SPECIAL REPORT

The British Society of Gastroenterology early gastric cancer/dysplasia survey: an interim report

F T de Dombal, A B Price, H Thompson, G T Williams, A G Morgan, A Softley, S E Clamp, B J Unwin

Abstract

This presentation describes interim findings in a series of 319 patients referred from 41 hospitals on the basis of histopathological findings of 'early gastric cancer', 'dysplasia', or 'worrying mucosal appearances'. Data were recorded using a predefined proforma, and histopathological material circulated amongst a 'panel' of three further pathologists. After this process, 132 patients were classified as having early gastric cancer and 63 as dysplasia. There was good agreement between pathologists as to whether the cases had cancer or dysplasia – but 39 cases said by referring pathologists to have early gastric cancer were classified by the panel as having more extensive disease. Most early gastric cancer cases were diagnosed only after histopathological examination. Cancer or 'possible cancer' was only mentioned after 36% of the radiological investigations and 40·5% of the endoscopies. Computer aided analysis of the patients' symptoms placed 91·3% of the early gastric cancer cases into a 'high risk' group – but was unable to distinguish between early gastric cancer and dysplasia. The five year survival rate of the cases agreed to be early gastric cancer by the panel was well over 90%, but the four year survival rate of cases registered as 'early gastric cancer' but said by the panel to have more advanced disease was under 75%. These findings may account for some of the differences between series, and emphasise the need for precise, widely agreed criteria for the diagnosis of early gastric cancer and gastric dysplasia.

Clinical Information Science Unit, Leeds
F T de Dombal
A Softley
S E Clamp
B J Unwin

Department of Histopathology, Northwick Park Hospital and MRC, Harrow Middlesex
A B Price

The General Hospital, Birmingham
H Thompson

University of Wales, Department of Pathology, Cardiff
G T Williams

Airedale District Hospital, Keighley, West Yorks
A G Morgan

Correspondence to: F T de Dombal, Clinical Information Science Unit, 22 Hyde Terrace, Leeds LS2 9LN.

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The frequency with which gastric cancer occurs (accounting for over 10% of cancer deaths per year in the United Kingdom), and the poor survival rate despite modern forms of surgery (under 10% at five year overall) are well recognised.[1] These depressing statistics are doubly disquieting because exhaustive studies have shown beyond reasonable doubt that the prognosis of gastric cancer is related to its clinicopathological staging.[2]

In the last decades, an increasing number of reports concerning 'early gastric cancer' have been stimulated by original work carried out in Japan.[3–7] At least two studies from the United Kingdom have attempted to delineate the features of cancers where invasion by the primary tumour is restricted to the mucosa and submucosa of the stomach by the time the cancer is resected.[8,9]

Evans and colleagues[8] reported 14 such cases with clinical and histopathological characteristics similar to those found in Japanese patients. Fielding and colleagues[1,9] have, however, shown that in current practice, the number of 'early gastric cancers' remains depressingly small. In the Birmingham series out of over 13 000 patients with gastric cancer, only 90 fully filled the above criteria for early disease.

Both these previous excellent surveys suggested that earlier and more effective investigation of patients with dyspepsia might increase the detection rate for early gastric cancer; but over the years there has been lively debate about the mode of presentation of early gastric cancer in the United Kingdom, and also about means of classifying such cases.

At the Second BSG SK&F International Workshop on early gastric cancer, delegates agreed widely that it would be helpful to develop a 'national picture' of early gastric cancer; but that on a prospective basis, no single centre or even region in the United Kingdom could readily and quickly collect sufficient cases to warrant more than limited conclusions. It was also agreed that the prognostic significance of 'gastric dysplasia' (and its relationship to the development of subsequent gastric cancer) had not yet been established.

Given that such problems could only be studied by careful analysis and follow up of a reasonably large cohort of patients, with the support and approval of the Education and Science Committee of the BSG, together with the Society's Council and Pathology Section, a multicentre collaborative study was started. The study results to date form the basis for this interim presentation.

Aims of study

The aims of the study may be summarised as follows:

1 The setting up of a register of patients diagnosed as having 'early gastric cancer' or 'gastric dysplasia' in Great Britain; and the generation of a databank of information about these patients on a prospective basis, using wherever possible, standardised criteria and pre-agreed definitions.
2 The investigation of observer reliability in

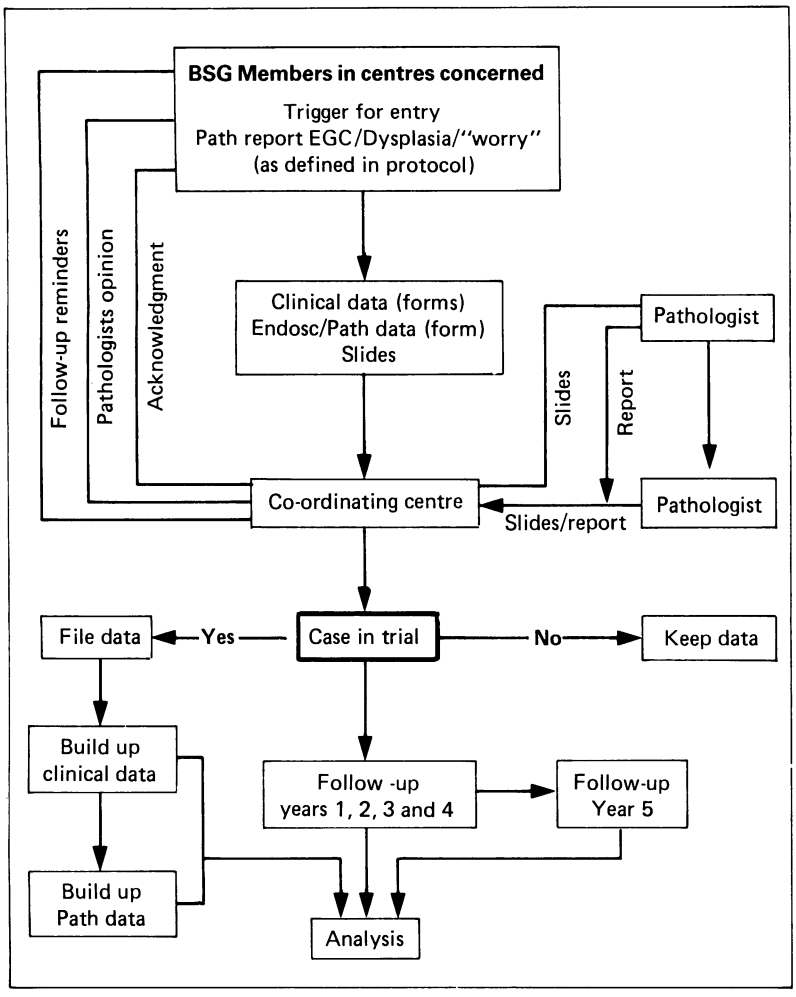

Figure 1: Flow diagram showing survey modus operandi.

the definition of early gastric cancer and dysplasia.

3 Comparison of the clinical characteristics of patients with early gastric cancer, gastric dysplasia and other causes of dyspepsia.

4 Delineation of diagnostic standards for early gastric cancer and gastric dysplasia which might form the basis of possible future comparisons between patients in Britain and those in other countries.

5 Establishment of a cohort of patients (with either 'early gastric cancer' or 'dysplasia') for clinical follow-up so as to investigate the prognostic significance of initial findings on endoscopy, biopsy and histopathology.

Methods

SUBJECTS

Entