribution at diagnosis.

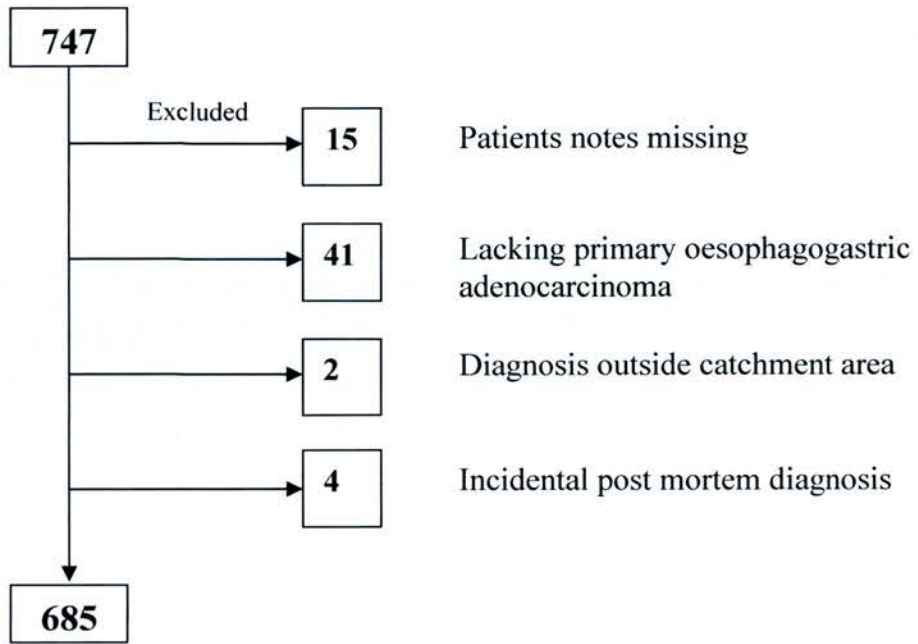
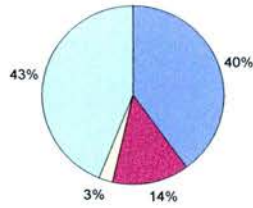
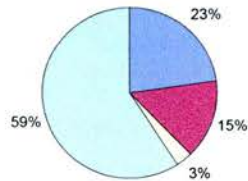


Figure 2.2. Details of study cohort.

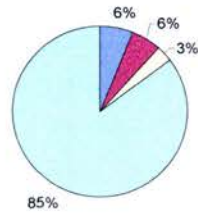
FIRST SYMPTOMS - ADENOCARCINOMA OESOPHAGUS



SYMPTOMS AT 1ST GP CONSULT - ADENOCARCINOMA OESOPHAGUS



SYMPTOMS AT REFERRAL - ADENOCARCINOMA OESOPHAGUS



SYMPTOMS AT DIAGNOSIS - ADENOCARCINOMA OESOPHAGUS

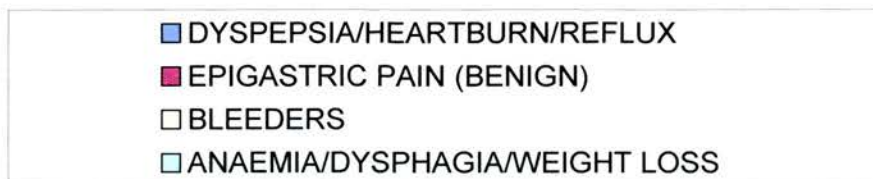
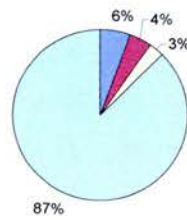
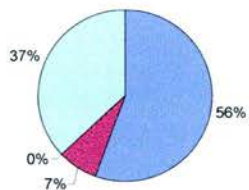
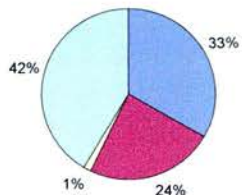


Figure 2.3 Symptoms as recorded in the GP notes at the various stages of the diagnostic pathway with and without the patient taking AST.

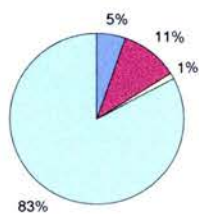
FIRST SYMPTOMS - ADENOCARCINOMA OESOPHAGUS ON AST



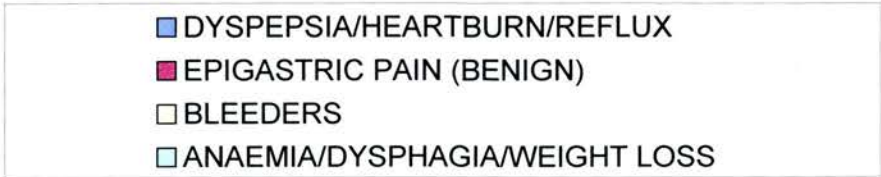
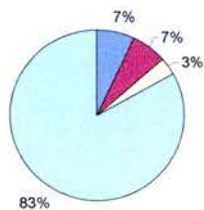
SYMPTOMS AT 1ST GP CONSULT - ADENOCARCINOMA OESOPHAGUS ON AST



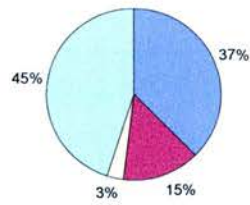
SYMPTOMS AT REFERRAL - ADENOCARCINOMA OESOPHAGUS ON AST



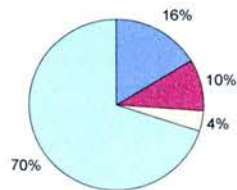
SYMPTOMS AT DIAGNOSIS - ADENOCARCINOMA OESOPHAGUS ON AST



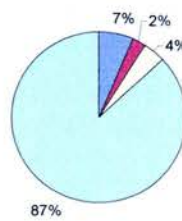
**FIRST SYMPTOMS - ADENOCARCINOMA OESOPHAGUS
NOT ON AST**



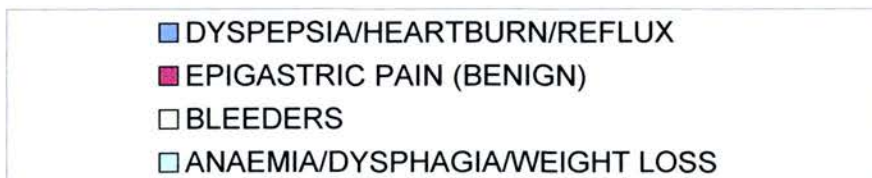
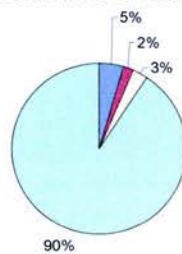
**SYMPTOMS AT 1ST GP CONSULT - ADENOCARCINOMA
OESOPHAGUS NOT ON AST**



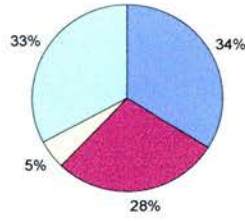
**SYMPTOMS AT REFERRAL - ADENOCARCINOMA
OESOPHAGUS NOT ON AST**



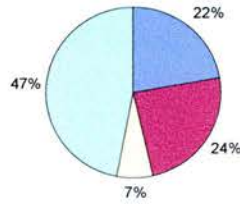
**SYMPTOMS AT DIAGNOSIS - ADENOCARCINOMA
OESOPHAGUS NOT ON AST**



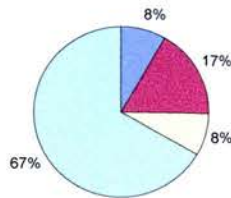
FIRST SYMPTOMS - ADENOCARCINOMA STOMACH



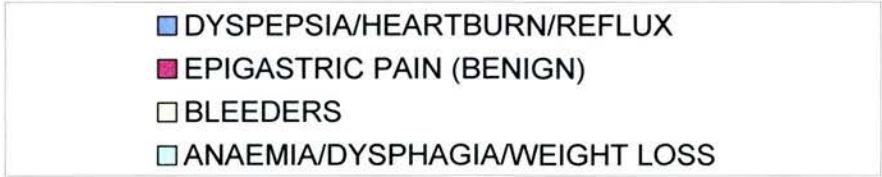
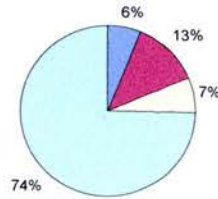
SYMPTOMS AT 1ST GP CONSULT - ADENOCARCINOMA STOMACH



SYMPTOMS AT REFERRAL - ADENOCARCINOMA STOMACH



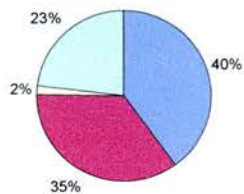
SYMPTOMS AT DIAGNOSIS - ADENOCARCINOMA STOMACH



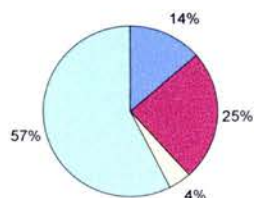
FIRST SYMPTOMS - ADENOCARCINOMA STOMACH ON AST



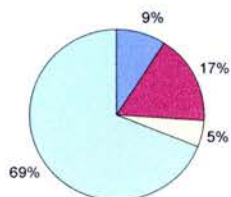
SYMPTOMS AT 1ST GP CONSULT - ADENOCARCINOMA STOMACH ON AST



SYMPTOMS AT REFERRAL - ADENOCARCINOMA STOMACH ON AST

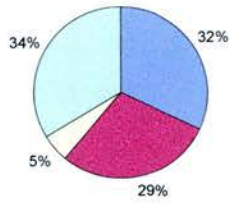


SYMPTOMS AT DIAGNOSIS - ADENOCARCINOMA STOMACH ON AST

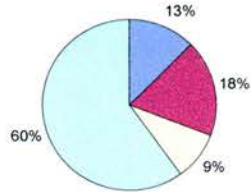


- DYSPEPSIA/HEARTBURN/REFLUX
- EPIGASTRIC PAIN (BENIGN)
- BLEEDERS
- ANAEMIA/DYSPHAGIA/WEIGHT LOSS

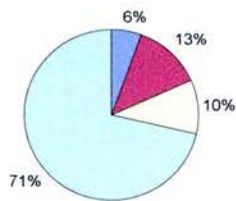
FIRST SYMPTOMS - ADENOCARCINOMA STOMACH NOT ON AST



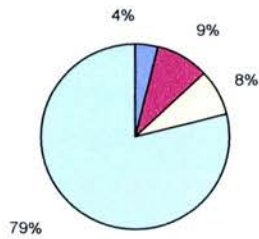
SYMPTOMS AT 1ST GP CONSULT - ADENOCARCINOMA STOMACH NOT ON AST



SYMPTOMS AT REFERRAL - ADENOCARCINOMA STOMACH NOT ON AST



SYMPTOMS AT DIAGNOSIS - ADENOCARCINOMA STOMACH NOT ON AST



- DYSPEPSIA/HEARTBURN/REFLUX
- EPIGASTRIC PAIN (BENIGN)
- BLEEDERS
- ANAEMIA/DYSPHAGIA/WEIGHT LOSS

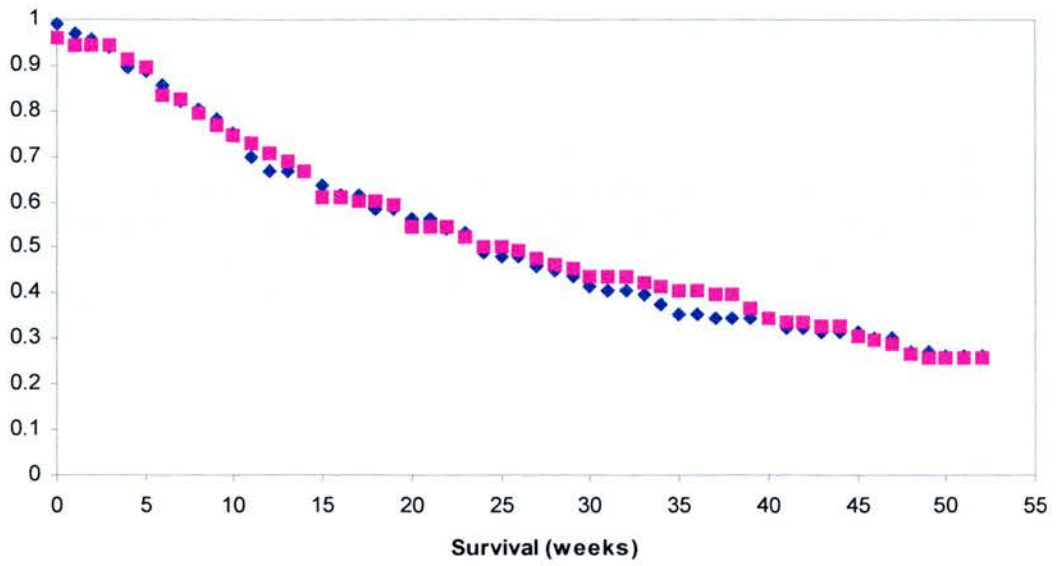


Figure 2.4 Kaplan Meier Survival curve for oesophageal carcinoma and the effect of antiseccretory drug therapy (AST)

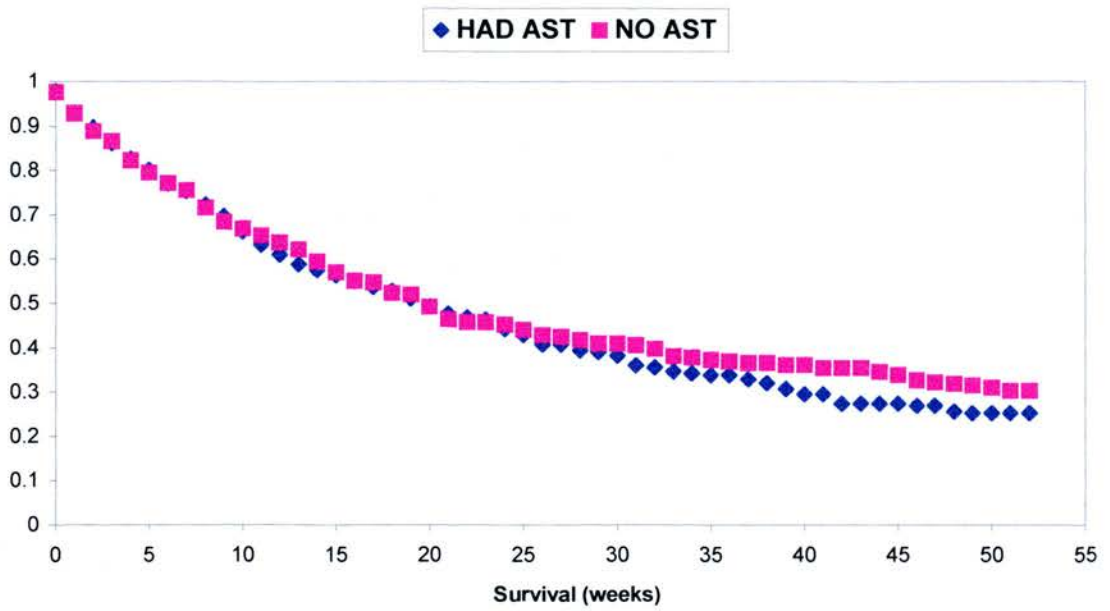


Figure 2.5 Kaplan Meier Survival curve for gastric carcinoma and the effect of antiseccretory drug therapy

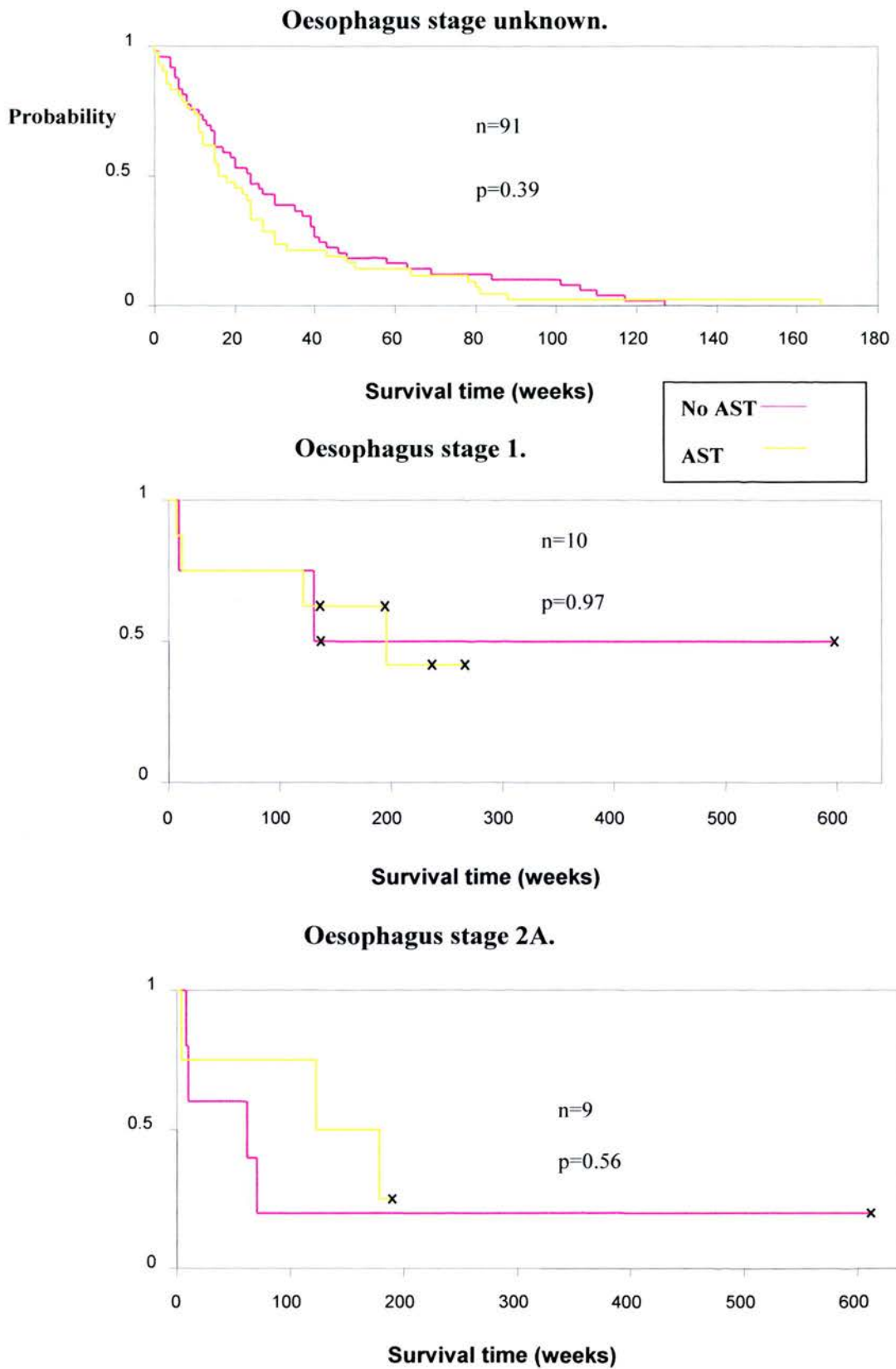
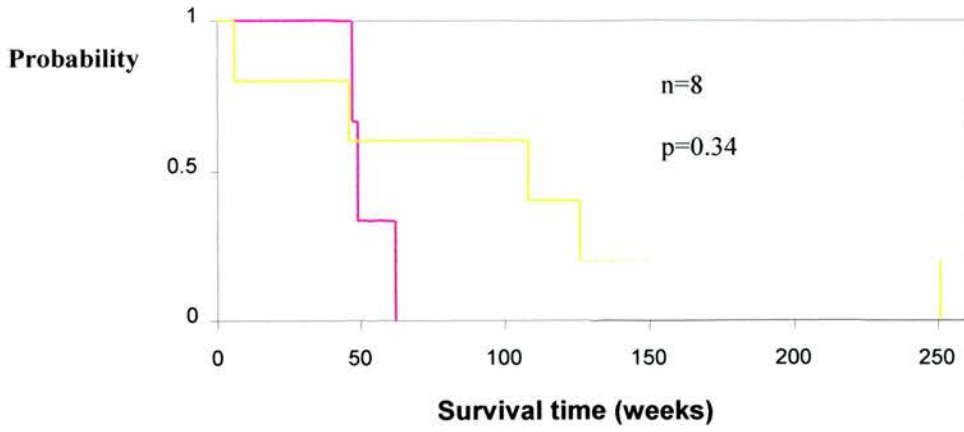
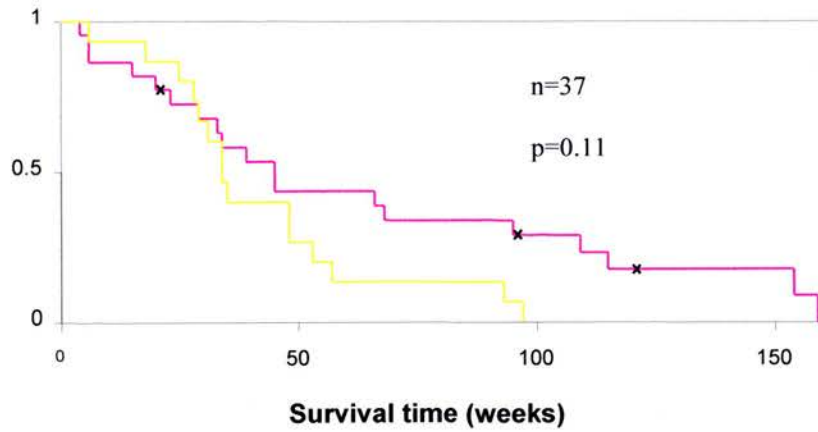


Figure 2.6 (a). Kaplan Meier Survival Curves for oesophageal adenocarcinoma and the effect of anti-secretory drug therapy

Oesophagus stage 2B.



Oesophagus stage 3.



Oesophagus stage 4.

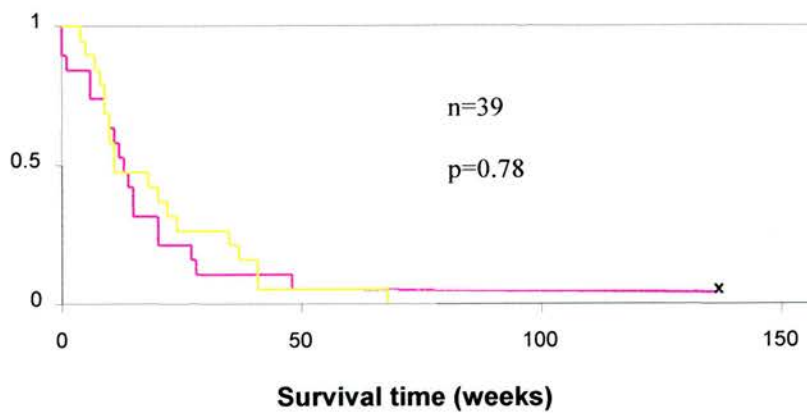


Figure 2.6 (b). Kaplan Meier Survival Curves for oesophageal adenocarcinoma and the effect of anti-secretory drug therapy

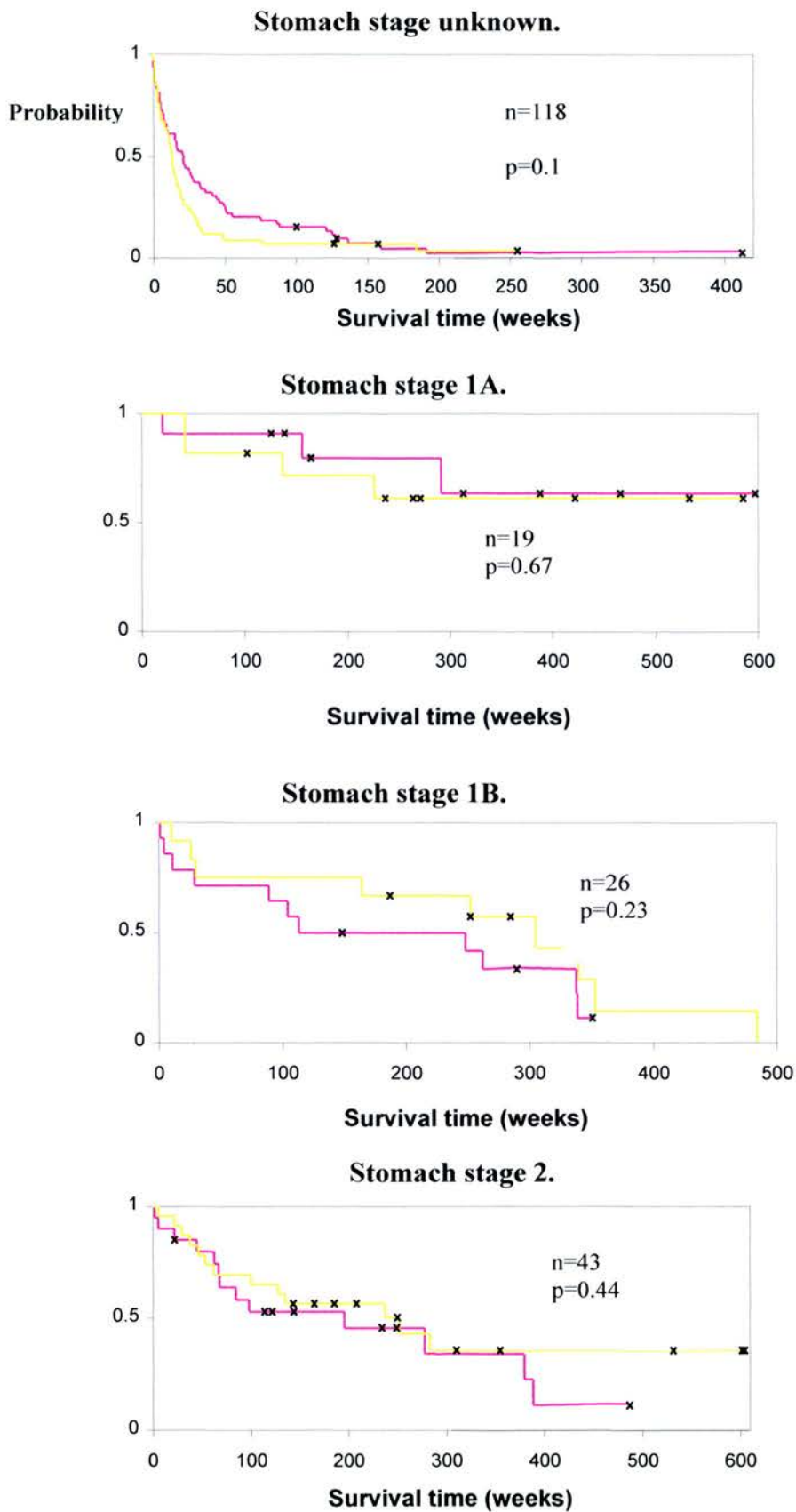


Figure 2.6 (c). Kaplan Meier Survival Curves for gastric adenocarcinoma and the effect of anti-secretory drug therapy

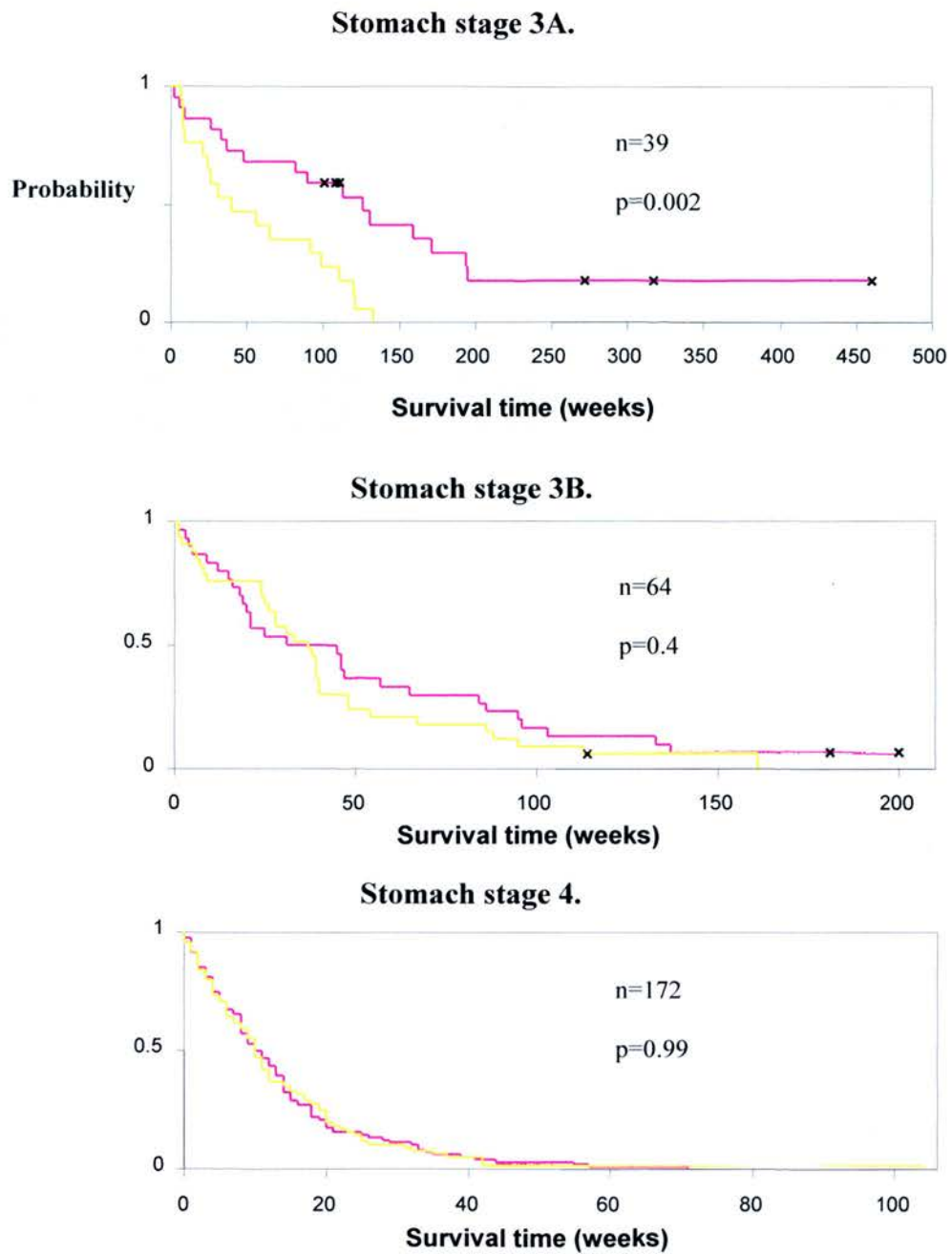


Figure 2.6 (d). Kaplan Meier Survival Curves for gastric adenocarcinoma and the effect of anti-secretory drug therapy

Chapter 3. Effect of strategies to facilitate referral

3.1 Introduction

In the National Cancer Plan ¹⁷⁰ the UK government introduced Urgent Cancer Referral Guidelines (the 'two-week rule') to ensure that everyone with suspected cancer would be referred to a specialist by their general practitioner and seen within two weeks of the referral date. Clearly this was intended to reduce some of the delays highlighted in Chapter 2. From the outset however there were doubts that these guidelines would actually improve the outcome of patients diagnosed with upper GI cancer given the poor correlation of symptoms with diagnosis and the emphasis on “alarm” symptoms as the trigger for endoscopy.

Although the onus may seem to be solely on the secondary care sector, there are undoubtedly issues for primary care. This is particularly evident in the area of UGI symptomatology where annually large numbers of dyspeptic patients are seen, few of whom will have malignancy ^{85;171;172}.

In the past General Practitioners have been reluctant to use 'open access' gastroscopy for patients with suspected cancer ¹⁶² and targeted two-week rule referrals have the potential to overwhelm individual clinicians and increase referral times for cancer patients with less obvious symptoms¹⁷³. This strategy may therefore be detrimental.

In June 2000 the guidelines were issued to General Practitioners highlighting the symptom complexes experienced by patients with UGI malignancy but the evidence base is acknowledged to be poor^{174;175}. The cancer detection rate from the new policy has been low ^{171;172} and the majority of patients with 'two-week' criteria will not have upper GI malignancy¹⁷⁶.

We were interested to see how far we had been historically from this ideal during the last ten years and how many of our patients with known UGI malignancy would have fulfilled the "2-week rule" had the same criteria been in place.

3.2 Aims

The aim of this study was to examine referral practice utilising the "two-week" criteria for all patients diagnosed as having UGI AC during the 10-year period April 1991-April 2001 to see whether lessons could be learned from previous referral practices.

3.3 Patients and methods

The previously identified cohort of patients with oesophago-gastric adenocarcinoma was studied. Primary care, hospital and pathology records were reviewed with respect to the Urgent Cancer Referral Guidelines and the data analysed using Epi Info™.

3.3.1 Statistics

Data was analysed using parametric methods for normally distributed continuous data (*t* test, ANOVA) and non-parametric methods (χ^2 Kruskal Wallis) for categorical data and non-normally distributed continuous data. Results were considered to be statistically significant with p values <0.05 (95% confidence limits)

3.4 Results

Of the study cohort a total of 494 patients (72.1%) fulfilled the major two-week rule criteria in terms of symptoms at the initial consultation with the General Practitioner (table 3.1) comprising 338 (69.1%) males, mean age 69.3 years (range 40-92). Males were more likely to fulfil the two-week rule criteria ($p<0.03$) and females were significantly older (mean 74.3 years, range 35-94) $p<0.001$.

3.4.1 Individual symptom complexes

The largest group of patients fulfilling the two-week rule criteria were those aged 55 years and over with dyspepsia or epigastric pain less than 1 year with continuous symptoms since onset ($n=244$). The mean time from first symptoms to seeing the GP was 6.6 weeks and 68 were referred immediately to secondary care (27.9%) increasing to 119 (48.8%) by four weeks. The second largest group comprised patients with dysphagia ($n=115$) of whom 80 (69.6%) had this as the main presenting symptom. The duration of dysphagia varied from within 1-26 weeks with a mean time of 5.1 weeks before consulting the GP. There were 49 patients with dyspepsia or epigastric pain with weight loss at their first consultation of whom 39 (79.6%) recalled simple dyspepsia or epigastric pain (without weight loss) as the first presenting symptom (mean duration 24.8 weeks, range 1-208). Dyspepsia or epigastric pain associated with anaemia accounted for 14 (3.8%) patients (mean time to initial consultation 39.0 weeks range 1-208). There were 11 patients (3%) with dyspepsia or epigastric pain associated vomiting and nine patients (2.4%) with an epigastric mass. All 29 patients presenting with acute GI bleeding had a short history of dyspepsia or epigastric pain and 25 (86.2%) were acute admissions. The minimal times to referral (mean 0.2 weeks) and being seen at the hospital (0.6 weeks) reflect

the acute nature of their symptoms. In the whole group (685 patients) referral to secondary care within four weeks varied from 41.2% to 100%. The proportion of patients seen within two weeks varied from 39.9% to 89.7% and was lowest in the most common symptom group (39.3%). At four weeks all patients with an epigastric mass had been seen but only 66.8% of patients over the age of 55 years and a short history of dyspepsia had been seen.

3.4.2 Correlation between GP priority and Specialist priority

The time taken for the GP to refer a patient following initial consultation would have been largely unknown to the specialist receiving the referral. However the priority placed on the referral by the GP (in terms of the number referred by four weeks) was closely matched by the percentage of patients seen with a particular symptom complex within four weeks (Spearman-rank correlation coefficient = 0.79 $p < 0.05$).

3.4.3 Patients for whom the two-week rule did not apply

There were 191 patients (27.9%) who did not fit the major urgent referral criteria for suspected UGI malignancy at the first consultation in primary care (table 3.2), of whom 113 (59.2%) were males, mean age 66.6 years (range 28-93). Females were significantly older (mean age 72.0 years, range 37-88 ; $p < 0.001$). Within the group there were no significant differences between the sexes in the mean time to referral or being seen by secondary care. The mean time to referral was 7.1 weeks (range within 1-137 weeks). Almost half (49.2%) were seen within two weeks and 69.6% by four weeks. The majority of these patients subsequently developed symptoms fitting referral criteria. There were 53 patients (16.8%) with weight loss but no upper GI symptoms at initial consultation, although 34 patients subsequently developed

these. Patients without UGI symptoms but with anaemia accounted for 31 patients (9.8%). There were 14 emergency admissions with severe anaemia but no GI symptoms, seven patients with sudden collapse, four patients with chest pain and seven patients with ill-defined symptoms such as fatigue and lethargy.

31 patients aged 55 years or under presented with benign symptoms (dyspepsia or epigastric pain alone). Almost all (93.5%) had symptoms for less than one year and 45.2% had symptoms for less than one month prior to consulting their GP. Time to referral ranged from 1-137 weeks (mean 17.7 weeks) but only 6 patients (19.4%) had worrying symptoms at the time of referral. Only 16 patients over 55 years of age had a history longer than 12 months and the referral time was also long (26.9 weeks). At the time of referral 5 patients (31.3%) had developed worrying symptoms.

3.4.4 Differences between the two groups

Females were significantly older than males in both groups and patients under the age of 55 were more likely to have benign symptoms than patients over this age ($p<0.03$). Males were more likely to have symptoms fitting the two-week referral criteria ($p=0.03$)

3.5 Discussion

The aim of this study was to assess the robustness of the current referral guidelines, viewed from the primary care perspective. At present the evidence base relating to symptoms comes from hospital based studies based on symptoms present in patients found to have malignancy on gastroscopy^{174;175}. The precise percentage of patients presenting with alarm symptoms in primary care is unknown, although recently a figure of 10% has been reported in patients presenting with dyspepsia¹⁷⁷, and yet the current guidelines are primarily aimed at general practitioners. It therefore seemed appropriate to examine symptoms before the patient was referred to hospital. In addition we wanted to assess the past performance of both primary and secondary care, in terms of the referral pathway, for patients subsequently diagnosed with UGI ACA.

The results indicate that there is good correlation between the priority General Practitioners' place on symptoms, as judged by speed of referral and the specialist's priority as determined by the time to be seen. Despite this agreement, before the inception of the 'two-week rule', specialists were able to see only 46.4% of patients with alarm symptoms within two weeks. In a system with a finite number of endoscopy sessions, diagnosis of patients without alarm symptoms is likely to be delayed¹⁷³. In this series the largest group not fulfilling the new upper GI urgent referral guidelines were patients with weight loss but no upper GI symptoms (n=53) or patients below 55 years of age with benign symptoms (n=31). Only a third of patients in the latter group were referred by two weeks, one third of whom, were seen by two weeks. At present lowering the referral age threshold and increasing the index of suspicion appear to be the only way of diagnosing this group (9% of the total) but

such a strategy would be difficult to justify on cost grounds. Weight loss or anaemia without GI symptoms represented 44% of those not meeting the guidelines. The burden upon endoscopy services by the need to investigate these extra patients will be compounded by the need to investigate all the other patients with worrying symptoms but no malignant disease^{85;171;172;176}. Preliminary results from other centres would suggest that the pick up rate for the over 55 years of age with new dyspepsia group is very low, whereas in this study the largest group of patients fell into this category. Nevertheless, if these patients are not gastroscoped it will inevitably diminish our ability to improve the detection rate of early disease^{103;178}. Without more endoscopy resources or better targeting of 'at risk' patients this study shows that 1 in 5 patients will have their gastroscopy delayed even longer as two-week rule patients are prioritised. Our results indicate younger patients (45-55 years of age) and those with early disease and simple dyspepsia¹⁰³ will be disadvantaged unless the current system changes.

The main limitation of this study is the lack of a denominator to be sure that adopting these new strategies would not lead to an increase in urgent referrals with little improvement in the overall delay in diagnosis

The NICE dyspepsia guidance document advocates investigation only for patients with "alarm symptoms" (defined by NICE as GI bleeding, dysphagia, unintentional weight loss and persistent vomiting) or those over 55 years with high risk factors (defined by NICE as pernicious anaemia, previous gastric surgery or gastric ulcer) or those taking NSAIDs. These guidelines are at odds with the Urgent referral guidelines as they have no provision advocating endoscopy for patients with new

onset dyspepsia. By adopting a high threshold for investigation the concern would be that by diagnosis the patient will have advanced disease or at the very least have endured a delay in diagnosis as a result of the now advocated “test and treat” strategies.

The second issue relating to the two-week rule is the apparent reluctance of General Practitioners to investigate patients over 55 years of age despite recent onset dyspepsia. Half the patients seen in this category had been prescribed acid suppression therapy, which is known to delay diagnosis further^{115;147}. If hospitals have to improve access to endoscopy for these patients it is equally necessary for GPs to identify 'at risk' patients and refer early when symptoms are not necessarily indicative of malignancy. From a primary care perspective there is a conflict between guidelines with respect to older dyspeptic patients

More 'open access' gastroscopy might seem to be the logical solution to this problem and most units now offer such a service¹⁴⁹, but present demand will be greatly exceeded by increasing acceptance of the two-week rule. Whilst this may seem to be a secondary care problem, the creation of Primary Care Trusts means that the commissioning of these services will be theirs. In addition the crucial decision as to whether a patient over the age of 55 years should be referred for gastroscopy, irrespective of whether alarm symptoms are present or not, will impact most on individual general practitioners.

In conclusion these findings indicate that the current referral guidelines will identify only 72% of patients with UGI ACA at their initial GP visit. Patients with 'epigastric

mass' represent only 2.4% of patients whereas patients with weight loss or iron deficiency anaemia *in the absence of upper GI symptoms* together constitute 12.3% of patients.

The "two-week" referral guidelines are aimed at identifying patients with cancer and so speed referral. Unfortunately the current guidelines are neither sensitive nor specific and risk delaying the diagnosis in a significant number of patients. The capacity to gastroscopise more patients in the "at risk" age group (>55 years) could be created by severely limiting access to those under this age (NICE). In addition GPs should consider gastroscopy for any at risk patients with new onset symptoms. There may well be a value to a "negative" endoscopy. By increasing the index of suspicion and improving access to endoscopy it may be possible to improve the detection of early stage disease and hence improve outcome.

"2 week rule" criteria (mutually exclusive) male n=338 (68.4%) female n=156 (31.6%)	Mean time GP consult to referral weeks	% referred within 4 weeks	Mean time referral to seen weeks	% seen within 2 weeks	% seen within 4 weeks
All (n=494)	6.7 (1-174)	65.4	2.6 (1-30)	46.4	71.9
Age >55 with dyspepsia/ heartburn/ reflux < 1 year duration (n=244)	10.8 (1-174)	48.8	2.8 (1-17)	39.3	66.8
Age >55 with GI bleeding first symptoms dyspepsia/reflux/ epigastric pain (n=29)	0.2 (1-5)	96.6	0.6 (1-9)	89.7	93.1
Dysphagia (n=115)	2.4 (1-120)	86.1	2.5 (1-18)	44.3	78.3
Dyspepsia or epigastric pain with weight loss (n=49)	1.6 (1-10)	83.7	3.0 (1-22)	46.9	67.3
Dyspepsia or epigastric pain with past history of gastric surgery/ Barrett's/ dysplasia (n=23)	6.9 (1-24)	43.5	3.1 (1-9)	43.5	60.9
Dyspepsia or epigastric pain with anaemia (n=14)	5.8 (1-30)	71.4	2.5 (1-11)	64.3	78.6
Dyspepsia or epigastric pain with vomiting (n=11)	6.6 (1-34)	54.5	3.7 (1-30)	72.7	72.7
Palpable mass (n=9)	0.1 (1)	100	1.0 (1-3)	66.7	100

Table 3.1. Details of patients' symptoms are shown along with the time taken for the General Practitioner to refer the patient to a specialist or open access gastroscopy. The range, in brackets, refers to the time period within which the patient was seen or referred.

"2 week rule" did not apply Male n=113 (62.0%) Female n=78 (38.0%)	Mean time GP consult to referral weeks	% referred within 4 weeks	Mean time referral to seen weeks	% seen within 2 weeks	% seen within 4 weeks
All (n=191)	7.1 (1-137)	62.3	2.8 (1-18)	49.2	69.6
Age <55 with dyspepsia or heartburn/reflux or epigastric pain (n=31)	17.7 (1-137)	32.3	4.1 (1-18)	32.3	61.3
Age >55 with dyspepsia or heartburn/reflux or epigastric pain >1 year (n=16)	26.9 (1-126)	12.5	4.6 (1-13)	37.5	43.8
Weight loss, no upper GI symptoms (n=53)	2.5 (1-20)	69.8	2.4 (1-16)	45.3	75.5
Anaemia, no upper GI symptoms (n=31)	2.8 (1-40)	77.4	2.6 (1-13)	48.4	67.7
Dyspepsia or epigastric pain with anorexia (n=15)	4.1 (1-14)	60.0	1.7 (1-8)	66.7	86.7
Fatigue and/ or Lethargy (n=15)	4.0 (3-5)	80.0	1.5 (1-3)	53.3	73.3
Chest pain and/ or breathlessness (n=10)	3.0 (1-21)	80.0	3.0 (1-12)	60.0	60.0
Collapse (n=9)	1.1 (1-5)	88.9	1.0 (1-5)	77.8	77.8
Nausea and vomiting (n=8)	1.3 (1-3)	100.0	3.0 (1-18)	75.0	75.0
Lower abdominal pain (n=3)	3.0 (1-5)	66.7	1.0 (1-3)	66.7	100.0

Table 3.2. Details of patient's symptoms are shown along with the time taken for the General Practitioner to refer the patient to a specialist or open access gastroscopy. The range, in brackets, refers to the time period within which the patient was seen or referred.

Chapter 4. Cancers missed at endoscopy.

4.1 Introduction.

Despite the widespread use of endoscopy, early gastric cancer remains uncommon in the UK and delays to diagnosis may play some part in this picture¹¹³. It has been reported that as many as 1 in 6 oesophago-gastric cancers may be missed at endoscopy within the 3 years leading up to diagnosis^{162;179} and that the prior use of anti-secretory drug therapy may contribute to this delay¹¹⁵. This suggests that even if the causes of the delays outlined in Chapters 2 and 3 are addressed, opportunities to diagnose a significant number of these cancers earlier are being missed. In many cases the failure to diagnose malignancy at initial gastroscopy will be a direct result of inconclusive histology. Such patients are not 'missed' as the suspicion of malignancy results in a second endoscopy and further biopsy. If the endoscopic appearances are not 'suspicious' the patient's real pathology may be missed, particularly if symptoms respond to acid suppression therapy. Gastric ulcers are usually re-gastroscooped after 6-8 weeks treatment to ensure healing and exclude malignancy. Again, a malignant gastric ulcer could not be deemed to have been "missed" if diagnosed in this way, despite a delay of up to 8 weeks.

The "real" missed cases of malignancy are those not diagnosed at initial gastroscopy and includes the following groups, some of whom might still have been diagnosed within a short time of the initial gastroscopy:-

1. Patients with a normal gastroscopy or minor abnormality (oesophagitis, gastritis, hiatus hernia, gastric polyp) and whose symptoms failed to resolve

on treatment, relapsed on treatment or the patient developed new ‘worrying’ symptoms and who subsequently had an unplanned follow up endoscopy;

2. Patients with a definite abnormality (erosions, ulcer)
 - a) where malignancy was detected at planned follow up in addition to the previously diagnosed abnormality
 - b) where the abnormality was deemed to be benign, no biopsies taken or were negative and no follow up was arranged
3. Patients with suspicious lesions but with negative histology who were not followed up.

Thus some patients with short delays should still be classified as ‘missed’ whereas some patients with long delays were not ‘missed’ because the suspicion remained that the pathology was not representative of the clinical and/or endoscopic diagnosis. Only by examining all the factors surrounding a diagnosis would a true figure of ‘missed’ cancers emerge.

4.2 Aims.

The aim of this study was to determine the number of patients with upper GI adenocarcinoma who were truly missed as a result of not being diagnosed with cancer at their initial endoscopy and to examine the potential variables, including operator experience, nature of prior reported abnormalities, biopsy/cytology rates and prior anti-secretory drug therapy, that may have contributed

4.3 Patients and methods.

The previously identified cohort of patients with oesophago-gastric adenocarcinoma was studied. The records were reviewed (by SP and HO'F) to identify the demographics of the cohort and details of the referral pathway. A "missed cancer" was identified when there was a prior opportunity to diagnose the cancer within 3 years of diagnosis. If this penultimate investigation was endoscopy it was known as the *prior* endoscopy. The above criteria were used to identify "real" missed cancers. Records were reviewed to determine details of the operator, original endoscopic diagnosis, frequency of biopsy and/or cytology samples and any previous investigations. Data was collected on the prescribing of anti-secretory drug therapy. All data was password protected and stored on a PC based spreadsheet/database only accessible to the investigators. The data were entered and analysed using Epi Info™ epidemiological database and statistical analysis package (US department of Health and Human Services, Centre for Disease Control and Prevention, Atlanta, Georgia, USA). Accuracy of data entry was optimised using the double data entry (by two different operators) and cross checking facility.

4.3.1 Statistics

Data was analysed using parametric methods for normally distributed continuous data (*t* test, ANOVA) and non parametric methods (χ^2 , Kruskal Wallis) for categorical data and non normally distributed continuous data. Results were considered to be statistically significant with p values <0.05 (95% confidence limits).

4.4 Results.

Of the 685 patients a prior investigation was recorded within 3 years of diagnosis in 242 (35.3%). In 183 patients (26.6%) the prior investigation was endoscopy (+/- other investigation such as abdominal ultrasound scan or barium study). Details are shown in table 4.1.

39 patients (5.7%) had 2 endoscopies within 3 years, and 18 (2.6%) had 3 endoscopies within 3 years.

There was no statistically significant difference in age, sex, or diagnosis between those in the missed cancer group and the diagnosed at first endoscopy group.

4.4.1 Patients

At least one prior endoscopy was performed in 50 patients (25.3%) subsequently diagnosed with oesophageal adenocarcinoma and 133 patients (27.3%) later diagnosed with gastric adenocarcinoma (as shown in table 4.1).

4.4.2 Endoscopy.

The findings at the most recent prior endoscopy along with the macroscopic appearance, with regards "suspiciousness" of the findings, are shown in table 4.3.

4.4.3 Endoscopist.

The diagnosis of cancer was made at endoscopy in 652 cases out of a total of 685 patients (194 oesophagus, 458 gastric). In 494 the diagnosis was made at the first endoscopy (148 oesophagus, 346 gastric), and a senior endoscopist (consultant, associate specialist, GP hospital practitioner) performed this in 68.6% of cases (339/494).

A total of 158 patients had at least one prior endoscopy where the diagnosis of cancer was missed (46 oesophageal, 112 gastric), and a senior endoscopist performed the endoscopy in 62.7% of these cases (99/158), with the remaining endoscopies being performed by a trainee ($p=0.2$). Details in table 4.4.

4.4.4 Method of diagnosis of cancer after a prior endoscopy.

Where a prior endoscopy had failed to diagnose the cancer, the majority of cases were subsequently diagnosed at endoscopy (158/183).

In 25 (13.7%) patients (four oesophageal, 21 gastric) the cancer diagnosis was not made at gastroscopy but at surgery in 17, ultrasound (US) guided biopsy in four, liver biopsy in one, endoscopic retrograde cholangiopancreatography (ERCP) in one, abdominal US in one and with a barium study in one. In 80.0% (20/25) cancer was suspected and the majority (84%) had the diagnosis made within 12 weeks.

Of the 502 patients who did not have a prior endoscopy, only 8 (0.2%) (0 oesophageal, 8 gastric) had their cancer diagnosis made by other means (five surgery, two US guided biopsy, one ERCP) ($p<0.00001$).

4.4.5 Delay to diagnosis after a prior endoscopy.

The mean time to diagnosis after a prior endoscopy was 24.4 weeks (range 0-153).

Figure 4.1.

For those with oesophageal cancer the mean time from prior endoscopy to diagnosis was 28.7 weeks (range 0-131). For those with gastric cancer the time from prior endoscopy to diagnosis was 22.8 weeks (range 0-153) ($p=0.19$).

45.9% of patients (84/183) had the prior endoscopy within 6 weeks of the diagnostic endoscopy (oesophagus 18/50 (36.0%), gastric 66/133 (49.6%). In 63.4% (116/184)

the prior endoscopy was within 12 weeks (oesophagus 25/50 (50.0%), gastric 91/133 (67.7%) and in 68.5% (126/184) the prior endoscopy was within 16 weeks (oesophagus 30/50 (60.0%), gastric 96/133 (72.2%). The remainder were delayed for longer. There was no significant difference between the mean time to diagnosis in oesophageal and gastric cancer cases overall but the difference in the median times implies oesophageal cases more likely to be delayed longer.

4.4.6 "Real" missed cases

Using the criteria above there were 63 patients (9.2%) who were "truly" missed.

43 patients had a normal prior gastroscopy or had only minor abnormalities seen and had symptoms that failed to resolve on treatment, relapsed on treatment or they developed new 'worrying' symptoms and so had an unplanned follow up endoscopy. One patient had a definite abnormality at the prior endoscopy but the malignancy was only detected at the planned follow up in addition to the previously diagnosed abnormality.

Two patients had a definite abnormality at the prior endoscopy but the malignancy was only detected at an unplanned follow up and was unrelated to the previously diagnosed abnormality.

12 patients had an abnormality (all gastric ulcers) deemed to be benign and either no biopsies were taken or the histology negative and no follow up was arranged. The diagnosis was made later at an unplanned further endoscopy.

Five patients had a suspicious lesion seen at the prior endoscopy but the histology was negative. They were not followed up and were later diagnosed with malignancy at an unplanned endoscopy.

4.4.7 Biopsy and cytology rates.

Where a prior endoscopy had occurred a mean of 1.8 biopsies were taken (median 1, range 0-14) (n=170, 2 missing data; 11 normal endoscopies with no biopsies taken were excluded). In the 493 cases where the diagnosis was made by endoscopy at the first opportunity (i.e. no prior endoscopy had occurred) the mean number of biopsies taken was 3.8 (median 4 range 1-14).

Of the oesophageal cases that appeared to be potentially malignant at the prior endoscopy, biopsies revealed worrying histology (cytological atypia or dysplasia of any type) in 27.6% (8/29). Although the endoscopy showed a potentially malignant lesion, biopsies were not taken in 24.1% (7/29). In the cases where the penultimate endoscopy was normal or revealed a benign looking lesion no worrying histology was obtained. In 47.4% (9/17 missing data in 2) no biopsies were taken.

Of the gastric cases, the penultimate endoscopy findings were considered potentially malignant in 49.6% (66/133). In 30.3% (20/66) of the endoscopies where suspicious findings were seen no biopsies were taken; 10 had unsatisfactory examinations and 10 had gastric ulcers. Of the gastric ulcers, 6 had active bleeding, 1 was on warfarin and 2 had cytology taken. In one case where no biopsies were taken there was a strong clinical suspicion of malignancy and the patient had a laparotomy with the resected specimen confirming carcinoma. For those with potentially malignant findings at the prior endoscopy, 24.3% (17/66) had worrying histology. For those with benign looking lesions at the prior endoscopy none had worrying histology.

Cytology was only taken in 34/170 cases (20%) and cytology rates varied according to the findings at the prior endoscopy. In the case of oesophagitis 7/23 (30.4%) had cytology taken, strictures 5/21 (23.8%), ulcers 31/71 (18.3%) and gastritis 2/14 (14.3%). When comparing lesions considered to be potentially malignant with those that appeared benign, cytology rates were significantly higher in the potentially malignant (30/100 vs. 4/70, $p=0.0002$).

Biopsy rates were similar for junior and senior endoscopists (senior mean 1.94, median 2, range 0-14 vs. junior 1.94, 1, 0-8, $p=0.9$)

4.4.8 Antisecretory drug therapy

Of the 685 total, 326 (47.6%) had been prescribed antisecretory drug therapy prior to diagnosis.

502 patients had their diagnosis made at the first opportunity and in 494 this was made by endoscopy. Of those that were diagnosed by endoscopy at the first opportunity 191/494 (38.7%) had been prescribed antisecretory drug therapy whereas of the 183 cases where the diagnosis was not made at prior endoscopy, 93 (50.8%) had antisecretory drug therapy prior to this endoscopy ($p=0.005$) i.e. those patients who had a prior endoscopy were more likely to have been prescribed antisecretory drug therapy.

Of the oesophageal cases ($n=198$), 85 (42.9%) had been prescribed antisecretory drug therapy prior to diagnosis. 148 had their diagnosis made at the first opportunity and in all cases this was made by endoscopy. Of those that were diagnosed by endoscopy at the first opportunity 58 (39.2%) had been prescribed antisecretory drug

therapy whereas of the 50 cases where the diagnosis was not made at the prior endoscopy 27 (54.0%) had antisecretory drug therapy prior to this endoscopy ($p=0.07$) i.e. no significant difference between prior endoscopy group and diagnostic endoscopy group and antisecretory drug therapy prescription but a strong trend towards misdiagnosis with AST use.

Of the gastric cases ($n=487$), 230 (47.2%) had been prescribed antisecretory drug therapy. 354 had their diagnosis made at the first opportunity and in 346 cases this was made by endoscopy. Of those that were diagnosed by endoscopy at the first opportunity 133 (38.4%) had been prescribed antisecretory drug therapy whereas of the 133 cases where the diagnosis was not made at prior endoscopy 66 (49.6%) had antisecretory drug therapy prior to this endoscopy ($p=0.03$) i.e. those patients who had a prior endoscopy were more likely to have been prescribed antisecretory drug therapy.

4.5 Discussion.

This study looked at the extent of the failure to detect oesophago-gastric ACA in South Tees and has shown that in 35.3% (242) of patient's there was a prior investigation within 3 years of the cancer diagnosis and in 26.7% (183) this was endoscopy. In these patients the mean delay to diagnosis was over 6 months. On examining the cases where there was a delay in diagnosis there were clearly two groups of patients – (i) those where the diagnosis was delayed as the diagnosis was not made at the first endoscopy *but* a follow up endoscopy was planned and (ii) those where no follow up was planned and it took until the patient represented for the diagnosis to be made – the “real” missed cases. These account for 9.2% of the total. At the prior endoscopy abnormalities were reported in 92% of the patients (excluding failed endoscopies and those reported as normal). It is beyond the ability of this retrospective study to say that all the lesions seen were the precursors of the cancers and clearly some findings were irrelevant to the final diagnosis. However, due to the natural history of oesophago-gastric cancer, it is likely that in some patients malignant lesions would have been present at the earlier endoscopy but were not diagnosed. Almost certainly in the two thirds who had a prior endoscopy within 12 weeks of diagnosis a malignant lesion would have been present. Although this delay is unlikely to have an effect on prognosis, given the natural history of oesophago-gastric cancer, it is still unacceptable. The patient will have endured avoidable investigations and the endoscopy service capacity will have been unnecessarily reduced.

If gastric ulcers alone are considered, all the cancers were diagnosed in the same geographical area and thus this demonstrates that the problem is one of inadequate biopsying. In 39% of cases it appears to be that lesions were detected but insufficient biopsies are being taken to make the diagnosis, resulting in a requirement for a repeat examination. Biopsy numbers were generally low and especially so if the lesion appeared benign or the endoscopy was done as an emergency. Biopsy rates were well below those shown in previous studies to be most likely not to miss cancer within an ulcer. Considering the natural history of gastric cancer a delay of 12 weeks is unlikely to effect prognosis but from the patient's perspective any delay is often perceived as unacceptable and for endoscopy capacity these repeat endoscopies are an avoidable wastage.

There are a number of factors why biopsies are not taken but this was not influenced by the experience of the endoscopist. AST treatment was more commonly prescribed in the "missed" group supporting the hypothesis that AST therapy allows lesions to heal and so masking their true potential at endoscopy. It seems that an important determinant as to whether biopsies are taken, or not, is the suspicion of the endoscopist irrespective of the nature of the lesion.

In order to minimise delay and reduce the miss rate symptoms should be reviewed regularly, AST not prescribed in high risk groups until after endoscopy and a high level of suspicion maintained with a low threshold for endoscopy. Improved endoscopic technique and a policy to perform multiple biopsies (seven or more) when a lesion is seen, especially when it looks potentially malignant or represents

ulcer disease, should reduce the rate of "missed" cancers and delays from 27% to less than 10%.

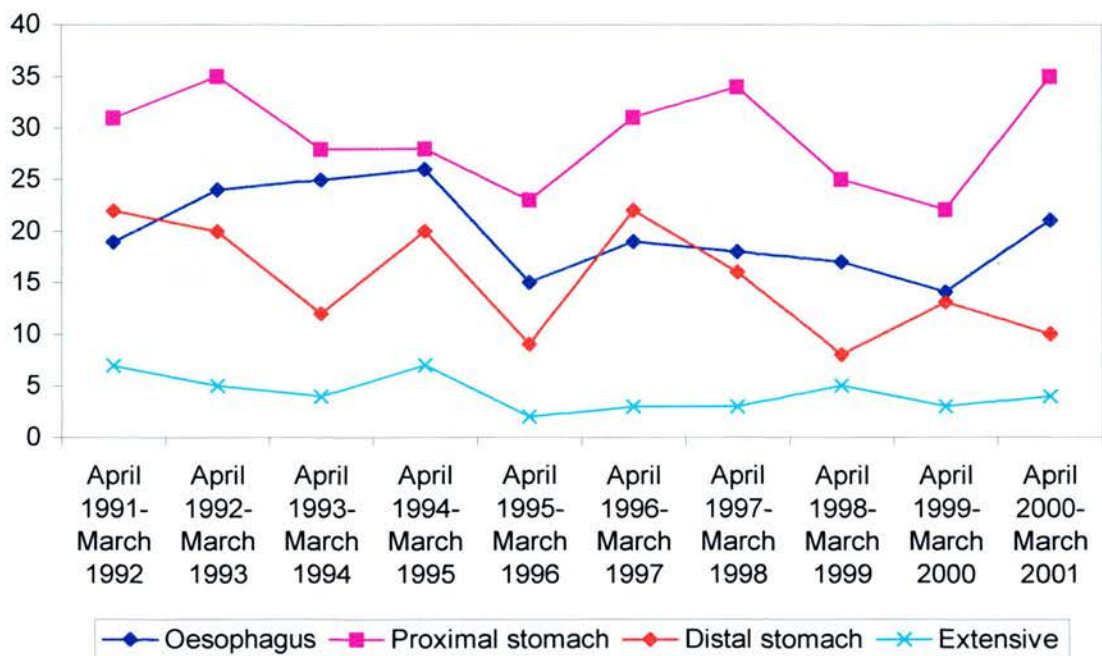


Figure 4.1 Change in site over time.

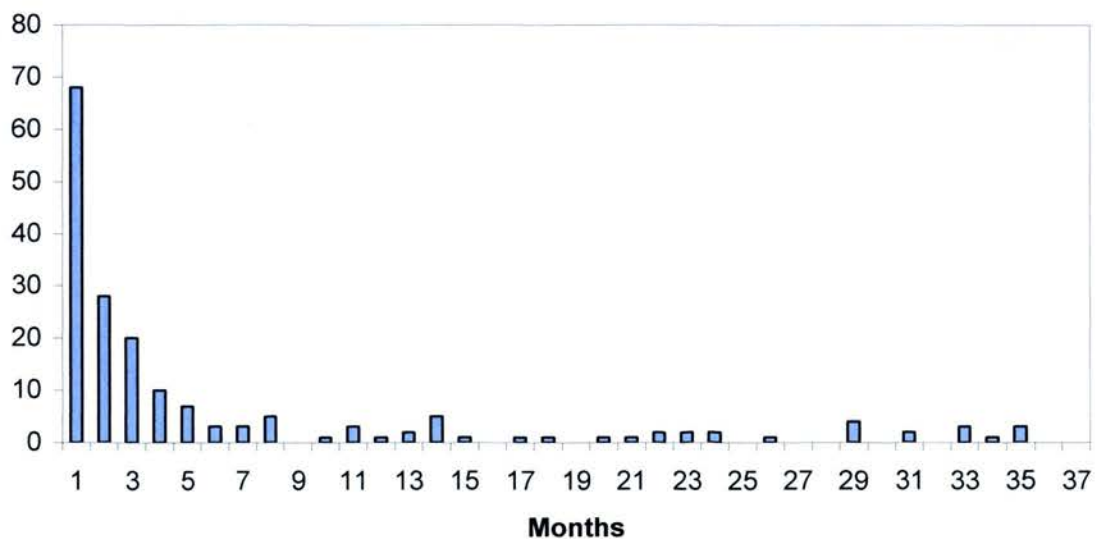


Figure 4.2 Time from prior endoscopy to diagnosis.

	All UGI ACA	Oesophageal	Gastric
Total number	685	198	487
Male	451	143	308
Female	234	55	179
Mean age at diagnosis (range) in years	70.3 (28-94)	69.4 (41-94)	70.7 (28-92)
Site of cancer at diagnosis	-	Middle third 5% Lower third 95%	Proximal 45% Mid-stomach 15% Distal 31% Extensive 9% (Lesser curve 69%)
Prior investigation (n)			
Overall	242	78	164
Endoscopy +/- other	183 (75.6%)	50 (64.1%)	133 (81.1%)
Barium studies alone	36 (14.9%)	24 (30.8%)	12 (7.3%)
US Scan alone	23 (9.5%)	4 (5.1%)	19 (11.6%)
Site of "missed" cancer at diagnosis	-	Middle third 1 Lower third 36 OGJ (oesophageal side) 13	OGJ (gastric side) 11 (8.3%) Upper 36 (27.1%) Body 15 (11.3%) Lower 58 (43.6%) Extensive 13 (9.8%)
Mean time to diagnosis in weeks following prior endoscopy (median, range)	24.4 (6, 1-153)	28.7 (11, 1-131)	22.7 (6, 1-153)
Nature of finding at prior endoscopy	n=183 (%)	N=50	n=133
Normal	11 (6%)	1	10
Oesophagitis	25 (14%)	20	5
Gastritis	14 (8%)	1	13
GU	71 (39%)	2	69
DU	4 (2%)	1	3
Stricture	21 (11%)	18	3
Other	37 (20%)	7	30

Nature of finding at prior endoscopy – when diagnosis made within 12 weeks	n=116	N=25	n=91
Normal	3	0	3
Oesophagitis	7	6 (severe or Barrett's)	1
Gastritis	7	0	7
GU	52	1 (at OGJ)	51
DU	1	0	1 (also gastric erosions)
Stricture	17	15	2
Other	29	3 (suspicious mass 3)	26 (suspicious mass 5, failed endoscopy 3, food debris 8, pyloric stenosis 6, mucosal abnormality 3, poor views ? tumour 1)
Nature of finding at prior endoscopy – when diagnosis delayed more than 12 weeks	n=67	N=25	n=42
Normal	8	1	7
Oesophagitis	18	14	4
Gastritis	7	1	6
GU	19	1	18
DU	3	1	2
Stricture	4	3	1
Other	8	4 (suspicious mass 1, failed endoscopy 1, hiatus hernia 2)	4 (mucosal abnormality 1, polyp 1, hiatus hernia 1, failed scope 1)

Table 4.1. Details of study cohort.

	All UGI ACA	Oesophageal	Gastric
% patients prescribed AST at any time	47.7	48.5	47.4
% PPI	57.8	65.6	54.5
% H ₂ RA	42.2	34.4	45.5
% on PPI at diagnosis previously treated with H ₂ RA	33.9	34.9	33.3

Table 4.2 Details of AST prescription.

	All UGI ACA	Oesophageal	Gastric
Macroscopic appearance of findings at prior endoscopy	n=		
“potentially malignant”	95	29	66
“benign”	72	19	53
“normal”	11	1	10
Macroscopic appearance of findings at prior endoscopy—when diagnosis made within 12 weeks			
“potentially malignant”	80	19 (oesophagitis 2, Barrett's 2, stricture 12, mass 3)	61 (GU 36, gastritis 2, stricture 2, mass 6, mucosal abnormality 3, pyloric stenosis 5, stomach full of food 7)
“benign”	30	6 (GU at OGJ 1, oesophagitis 2, stricture 3)	24 (DU 1, GU 15, gastritis 5, oesophagitis 1, pyloric stenosis 1, stomach full of food 1)
“normal” (Failed endoscopy 3)	3	0	3
Macroscopic appearance of findings at prior endoscopy—when diagnosis delayed more than 12 weeks			
“potentially malignant”	15	10 (oesophagitis 8, stricture 1, mass 1)	5 (GU 5)
“benign”	42	13 (DU 1, GU 1, gastritis 1, oesophagitis 6, stricture 2, hiatus hernia 2)	29 (DU 2, GU 13, hiatus hernia 1, gastritis 6, oesophagitis 4, stricture 1, mucosal abnormality 1, benign-looking polyp 1)
“normal” (Failed endoscopy 2)	8	1	7
Mean time to diagnosis in weeks after prior endoscopy if findings considered			
“potentially malignant”	7.5 (2.5, 0-91)	12.3 (4, 0-85)	5.4 (2, 0-91)
“benign”	40.2 (17, 0-150)	49.3 (44, 0-131)	37 (15, 2-150)
“normal” at prior endoscopy	74.5 (86, 5-153)	131 (131, 131)	68.8 (68.5, 5-153)

Table 4.3. Details of the macroscopic appearance and suspiciousness of the findings at the prior endoscopy, and time to diagnosis.

Endoscopist	No previous endoscopy n=494	Previous endoscopy n=158
Consultant, associate specialist, GP hospital practitioner	339 (68.6%)	99 (62.7%)
Registrar	120 (24.3%)	40 (25.3%)
SHO	5 (1.0%)	3 (1.9%)
Unknown	30 (6.1%)	16 (10.1%)

Table 4.4. Endoscopist performing procedure

Eventual site of cancer	Biopsy rate at prior endoscopy	Cytology rate
Oesophageal (n=47)	2.0, (2.0, 0-14)	27.7%
Gastric (n=123)	1.8, (1, 0-7)	17.1%

Table 4.5. Biopsy and cytology rates.

Principal finding at prior endoscopy (n=183)	(n)	Mean number of biopsies taken (median, range)
Normal/HH/DU	19	0
Oesophagitis	25	2.3, 2, 0-14 (n=23)
Oesophageal stricture	21	1.1, 1, 0-3
“Gastritis”	14	1.9, 1.5, 0-6
GU	71	2.0, 1, 0-7
Emergency diagnosis	28	1.3, 0.5, 0-7
Non-emergency diagnosis	43	2.5, 3, 0-7
Benign looking polyp	1	1
Suspicious mass	10	2.9, 3, 1-5
Mucosal abnormality	4	3.8, 3.5, 1-7
Pyloric stenosis	6	2.3, 2.5, 0-5
Stomach full of food	8	0.6, 0, 0-3
Failed endoscopy	5	0

Table 4.6. Diagnosis at prior endoscopy and biopsy rates.

Chapter 5. Prospective evaluation of endoscopic diagnosis in relation to histopathology for patients with gastric ulcer disease.

5.1 Introduction

As shown in chapter 4, malignant lesions are "missed" at endoscopy and that even when obvious lesions are seen, misdiagnosis occurs because insufficient biopsies are taken or histology is misleading. Graham *et al* showed that one biopsy was sufficient to make the diagnosis in only 70% of gastric cancers (93% of oesophageal cancers) whilst four biopsies were required to be accurate in 95% of cases and seven biopsies were required to ensure that no diagnosis was missed¹⁴¹. Ulcer healing drugs have been observed to heal malignant ulcers and this may also be a factor resulting in misdiagnosis¹⁴⁷.

5.2 Aim

The aim of this study was to investigate prospectively whether the endoscopist's assessment of the macroscopic appearance of a gastric ulcer was accurate and whether this determined biopsy rates.

5.3 Patients and methods

The study was performed at James Cook University Hospital during the period October 1999 until August 2001 with at least a 2-year follow up to ensure no patient presented later with a 'missed' upper gastrointestinal carcinoma

All patients diagnosed as suffering from a gastric ulcer (mucosal breach >5mm) during the study period were considered for inclusion. Theatre logbooks were also examined to identify patients diagnosed with gastric ulcer at laparotomy. Ulcers described as "superficial" or "small" were excluded.

Demographic and endoscopic details were collected for all patients including prior treatment with antisecretory drugs. . Whether the ulcer was considered "benign", "suspicious" or "malignant" by the endoscopist was recorded from information on the endoscopy report and histology request. The endoscopist was not aware of this process but did know that 'audit' was taking place.

Data was collected the following day (by SP) and results correlated with the histological findings (including the number of biopsies received by the pathology department).

Data handling and analysis was performed using the SPSS v11™ epidemiological database and statistical analysis package.

South Tees Acute Trust Ethics Committee approval was obtained.

5.4 Results

During the study period a total of 250 patients were diagnosed with gastric ulcer disease of which 196 met the inclusion criteria. Of these 32 (16%) were malignant ulcers. Details are shown in table 5.1.

The mean age at the diagnostic endoscopy was 67 years (median 70, range 23-98).

The male: female ratio was 1.25:1.

5.4.1 Factors influencing the endoscopist's judgement

5.4.1.1 Location of ulcer

The majority of the ulcers were distal (66.8%). Details are shown in table 5.1.

5.4.1.2 Size

The larger the ulcer, the more likely the endoscopists were to regard the ulcer as suspicious or malignant.

5.4.1.3 Experience

There was no difference between junior doctors' interpretation of ulcer appearances compared to more senior endoscopists (table 5.2).

5.4.1.4 Previous antisecretory drug therapy

The predictive value of the endoscopist's macroscopic judgement regarding the "suspiciousness" of an ulcer can be estimated as the proportion of correct macroscopic diagnoses (PV pos). Details can be seen in table 5.2. The overall

positive predictive value for suspicious or malignant looking ulcers was worse if patients had been on antisecretory drug therapy prior to endoscopy

5.4.2 Follow up

5.4.2.1 Immediate

Of the 196 cases, 17 patients underwent laparotomy. 10 ulcers presented with perforation requiring laparotomy. 7 patients required surgery for bleeding (6 patients having a prior endoscopy - biopsies taken in only 1 case).

5.4.2.2 Long term

No patient has subsequently developed an upper gastrointestinal carcinoma over a mean follow up of 3.4 years (2.5-4.4).

5.5 Discussion

Gastric ulcer disease accounts for 4-5% of all gastroscopy findings¹⁸⁰ and is now the commonest lesion seen at emergency gastroscopy performed to investigate upper GI haemorrhage¹⁸¹. The endoscopist usually makes a judgement about whether an ulcer looks “benign” or “malignant” based on a number of criteria. These include the presence or absence of rolled edges, ulcer depth, size and position. That interpretation, which may be subconscious, is influenced by numerous factors including presentation and the endoscopist’s experience. In the case of gastric ulceration well-established protocols involve multiple biopsy of the ulcer to exclude malignancy and then a follow up endoscopy of “benign” ulcers until healing. The purpose of this study was to determine if the endoscopist's visual determination of pathology in various clinical settings was accurate and whether this determination influenced the number of biopsies taken.

The results suggest that the endoscopists' judgement was good with regard to benign ulcers achieving an overall PVpos of 0.96. This was similar between junior and senior endoscopists suggesting that the experience of the endoscopist did not influence this judgement. The endoscopist was less adept at identifying "suspicious or malignant" ulcers with a PVpos of only 0.58. The ability of the endoscopist to determine if an ulcer was benign or suspicious appears to be influenced by treatment with antisecretory drugs prescribed prior to endoscopy. In this situation the endoscopist was less likely to recognise the ulcer as malignant suggesting that these agents alter the endoscopic appearance of malignant ulcers. One factor influencing the endoscopists' impression of an ulcer appeared to be size. “Malignant looking” ulcers were four times larger than ulcers considered “benign looking” whereas

“suspicious looking” ulcers were twice as large. The determination of "suspiciousness" also affected the ulcer biopsy rate with more biopsies being taken from the "suspicious" or "malignant" looking ulcers.

Although this was a prospective study no attempt was made to alter the behaviour of individual endoscopists as this may have biased the results. Clinicians were aware of an “ulcer audit” but not the purpose of the study.

This study is limited by an incomplete data set and the subjective nature of some data. For example, we do not know how “suspicious” the endoscopist really was that malignancy might be present as this group clearly contains many ulcers that turned out to be benign. In many cases details such as ‘rolled edges’ or ulcer depth were not recorded. However as we did not wish to influence the endoscopists’ opinion we accepted this limitation to the study, particularly as this sort of data is often incomplete. Paradoxically fewer biopsies were taken in the 'suspicious' group than those thought to be definitely malignant. It would be clinically more appropriate to increase the number of biopsies in this group rather than take a greater number of biopsies in patients where the endoscopist is more confident that an ulcer is malignant.

Another finding from this study relates to the small number of biopsies taken from ‘benign’ looking ulcers. In the emergency situation it is perhaps not surprising that the focus of the procedure was on treatment rather than diagnosis but lack of a biopsy protocol in this situation did result in 6 cancers being missed initially. Ulcer size appeared to be a factor in determining biopsy rates and small ulcers (5-10 mm) were biopsied less and very few ulcers were biopsied seven times, irrespective of size.

In conclusion this study has shown that endoscopists are good at diagnosing benign ulcers taking fewer biopsies but mis-diagnosing 4.4% (6/137) of cancers. Or for every 20 ulcers considered to be benign one will actually be malignant.

“Suspiciousness” of malignancy appears to relate to ulcer size as well as appearance although inadequate numbers of biopsies are taken compared to frankly malignant looking ulcers. Finally, antisecretory drug therapy does appear to mask the endoscopic appearance of "malignancy" making this a less likely endoscopic diagnosis. We are now encouraging endoscopists to increase the biopsy rate for patients with “suspicious” ulcers. In the emergency situation biopsy should be performed once endoscopic therapy has been completed, or a repeat gastroscopy should be performed prior to discharge in order to obtain biopsy material.

Ulcer n=196	All	"Looked benign"	"Looked suspicious"	"Looked malignant"
Diagnosed by Junior endoscopist	97	73	16	8
Senior endoscopist (missing data n=19)	80	60	11	9
Diagnosed at List	73	48	14	10
Open access	28	21	3	4
Emergency	82	66	11	3
PEG	2	2	0	0
Operative (missing data re endoscopic appearance n = 3)	11	0	0	0
Mean size (mm) (median, range)	16.7 (10, 5-100)	11.5 (10, 5-60)	24.3 (20, 5-100)	41.8 (42.5, 6-90)
Location (n=)				
OGJ	12	6	4	2
Proximal	49	35	7	6
Distal	123	91	17	8
Biopsy rate (% of endoscopies where biopsies taken)	70.0 (133/190)	62.1 (82/132)	96.2 (26/27)	87.5 (14/16)
List	95.4 (63/66)	-	-	-
OAG	96.4 (27/28)	-	-	-
Emergency	38.0 (30/79)	-	-	-
Number of biopsies (mean, median, range)	2.2, 2, 0-6	1.8, 2, 0-6	3.6, 4, 0-4	4.2, 4, 0-6
List	3.2, 3, 0-6	2.6, 3, 0-6	4.4, 5, 1-6	4.0, 4, 0-6
OAG	3.4, 4, 0-6	3.0, 3, 0-5	4.0, 4, 4	5.3, 6, 3-6
Emergency	1.0, 0, 0-6	0.75, 0, 0-4	2.4, 2.5, 0-5	3.3, 4, 0-6
Sclerotherapy rate at emergency endoscopy (%)	34.1 (28/82)	37.9 (25/66)	37.5 (3/11)	0 (0/3)
Patients taking AST prior to diagnosis (%)	21.4 (40/187)	21.6 (29/134)	32.0 (8/25)	12.5 (2/16)

Table 5.1. Ulcer demographics.

	Positive predictive value of macroscopic judgement	
	Benign	Suspicious or malignant
Junior	0.96 (70/73)	0.63 (12/19)
Senior	0.95 (57/60)	0.6 (12/20)
All	0.96 (131/137)	0.58 (26/45)
+AST	0.93 (27/29)	0.3 (3/10)
-AST	0.97 (102/105)	0.65 (20/31)
List	0.94 (45/48)	0.59 (14/24)
+AST	0.85 (11/13)	0.67 (2/3)
-AST	0.97 (31/32)	0.61 (11/18)
OAG	1.0 (21/21)	0.71 (5/7)
+AST	1.0 (13/13)	0.5 (1/2)
-AST	1.0 (8/8)	0.8 (4/5)
Emergency	0.95 (63/66)	0.50 (7/14)
+AST	1.0 (3/3)	0.4 (2/5)
-AST	1.0 (61/61)	0.5 (4/8)

Table 5.2. Positive predictive value of endoscopic judgement.

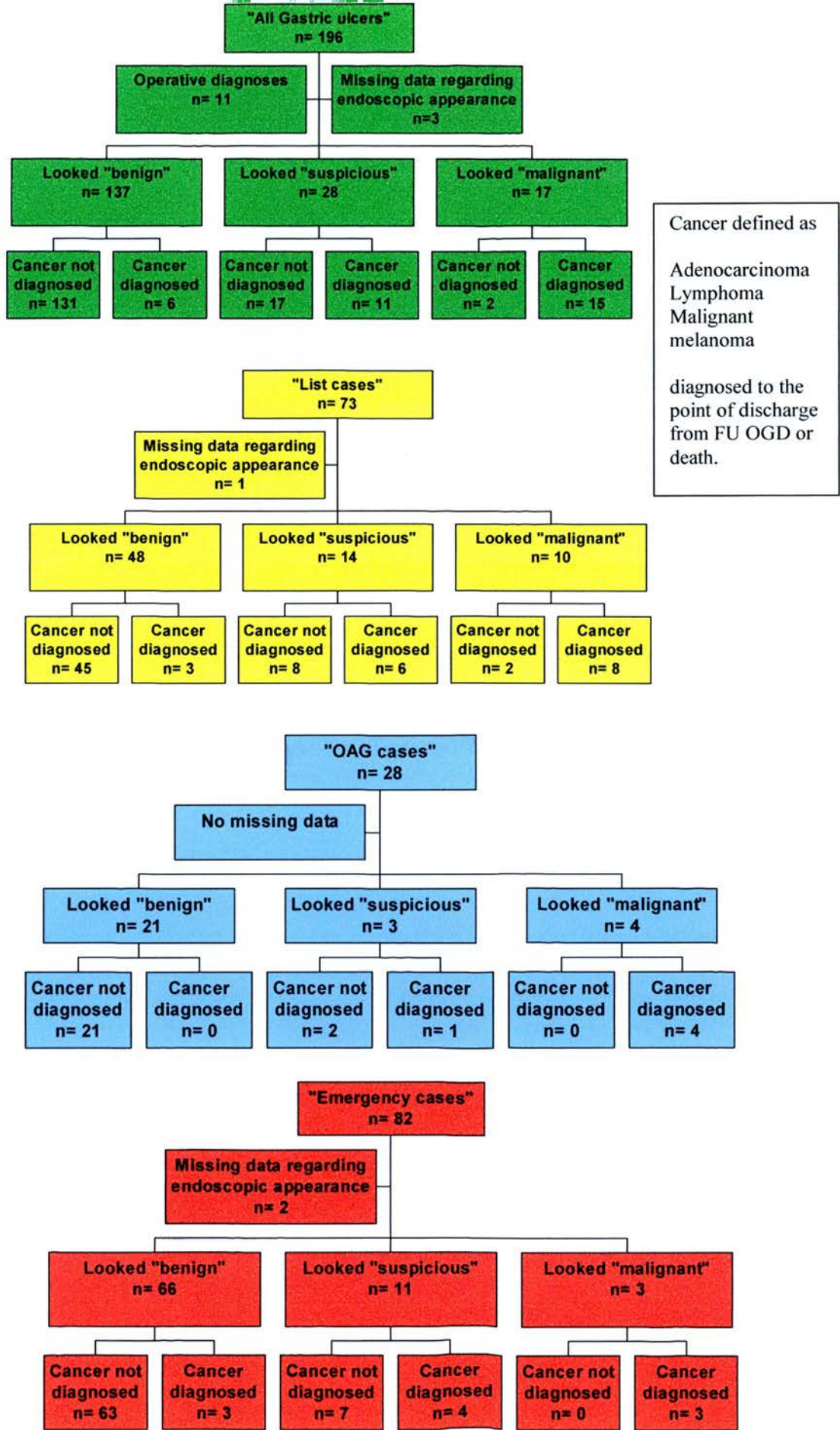


Figure 5.1. Endoscopic appearance by type of diagnostic list.

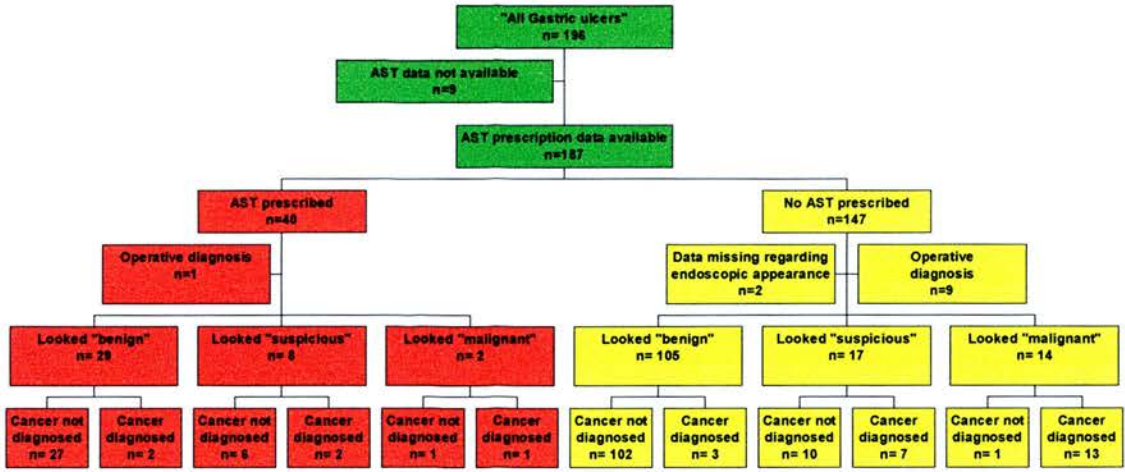


Figure 5.2 (a). Endoscopic appearance and the effect of AST.

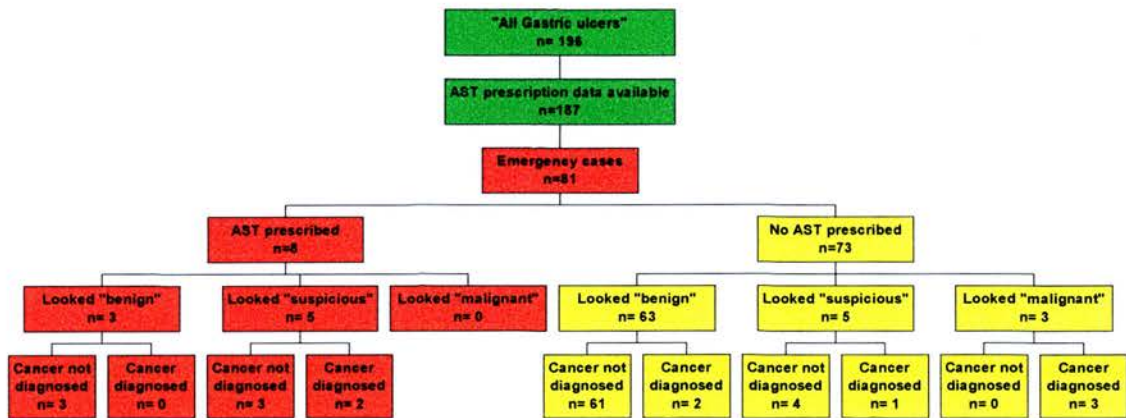
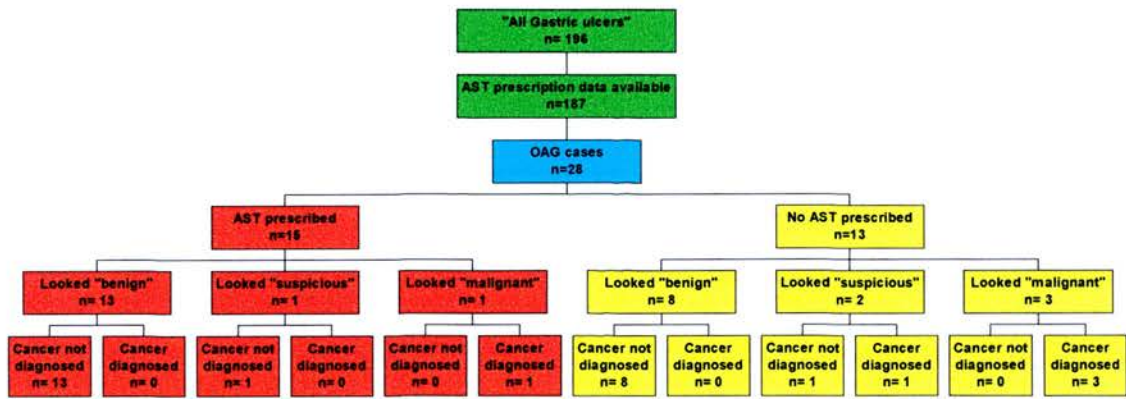
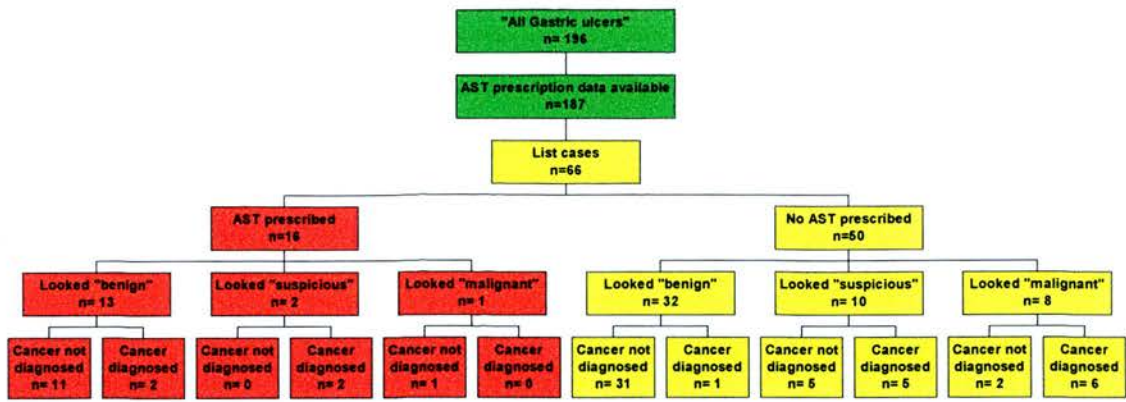


Figure 5.2 (b). Endoscopic appearance and the effect of AST by type of diagnostic list.

Chapter 6. Prospective study of the use of chromoendoscopy.

6.1 Introduction.

Endoscopy is considered to be the "gold standard" in the diagnosis of luminal upper gastro-intestinal disease being superior to radiological techniques¹⁸²⁻¹⁸⁵ but as shown in chapters 4 and 5 lesions are being missed and inadequately biopsied. In addition to this are we missing subtle mucosal abnormalities?

In Japan and elsewhere, chromoendoscopy (also known as dye-scattering, chromoscopy, dye staining, vital staining), is widely used to improve the detection of subtle mucosal changes which may represent early malignant lesions^{125;126;128-130;133;186} and to delineate the mucosa¹⁸⁷.

Chromoendoscopy is not routinely utilised in the UK and thus there is no published data regarding its efficacy in improving the endoscopic detection rate of clinically significant lesions when used in the UK.

Although endoscopists are encouraged to biopsy all irregularities within the stomach, to avoid missing early gastric cancer, in reality this strategy is likely to overwhelm the currently available pathology services in many hospitals. Indeed the Royal College of Pathologists have recognised this and recently published a report which advocates taking a biopsy of only clinically significant lesions¹⁸⁸.

6.2 Aim

This prospective study aimed to investigate the detection rate of additional clinically significant lesions, in a symptomatic population over the age of 50 years referred for open access endoscopy, by utilising chromoendoscopic techniques and to assess the impact on pathology services of a rigorous biopsy policy.

6.3 Patients and methods

All patients aged 50 years or over with upper GI symptoms referred for open access endoscopy to the James Cook University Hospital were eligible for the study during the period October 1999 until June 2001. The cancer referral guidelines advocate investigation of dyspepsia in those over 55 years when the symptoms are of recent onset although the guidelines allowed for this age to be lowered if thought appropriate locally. In this study we chose a lower age for pragmatic reasons to ensure that during the period of research an adequate number of patients would undergo chromoendoscopy.

Local Ethics Committee approval was obtained.

A patient information sheet explaining the nature of the study was enclosed with the appointment letter sent from the hospital. On arrival at the endoscopy centre the patients were clerked by the nursing staff and the study further explained. Patients who then did not wish to participate in the study underwent a standard endoscopy. Those who wished to participate in the study were consented by the investigator (SP) and an endoscopy was performed using local anaesthetic throat spray (1% lignocaine) or intravenous midazolam, depending on patient preference. The patient then underwent a “standard” endoscopy using an Olympus videoendoscope (XQ230, Q200, XP240, XQ240, T240) linked to an Olympus CV240 processor and the findings recorded. In the absence of contra-indications buscopan 20mg iv (repeated if necessary to a maximum dose of 40mg) was used if mucosal views were sub-optimal as a result of gastric contractions. The stomach and any Barrett’s oesophagus identified was then sprayed, using an Olympus dye spray catheter (PW 6P-1, PW5L-1) placed through the biopsy channel, with up to 20mls of a 0.5% methylene blue solution (Martindale pharmaceuticals, Romford) containing 0.5ml simethicone

(Infacol™, Pharmax Ltd, Bexley), after surface mucus had been cleared with simethicone (diluted up to 20mls). The spraying was performed from the pylorus proximally in a helical pattern with retroversion of the endoscope to spray the proximal stomach. The whole stomach was sprayed. Excess pooled dye was aspirated. Discrete changes in surface contour or discolouration compared with surrounding mucosa were recorded using a Sony digital still mini-disc recorder (DKR 700P). Biopsies from identified areas were sent for routine histological analysis.

Between patients the endoscope was cleaned as per BSG guidelines¹⁸⁹.

Patients were warned of the potential for discolouration of their urine and stools.

6.4 Results.

A total of 1008 patients, from 65 GP practices, were studied with a mean age of 62.8 years (range 50-88, median 61.8 years). There were 450 males with a mean age of 63.3 years (range 50-88) and 558 females with a mean age of 62.3 years (range 50-87).

6.4.1 Risk factors

All patients were over 50 years of age and 518 patients (51.4%) reported regular alcohol intake with a mean intake of 11.9 units per week (median 7.0, range 1-70 units) (men mean 15.8, median 12, range 0-70, women mean 6, median 4, range 0-40). Two hundred and five patients (20.3%) were smokers (mean 14.3 cigarettes/day, range 1-60).

6.4.2 Symptoms and prior treatment.

The nature of the symptoms at the time of the endoscopy is shown in table 6.1.

Acid suppression therapy (AST) was prescribed for 487 patients (48.3%) prior to endoscopy of whom 231 were prescribed H₂RA and 288 a PPI (with 32 having been prescribed a H₂RA earlier). A quarter (254) of patients had been prescribed a NSAID.

For those prescribed PPI the median duration of treatment prior to endoscopy was 61 days (mean 333, range 0- 4059). The median time off treatment prior to endoscopy was 23 days.

6.4.3 Expected diagnoses.

In 982 cases the referring GP stated the expected diagnosis or diagnoses as shown in table 6.2. Gastric cancer was considered as a possible diagnosis in only 3.0% of referrals.

6.4.4 Endoscopy

Topical anaesthesia was used in 48.9% of endoscopies. Buscopan iv was used in 19.6% of cases.

The mean time taken to complete chromoendoscopic examination of the upper gastro-intestinal tract was 14.7 minutes (median 15, range 2-30).

6.4.5 The findings with "standard" endoscopy.

Details of the findings are shown in table 6.3 and compared with the historical findings of the open access service in figure 6.1.

6.4.6 Extra findings within the stomach with chromoendoscopy.

Extra findings were present in 142 patients, 14% of endoscopies of which 100% were benign.

Details are shown in tables 6.4 and 6.5.

Examples of chromoendoscopy shown in figure 6.2.

6.4.7 Upper GI cancer

A total of 17 patients (1.7%) had upper GI cancer as shown in table 6.3. All were detected on initial endoscopy prior to the use of methylene blue.

Barrett's oesophagus was found in 33 patients none of which showed any abnormality on chromoendoscopy.

6.4.8 Findings "missed/masked" by chromoendoscopy.

After a mean follow up of 3.1 years (median 3.14, range 2.2-3.9) there have been 2 patients subsequently diagnosed with oesophago-gastric adenocarcinoma. In both cases the diagnosis was made within 8 weeks. In one case the patient could not be intubated with throat spray but endoscopy was successful with sedation; the second patient had extensive gastric erosions and was brought back for repeat endoscopy to ensure healing. It was at this follow up endoscopy that the superficial cancer (not seen on the original endoscopy) was diagnosed at the oesophago-gastric junction.

6.4.9 Pathology workload.

After chromoendoscopy an extra 326 biopsies were taken (mean 2.3 per endoscopy, 1-7). This equates to 3.7 weeks of extra work for the pathologists.

The number of clinically significant diagnoses was not increased by the extra biopsies taken after chromoendoscopy.

6.5 Discussion

In this study chromoendoscopy, with methylene blue used to detect additional clinically significant findings at upper GI endoscopy, was evaluated in a population aged over 50 years. This age group was chosen to yield a significant number of patients in whom it was expected there would be a reasonable chance of identifying pathology. Methylene blue in this study was used as a contrast dye to delineate the surface topography. It was decided to use methylene blue as opposed to indigo carmine, the usual contrast agent used to visualise the stomach, as it was readily available and it had a favourable side effect profile.

Chromoendoscopy proved to be easy to perform in the endoscopy unit without significantly prolonging the duration of the endoscopy and without any complications or adverse events.

A rigorous biopsy policy was adopted for this study. Widespread adoption of such a policy would clearly have practical implications due to the concerns surrounding potential transmission of vCJD in endoscopy and thus the move towards more costly disposable biopsy forceps.

There were additional findings noted in approximately 15% of the endoscopies performed. Of these potentially pre-malignant lesions were detected in 45 cases (31.7%). There is currently no accepted evidence for surveillance of these lesions however Whiting *et al* showed that with annual follow up endoscopies for atrophic gastritis and intestinal metaplasia the risk of malignancy was 11%. Thus they have

suggested that there should be a multicentre randomised control trial to examine the benefit of surveillance for these premalignant lesions⁸⁵.

As expected given the sample size and relative low incidence of gastric adenocarcinoma, along with the selection bias of the population studied, it was not possible to show an improvement in the detection of malignancy.

Follow up of these patients has shown that in one patient a significant lesion was missed at endoscopy. In this case a junctional tumour was diagnosed at a routine planned follow up endoscopy. Although all patients underwent a "standard" endoscopy prior to the use of the dye spray it is worth considering that dye does pool in the fundus and care should be taken to ensure that the proximal stomach is adequately visualised.

Thus, although chromoendoscopy did not reveal extra cancers it was useful to delineate the surface of the stomach and highlighted areas of potential abnormality. It proved practicable for day-to-day use and without side effects.

The extra burden generated however for the pathology department was significant, amounting to almost a month of a pathologist's time. In an era where pathology departments are under significant workload and staffing pressures it is hard to justify the extra work generated as a result of the "biopsy everything" ethos when the yield of significant pathologies was so low. If no biopsies had been taken at all from subtle mucosal abnormalities the mis-rate of early gastric cancer would have been 1 in 1000 patients endoscoped.

Using a “gold standard” method to identify small or subtle mucosal lesions seems not to be routinely worthwhile and simply adds to the burden of GI pathologists. It appears that early lesions are not being missed in any significant number. The main problem as outlined in chapter 4 is the failure to biopsy an obvious lesion because it looks benign.

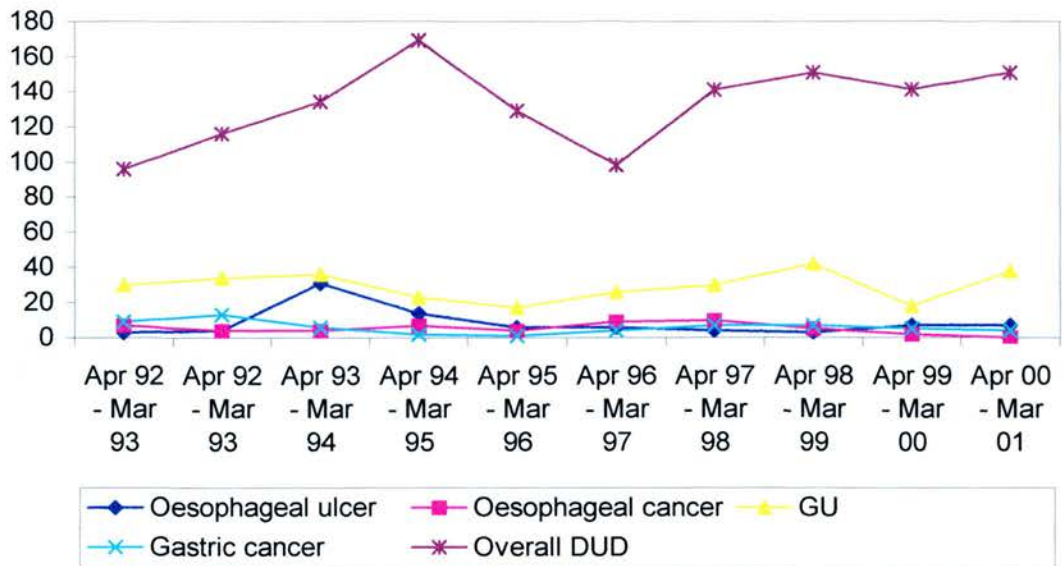


Figure 6.1 Comparison of historical open access findings and findings during research period.

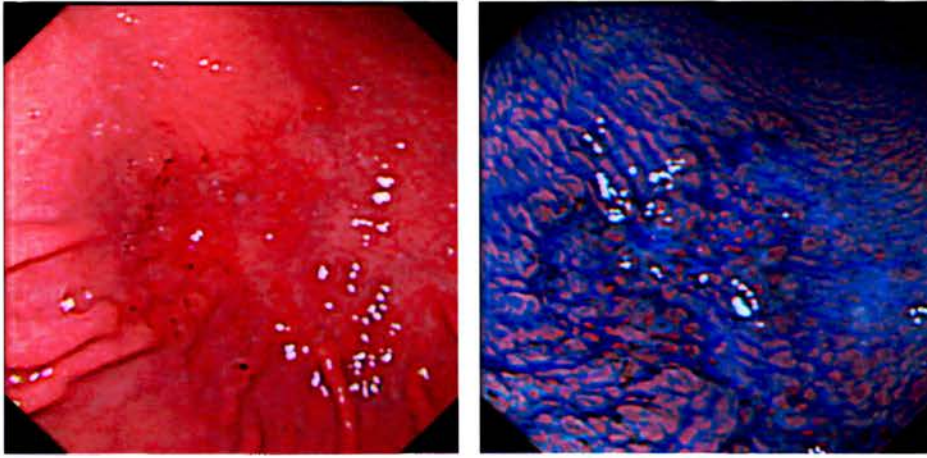


Fig. 6.2 (a). Early gastric cancer (a) before dye spray (b) after dye spray.

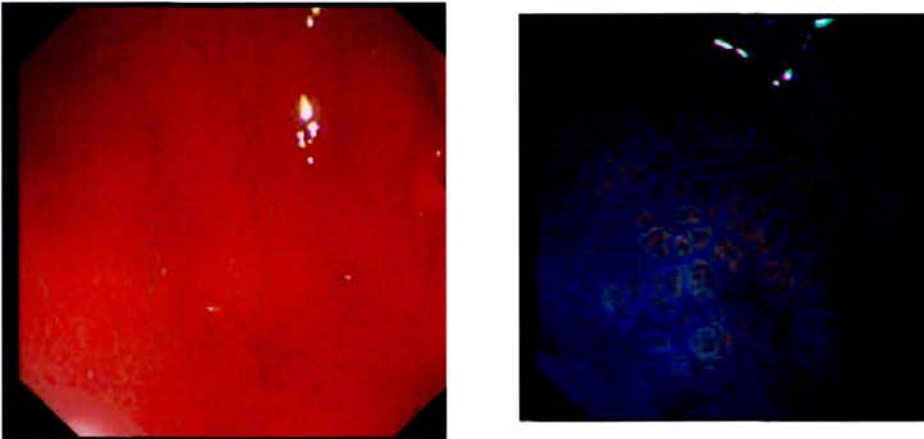
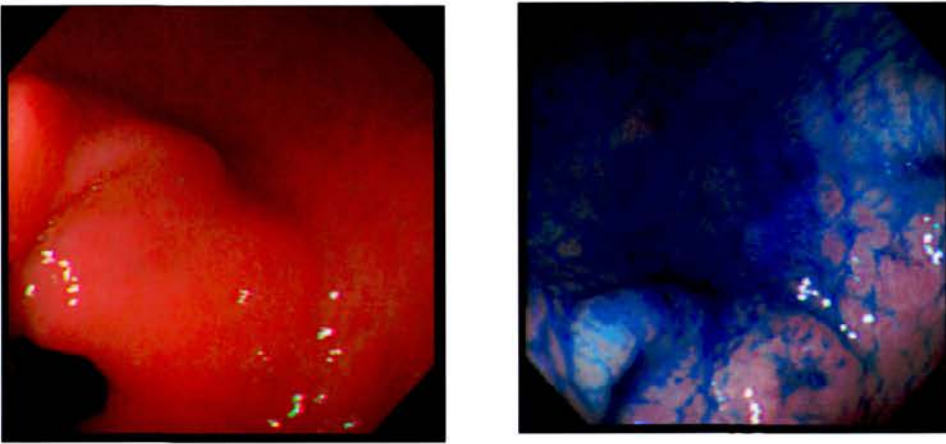


Figure 6.2 (b). Mucosa before dye spray (a) after dye spray showing intestinal metaplasia

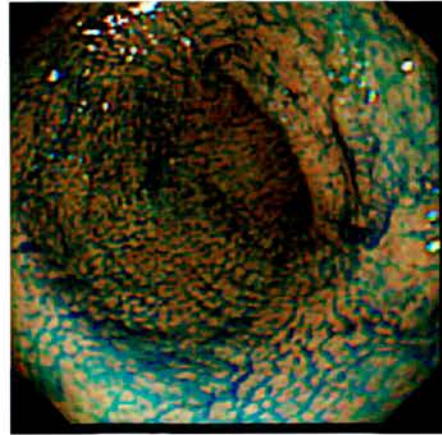
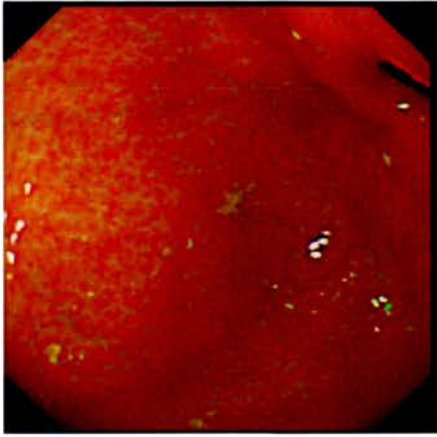


Figure 6.2 (c). Raised lesion seen after chromoendoscopy.

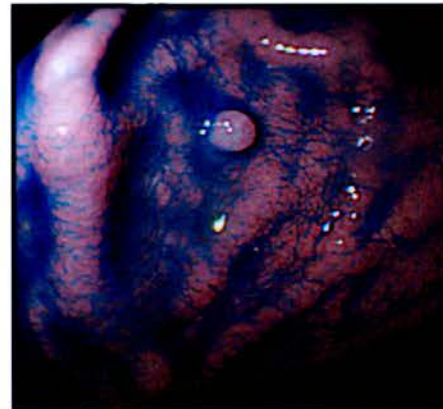
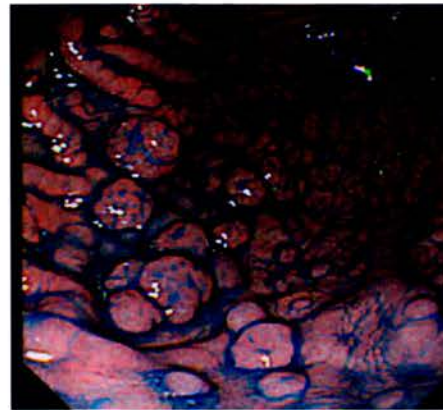
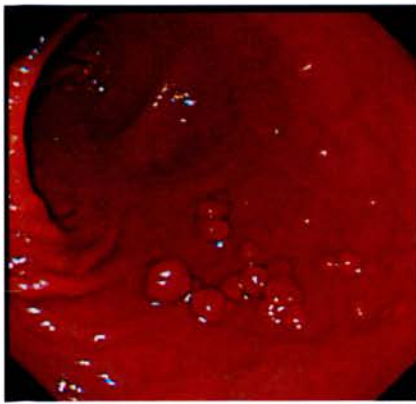


Figure 6.2 (d). Polyps delineated by chromoendoscopy.

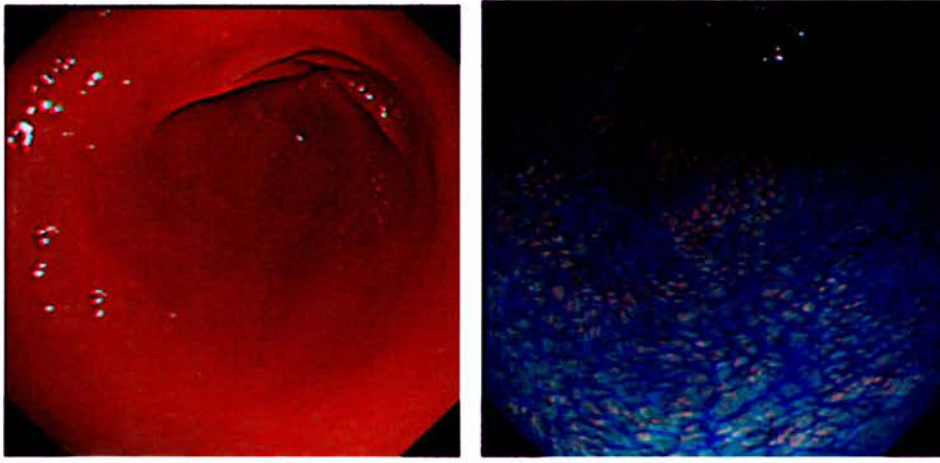


Figure 6.2 (e). Gastric mucosa (a) before dye spray (b) after dye.

	N=	%
Epigastric pain	694	68.8
Heartburn	452	44.8
Retrosternal pain	401	39.8
Nausea	265	26.3
Vomiting	111	11.0
Anorexia	87	8.8
Wt loss	75	7.4
Dyspepsia	6	0.6
Dysphagia	7	0.7
Haematemesis/ melaena	5	0.5
None	5	0.5
Other	72	7.1
"Alarm" symptoms (vomiting/dysphagia/anaemia/wt loss)	174	17.3

Table 6.1 Symptoms at time of endoscopy.

	Number	%
GERD	476	48.5
Hiatus hernia	205	20.9
Not known	158	16.1
Duodenal ulcer	147	15.0
Gastric ulcer	123	12.5
Normal	47	4.8
Gastric cancer	29	3.0

Table 6.2 Expected diagnoses as stated by GP.

Finding	Number
Normal oesophagus	603
Hiatus hernia	139
Oesophagitis- grade 1	119
Oesophagitis- grade 2	119
Oesophagitis- grade 3	31
Oesophagitis- grade 4	45
Oesophageal ulcer	10
Barrett's oesophagus	33
Other oesophagus	44
Normal stomach	143
Gastric erythema	789
Polyp	35
Gastric ulcer	45
Normal duodenum	778
Duodenitis	158
Duodenal scarring	11
Duodenal ulcer	42

Site	Finding	Number
Oesophagus	Squamous carcinoma	4
	Adenocarcinoma	3
	Small cell cancer	1
Stomach	Adenocarcinoma	7
	Early gastric cancer	1 (14%)
	Lymphoma	1

Unable to intubate in 3 cases, endoscopy abandoned (food residue, patient intolerance) in 6 cases.

Table 6.3 Findings with standard endoscopy.

Nature of finding	Number
Raised mucosal abnormality	19
Polypoidal lesion	36
Flat mucosal abnormality	33
Depressed lesion/erosion	37
Raised erosion	10
Other (scar, prominent fold)	7

Table 6.4. Additional findings following chromoendoscopy

Histological finding	Number
Normal	28
Gastritis	56
Atrophy	6
Incomplete intestinal metaplasia	3
Complete intestinal metaplasia	0
Unspecified intestinal metaplasia	32
Indefinite dysplasia	3
Mild dysplasia	1
Other	7

Table 6.5. Histological findings from extra biopsies.

Chapter 7 Conclusions

Flexible fiberoptic examination of the upper GI tract has been part of standard clinical practice for over 30 years. During this time, the incidence of upper GI adenocarcinoma has slowly declined but mortality has remained stubbornly high with a depressingly low 5-year survival, little different from the time when the barium meal was the standard investigation of the upper GI symptoms. Changing patterns of disease (decreasing distal gastric cancers and increasing numbers close to the cardia) do not explain the failure to improve prognosis but the prognosis of early gastric cancer is acknowledged to be very good with a 5-year survival rate in excess of 90%. Why have modern endoscopic methods of diagnosis not had any impact on the outcome of this truly awful disease and is there any prospect of improving the situation during the next 30 years?

A major factor in the UK is the late presentation of upper GI cancer and this thesis was concerned with clarifying and resolving the issues pertinent to this. Each chapter has addressed a different contributory element:-

- Quantifying the time course to diagnosis of oesophago-gastric adenocarcinoma in the South Tees population.
- Evaluating the effect of antisecretory drug therapy on the diagnostic process and the delay that antisecretory therapy engenders.
- Examining the long-term outcome of these delays in the clinical context.

- Analysing the effect of various strategies to improve early diagnosis, in particular the implementation of the Urgent Referral Guidelines for upper GI cancer, known more commonly as the “two week rule” guidelines.
- Identifying why not all upper GI cancers are diagnosed at the first endoscopy.
- Determining how many upper GI cancers are truly missed at endoscopy and how many are simply not diagnosed, even though an endoscopic abnormality is clearly recorded in the endoscopy report.
- Investigating the use of chromoendoscopy on the gastric mucosa to identify minor abnormalities which might represent early gastric cancer and determine the effect of an aggressive biopsy policy in patients “at risk” by virtue of age.

and

- Investigated the endoscopists' evaluation of histopathology from the appearance of gastric ulcer disease.

The research that forms the basis of this thesis has confirmed that there are unacceptable delays in the diagnosis of upper GI adenocarcinoma in the UK. The time from first symptom to diagnosis has been shown to be 30 weeks, with patients spending twice as long in the primary care phase of the diagnostic pathway as compared with the secondary care phase. Patients with oesophageal cancer take longer to present to their GP and longer to be seen in secondary care as a result of the more "benign reflux-like " nature of their symptoms. The interpretation of the patient's symptoms by their GP and the patient's perception of their presenting symptoms is crucial to the diagnosis of the patient with cancer. Much effort has been made to use symptoms to identify patients at most risk of cancer through the "2 week

rule urgent referral guidelines". However this thesis has shown that only 50% of patients present to their GP with "alarm" symptoms and only 78% of patients have "alarm" symptoms at diagnosis. Over time patients with "benign" symptoms develop "alarm" symptoms and are referred but using "alarm" symptoms alone as the trigger for referral is associated with a delay in diagnosis. Patients with "benign" symptoms were prescribed powerful acid suppressing medications prior to referral for endoscopy, which was often delayed as a result. Surprisingly patients with "alarm" symptoms were also treated, although less often. This treatment was initiated at the patients' first visit to the GP and delayed diagnosis by 18 weeks. Over this time patients with "benign" symptoms developed "alarm" symptoms but patients with "alarm" symptoms did not have resolution of their symptoms. It might be anticipated that widespread use of powerful acid suppressing drugs would inevitably delay diagnosis in treated patients by a sufficient amount as to worsen prognosis compared to their untreated counterparts. However work in this thesis did not show this and those given treatment did not experience a worse outcome.

As stated earlier, the "2 week urgent referral guidelines" were introduced to speed referral, for out patient review and investigation, those patients with "alarm" symptoms. This thesis demonstrates that a significant number of patients with an ultimate diagnosis of upper GI cancer did not meet the referral criteria at their first GP visit or indeed at diagnosis. Extending these criteria to include patients with unexplained weight loss and anaemia would improve this but would be unlikely to improve prognosis as such symptoms denote advanced disease. The newly released NICE dyspepsia guidelines (www.nice.org.uk) advocate the investigation of these two groups of patients *only if dyspepsia is present* but do not recommend

investigation of those with new onset dyspepsia without a therapeutic trial of *H. pylori* eradication therapy or acid suppressing medication first. With this approach there is a danger of delaying the diagnosis further in this group of patients (which is the largest group identified in this thesis). Clearly these NICE dyspepsia guidelines are aimed at reducing unnecessary gastroscopy but they do so at the very great risk of decreasing still further our ability to diagnose upper GI malignancy at an early (potentially curable) stage. New strategies need to be developed to identify high-risk patients who would qualify for endoscopy before developing classic "alarm" symptoms.

The delays in the referral pathway are only one element in the overall delay in diagnosis. Essential to the process of diagnosing the upper GI adenocarcinoma is endoscopy. This thesis has demonstrated that over 1/3 of patients have had prior investigations in the 3 years prior to when the diagnosis was made. In three-quarters of these cases the prior test was endoscopy. When all reasons why a diagnosis was not made at the initial endoscopy were considered, 10% of patients had their cancer truly "missed" at endoscopy. These patients represented later and were diagnosed. The larger group who were delayed and diagnosed at a planned follow up endoscopy constitutes a huge waste of endoscopic resource. The reason these cancers were not diagnosed at the first endoscopy was not inexperience of the operator (most endoscopies were performed by senior doctors) or that lesions were not seen (in the majority of cases) but rather that insufficient biopsies were taken from lesions that were in the main ulcerated. Acid suppressing medication may play a role by "masking" the true nature of a lesion under a blanket of benign-looking re-epithelialisation.

The use of chromoendoscopic techniques to examine the gastric mucosa yielded extra findings in 14% of endoscopies performed in a high-risk population (those over 55 years). All the lesions biopsied were benign although 1/3 were potentially pre-malignant lesions. The rigorous biopsy policy used generated 3.7 weeks extra work for the pathologists which is hard to justify given that no extra cases of malignancy were found and considering the results from the retrospective review, which suggested that even obvious lesions are being seen but not being diagnosed due to lack of biopsies. The inability to diagnose obvious lesions, through inadequate biopsies, needs to be fully addressed before time and effort is spent looking for subtle lesions. In some instances when there was an obvious lesion biopsies were not taken at all, or the biopsies taken were inadequate in quantity or quality. It is apparent, from the data presented in this thesis on gastric ulcer biopsy rates, that the endoscopist, when looking at a lesion makes a decision (which may be subconscious) as to the nature of the lesion and its malignant potential. This operator bias has been shown in this thesis to influence the number of biopsies that are taken. More biopsies were taken from "suspicious-" or "malignant-looking" ulcers than from "benign-looking" ulcers. However the endoscopists' ability to tell whether an ulcer was "benign" or "malignant" was poor. This ability was hampered further by acid suppressing medication, which reduced the positive predictive value of the macroscopic judgement. It seems likely therefore that this type of medication does alter the macroscopic appearance of ulcers in some way such that it influences the endoscopist.

In summary, patients delay seeing their GP with symptoms and because of the often benign nature of those symptoms referral is delayed especially if the patient is treated with acid suppressing medication. Further delay occurs because the cancer is not diagnosed at endoscopy due to inadequate biopsies being taken. The NICE dyspepsia guidelines will not improve the outcome of patients with oesophago-gastric cancer as patients with early disease lacking “alarm symptoms” will not be offered an endoscopy and those that are eventually investigated will have been on acid suppression for some time. Some of the data from this thesis may influence the debate on this subject.

If the delay in the diagnosis of upper GI cancer is to be improved patients with upper GI symptoms who are “at risk” should be endoscoped irrespective of the nature of the symptoms. An adequate number of biopsies should be taken from the lesions routinely as part of a biopsy protocol. Acid suppressing medication should be withheld until after endoscopy.

The difficulty is identifying the “high risk” population given the extremely high prevalence of dyspepsia in the population and balancing the cost-benefit of any strategy that increases endoscopy demand. As symptoms fail to discriminate those with early malignancy, which is the group most likely to benefit from diagnosis, a new approach is needed if outcome is to be improved. This should focus on reducing the incidence of upper GI cancer in the population through risk reduction strategies and be linked to a new method to identify “at risk” individuals through multifactorial risk profiling.

Current strategies are more likely to worsen survival by excluding curable patients from early investigation and despite the NICE guidelines the debate is far from over.

The results of the studies outlined in this thesis will inform that debate and in particular re-examine the guidance that new onset dyspepsia (without “alarm” symptoms) in the over 55 year age group does not require endoscopy.

Publications

Panter SJ, Bramble MG, O'Flanagan H, Hungin APS. Urgent cancer referral guidelines – a retrospective cohort study of referrals for upper GI adenocarcinoma. *British Journal of General Practice*, 2004, **54**,611-13.

Panter SJ, Bramble MG, O'Flanagan H, Hungin APS. Empirical acid suppression therapy delays diagnosis of upper gastrointestinal adenocarcinoma but does not effect outcome. *AP&T*, 2004, **19**, 981-88.

(Appendix

Posters and Oral Presentations.

Irish Society of Gastroenterology G2K meeting 7th-9th September 2000

Panter SJ, Bramble MG. Is gastric ulcer disease changing? A prospective study. *Irish Journal Med Sci* 169 (3); 20

BSG meeting 18th-21st March 2001

Panter SJ, Bramble MG “Routine“ chromoendoscopic imaging in the UK- is it worthwhile? *Gut* (suppl) **48** (1) Mar 2001

Panter SJ *et al.* A 9 year retrospective study of upper GI adenocarcinoma. How many cancers are we missing? *Gut* (suppl) **48** (1) Mar 2001

Panter SJ, Bramble MG. Do gastric “ulcer-cancers” present differently to “mass-cancers”? *Gut* (suppl) **48** (1) Mar 2001 (**Oral presentation in Plenary session**).

Northern Primary Care Research Network and Royal College General Practitioners Annual Research Presentation Conference, Durham 22nd November 2001.

Panter SJ, O'Flanagan H, Bramble MG. Do gastric "ulcer-cancers" present differently to "mass-cancers"? (**Oral presentation**)

BSG meeting 18th-21st March 2002.

Panter SJ, O'Flanagan H, Bramble MG, Hungin APS. A 10 year retrospective study of upper GI adenocarcinoma. How can we improve early diagnosis? *Gut* (suppl) **50** (11); A11 Mar 2002 (**Oral presentation**)

Panter SJ, O'Flanagan H, Bramble MG, Hungin APS. Empirical acid-suppressing drug therapy (AST) is associated with delayed diagnosis of oesophago-gastric cancer *Gut* (suppl) **50** (11); A11 Mar 2002 (**Oral presentation**)

Panter SJ, Bramble MG. Is it necessary to biopsy acutely bleeding gastric ulcers at the initial endoscopy? *Gut* (suppl) **50** (11); A51 Mar 2002 (**Plenary poster**)

American Gastroenterology Association - Digestive Diseases Week 19th-22nd May 2002.

Panter SJ, O'Flanagan H, Bramble MG, Hungin APS. Does acid-suppressing therapy delay the diagnosis of upper GI adenocarcinoma? (**Poster of Distinction**). *Gastroenterology* **122** (4), Suppl. 1, A-591.

Association of Physicians Meeting July 2003

Panter SJ, O'Flanagan H, Bramble MG, Hungin APS. Empirical AST delays the diagnosis of upper GI adenocarcinoma but does not effect outcome? (**Oral presentation**)

BSG meeting 18th-21st March 2005.

Panter SJ. Delays in the diagnosis of upper GI cancer (**Invited Keynote lecture to Primary Care Section**)

BSG meeting 26th-29th March 2007.

Panter SJ, Bramble M, Hungin APS, Jones R, O'flanagan, H. Inadequate numbers of biopsies results in delayed diagnosis of upper GI adenocarcinoma *Gut* (suppl) **56** (11); A98 Mar 2007 .

Panter SJ, Bramble M, Hungin APS, Jones R. Perception of the malignant potential of gastric ulcers is influenced by acid suppressing medication *Gut* (suppl) **56** (11); A98 Mar 2007 .

Appendix I. GASTRIC CANCER STUDY

Study Number **CANCERIID** Practice Code **GP**
D number **DNUMBER** NHS number **NHSNUMBER**
Name **FIRSTNAME** **SURNAME** Address **ROAD**
Date of birth **DOB** **TOWN**
Sex **SEX** Male **M** Female **F** Postcode
POSTCODE

SECTION A – CANCER DIAGNOSIS

Date cancer diagnosed **DATECANCER** Age at diagnosis in years **AGEATDIAGN**

Diagnosis investigation **CANCERINVE**

Barium Studies **DB** Gastroscopy **DG** Other **DO** If other, please specify **OTHERINVES**

Diagnosis **DIAGNOSIS** Squamous carcinoma oesophagus **SCO**
Adenocarcinoma oesophagus **ACO**
Adenocarcinoma stomach **ACS**
Other **OTH**

If other please specify histology and site **HISTOLOGYS**

Symptoms at time of cancer diagnosis **CANCERSYMP** Dyspepsia / Heartburn / Reflux **1**
Epigastric Pain ± other symptom(s) **2**
Heamatemesi s ± Melaena **3**
Other **4**

If other please specify **OTHERSYMP0**
(e.g. Anaemia, Dysphagia, Vomiting, Weight Loss, Early Satiety)

If Gastroscopy, **CANCEROGD** OAG **1** List **2** Emergency **3**

Operator name **OPCANCER** Number of gastric biopsies taken **INDEXBIOPS**

Cytology taken **INDEXCYTOL** Yes **Y** No **N**

Result **CYTO0RES** Malignant **M** Benign **B**

Naked eye appearance of lesion **NAKEDEYE0**

Protuberant mass **1** Ulcerated lesion **2** Mucosal abnormality **3**

Oesophageal stricture **4** Other **5** If other, please specify **OTHEREYE0**

Date first GP consultation with present symptoms **GPDATEINDX**

Time from consultation to cancer diagnosis **GPINDXTIME** weeks

Was the patient on concurrent Aspirin or NSAIDs **NSAIDINDEX** Yes **Y** No **N**

Patient on AST in time from consultation to cancer diagnosis **ASTINDEX** Yes **Y** No **N**

If Yes, Time from consultation to AST initiated **ASTTIME0** weeks

Duration of AST prior to cancer diagnosis **DURATION0** weeks

Which medication? **H2RA0** H₂RA for **H2RAWEEKS0** weeks **H2RASCRIPT0**
Monthly scripts

PPI0 PPI for **PPIWEEKS0** weeks **PPISCRIP0**
Monthly scripts

Was treatment stepped up from an H₂RA to a PPI in this time? **STEPUP0** Yes **Y** No **N**

Was treatment stopped by GP prior to cancer OGD? **STOPGP0** Yes **Y** No **N**

If Yes.. Date stopped **STOPDATE0** No. of weeks prior to cancer OGD **STOPWEEKS0**

Was the patient on antisecretory therapy at the time of the cancer OGD (i.e. 3 weeks or less)
ONAST0

Yes **Y**

No **N**

Was cancer suspected by GP at this time **GPSUSPECT** Yes **Y** No **N**

Previous GI investigation within 3 years of cancer diagnosis? **PREV3YRS**

Yes **Y** No **N**

If Yes, continue with section B If No, go to section C

SECTION B – PREVIOUS GI INVESTIGATIONS WITHIN 3 YEARS

Investigation(s) **INVESTIGAT**

Barium Studies **1** Gastroscopy **2** Other **3** If other, please specify
INVES3YRS

If Barium Studies is Yes, Date performed **BARIUMDATE** Age in years **BARIUMAGE**
BARIUMDIAG

Diagnosis Normal **0** Abnormal (suspicious) **1** Abnormal (not suspicious) **2**

BARIUMFIND

- DU 1
- GU 2
- GORD 3
- HH 4
- Oesophageal Stricture 5
- Other 6

If other please specify

OTHERBARIU

If Gastroscopy is Yes, number of gastroscopies within last 3 years **OGDLAST3Y**

**Details of previous gastroscopies (in reverse date order from cancer OGD)
GASTROSCOPY 1**

Date previous gastroscopy 1 **DATEGAST1**

Age at gastroscopy 1 **AGEGAST1**

Operator name **OPGAST1**

GASTITYPE OAG 1 List 2 Emergency 3

GASTIDIAG Diagnosis Normal 0 Abnormal (suspicious) 1 Abnormal (not susp) 2

GASTIFIND

DU 1

GU 2

GORD 3

HH 4

Gastritis 5

Oesophagitis 6 Grade 1,2,3,4,5 **GASTIGRADE**

Oesophageal Stricture 7

Other 8

If other please specify **GASTIOTHER**

Number of gastric biopsies taken **GASTIBIPOS**

GASTICYTO Cytology taken Yes Y No N

CYTOIRES Result Malignant M Benign B

Naked eye appearance of lesion **NAKEDEYE1**

Protuberant mass 1 Ulcerated lesion 2 Mucosal abnormality 3 Oesophageal stricture 4

Other 5 If other, please specify **OTHEREYE1**

CLO1 Clo taken Yes Y No N Don't know

U

CLOIRESLT Result Positive Y Negative N Don't know

U

Any other relevant diagnosis at OGD? **GASTISECON**

No 0 DU 1 Oesophagitis 2 HH 3 Stricture 4

Other 5

Treatment received **GASTITREAT** None N

H₂RA H

PPI **P** for **GASTIWEEKS** weeks
Eradication **E**

Symptoms on referral for investigation Dyspepsia / Heartburn / Reflux **1**
GASTISYMPT Epigastric Pain ± other symptom(s) **2**
Heamatemesi s ± Melaena **3**
Other **4**

If other please specify **OTHERSYMPT**
(e.g. Anaemia, Dysphagia, Vomiting, Weight Loss, Early Satiety)

Date first GP consultation with symptoms this episode **GPDATEI**

Time from consultation to OGD 1 **GPTIMEI** weeks

Was the patient on concurrent Aspirin or NSAIDs **NSAIDI** Yes **Y** No **N**

Patient on AST in time from consultation to OGD 1 **ASTI** Yes **Y** No **N**

If Yes, Date start of AST (antise cretory therapy) prior to OGD 1 **ASTIDATE**

Time from consultation to AST initiated **ASTTIMEI** weeks

Duration of AST prior to OGD 1 **DURATIONI** weeks

Which medication this episode? **H2RAI** H₂RA for **H2RAWEEKSI** weeks **H2RASCRIP I**
PPII PPI for **PPIWEEKSI** weeks **PPISCRIP I**

Was treatment stepped up from an H₂RA to a PPI in this time? **STEPUPI** Yes **Y** No **N**

Was treatment stopped by GP prior to OGD 1? **STOPGPI** Yes **Y** No **N**

If Yes.. Date stopped **STOPDATEI** No. of weeks prior to OGD **STOPWEEKSI**

Was the patient on antise cretory therapy at the time of OGD 1 (i.e. within 3 weeks)

ASTGASTROI

Yes **Y**

No **N**

No. of (monthly) prescriptions of AST in time period from OGD 1 to cancer OGD

SCRIPTASTI

No. of (monthly) prescriptions of AST type H₂RA **ASTTYPEHI** PPI

ASTTYPEPI

Therefore, AST **ASTTREATI** None **N** Continuous **C** Intermittent **I**

Time from OGD 1 to diagnosis of cancer **OGDIINDEX** weeks

Did the patient have another OGD prior to OGD 1 (within 3 years of Cancer OGD)?
OTHEROGD1

Yes **Y** No **N**

If Yes, continue with section B **If No**, go to section C

GASTROSCOPY 2

Date previous gastroscopy 1 **DATEGAST2**

Age at gastroscopy 1 **AGEGAST2**

Operator name **OPGAST2** **GAST2TYPE** OAG **1** List **2** Emergency **3**

GAST2DIAG Diagnosis Normal **0** Abnormal (suspicious) **1** Abnormal (not susp) **2**

GAST2FIND

DU	<input type="checkbox"/> 1
GU	<input type="checkbox"/> 2
GORD	<input type="checkbox"/> 3
HH	<input type="checkbox"/> 4
Gastritis	<input type="checkbox"/> 5
Oesophagitis	<input type="checkbox"/> 6 Grade 1,2,3,4,5 GAST2GRADE
Oesophageal Stricture	<input type="checkbox"/> 7
Other	<input type="checkbox"/> 8
If other please specify	GAST2OTHER

Number of gastric biopsies taken **GAST2BIPOS**

GAST2CYTO Cytology taken Yes **Y** No **N**

CYTO2RES Result Malignant **M** Benign **B**

Naked eye appearance of lesion **NAKEDEYE2**

Protuberant mass **1** Ulcerated lesion **2** Mucosal abnormality **3** Oesophageal stricture **4**
Other **5** If other, please specify **OTHEREYE2**

CLO2 Clo taken Yes **Y** No **N** Don't know **U**

CLO2RESULT Result Positive **Y** Negative **N** Don't know **U**

Any other relevant diagnosis at OGD? **GAST2SECON**

No **0** DU **1** Oesophagitis **2** HH **3** Stricture **4**
Other **5**

Treatment received **GAST2TREAT** None **N**
 H₂RA **H**
 PPI **P** for **GAST2WEEKS** weeks
 Eradication **E**

Symptoms on referral for investigation Dyspepsia / Heartburn / Reflux **1**
GAST2SYMPT Epigastric Pain ± other symptom(s) **2**
 Heamatemesis ± Melaena **3**
 Other **4**

If other please specify **OTHERSYMPT2**
 (e.g. Anaemia, Dysphagia, Vomiting, Weight Loss, Early Satiety)

Date first GP consultation with symptoms this episode **GDATE2**

Time from consultation to OGD 2 **GPTIME2** weeks

Was the patient on concurrent Aspirin or NSAIDs **NSAID2** Yes **Y** No **N**

Patient on AST in time from consultation to OGD 2 **AST2** Yes **Y** No **N**

If Yes, Date start of AST (antisecretory therapy) prior to OGD 2 **AST2DATE**

Time from consultation to AST initiated **ASTTIME2** weeks

Duration of AST prior to OGD 2 **DURATION2** weeks

Which medication this episode? **H2RA2** H₂RA for **H2RAWEEKS2** weeks **H2RASCRIPT2**
PPI2 PPI for **PPIWEEKS2** weeks **PPISCRIP2**

Was treatment stepped up from an H₂RA to a PPI in this time? **STEPUP2** Yes **Y** No **N**

Was treatment stopped by GP prior to OGD 2? **STOPGP2** Yes **Y** No **N**

If Yes.. Date stopped **STOPDATE2** No. of weeks prior to OGD **STOPWEEKS2**

Was the patient on antisecretory therapy at the time of OGD 2 (i.e. within 3 weeks)
ASTGASTRO2

Yes **Y**

No **N**

No. of (monthly) prescriptions of AST in time period from OGD 2 to cancer OGD
SCRIPTAST2

No. of (monthly) prescriptions of AST type
ASTTYPEP2

H₂RA **ASTTYPEH2** PPI

Therefore, AST **ASTTREAT2** None **N** Continuous **C** Intermittent **I**

Time from OGD 1 to diagnosis of cancer **OGD2INDEX** weeks

Did the patient have another OGD prior to OGD 2 (within 3 years of Cancer OGD)?
OTHEROGD2

Yes **Y** No **N**

If Yes, continue with section B

If No, go to section C

Time from OGD 2 to diagnosis of cancer **OGD2INDEX** weeks

Did the patient have another OGD prior to OGD 2 (within 3 years of Cancer OGD)?
OTHEROGD2

Yes **Y** No **N**

If Yes, continue with section B **If No,** go to section C

SECTION C – SIGNIFICANT PAST HISTORY

Previous Cholecystectomy Yes **Y** No **N** If Yes, date
PREVCHOLE **DATECHOLE**

Previous Gastric Surgery Yes **Y** No **N** If Yes, date
PREVSURG **DATESURG**

Previous upper GI investigations more than 3 years from cancer diagnosis?
PREVINVEST

Yes **Y** No **N**

If Yes, Investigation **INVEST1** Date **DATE1** Diagnosis **DIAGNOSE1**

Investigation **INVEST2** Date **DATE2** Diagnosis **DIAGNOSE2**

Investigation **INVEST3** Date **DATE3** Diagnosis **DIAGNOSE3**

Investigation **INVEST3** Date **DATE4** Diagnosis **DIAGNOSE4**

SECTION D

Is the patient alive **ALIVE** Yes **Y** No **N** Today's date
TODAYSDATE

If Yes, time since diagnosis of cancer **TIMESINCED**

If No, date of death **DATEDEATH**

Cause of death **CAUSEDEATH**

Was patient alive at **LIVEDFOR** Less than 1 month **0**
1 month **1**
6 months **6**
1 year **12**

2 years

24

If more than 2 years, number of years since diagnosis **LIVEDYEARS**

Did the patient undergo surgical resection? **SURGERY** Yes **Y** No **N**

If Yes.. Curative intent **CURE** Palliative **PALLIATIVE**

Final staging EGC **0** Stage 1 **1** Stage 2 **2** Greater **3**
FINALSTAGI

MASS/ULCER CANCERIID

Study Number **MASSID** Practice Code **GP**

D number **DNUMBER** NHS number **NHSNUMBER**

Name **FIRSTNAME SURNAME** Address **ROAD**

Date of birth **DOB** **TOWN**

Sex **SEX** Male **M** Female **F** Postcode

POSTCODE

First symptoms Date **FIRSTSYMPT** or Duration **ORDURATION**

On continuous AST prior to 1st GP consult? **ONAST1 (N, H, P, B, E)**

Number of weeks treatment **TREATMENT1**

Nature of symptoms as recalled **NATURESYMP**

Dyspepsia / Heartburn / Reflux **1**

Epigastric Pain ± other symptom(s) **2**

Heamatemesis ± Melaena **3**

Other **4**

If other please specify

OTHERPLEAS

(e.g. Anaemia=5, Dysphagia=6, Vomiting=7, Weight Loss=8, Early Satiety=9, Anorexia=10, Mass=11, Other=12)

OTHER1ST1 OTHER1ST2 OTHER1ST3 OTHER1ST4

If bleeder, benign or worrying **BLEEDERSWO (B, W)**

First consultation GP Date **FIRSTCONSU** duration from 1st symptoms **DURATION2R**

On AST 1st GP consult to referral? **ONAST2 (N, H, P, B, E)**

Number of weeks treatment **TREATMENT2**

Symptoms at first consultation GP **SYMPTOMSAT**

Dyspepsia / Heartburn / Reflux **1**

Epigastric Pain ± other symptom(s) **2**

Heamatemesis ± Melaena **3**

Other **4**

If other please specify

OTHERPLE01

(e.g. Anaemia=5, Dysphagia=6, Vomiting=7, Weight Loss=8, Early Satiety=9, Anorexia=10, Mass=11, Other=12)

OTHER2ND1 OTHER2ND2 OTHER2ND3 OTHER2ND4

If bleeder, benign or worrying **BLEEDERS01 (B, W)**

Referral date **REFERRALDA** Date first seen at Hospital **DATEFIRSTS**

GP suspect cancer? **GPSUSPECT (Y, N)** Time in weeks from referral to seen at hospital

DURATION3F

On AST from referral to seen? **ONAST3 (N, H, P, B, E)**

Number of weeks treatment **TREATMENT3**

Symptoms on referral **SYMPTOMSON**

Dyspepsia / Heartburn / Reflux	<input type="checkbox"/>	1
Epigastric Pain ± other symptom(s)	<input type="checkbox"/>	2
Heamatemesis ± Melaena	<input type="checkbox"/>	3
Other	<input type="checkbox"/>	4

If other please specify **OTHERPLE02**
(e.g. Anaemia=5, Dysphagia=6, Vomiting=7, Weight Loss=8, Early Satiety=9, Anorexia=10, Mass=11, Other=12)

If bleeder, benign or worrying **BLEEDERS02 (B, W)**
OTHER3RD1 OTHER3RD2 OTHER3RD3 OTHER3RD4

Date of cancer diagnosis **DATECANCER** Time in weeks from seen at hospital to diagnosis
DURATION4F

On AST from seen at hospital to cancer diagnosis? **ONAST4 (N, H, P, B, E)**

Number of weeks treatment **TREATMENT4**

Symptoms at time of cancer diagnosis **SYMPTOMS01**

Dyspepsia / Heartburn / Reflux	<input type="checkbox"/>	1
Epigastric Pain ± other symptom(s)	<input type="checkbox"/>	2
Heamatemesis ± Melaena	<input type="checkbox"/>	3
Other	<input type="checkbox"/>	4

If other please specify **OTHERPLE03**
(e.g. Anaemia=5, Dysphagia=6, Vomiting=7, Weight Loss=8, Early Satiety=9, Anorexia=10, Mass=11, Other=12)

OTHER4TH1 OTHER4TH2 OTHER4TH3 OTHER4TH4
If bleeder, benign or worrying **BLEEDERS03 (B, W)**

Histology	HISTOLOGYD	Diffuse	<input type="checkbox"/>	Y, N
	INTESTINAL	Intestinal	<input type="checkbox"/>	Y, N

PH Gastric Surgery? **PHGASTRICS Y, N**

PH Barretts? **PHBARRETTS Y, N**

PH Dysplasia? **PHDYSPLASI Y, N**

PH GI Investigations within 3 years of diagnosis? **PHGIINVEST Y, N**

If yes, type of investigation? **TYPEINVESTI OGD, BAR, USS, LAP**

Number of OGDS? **NUMBEROGDS 0, 1, 2, 3**

Appendix II. Oesophageal and gastric cancer staging¹⁶⁵.

Oesophagus

Primary tumour (T)

- TX primary tumour cannot be assessed
- T0 no evidence of primary tumour
- Tis carcinoma in situ
- T1 tumour invades lamina propria or submucosa
- T2 tumour invades muscularis propria
- T3 tumour invades adventitia
- T4 tumour invades adjacent structures

Regional lymph nodes

- NX regional lymph nodes cannot be assessed
- N0 no regional lymph node metastasis
- N1 regional lymph node metastasis

Distal metastasis

- MX presence of distal metastasis cannot be assessed
- M0 no distant metastasis
- M1 distant metastasis

Staging

0	Tis	N0	M0
1	T1	N0	M0
2a	T2	N0	M0
	T3	N0	M0
2b	T1	N1	M0
	T2	N1	M0
3	T3	N1	M0
	T4	Any N	M0
4	Any T	Any N	M1

Gastric

Primary tumour (T)

- TX primary tumour cannot be assessed
- T0 no evidence of primary tumour
- Tis carcinoma in situ
- T1 tumour invades lamina propria or submucosa
- T2 tumour invades muscularis propria
- T3 tumour invades adventitia
- T4 tumour invades adjacent structures

Lymph nodes

- N0 no nodal involvement
- N1 involvement of perigastric nodes within 3cm of primary
- N2 involvement of more distant perigastric and regional nodes that are amenable to removal at gastrectomy
- N3 involvement of more distant intra-abdominal nodes including mesenteric, hepato-duodenal and retropancreatic.

Distal metastasis

- M0 no distant metastasis
- M1 distant metastasis

Staging

		M0				M1
		N0	N1	N2	N3	
M0	Tis	0	-	-	-	-
	T1	1A	1B	2	4	4
	T2	1B	2	3A	4	4
	T3	2	3A	3B	4	4
	T4	3A	3B	4	4	4
M1		4	4	4	4	4

This staging system was used for this thesis. There have been further modifications¹⁹⁰.

Appendix III. ASA Classification.

- Stage 1** **Normally healthy.**
- Stage 2** **Mild systemic disease**
- Stage 3** **Severe systemic disease that limits activity; not
incapacitating**
- Stage 4** **Incapacitating systemic disease that poses a threat to life**
- Stage 5** **Moribund. Not expected to survive 24 hours even with
operation**

ASA grading. *Anaesth.* 1963. **24**; 111

Appendix IV.

(see over)

Empirical use of antisecretory drug therapy delays diagnosis of upper gastrointestinal adenocarcinoma but does not effect outcome

S. J. PANTER*, H. O'FLANAGAN*, M. G. BRAMBLE* & A. P. S. HUNGIN†

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SUMMARY

Background: Upper gastrointestinal cancer carries a poor prognosis. Although the incidence of gastric adenocarcinoma is falling, oesophageal adenocarcinoma is increasing. This has been attributed to an increasing prevalence of gastro-oesophageal reflux disease, commonly treated empirically in primary care with antisecretory drugs. Treatment has been associated with delayed diagnosis but it is unclear if this influences prognosis.

Aims: To ascertain the effect of antisecretory drugs on time to diagnosis, symptoms, tumour stage and outcome.

Methods: A retrospective cohort study of primary care records for 747 patients diagnosed with upper gastrointestinal adenocarcinoma at South Tees NHS Trust between 1991 and 2001.

Results: Mean time from the onset of symptoms to diagnosis was 30 weeks. Mean and median times at the primary care stage were longer than at the hospital stage for both oesophageal and gastric cancer ($P < 0.0001$). Patients with benign symptoms prescribed antisecretory drugs were referred later than those not on antisecretory drugs ($P < 0.0001$), as were patients with alarm symptoms ($P = 0.0008$). Prior use of antisecretory drugs delayed diagnosis by 17.6 weeks (mean) but had no effect on tumour stage at diagnosis or survival.

Conclusion: Prior antisecretory drug therapy was associated with delayed diagnosis of upper gastrointestinal adenocarcinoma irrespective of presenting symptoms. Concerns that delays might adversely affect tumour stage or long-term survival were not substantiated.

INTRODUCTION

For more than half a century the overall incidence and mortality rates of gastric cancer have been slowly declining¹ although adenocarcinoma of the gastric cardia is becoming more common.^{2–4} The incidence of adenocarcinoma of the oesophagus is also increasing; this has been attributed to the increasing prevalence of gastro-oesophageal reflux.⁵ It is now the commonest form of oesophageal cancer.^{5–7} In the UK there are often delays in the diagnosis of oesophago-gastric cancer^{8, 9}

for reasons that are unclear. Patients may delay seeing a doctor and referral to hospital may be deferred by a previous history of dyspepsia¹⁰ or absence of alarm symptoms.¹¹ These factors influence the process leading to endoscopy and diagnosis. In addition the empirical use of antisecretory drugs prior to diagnosis, particularly proton pump inhibitors (PPIs) can contribute to the delay through the modification of symptoms and the potential healing of early malignant ulcers.¹² Also, dyspepsia management guidelines increasingly advocate empirical therapy for *Helicobacter pylori* negative patients under 55 years without alarm symptoms;¹¹ thus people who have previously received antisecretory drug therapy are likely to receive further prescriptions when symptoms recur.

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E-mail: simon.panter@sthct.nhs.uk

AIMS

The aim of this study was to identify the patterns of presentation of oesophago-gastric adenocarcinomas, to ascertain the effect of prior antisecretory drug therapy on the time to a definitive diagnosis and the effect on symptoms, tumour stage and outcome.

PATIENTS AND METHODS

The study design was a survey of the records of all patients with an established diagnosis of primary oesophageal or gastric adenocarcinoma over a 10-year period.

The study was based in the South Tees health district of Teesside, a mixed industrial and rural area with a catchment population of *c.* 300 000. Because of the centralization of gastroenterology services it is estimated that over 95% of all patients referred with gastrointestinal problems are seen at one hospital, the James Cook University Hospital. This enabled central access to patient records, and endoscopy and pathology reports. Both primary and secondary care records were accessed.

To meet the inclusion criteria patients had to have a definitive cancer diagnosis established within the population area, for the first time, in the 10 years to April 2001.

Patients were initially identified from the computerized pathology database. The list obtained was cross-referenced with the regional cancer registry (Northern and Yorkshire Cancer Registry and Information Service) and the hospital's own cancer records to ensure completeness and accuracy of the patient cohort. The identified patients' primary care records were reviewed at their general practices or, where the patients were dead, retrieved from the central registry of Tees and North Yorkshire Health Authorities. These were reviewed to record demographic characteristics and to detail the diagnostic pathway leading to the definitive diagnosis and eventual outcomes. These details included the timings of the onset of symptoms, first General Practitioner (GP) consultation with new onset symptoms and the timings of referral and investigations. Details about the prescribing of antisecretory drugs prior to investigation were also recorded and the hospital records reviewed for endoscopy findings, including the endoscopist, number of biopsies taken, tumour stage at diagnosis and long-term outcome.

Statistics

Data handling and analysis was performed using the Epi Info™ epidemiological database and statistical analysis package (US Dept. of Health and Human Services Center for Disease Control and Prevention, Atlanta, GA, USA). The accuracy of data entry was optimized by using double data entry and cross checking. Data were analysed using parametric methods for normally distributed continuous data (*t*-test, ANOVA) and nonparametric methods (χ^2 , Kruskal–Wallis) for categorical data and non-normally distributed continuous data. Results were considered to be statistically significant with *P*-values <0.05 (95% confidence limits).

RESULTS

A total of 747 patients were identified of whom 685 (92%) were included in the study. Table 1 and Figure 1 details patient numbers.

REFERRAL PATTERNS

The mean time from first symptoms, as recorded in the notes from the patients' history, to diagnosis, was 30 weeks (median 14, range 1–428). Compared to patients with gastric cancer those with oesophageal cancer took longer to present to their GP (*P* = 0.003) and longer to be seen in secondary care once referred (*P* = 0.03). All the other time periods (time to be referred, time to definitive diagnosis) showed no statistically significant differences. The mean and median time durations during which the patient remained under primary care management only was double the hospital phase times, for both oesophageal and gastric cancer (*P* < 0.0001). There were no significant differences between the time periods the patient remained in primary care alone or in hospital management for either oesophageal or gastric cancer.

Details are shown in Table 1.

Symptoms

Figure 2 shows the symptoms as recorded in the GP and hospital notes at the various stages in the diagnostic process. Initially only 50% of patients had alarm symptoms (i.e. anaemia/dysphagia/weight loss/vomiting). By the time of referral this had risen to 71% and at diagnosis to 78%.

Table 1. Demographics for all upper gastrointestinal adenocarcinomas with oesophageal and gastric subsets

	All	Oesophageal	Gastric
Total number	685	198	487
Male	451	143	308
Female	234	55	179
Mean age at diagnosis (range) in years	70.3 (28-94)	69.4 (41-94)	70.7 (28-92)
% Under 45 years at diagnosis	2.6 (n = 18)	1.5 (n = 3)	3.1 (n = 15)
% Under 55 years at diagnosis	8.9 (n = 61)	10.1 (n = 20)	8.4 (n = 41)
Mean time to diagnosis in weeks (median, range)	29.7 (14, 1-428)	32.0 (15, 1-428)	28.8 (13, 1-415)
Mean primary care stage time in weeks (median, range)	20.2 (7, 1-423)	22.0 (8, 1-423)	19.4 (6, 1-408)
Mean hospital stage time in weeks (median, range)	9.6 (3, 1-165)	10.0 (3, 1-164)	9.4 (3, 1-165)
% Patients prescribed AST at any time	47.7	48.5	47.4
% PPI	57.8	65.6	54.5
% H ₂ RA	42.2	34.4	45.5
% on PPI at diagnosis previously treated with H ₂ RA	33.9	34.9	33.3
Mean time to diagnosis in weeks (median, range)	44.3 (21, 1-428)	48.0 (27, 2-428)	42.7 (21, 1-415)
+AST	16.5 (10, 1-294)	17.0 (12, 1-294)	16.3 (9, 1-260)
-AST			
Mean stage times in weeks (median)			
First symptom to first GP visit	13.4 (4)	16.4 (4)	12.1 (3)
	P < 0.0001	P < 0.0001	P < 0.0001
	+AST, -AST	+AST, -AST	+AST, -AST
	58.6 (6), 9.3 (4)	59.4 (4), 9.6 (4)	57.8 (12), 9.1 (2)
First GP visit to referral	6.8 (1)	5.6 (1)	7.3 (1)
	P < 0.0001	P = 0.04	P < 0.0001
	13.3 (5), 3.2 (0)	9.7 (3), 3.2 (0)	14.9 (6), 3.2 (0)
Referral to first hospital contact	2.7 (2)	2.8 (2)	2.6 (2)
	P < 0.0001	P < 0.0001	P < 0.0001
	3.0 (2), 2.5 (1)	2.9 (2), 2.8 (2)	3.1 (2), 2.3 (1)
First hospital contact to diagnosis	6.9 (0)	7.2 (0)	6.8 (0)
	P = 0.003	P = 0.6	P = 0.002
	12.7 (1), 2.5 (0)	14.2 (1/2), 1.5 (0)	12.1 (1), 2.9 (0)
	P < 0.0001	P = 0.0005	P < 0.0001
	+AST, -AST	+AST, -AST	+AST, -AST
TMN stage at diagnosis			
0 (Tis)	-	2	3
I	-	10	45
II	-	19	43
III	-	37	107
IV	-	39	172
Stage unknown	-	91	117
		42.49	58.59

PPI, proton pump inhibitor; AST, antiseecretory drug therapy; GP, General Practitioner; TNM, staging classification.

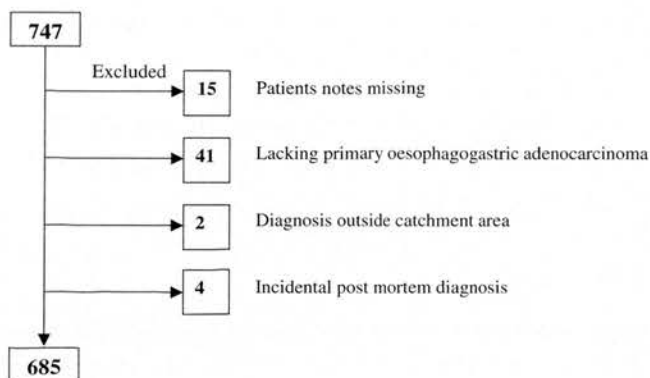


Figure 1. Details of study cohort.

Empirical treatment

Overall, of the 685 patients with adenocarcinoma 47.7% had antisecretory drug treatment between the onset of symptoms and diagnosis. In 66.8% this was initiated at the first GP visit. Patients with oesophageal

adenocarcinoma were more likely than patients with gastric adenocarcinoma to be taking antisecretory drugs prior to their first GP consultation with new onset symptoms (13.6% vs. 6.2%) ($P = 0.002$). Patients were predominantly prescribed PPIs although 33.9% were on a H₂RA beforehand. There was no significant difference between males and females in relation to rates of antisecretory drugs prescribing at any stage. Details are shown in Table 1.

Antisecretory drug prescribing and time to diagnosis of cancer

An increase in the time to diagnosis was associated with the use of antisecretory drugs at all stages (Table 1). The time interval before referral from primary care to hospital was significantly longer in those prescribed antisecretory drugs compared with those who were not prescribed these. This was irrespective of the presenting

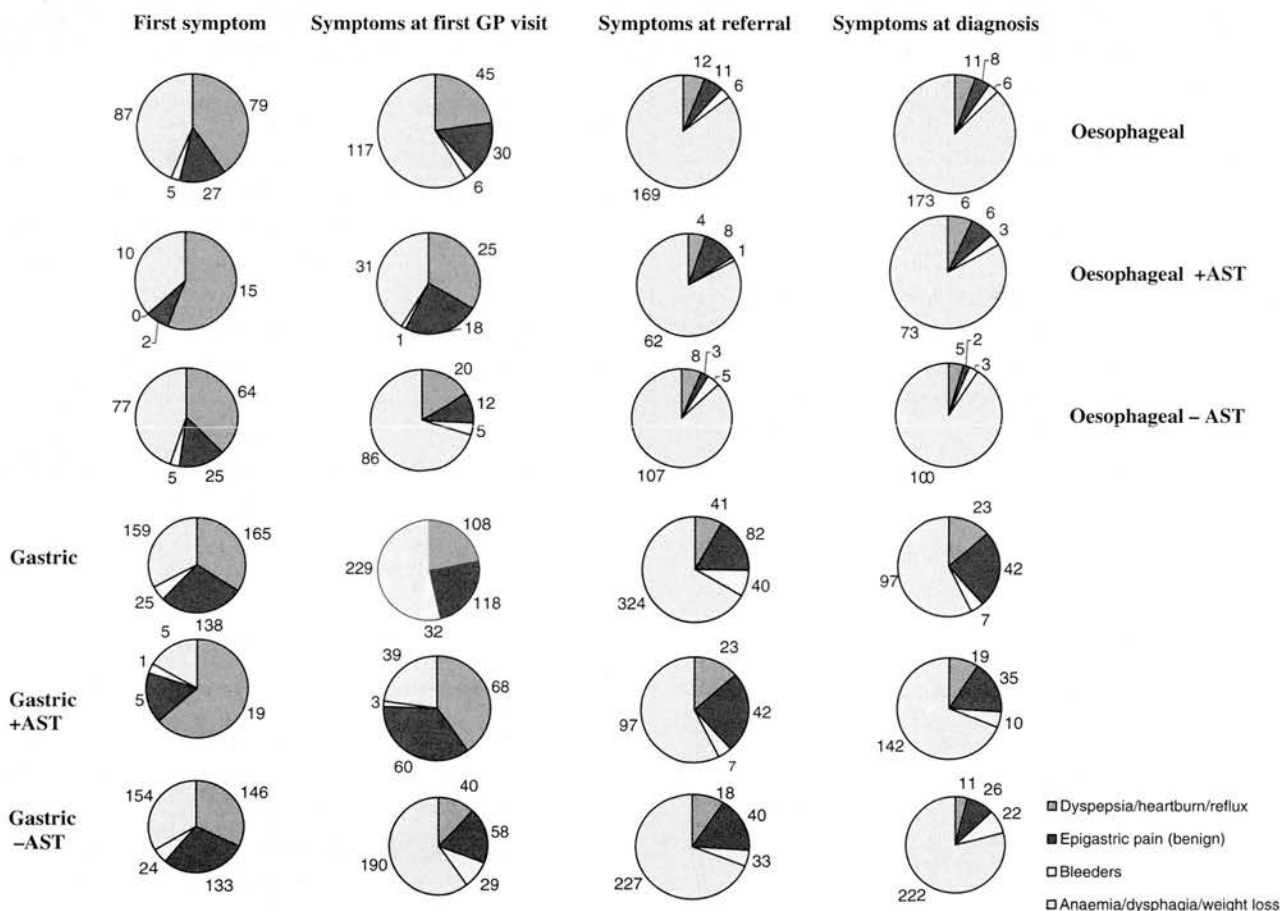


Figure 2. Symptoms as recorded in the General Practitioner (GP) notes at the various stages of the 'diagnostic pathway'. AST, antisecretory drug therapy.

symptoms except for those presenting with haematemesis/melaena. For those treated with antisecretory drugs prior to gastroscopy the mean time from their first GP visit with new onset symptoms to diagnosis was increased by 17.6 weeks ($P < 0.001$).

Effect of antisecretory drug therapy on symptoms

The number of patients with alarm symptoms at each stage of the diagnostic pathway, in relation to whether or not they were prescribed antisecretory drugs is shown in Figure 2. In total 339 (49.5%) of patients had benign symptoms at their first GP consultation; of these 175 (51.6%) were given antisecretory drugs. For patients with alarm symptoms 20.2% were prescribed antisecretory drugs. Thus patients with more benign sounding symptoms were more likely to have been prescribed antisecretory drugs ($P < 0.0001$).

Patients with benign symptoms prescribed antisecretory drugs ($n = 175$) were referred later than patients with benign symptoms not given antisecretory drugs ($n = 164$) (mean 16.4 vs. 5.54 weeks, median 8 vs. 1 weeks, $P < 0.0001$). Similarly, patients with alarm symptoms were referred later if antisecretory drugs had been prescribed (5.6 vs. 1.8 weeks, median 1 vs. 0, $P = 0.0008$). Thus the use of antisecretory drugs was associated with a longer time to referral. During this period more patients developed alarm symptoms. However, 98.6% of patients with alarm symptoms at the first GP consultation and who were prescribed antisecretory drugs still had alarm symptoms by the time of hospital consultation. This suggests that the use of antisecretory drugs did not change alarm symptoms to benign sounding symptoms.

Effect of antisecretory drug therapy on tumour stage at diagnosis

Staging data using the TNM classification¹³ was available for 477 patients (70% of total). Of these 287 underwent surgery. Treatment with antisecretory drugs was not associated with the tumour stage at diagnosis for either oesophageal or gastric adenocarcinoma ($P = 0.49$ and $P = 0.31$ respectively) as shown in Table 1.

Effect of antisecretory drug therapy on survival

The effects of empirical antisecretory drugs on survival (Kaplan–Meier) following diagnosis are shown for

both oesophageal and gastric adenocarcinoma in Figure 3. No significant differences were observed between the two groups except for gastric adenocarcinoma where patients with stage IIIa disease had a worse prognosis with prior empirical antisecretory drugs.

DISCUSSION

Upper gastrointestinal cancer carries a poor prognosis in Western countries where the incidence of oesophageal adenocarcinoma is increasing⁵ on a background of falling rates for gastric adenocarcinoma.¹ This change has been attributed to the increasing prevalence of gastro-oesophageal reflux disease,¹⁴ a condition commonly treated by empirical antisecretory drugs. PPIs are now the drugs of choice for treating symptomatic reflux and their efficacy means that increased prescribing of these powerful acid suppressants is a modern phenomenon seen in many western countries.^{15, 16} Concern about these drugs masking cancer or delaying diagnosis^{10, 12, 17} is therefore important if the net effect is a worse prognosis.

Symptoms are the major influence on the timing and presentation of patients to their GP and subsequent referral for investigation. The vast majority of dyspeptic patients in the 'at risk' age group will have benign disease, even if some of their symptoms are 'worrying', as symptoms are a poor predictor of pathology.^{18–20} Some patients are also very elderly and would potentially not be suitable for surgery even if diagnosed early. However the mean age was 70.3 years at diagnosis and we can find no evidence that age *per se* delayed referral.

A limitation of this study is its retrospective nature and that only those with cancer were studied rather than the dyspeptic population as a whole. However, the fact that patients with oesophageal adenocarcinoma took longer to present to their GP suggested that they were not concerned by their symptoms until relatively later. These patients were also more likely to have been on antisecretory drugs previously, compared with those with gastric adenocarcinoma, with 26% of the oesophageal adenocarcinoma patients on antisecretory drug therapy prior to their first GP consultation having a past history of Barrett's oesophagus.

This study confirms previous work showing that patients given antisecretory drugs endure a delay to a definitive morphological diagnosis. Patients given antisecretory drugs on their first visit to the GP had a longer

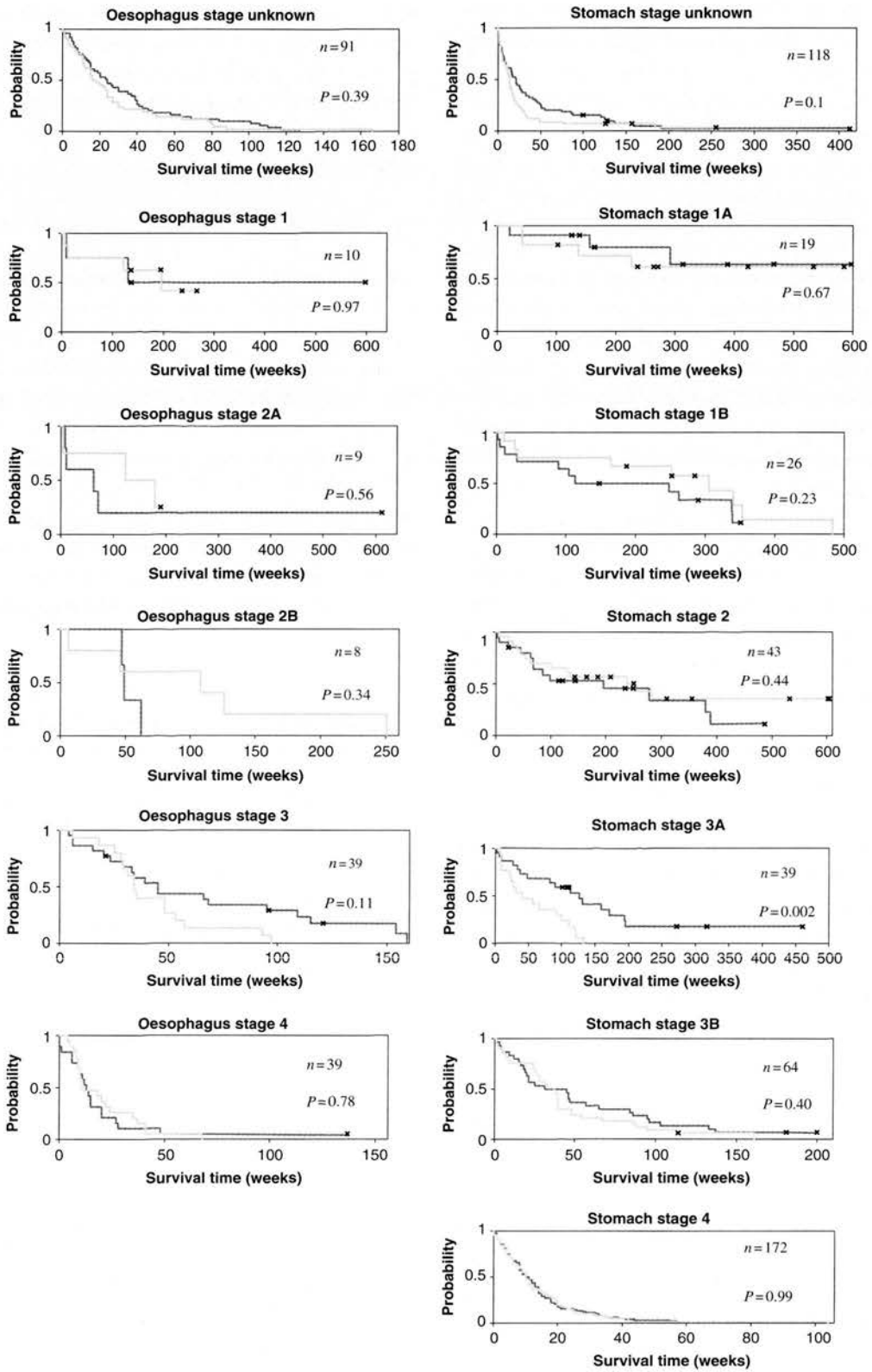


Figure 3. Kaplan–Meier survival curves for oesophageal and gastric adenocarcinoma and the effect of antisecretory drug therapy.

time to diagnosis at all stages of the process but the longest delay occurred because patients previously prescribed antisecretory drugs did not seek a further medical opinion and when they did, the GP was likely to restart the antisecretory drugs rather than refer for investigation. Patients with worrying symptoms received antisecretory drugs less frequently and were referred quickly compared to those with more dyspeptic symptoms. In many cases the delay was many months during which time it might be assumed that the tumour would progress significantly and worsen both the stage of the disease at diagnosis and long-term survival. The results indicate this did not happen. Those patients with early stage disease (early gastric cancer or stage I disease) had the longest period on treatment but were still 'early' when eventually diagnosed.

The reasons for this are probably explained by the natural history of upper gastrointestinal adenocarcinoma. In the oesophagus the disease spreads relatively early²¹ and even those patients referred quickly are likely to have disease that has infiltrated the lymphatics, making curative resection less likely. Thus delays resulting from prior antisecretory drugs are unlikely to affect prognosis. In relation to stomach cancer, patients with early disease were more likely to have benign symptoms and more likely to have been prescribed antisecretory drugs. Tumour-doubling time is long in early stage disease²¹⁻²³ making a delay less critical in terms of tumour stage at diagnosis. Patients with alarm symptoms have more advanced disease³ associated with a rapid tumour doubling time.²³ In this study patients with alarm symptoms were less likely to receive antisecretory drugs and were referred more quickly. Thus those patients presenting with mucosal disease and benign sounding symptoms in primary care still had mucosal disease when diagnosed at gastroscopy despite many months' delay.

In conclusion, this study confirmed that empirical antisecretory drug therapy was associated with a significant delay in the definitive diagnosis but that this did not affect the tumour stage at diagnosis. The long-term outcomes were identical in those who had been prescribed antisecretory drugs prior to diagnosis and those who had not. Withholding antisecretory drugs prior to investigation may accelerate a definitive diagnosis but is not likely to affect the eventual outcome. We cannot recommend routinely treating 'at risk' patients with antisecretory drugs prior to gastroscopy, as patients will still perceive this as a delay.

However this paper does support the concept that such a delay has little significance, as outcome is poor in both groups. These findings have important clinical, management and medico-legal implications.

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CONFLICT OF INTEREST

Professors M.G. Bramble and A.P.S. Hungin have advised pharmaceutical companies marketing PPIs. Dr S.J. Panter has participated on Advisory boards for Astra-Zeneca. H. O'Flanagan has no conflict of interest.

REFERENCES

- 1 Howson CP, Hiyama T, Wynder EL. The decline in gastric cancer: epidemiology of an unplanned triumph. *Epidemiol Rev* 1986; 8: 1-27.
- 2 Powell J, McConkey CC. The rising trend in oesophageal adenocarcinoma and gastric cardia. *Eur J Cancer Prev* 1992; 1: 265-9.
- 3 Allum WH, Fielding JW. Gastric cancer: a 25-year review. *Br J Surg* 1990; 77: 353.
- 4 Wayman J, Craig DJ, Biggin CS, Raimes SA, Griffin SM. The changing pattern of oesophago-gastric cancer. *Gut* 1997; 40(3S, Suppl. 1): 8.
- 5 Devesa SS, Blot WJ, Fraumeni JF Jr. Changing patterns in the incidence of esophageal and gastric carcinoma in the United States. *Cancer* 1998; 83: 2049-53.
- 6 Devesa SS, Fraumeni JF Jr. The rising incidence of gastric cardia cancer. *J Natl Cancer Inst* 1999; 91: 747-9.
- 7 Thomas RJ, Lade S, Giles GG, Thursfield V. Incidence trends in oesophageal and proximal gastric carcinoma in Victoria. *Aust N Z J Surg* 1996; 66: 271-5.
- 8 Wayman J, Raimes S, Griffin SM, Hayes N. Delays in diagnosing oesophagogastric cancer. Small study found that four fifths of delay was due to patients. *BMJ* 1997; 315: 428.
- 9 Martin IG, Young S, Sue-Ling H, Johnston D. Delays in the diagnosis of oesophagogastric cancer: a consecutive case series. *BMJ* 1997; 314: 467-70.
- 10 Suvakovic Z, Bramble MG, Jones R, Wilson C, Idle N, Ryott J. Improving the detection rate of early gastric cancer requires more than open access gastroscopy: a five year study. *Gut* 1997; 41: 308-13.

- 11 Dyspepsia guidelines. 2003. <http://www.sign.ac.uk>
- 12 Wayman J, Hayes N, Griffin SM. The response of early gastric cancer to proton-pump inhibitors. *N Engl J Med* 1998; 338: 1924–5.
- 13 Kennedy BJ. The unified international gastric cancer staging classification. *Scand J Gastroenterol* 1987; 22(Suppl. 133):11–3.
- 14 Lagergren J, Bergstrom R, Lindgren A, Nyren O. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. *N Engl J Med* 1999; 340: 825–31.
- 15 Bashford JN, Norwood J, Chapman SR. Why are patients prescribed proton pump inhibitors? Retrospective analysis of link between morbidity and prescribing in the General Practice Research Database. *BMJ* 1998; 317: 452–6.
- 16 Jones MI, Greenfield SM, Jowett S, Bradley CP, Seal R. Proton pump inhibitors: a study of GPs' prescribing. *Fam Pract* 2001; 18: 333–8.
- 17 Bramble MG, Suvakovic Z, Hungin AP. Detection of upper gastrointestinal cancer in patients taking antisecretory therapy prior to gastroscopy. *Gut* 2000; 46: 464–7.
- 18 Talley NJ, Weaver AL, Tesmer DL, Zinsmeister AR. Lack of discriminant value of dyspepsia subgroups in patients referred for upper endoscopy. *Gastroenterology* 1993; 105: 1378–86.
- 19 Bytzer P, Hansen JM, Schaffalitzky De Muckadell OB, Malchow-Moller A. Predicting endoscopic diagnosis in the dyspeptic patient. The value of predictive score models. *Scand J Gastroenterol* 1997; 32: 118–25.
- 20 Hansen JM, Bytzer P, Schaffalitzky De Muckadell OB. Management of dyspeptic patients in primary care. Value of the unaided clinical diagnosis and of dyspepsia subgrouping. *Scand J Gastroenterol* 1998; 33: 799–805.
- 21 Fujita S. Biology of early gastric carcinoma. *Pathol Res Pract* 1978; 163: 297–309.
- 22 Eckardt VF, Willems D, Kanzler G, Remmele W, Bettendorf U, Paulus W. Eighty months persistence of poorly differentiated early gastric cancer. *Gastroenterology* 1984; 87: 719–24.
- 23 Kohli Y, Kawai K, Fujita S. Analytical studies on growth of human gastric cancer. *J Clin Gastroenterol* 1981; 3: 129–33.

Urgent cancer referral guidelines: a retrospective cohort study of referrals for upper gastrointestinal adenocarcinoma

Simon J Panter, Mike G Bramble, Hilda O'Flanagan and A Pali S Hungin

SUMMARY

Dyspepsia in primary care is common and guidelines indicate that patients with alarm symptoms, as defined by the urgent cancer referral guidelines, should be investigated by gastroscopy. The specificity and sensitivity of alarm symptoms is poor and only a small percentage of patients will turn out to have malignant disease. This primary care study shows that employing current guidelines will identify only 72% of patients at their initial visit to a general practitioner, but this figure could be increased to 86% if the guidelines included patients with weight loss or anaemia in the absence of dyspepsia. Past performance indicates that the majority of patients with the commonest symptom complex were not referred quickly and less than half were seen within 4 weeks.

Keywords: adenocarcinoma; diagnosis; gastrointestinal diseases; referral; upper gastrointestinal tract.

Introduction

IN *The NHS Cancer plan*,¹ the United Kingdom government introduced urgent cancer referral guidelines (the '2-week rule') to ensure that everyone with suspected cancer would be referred to a specialist by their general practitioner (GP) and seen within 2 weeks of the referral date.² In June 2000 guidelines were issued to general practitioners highlighting the symptom complexes experienced by patients with upper gastrointestinal (UGI) malignancy,³ but the evidence base is acknowledged to be poor^{4,5} and data from hospital studies suggest that nearly all patients with UGI malignancy will have 2-week rule symptoms.⁶

The aim of this study was to examine referral practice and outcome, utilising the 2-week rule criteria for all patients diagnosed as having UGI adenocarcinoma during the 10-year period 1991–2001 in order to identify what proportion of patients fulfilled the 2-week rule criteria, and to determine how primary care had managed these patients before referral.

Method

All patients with UGI adenocarcinoma (excluding pancreatic) diagnosed in the South Tees Health Authority area, where a single endoscopy unit serves the entire population, were identified from the hospital computerised pathology database for the period April 1991–April 2001. Completeness of the data was verified with the regional cancer registry (NYCRIS). Primary care records were reviewed with respect to the government's urgent cancer referral guidelines and data analysed using parametric methods for normally distributed continuous data (*t*-test, ANOVA) and non-parametric methods (χ^2 , Kruskal–Wallis) for categorical and non-normally distributed data.

Results

A total of 747 patients were identified, of whom 685 (92%) were included in the study. Of those excluded, the majority (35) did not have a primary gastric or oesophageal adenocarcinoma. A total of 494 (72.1%) patients fulfilled the 2-week rule criteria in terms of symptoms at the initial consultation with the GP (Table 1). The largest group of patients fulfilling the 2-week rule criteria were those aged 55 years and over, with dyspepsia or epigastric pain for less than 1 year, with continuous symptoms since onset ($n = 244$, 40.1%). The mean time to referral was 6.7 weeks (range within 1–174 weeks) with 68 (27.9%) being referred immediately to secondary care, increasing to 119 (48.8%) by 4 weeks. The second largest group comprised patients with

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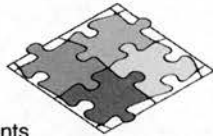
©British Journal of General Practice, 2004, 54, 611–613.

HOW THIS FITS IN*What do we know?*

Dyspepsia in primary care is common and recent guidelines indicate that patients with alarm symptoms should be investigated.

What does this paper add?

This primary care study shows that employing current guidelines will identify only 72% of patients at their first visit to a general practitioner, but if the guidelines included patients with weight loss or anaemia in the absence of dyspepsia this figure could be increased to 86%.



dysphagia ($n = 115$) of whom 80 (69.6%) had this as the main presenting symptom. Dyspepsia associated with anaemia accounted for 14 (3.8%) patients. Nine patients (2.4%) had an epigastric mass. Twenty patients presented with acute bleeding. Patients referred quickly from primary care were seen more quickly in hospital (Spearman rank correlation coefficient = 0.79, $P < 0.05$). Males were more likely to fit the 2-week rule ($P = 0.022$) and females were significantly older ($P < 0.001$).

There were 191 (27.9%) patients who did not fit the major urgent referral criteria for suspected UGI malignancy at the first consultation in primary care (Table 2). The mean time to referral was 7.1 weeks (range within 1–137 weeks) with 75 (39.3%) being referred immediately to secondary care,

Table 1. Details of patients' symptoms shown along with the time taken for the general practitioner (GP) to refer the patient to a specialist or open access gastroscopy.

2-week rule criteria (mutually exclusive)	Mean time from GP consultation to referral in weeks (range)	% referred within 4 weeks	Mean time from referral to appointment in weeks (range)	% seen within 2 weeks	% seen within 4 weeks
Total ($n = 494$) ^a	6.7 (1–174)	65.4	2.6 (1–30)	46.4	71.9
Aged >55 years with dyspepsia/heartburn/reflux <1 year duration ($n = 244$)	10.8 (1–174)	48.8	2.8 (1–17)	39.3	66.8
Aged >55 years with GI bleeding first symptoms dyspepsia/reflux/epigastric pain ($n = 29$)	0.2 (1–5)	96.6	0.6 (1–9)	89.7	93.1
Dysphagia ($n = 115$)	2.4 (1–120)	86.1	2.5 (1–18)	44.3	78.3
Dyspepsia or epigastric pain with weight loss ($n = 49$)	1.6 (1–10)	83.7	3.0 (1–22)	46.9	67.3
Dyspepsia or epigastric pain with past history of gastric surgery/Barretts oesophagus/dysplasia ($n = 23$)	6.9 (1–24)	43.5	3.1 (1–9)	43.5	60.9
Dyspepsia or epigastric pain with anaemia ($n = 14$)	5.8 (1–30)	71.4	2.5 (1–11)	64.3	78.6
Dyspepsia or epigastric pain with vomiting ($n = 11$)	6.6 (1–34)	54.5	3.7 (1–30)	72.7	72.7
Palpable mass ($n = 9$)	0.1 (1)	100	1.0 (1–3)	66.7	100

^aMen $n = 338$ (68.4%), women $n = 156$ (31.6%). GI = gastrointestinal.

Table 2. Details of patients' symptoms shown along with the time taken for the general practitioner (GP) to refer the patient to a specialist or open access gastroscopy.

2-week rule did not apply	Mean time from GP consultation to referral in weeks (range)	% referred within 4 weeks	Mean time from referral to appointment in weeks (range)	% seen within 2 weeks	% seen within 4 weeks
Total ($n = 191$) ^a	7.1 (1–137)	62.3	2.8 (1–18)	49.2	69.6
Aged <55 years with dyspepsia/heartburn/reflux or epigastric pain ($n = 31$)	17.7 (1–137)	32.3	4.1 (1–18)	32.3	61.3
Aged >55 years with dyspepsia or heartburn/reflux or epigastric pain >1 year ($n = 16$)	26.9 (1–126)	12.5	4.6 (1–13)	37.5	43.8
Weight loss, no upper GI symptoms ($n = 53$)	2.5 (1–20)	69.8	2.4 (1–16)	45.3	75.5
Anaemia, no upper GI symptoms ($n = 31$)	2.8 (1–40)	77.4	2.6 (1–13)	48.4	67.7
Dyspepsia or epigastric pain with anorexia ($n = 15$)	4.1 (1–14)	60.0	1.7 (1–8)	66.7	86.7
Fatigue and/or lethargy ($n = 15$)	4.0 (3–5)	80.0	1.5 (1–3)	53.3	73.3
Chest pain and/or breathlessness ($n = 10$)	3.0 (1–21)	80.0	3.0 (1–12)	60.0	60.0
Collapse ($n = 9$)	1.1 (1–5)	88.9	1.0 (1–5)	77.8	77.8
Nausea and vomiting ($n = 8$)	1.3 (1–3)	100.0	3.0 (1–18)	75.0	75.0
Lower abdominal pain ($n = 3$)	3.0 (1–5)	66.7	1.0 (1–3)	66.7	100.0

^aMen $n = 113$ (62.0%), women $n = 78$ (38.0%). GI = gastrointestinal.

increasing to 119 (62.3%) by 4 weeks. Almost half (49.2%) were seen within 2 weeks and 69.6% by 4 weeks. The majority of these patients subsequently developed symptoms fitting referral criteria. There were 53 patients (16.8%) with weight loss but no UGI symptoms at initial consultation. Patients without UGI symptoms but with anaemia accounted for 31 patients (9.8%). There were 14 emergency admissions with severe anaemia but no GI symptoms. Thirty-one patients aged 55 years or under presented with benign symptoms (dyspepsia or epigastric pain alone). Almost all (93.5%) had symptoms for less than 1 year and 45.2% had symptoms for less than 1 month prior to consulting their GP. Time to referral ranged from 1–137 weeks (mean = 17.7 weeks) but only 6 patients (19.4%) had worrying symptoms at the time of referral.

Discussion

The aim of this study was to assess the robustness of the current referral guidelines, viewed from the primary care perspective. At present, the evidence for identifying 2-week rule patients comes from hospital-based studies based on symptoms present in patients found to have malignancy on gastroscopy.^{4,5} The percentage of cancer patients presenting with alarm symptoms in primary care is estimated to be close to 100%, but this is largely based on symptoms at endoscopy.^{6,7} It is clear that, prior to the new guidelines, less than half of all patients with alarm symptoms were referred within 4 weeks, indicating a high referral threshold.

In this series the largest group not fulfilling the new UGI urgent referral guidelines were patients with weight loss but no UGI symptoms ($n = 53$) or patients below 55 years of age with benign symptoms ($n = 31$). Only a third of patients in the latter group were referred by 2 weeks and one-third seen by 2 weeks. Although weight loss or anaemia without GI symptoms represented 44% of those not meeting the guidelines GPs felt that UGI malignancy was a possibility and hence referred patients with the same degree of urgency as those with 2-week rule criteria. Our results indicate that younger patients (45–55 years of age) and those with early disease and simple dyspepsia will be disadvantaged by the new guidelines.^{8,9} Unexplained weight loss or iron deficiency anaemia in the absence of UGI symptoms account for 12.3% of patients and should be considered for inclusion in any new guidance. Elderly patients with new onset dyspepsia should be followed up closely in primary care in case alarm symptoms develop, and referred urgently if symptoms fail to settle. Clearly, this study lacks the denominator to be sure that adopting these new strategies would not lead to an increase in urgent referrals with little improvement in the overall delay in diagnosis. Even allowing for this, our findings indicate that the current referral guidelines will not identify one in seven patients with UGI adenocarcinoma at their initial GP visit.

References

1. Department of Health. *The NHS Cancer plan. A plan for investment: a plan for reform*. London: Department of Health, 2000. http://www.dh.gov.uk/PublicationsAndStatistics/Publications/PublicationsPolicyAndGuidance/PublicationsPolicyAndGuidanceArticle/fs/en?CONTENT_ID=4009609&chk=n4LXTU (accessed 29 Apr 2004).

2. Department of Health. *Referral guidelines for suspected cancer*. London: Department of Health, 2000. http://www.dh.gov.uk/PublicationsAndStatistics/Publications/PublicationsPolicyAndGuidance/PublicationsPolicyAndGuidanceArticle/fs/en?CONTENT_ID=4008746&chk=jtslsg (accessed 29 Apr 2004).
3. NHS Executive. *Guidance on commissioning cancer services. Improving outcomes in upper gastrointestinal cancers. The Manual*. London: Department of Health, 2001. www.dh.gov.uk/assetRoot/04/08/02/78/04080278.pdf (accessed 29 Apr 2004).
4. Stoker E, Elsener A, Bradbury D, et al. Audit of fast track 2-week cancer wait [Abstract]. *Gut* 2002; **50**(suppl 2): A11.
5. Wallace MB, Durkalski VL, Vaughan J, et al. Age and alarm symptoms do not predict endoscopic findings among patients with dyspepsia: a multicentre database study. *Gut* 2001; **49**: 29-34.
6. Christie J, Shepherd NA, Codling BW, Valori RM. Gastric cancer below the age of 55: implications for screening patients with uncomplicated dyspepsia. *Gut* 1997; **41**: 513-517.
7. Kapoor N, Bassi A, Sturgess R, Bodger K. Predictive value of alarm features in patients referred to a rapid access upper gastrointestinal cancer service [Abstract]. *Gastroenterology* 2003; **124**(S1): A1247.
8. Hallissey MT, Allum WH, Jewkes AJ, et al. Early detection of gastric cancer. *BMJ* 1990; **301**: 513-515.
9. Sue-Ling HM, Johnson D, Martin IG, et al. Gastric cancer: a curable disease in Britain. *BMJ* 1993; **307**: 591-596.

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Requiring one day of attendance per week, this taught course emphasises scientific knowledge, clinical skills, psychology, public health, policy and management, in relation to substance misuse and dependence on drugs, alcohol and tobacco. There is a strong research element and a research dissertation of clinical relevance to the candidate will be undertaken.

For further information and enrolment details please contact Dr Kim Wolff (Programme Leader) or Rosie Bellinger (Course Administrator) National Addiction Centre, 4 Windsor Walk, Denmark Hill, London SE5 8AF. Tel: +44 (0)20 7848 0823, fax: +44 (0)20 7708 5658, email: r.bellinger@iop.kcl.ac.uk

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Equality of opportunity is College policy

Reference List

1. Office of National Statistics. Office for National Statistics. Mortality Statistics, Cause. 1999.
2. HMSO. Office of Population Censuses and Surveys. Mortality statistics by cause. 1989.
3. Everett SM, Axon AT. Early gastric cancer: disease or pseudo-disease? *Lancet* 1998;351:1350-2.
4. Howson CP, Hiyama T, Wynder EL. The decline in gastric cancer: epidemiology of an unplanned triumph. *Epidemiol.Rev.* 1986;8:1-27.
5. Powell J, McConkey CC. The rising trend in oesophageal adenocarcinoma and gastric cardia. *Eur.J.Cancer Prev.* 1992;1:265-9.
6. Allum WH, Fielding JW. Gastric cancer: a 25-year review. *Br.J.Surg.* 1990;77:353.
7. Wayman, J. and . The changing pattern of oesophago-gastric cancer. Craig, D. J, Biggin, C. S., Raimes, S. A., and Griffin, S. M. *Gut* 40 (3S) Suppl 1, 8. 1997.
8. Kocher HM, Linklater K, Patel S, Ellul JP. Epidemiological study of oesophageal and gastric cancer in south-east England. *Br.J.Surg.* 2001;88:1249-57.
9. Devesa SS, Blot WJ, Fraumeni JF, Jr. Changing patterns in the incidence of esophageal and gastric carcinoma in the United States. *Cancer* 1998;83:2049-53.
10. Devesa SS, Fraumeni JF, Jr. The rising incidence of gastric cardia cancer. *J.Natl.Cancer Inst.* 1999;91:747-9.
11. Thomas RJ, Lade S, Giles GG, Thursfield V. Incidence trends in oesophageal and proximal gastric carcinoma in Victoria. *Aust.N.Z.J.Surg.* 1996;66:271-5.
12. Brown LM, Devesa SS. Epidemiologic trends in esophageal and gastric cancer in the United States. *Surg.Oncol.Clin.N.Am.* 2002;11:235-56.
13. Faivre J, Forman D, Esteve J, Gatta G. Survival of patients with oesophageal and gastric cancers in Europe. *Eur.J.Cancer* 1998;34:2167-75.
14. Vaughan TL, Davis S, Kristal A, Thomas DB. Obesity, alcohol, and tobacco as risk factors for cancers of the esophagus and gastric cardia: adenocarcinoma versus squamous cell carcinoma. *Cancer Epidemiol.Biomarkers Prev.* 1995;4:85-92.
15. Tuyns AJ, Pequignot G, Jensen OM. [Esophageal cancer in Ille-et-Vilaine in relation to levels of alcohol and tobacco consumption. Risks are multiplying]. *Bull.Cancer* 1977;64:45-60.
16. Hu J, Nyren O, Wolk A, Bergstrom R, Yuen J, Adami HO *et al.* Risk factors for oesophageal cancer in northeast China. *Int.J.Cancer* 1994;57:38-46.

17. Brown LM, Silverman DT, Potters LM, Schoenberg JB, Greenberg RS, Swanson GM *et al.* Adenocarcinoma of the esophagus and esophagogastric junction in white men in the United States: alcohol, tobacco, and socioeconomic factors. *Cancer Causes Control* 1994;5:333-40.
18. Rolon PA, Castellsague X, Benz M, Munoz N. Hot and cold mate drinking and esophageal cancer in Paraguay. *Cancer Epidemiol.Biomarkers Prev.* 1995;4:595-605.
19. Castelletto R, Castellsague X, Munoz N, Iscovich J, Chopita N, Jmelnitsky A. Alcohol, tobacco, diet, mate drinking, and esophageal cancer in Argentina. *Cancer Epidemiol.Biomarkers Prev.* 1994;3:557-64.
20. Gao YT, McLaughlin JK, Blot WJ, Ji BT, Benichou J, Dai Q *et al.* Risk factors for esophageal cancer in Shanghai, China. I. Role of cigarette smoking and alcohol drinking. *Int.J.Cancer* 1994;58:192-6.
21. Gao YT, McLaughlin JK, Gridley G, Blot WJ, Ji BT, Dai Q *et al.* Risk factors for esophageal cancer in Shanghai, China. II. Role of diet and nutrients. *Int.J.Cancer* 1994;58:197-202.
22. Tavani A, Negri E, Franceschi S, La Vecchia C. Risk factors for esophageal cancer in women in northern Italy. *Cancer* 1993;72:2531-6.
23. Kennedy T., Jones R. The prevalence of gastro-oesophageal reflux symptoms in a UK population and the consultation behaviour of patients with these symptoms. *Aliment.Pharmacol.Ther.* 2000;14:1589-94.
24. Iftikhar SY, James PD, Steele RJ, Hardcastle JD, Atkinson M. Length of Barrett's oesophagus: an important factor in the development of dysplasia and adenocarcinoma. *Gut* 1992;33:1155-8.
25. Velanovich V, Hollingsworth J, Suresh P, Ben Menachem T. Relationship of gastroesophageal reflux disease with adenocarcinoma of the distal esophagus and cardia. *Dig.Surg.* 2002;19:349-53.
26. Chow WH, Finkle WD, McLaughlin JK, Frankl H, Ziel HK, Fraumeni JF, Jr. The relation of gastroesophageal reflux disease and its treatment to adenocarcinomas of the esophagus and gastric cardia. *JAMA* 1995;274:474-7.
27. Salminen JT, Ramo OJ, Ahotupa MO, Farkkila MA, Salo JA. Increased DNA adducts in Barrett's esophagus and reflux-related esophageal malignancies. *Ann.Med.* 2002;34:565-70.
28. Attwood SE, Smyrk TC, DeMeester TR, Mirvish SS, Stein HJ, Hinder RA. Duodeno-esophageal reflux and the development of esophageal adenocarcinoma in rats. *Surgery* 1992;111:503-10.
29. Fein M, Peters JH, Chandrasoma P, Ireland AP, Oberg S, Ritter MP *et al.* Duodeno-esophageal reflux induces esophageal adenocarcinoma without exogenous carcinogen. *J.Gastrointest.Surg.* 1998;2:260-8.
30. Theisen J, Peters JH, Fein M, Hughes M, Hagen JA, Demeester SR *et al.* The mutagenic potential of duodeno-esophageal reflux. *Ann.Surg.* 2005;241:63-8.
31. Shaheen NJ, Crosby MA, Bozymski EM, Sandler RS. Is there publication bias in the reporting of cancer risk in Barrett's esophagus? *Gastroenterology* 2000;119:333-8.

32. Cameron AJ, Zinsmeister AR, Ballard DJ, Carney JA. Prevalence of columnar-lined (Barrett's) esophagus. Comparison of population-based clinical and autopsy findings. *Gastroenterology* 1990;99:918-22.
33. Csendes A, Smok G, Burdiles P, Quesada F, Huertas C, Rojas J *et al.* Prevalence of Barrett's esophagus by endoscopy and histologic studies: a prospective evaluation of 306 control subjects and 376 patients with symptoms of gastroesophageal reflux. *Dis. Esophagus.* 2000;13:5-11.
34. Corder AP, Jones RH, Sadler GH, Daniels P, Johnson CD. Heartburn, oesophagitis and Barrett's oesophagus in self-medicating patients in general practice. *Br.J.Clin.Pract.* 1996;50:245-8.
35. Winters C, Jr., Spurling TJ, Chobanian SJ, Curtis DJ, Esposito RL, Hacker JF, III *et al.* Barrett's esophagus. A prevalent, occult complication of gastroesophageal reflux disease. *Gastroenterology* 1987;92:118-24.
36. Lagergren J, Ye W, Lindgren A, Nyren O. Heredity and risk of cancer of the esophagus and gastric cardia. *Cancer Epidemiol.Biomarkers Prev.* 2000;9:757-60.
37. Dhillon PK, Farrow DC, Vaughan TL, Chow WH, Risch HA, Gammon MD *et al.* Family history of cancer and risk of esophageal and gastric cancers in the United States. *Int.J.Cancer* 2001;93:148-52.
38. Tominaga K, Koyama Y, Sasagawa M, Hiroki M, Nagai M. A case-control study of stomach cancer and its genesis in relation to alcohol consumption, smoking, and familial cancer history. *Jpn.J.Cancer Res.* 1991;82:974-9.
39. Zaridze D, Borisova E, Maximovitch D, Chkhikvadze V. Alcohol consumption, smoking and risk of gastric cancer: case-control study from Moscow, Russia. *Cancer Causes Control* 2000;11:363-71.
40. De Stefani E, Correa P, Fierro L, Carzoglio J, Deneo-Pellegrini H, Zavala D. Alcohol drinking and tobacco smoking in gastric cancer. A case-control study. *Rev.Epidemiol.Sante Publique* 1990;38:297-307.
41. De Stefani E, Boffetta P, Carzoglio J, Mendilaharsu S, Deneo-Pellegrini H. Tobacco smoking and alcohol drinking as risk factors for stomach cancer: a case-control study in Uruguay. *Cancer Causes Control* 1998;9:321-9.
42. Tredaniel J, Boffetta P, Buiatti E, Saracci R, Hirsch A. Tobacco smoking and gastric cancer: review and meta-analysis. *Int.J.Cancer* 1997;72:565-73.
43. Hansson LE, Baron J, Nyren O, Bergstrom R, Wolk A, Adami HO. Tobacco, alcohol and the risk of gastric cancer. A population-based case-control study in Sweden. *Int.J.Cancer* 1994;57:26-31.
44. Harrison LE, Zhang ZF, Karpeh MS, Sun M, Kurtz RC. The role of dietary factors in the intestinal and diffuse histologic subtypes of gastric adenocarcinoma: a case-control study in the U.S. *Cancer* 1997;80:1021-8.
45. Boeing H, Jedrychowski W, Wahrendorf J, Popiela T, Tobiasz-Adameczyk B, Kulig A. Dietary risk factors in intestinal and diffuse types of stomach cancer: a multicenter case-control study in Poland. *Cancer Causes Control* 1991;2:227-33.
46. Mirvish SS. The etiology of gastric cancer. Intra-gastric nitrosamide formation and other theories. *J.Natl.Cancer Inst.* 1983;71:629-47.

47. Bartsch H, Ohshima H, Pignatelli B, Calmels S. Human exposure to endogenous N-nitroso compounds: quantitative estimates in subjects at high risk for cancer of the oral cavity, oesophagus, stomach and urinary bladder. *Cancer Surv.* 1989;8:335-62.
48. Choi NW, Miller AB, Fodor JG, Jain M, Howe GR, Risch HA *et al.* Consumption of precursors of N-nitroso compounds and human gastric cancer. *IARC Sci.Publ.* 1987;492-6.
49. Xu GP, Song PJ, Reed PI. Effects of fruit juices, processed vegetable juice, orange peel and green tea on endogenous formation of N-nitrosoproline in subjects from a high-risk area for gastric cancer in Moping County, China. *Eur.J.Cancer Prev.* 1993;2:327-35.
50. Working group on diet and cancer, Committee on Medical Aspects of Food and Nutrition Policy. *Nutritional Aspects of the Development of Cancer.* 1998. Department of Health.
51. Buiatti E, Palli D, Decarli A, Amadori D, Avellini C, Bianchi S *et al.* A case-control study of gastric cancer and diet in Italy. *Int.J.Cancer* 1989;44:611-6.
52. Hu JF, Zhang SF, Jia EM, Wang QQ, Liu SD, Liu YY *et al.* Diet and cancer of the stomach: a case-control study in China. *Int.J.Cancer* 1988;41:331-5.
53. Terry P, Lagergren J, Ye W, Wolk A, Nyren O. Inverse association between intake of cereal fiber and risk of gastric cardia cancer. *Gastroenterology* 2001;120:387-91.
54. Risch HA, Jain M, Choi NW, Fodor JG, Pfeiffer CJ, Howe GR *et al.* Dietary factors and the incidence of cancer of the stomach. *Am.J.Epidemiol.* 1985;122:947-59.
55. Munoz N, Vivas J, Buiatti E, Kato I, Oliver W. Chemoprevention trial on precancerous lesions of the stomach in Venezuela: summary of study design and baseline data. *IARC Sci.Publ.* 1996;125-33.
56. De Stefani E, Correa P, Boffetta P, Ronco A, Brennan P, Deneo-Pellegrini H *et al.* Plant foods and risk of gastric cancer: a case-control study in Uruguay. *Eur.J.Cancer Prev.* 2001;10:357-64.
57. Neugut AI, Hayek M, Howe G. Epidemiology of gastric cancer. *Semin.Oncol.* 1996;23:281-91.
58. Cho NH, Moy CS, Davis F, Haenszel W, Ahn YO, Kim H. Ethnic variation in the incidence of stomach cancer in Illinois, 1986- 1988. *Am.J.Epidemiol.* 1996;144:661-4.
59. Parsonnet J. Helicobacter pylori and gastric cancer. *Gastroenterol.Clin.North Am.* 1993;22:89-104.
60. Haenszel W, Kurihara M, Segi M, Lee RK. Stomach cancer among Japanese in Hawaii. *J.Natl.Cancer Inst.* 1972;49:969-88.
61. Malaty HM, Graham DY. Importance of childhood socioeconomic status on the current prevalence of Helicobacter pylori infection. *Gut* 1994;35:742-5.
62. Megraud, F. Epidemiology of Helicobacter pylori infection. 2nd, 107-123. 1992. Oxford: Blackwell Scientific Publications. Helicobacter pylori and Gastroduodenal Disease. Rathbone B.J. and Heatley, R. V.

63. Nomura A, Stemmermann GN. *Helicobacter pylori* and gastric cancer. *J.Gastroenterol.Hepatol.* 1993;8:294-303.
64. Nomura A, Stemmermann GN, Chyou PH, Kato I, Perez-Perez GI, Blaser MJ. *Helicobacter pylori* infection and gastric carcinoma among Japanese Americans in Hawaii. *N.Engl.J.Med* 1991;325:1132-6.
65. Parsonnet J, Friedman GD, Vandersteen DP, Chang Y, Vogelman JH, Orentreich N *et al.* *Helicobacter pylori* infection and the risk of gastric carcinoma. *N.Engl.J.Med* 1991;325:1127-31.
66. Forman D. The prevalence of *Helicobacter pylori* infection in gastric cancer. *Aliment.Pharmacol.Ther.* 1995;9 Suppl 2:71-6.
67. An international association between *Helicobacter pylori* infection and gastric cancer. The EUROGAST Study Group. *Lancet* 1993;341:1359-62.
68. Graham DY, Malaty HM, Evans DG, Evans DJ, Jr., Klein PD, Adam E. Epidemiology of *Helicobacter pylori* in an asymptomatic population in the United States. Effect of age, race, and socioeconomic status. *Gastroenterology* 1991;100:1495-501.
69. Malaty HM, Paykov V, Bykova O, Ross A, Graham DP, Anneger JF *et al.* *Helicobacter pylori* and socioeconomic factors in Russia. *Helicobacter.* 1996;1:82-7.
70. Parsonnet J, Friedman GD, Orentreich N, Vogelman H. Risk for gastric cancer in people with CagA positive or CagA negative *Helicobacter pylori* infection. *Gut* 1997;40:297-301.
71. Kuipers EJ. *Helicobacter pylori* and the risk and management of associated diseases: gastritis, ulcer disease, atrophic gastritis and gastric cancer. *Aliment.Pharmacol.Ther.* 1997;11 Suppl 1:71-88.
72. Kuipers EJ. Review article: exploring the link between *Helicobacter pylori* and gastric cancer. *Aliment.Pharmacol.Ther.* 1999;13 Suppl 1:3-11.
73. Dixon MF, Martin IG, Sue-Ling HM, Wyatt JI, Quirke P, Johnston D. Goseki grading in gastric cancer: comparison with existing systems of grading and its reproducibility. *Histopathology* 1994;25:309-16.
74. Dixon MF. Commentary: role of *Helicobacter pylori* on gastric mucosal damage, gastric cancer, and gastric MALT lymphoma. *Gastroenterology* 1997;113:S65-S66.
75. Cheli R, Santi L, Ciancamerla G, Canciani G. A clinical and statistical follow-up study of atrophic gastritis. *Am.J.Dig.Dis.* 1973;18:1061-5.
76. Uemura N, Okamoto S, Yamamoto S, Matsumura N, Yamaguchi S, Yamakido M *et al.* *Helicobacter pylori* infection and the development of gastric cancer. *N.Engl.J.Med* 2001;345:784-9.
77. Correa P. Human gastric carcinogenesis: a multistep and multifactorial process-- First American Cancer Society Award Lecture on Cancer Epidemiology and Prevention. *Cancer Res.* 1992;52:6735-40.
78. Kikuchi S, Wada O, Nakajima T, Nishi T, Kobayashi O, Konishi T *et al.* Serum anti-*Helicobacter pylori* antibody and gastric carcinoma among young adults. Research Group on Prevention of Gastric Carcinoma among Young Adults. *Cancer* 1995;75:2789-93.

79. Kokkola A, Valle J, Haapiainen R, Sipponen P, Kivilaakso E, Puolakkainen P. Helicobacter pylori infection in young patients with gastric carcinoma. *Scand.J.Gastroenterol.* 1996;31:643-7.
80. You WC, Blot WJ, Li JY, Chang YS, Jin ML, Kneller R *et al.* Precancerous gastric lesions in a population at high risk of stomach cancer. *Cancer Res.* 1993;53:1317-21.
81. Walker IR, Strickland RG, Ungar B, Mackay IR. Simple atrophic gastritis and gastric carcinoma. *Gut* 1971;12:906-11.
82. Craanen ME, Dekker W, Blok P, Ferwerda J, Tytgat GN. Intestinal metaplasia and Helicobacter pylori: an endoscopic bioptic study of the gastric antrum. *Gut* 1992;33:16-20.
83. Craanen ME, Blok P, Dekker W, Ferwerda J, Tytgat GN. Subtypes of intestinal metaplasia and Helicobacter pylori. *Gut* 1992;33:597-600.
84. Boland, C. R. Tumours of the stomach. Yamada, T. 1494-1523. 1996. Philadelphia, JB Lippincott. Textbook of Gastroenterology.
85. Whiting JL, Sigurdsson A, Rowlands DC, Hallissey MT, Fielding JW. The long term results of endoscopic surveillance of premalignant gastric lesions. *Gut* 2002;50:378-81.
86. Correa P. A human model of gastric carcinogenesis. *Cancer Res* 1988;48:3554-60.
87. Rokkas T, Filipe MI, Sladen GE. Detection of an increased incidence of early gastric cancer in patients with intestinal metaplasia type III who are closely followed up. *Gut* 1991;32:1110-3.
88. Goldstein NS, Lewin KJ. Gastric epithelial dysplasia and adenoma: historical review and histological criteria for grading. *Hum.Pathol.* 1997;28:127-33.
89. Tsukuma H, Oshima A, Narahara H, Morii T. Natural history of early gastric cancer: a non-concurrent, long term, follow up study. *Gut* 2000;47:618-21.
90. Tsukuma H, Mishima T, Oshima A. Prospective study of "early" gastric cancer. *Int.J.Cancer* 1983;31:421-6.
91. Oshima, A. Screening for stomach cancer: the Japanese program. 65-70. 1988. UICC, Toronto, Hans Huber. Screening for gastrointestinal cancer. Chamberlan J and Miller AB.
92. Hisamichi S. Screening for gastric cancer. *World J.Surg.* 1989;13:31-7.
93. Fujita S. Biology of early gastric carcinoma. *Pathol.Res Pract.* 1978;163:297-309.
94. Kohli Y, Kawai K, Fujita S. Analytical studies on growth of human gastric cancer. *J.Clin.Gastroenterol.* 1981;3:129-33.
95. Peddanna N, Holt S, Verma RS. Genetics of gastric cancer. *Anticancer Res.* 1995;15:2055-64.
96. Oliveira C, Seruca R, Carneiro F. Genetics, pathology, and clinics of familial gastric cancer. *Int.J.Surg.Pathol.* 2006;14:21-33.
97. Murakami T. Pathomorphological diagnosis. Definition and gross classification of early gastric cancer. *Gann Monogr Cancer Res* 11, 53-55. 1971.

98. Sue-Ling HM, Martin I, Griffith J, Ward DC, Quirke P, Dixon MF *et al.* Early gastric cancer: 46 cases treated in one surgical department. *Gut* 1992;33:1318-22.
99. Yamazaki H, Oshima A, Murakami R, Endoh S, Ubukata T. A long-term follow-up study of patients with gastric cancer detected by mass screening. *Cancer* 1989;63:613-7.
100. Saeki J. Uber die histologische prognostic dens magenkazinomas. *Mitteil Med Gessellsch Tokyo* , 191. 1938.
101. Ballantyne KC, Morris DL, Jones JA, Gregson RH, Hardcastle JD. Accuracy of identification of early gastric cancer. *Br.J.Surg.* 1987;74:618-9.
102. Everett SM, Axon AT. Early gastric cancer in Europe. *Gut* 1997;41:142-50.
103. Hallissey MT, Allum WH, Jewkes AJ, Ellis DJ, Fielding JW. Early detection of gastric cancer. *BMJ* 1990;301:513-5.
104. O'Brien MJ, Burakoff R, Robbins EA, Golding RM, Zamcheck N, Gottlieb LS. Early gastric cancer. Clinicopathologic study. *Am.J.Med.* 1985;78:195-202.
105. Houghton PW, Mortensen NJ, Allan A, Williamson RC, Davies JD. Early gastric cancer: the case for long term surveillance. *Br.Med.J.(Clin.Res.Ed)* 1985;291:305-8.
106. Nishi M, Ishihara S, Nakajima T, Ohta K, Ohyama S, Ohta H. Chronological changes of characteristics of early gastric cancer and therapy: experience in the Cancer Institute Hospital of Tokyo, 1950- 1994. *J.Cancer Res.Clin.Oncol.* 1995;121:535-41.
107. Hisamichi S, Nozaki K, Kitagawa M, Mochizuki F, Gomi T. Evaluation of mass screening program for stomach cancer. *Tohoku J.Exp.Med.* 1976;118 Suppl:69-77.
108. NHS centre for reviews and dissemination. Management of upper gastro-intestinal cancers. 2000.
109. Maruyama K, Okabayashi K, Kinoshita T. Progress in gastric cancer surgery in Japan and its limits of radicality. *World J.Surg.* 1987;11:418-25.
110. Nakajima T, Nishi M. Surgery and adjuvant chemotherapy for gastric cancer. *Hepatogastroenterology* 1989;36:79-85.
111. Geoghegan JG, Keane TE, Rosenberg IL, Dellipiani AW, Peel AL. Gastric cancer: the case for a more selective policy in surgical management. *J.R.Coll.Surg.Edinb.* 1993;38:208-12.
112. Wayman J, Raimes S, Griffin SM, Hayes N. Delays in diagnosing oesophagogastric cancer. Small study found that four fifths of delay was due to patients. *BMJ* 1997;315:428.
113. Martin IG, Young S, Sue-Ling H, Johnston D. Delays in the diagnosis of oesophagogastric cancer: a consecutive case series. *BMJ* 1997;314:467-70.
114. Jones RV, Dudgeon TA. Time between presentation and treatment of six common cancers: a study in Devon. *Br.J.Gen.Pract.* 1992;42:419-22.
115. Bramble MG, Suvakovic Z, Hungin AP. Detection of upper gastrointestinal cancer in patients taking antisecretory therapy prior to gastroscopy. *Gut* 2000;46:464-7.

116. Jones RH, Lydeard SE, Hobbs FD, Kenkre JE, Williams EI, Jones SJ *et al.* Dyspepsia in England and Scotland. *Gut* 1990;31:401-5.
117. Howell S, Talley NJ. Does fear of serious disease predict consulting behaviour amongst patients with dyspepsia in general practice? *Eur.J.Gastroenterol.Hepatol.* 1999;11:881-6.
118. Hu WH, Wong WM, Lam CL, Lam KF, Hui WM, Lai KC *et al.* Anxiety but not depression determines health care-seeking behaviour in Chinese patients with dyspepsia and irritable bowel syndrome: a population-based study. *Aliment.Pharmacol.Ther.* 2002;16:2081-8.
119. McCulloch P, Williams E, McCulloch C, Mullins D. Can we improve the uptake of gastroscopy in the population at risk for gastric cancer? The effect of home letter information. *J.R.Coll.Surg.Edinb.* 1998;43:385-9.
120. Cass OW, Freeman ML, Peine CJ, Zera RT, Onstad GR. Objective evaluation of endoscopy skills during training. *Ann.Intern.Med* 1993;118:40-4.
121. Gjorup T, Agner E, Bording JL, Mollmann KM. Accuracy of radiologic and endoscopic diagnosis of duodenal ulcer. *Acta Radiol.* 1988;29:661-4.
122. Rembacken BJ, Fujii T, Cairns A, Dixon MF, Yoshida S, Chalmers DM *et al.* Flat and depressed colonic neoplasms: a prospective study of 1000 colonoscopies in the UK. *Lancet* 2000;355:1211-4.
123. Rutter MD, Saunders BP, Schofield G, Forbes A, Price AB, Talbot IC. Pancolonic indigo carmine dye spraying for the detection of dysplasia in ulcerative colitis. *Gut* 2004;53:256-60.
124. Yoshida S, Yamaguchi H, Tajiri H, Saito D, Hijikata A, Yoshimori M *et al.* Diagnosis of early gastric cancer seen as less malignant endoscopically. *Jpn.J.Clin.Oncol.* 1984;14:225-41.
125. Yokoyama A, Ohmori T, Makuuchi H, Maruyama K, Okuyama K, Takahashi H *et al.* Successful screening for early esophageal cancer in alcoholics using endoscopy and mucosa iodine staining. *Cancer* 1995;76:928-34.
126. Dawsey SM, Fleischer DE, Wang GQ, Zhou B, Kidwell JA, Lu N *et al.* Mucosal iodine staining improves endoscopic visualization of squamous dysplasia and squamous cell carcinoma of the esophagus in Linxian, China. *Cancer* 1998;83:220-31.
127. Canto MI, Setrakian S, Willis JE, Chak A, Petras RE, Sivak MV. Methylene blue staining of dysplastic and nondysplastic Barrett's esophagus: an in vivo and ex vivo study. *Endoscopy* 2001;33:391-400.
128. Tatsuta M, Okuda S, Tamura H, Taniguchi H. Endoscopic diagnosis of early gastric cancer by the endoscopic Congo red-methylene blue test. *Cancer* 1982;50:2956-60.
129. Tatsuta M, Iishi H, Okuda S, Taniguchi H. Diagnosis of early gastric cancers in the upper part of the stomach by the endoscopic Congo red-methylene blue test. *Endoscopy* 1984;16:131-4.
130. Iishi H, Tatsuta M, Okuda S. Diagnosis of simultaneous multiple gastric cancers by the endoscopic Congo red--methylene blue test. *Endoscopy* 1988;20:78-82.
131. Shim CS. Staining in gastrointestinal endoscopy: clinical applications and limitations. *Endoscopy* 1999;31:487-96.

132. Mashberg A. Tolonium (toluidine blue) rinse--a screening method for recognition of squamous carcinoma. Continuing study of oral cancer IV. *JAMA* 1981;245:2408-10.
133. Jung M, Kiesslich R. Chromoendoscopy and intravital staining techniques. (13 (1)), 11-19. 1999. Bailliere's Clinical Gastroenterology.
134. Ng TY, Datta TD, Kirimli BI. Reaction to indigo carmine. *J.Urol.* 1976;116:132-3.
135. Sills MR, Zinkham WH. Methylene blue-induced Heinz body hemolytic anemia. *Arch.Pediatr.Adolesc.Med* 1994;148:306-10.
136. Demirturk L, Hulagu S, Altin M, Ucmakli E, Dumanhan L, Ozel M. Does staining gastric mucosa with methylene blue spraying method affect diagnosis of Helicobacter pylori? *Gastrointest.Endosc.* 1996;43:81.
137. Lawrence M, Shiu MH. Early gastric cancer. Twenty-eight-year experience. *Ann.Surg.* 1991;213:327-34.
138. O'Donoghue J, Waldron R, Gough D, McCabe J, Kerin M, McGuire M *et al.* An analysis of the diagnostic accuracy of endoscopic biopsy and cytology in the detection of oesophageal malignancy. *Eur.J.Surg.Oncol.* 1992;18:332-4.
139. Tatsuta M, Iishi H, Okuda S, Oshima A, Taniguchi H. Prospective evaluation of diagnostic accuracy of gastrofiberscopic biopsy in diagnosis of gastric cancer. *Cancer* 1989;63:1415-20.
140. Lal N, Bhasin DK, Malik AK, Gupta NM, Singh K, Mehta SK. Optimal number of biopsy specimens in the diagnosis of carcinoma of the oesophagus. *Gut* 1992;33:724-6.
141. Graham DY, Schwartz JT, Cain GD, Gyorkey F. Prospective evaluation of biopsy number in the diagnosis of esophageal and gastric carcinoma. *Gastroenterology* 1982;82:228-31.
142. Martin RM, Lim AG, Kerry SM, Hilton SR. Trends in prescribing H2-receptor antagonists and proton pump inhibitors in primary care. *Aliment.Pharmacol.Ther.* 1998;12:797-805.
143. Bashford JN, Norwood J, Chapman SR. Why are patients prescribed proton pump inhibitors? Retrospective analysis of link between morbidity and prescribing in the General Practice Research Database. *BMJ* 1998;317:452-6.
144. Ross I, Edgehill J. Prescription of proton pump inhibitors. Ulcer healing drugs affect gastroscopy results. *BMJ* 1999;318:534.
145. Taylor RH, Menzies-Gow N, Lovell D, La Brooy SJ, Misiewicz JJ. Misleading response of malignant gastric ulcers to cimetidine. *Lancet* 1978;1:686-8.
146. Griffin SM, Raimes SA. Proton pump inhibitors may mask early gastric cancer. Dyspeptic patients over 45 should undergo endoscopy before these drugs are started. *BMJ* 1998;317:1606-7.
147. Wayman J, Hayes N, Griffin SM. The response of early gastric cancer to proton-pump inhibitors. *N.Engl.J.Med.* 1998;338:1924-5.
148. Bramble MG. Open access endoscopy--a nationwide survey of current practice. *Gut* 1992;33:282-5.

149. Silcock JG, Bramble MG. Open access gastroscopy: second survey of current practice in the United Kingdom. *Gut* 1997;40:192-5.
150. Quine MA, Bell GD, McCloy RF, Devlin HB, Hopkins A. Appropriate use of upper gastrointestinal endoscopy--a prospective audit. Steering Group of the Upper Gastrointestinal Endoscopy Audit Committee. *Gut* 1994;35:1209-14.
151. O'Neill L, Quirke M, Hogan S, Eustace-Ryan AM, O'Regan P. Uncensored open access gastroscopy--limited resources--unlimited demand. *Ir.J.Med.Sci.* 1998;167:89-91.
152. Hungin AP, Thomas PR, Bramble MG, Corbett WA, Idle N, Contractor BR *et al.* What happens to patients following open access gastroscopy? An outcome study from general practice. *Br.J.Gen.Pract.* 1994;44:519-21.
153. Bytzer P, Hansen JM, Schaffalitzky De Muckadell OB. Empirical H2-blocker therapy or prompt endoscopy in management of dyspepsia. *Lancet* 1994;343:811-6.
154. Holdstock G, Wiseman M, Loehry CA. Open-access endoscopy service for general practitioners. *Br.Med.J.* 1979;1:457-9.
155. Kerrigan DD, Brown SR, Hutchinson GH. Open access gastroscopy: too much to swallow? *BMJ* 1990;300:374-6.
156. Goy JA, Herold E, Jenkins PJ, Colman JC, Russell DM. "Open-access" endoscopy for general practitioners. Experience of a private gastrointestinal clinic. *Med.J.Aust.* 1986;144:71-4.
157. Gear MW, Ormiston MC, Barnes RJ, Rocyn-Jones J, Voss GC. Endoscopic studies of dyspepsia in the community: an "open-access" service. *Br.Med.J.* 1980;280:1135.
158. Quine MA, Bell GD, McCloy RF, Charlton JE, Devlin HB, Hopkins A. Prospective audit of upper gastrointestinal endoscopy in two regions of England: safety, staffing, and sedation methods. *Gut* 1995;36:462-7.
159. Office for National Statistics. Registrations of cancer diagnosed in 1993-1996, England and Wales. *Health Statistics Quarterly* 4, 59-70. 1999.
160. Suzuki S. Endoscopic dye method. 1996. Igaku Shoin. ABC of GI endoscopy.
161. Canto MI. Staining in gastrointestinal endoscopy: the basics. *Endoscopy* 1999;31:479-86.
162. Suvakovic Z, Bramble MG, Jones R, Wilson C, Idle N, Ryott J. Improving the detection rate of early gastric cancer requires more than open access gastroscopy: a five year study. *Gut* 1997;41:308-13.
163. Dyspepsia guidelines. 2003.
164. Banait G, Sibbald B, Thompson D, Summerton C, Hann M, Talbot S. Modifying dyspepsia management in primary care: a cluster randomised controlled trial of educational outreach compared with passive guideline dissemination. *Br.J.Gen.Pract.* 2003;53:94-100.
165. Kennedy BJ. The unified international gastric cancer staging classification. *Scand.J.Gastroenterol.* 1987;22 (suppl 133):11-3.
166. Jones MI, Greenfield SM, Jowett S, Bradley CP, Seal R. Proton pump inhibitors: a study of GPs' prescribing. *Fam.Pract.* 2001;18:333-8.

167. Bytzer P, Schaffalitzky De Muckadell OB. Prediction of major pathologic conditions in dyspeptic patients referred for endoscopy. A prospective validation study of a scoring system. *Scand.J.Gastroenterol.* 1992;27:987-92.
168. Fransen GA, Janssen MJ, Muris JW, Laheij RJ, Jansen JB. Meta-analysis: the diagnostic value of alarm symptoms for upper gastrointestinal malignancy. *Aliment.Pharmacol.Ther.* 2004;20:1045-52.
169. Eckardt VF, Willems D, Kanzler G, Remmele W, Bettendorf U, Paulus W. Eighty months persistence of poorly differentiated early gastric cancer. *Gastroenterology* 1984;87:719-24.
170. Department of Health. Improving outcomes in upper gastrointestinal cancers. The Manual 2001. 2001.
171. Stoker E, Elsener A, Bradbury D, Cullen M, Chirnside V, Thompson N. Audit of fast track 2 week cancer wait. *Gut* 50(suppl 2). 2002.
172. Subramanian S, Lloyd D, Poulis A, Millar-Smith J, Kang J, Neild P, Maxwell J. Few gastro-oesophageal malignancies are identified through the two week rule. *Gut* 50(suppl 2). 2002.
173. Jones R, Rubin G, Hungin P. Is the two week rule for cancer referrals working? *BMJ* 2001;322:1555-6.
174. Wallace MB, Durkalski VL, Vaughan J, Palesch YY, Libby ED, Jowell PS *et al.* Age and alarm symptoms do not predict endoscopic findings among patients with dyspepsia: a multicentre database study. *Gut* 2001;49:29-34.
175. Christie J, Shepherd NA, Codling BW, Valori RM. Gastric cancer below the age of 55: implications for screening patients with uncomplicated dyspepsia. *Gut* 1997;41:513-7.
176. Loehry J, Smith T, Vyas S. Achieving the two week standard for suspected upper GI cancers: continuing pain with little gain. *Gut* 50(Suppl 2). 2002.
177. Meineche-Schmidt V, Jorgensen T. 'Alarm symptoms' in patients with dyspepsia: a three-year prospective study from general practice. *Scand.J.Gastroenterol.* 2002;37:999-1007.
178. Sue-Ling HM, Johnston D, Martin IG, Dixon MF, Lansdown MR, McMahon MJ *et al.* Gastric cancer: a curable disease in Britain. *BMJ* 1993;307:591-6.
179. Hosokawa O, Tsuda S, Kidani E, Watanabe K, Tanigawa Y, Shirasaki S *et al.* Diagnosis of gastric cancer up to three years after negative upper gastrointestinal endoscopy. *Endoscopy* 1998;30:669-74.
180. Voutilainen M, Mantynen T, Kunnamo M, Juhoa M, Farkkila M. Impact of clinical symptoms and referral volume on endoscopy for detecting peptic ulcer and gastric neoplasms. *Scand.J.Gastroenterol.* 2003;38:109-13.
181. Rockall TA, Logan RFA, Devlin HB, Northfield TC. Influencing the practice and outcome in acute upper gastrointestinal haemorrhage. *Br.Med.J.* 1997;41:606-12.
182. Fung WP, Lee SK. Diagnosis of gastric malignancy by fiberoptic endoscopy and gastric biopsy: Comparison with radiology. *Med.J.Aust.* 1976;2:241-2.

183. Stevenson GW, Cox RR, Roberts CJ. Prospective comparison of double-contrast barium meal examination and fiberoptic endoscopy in acute upper gastrointestinal haemorrhage. *Br.Med.J.* 1976;2:723-4.
184. Martin TR, Vennes JA, Silvis SE, Ansel HJ. A comparison of upper gastrointestinal endoscopy and radiography. *J.Clin.Gastroenterol.* 1980;2:21-5.
185. Morris E. A comparison between upper gastro-intestinal endoscopy and barium meal examination in private practice. *S.Afr.Med.J.* 1980;57:870-2.
186. Yoshida, S., Yamaguchi, H., Saiton D, and Kido, M. Endoscopic diagnosis:latest trends. 246-262. 1993. Tokyo, Springer Verlag. Nishi M.
187. Kiesslich R, Mergener K, Naumann C, Hahn M, Jung M, Koehler HH *et al.* Value of chromoendoscopy and magnification endoscopy in the evaluation of duodenal abnormalities: a prospective, randomized comparison. *Endoscopy* 2003;35:559-63.
188. Howat A, Boyd K, Douce G, and et al. 2002. Royal College of Pathologists. SAC on histopathology of limited or no clinical value.
189. Cowan RE, Manning AP, Ayliffe GA, Axon AT, Causton JS, Cripps NF *et al.* Aldehyde disinfectants and health in endoscopy units. British Society of Gastroenterology Endoscopy Committee. *Gut* 1993;34:1641-5.
190. Debruyne PR, Waldman SA, Schulz S. Pathological staging and therapy of oesophageal and gastric cancer. *Expert.Opin.Pharmacother.* 2003;4:1083-96.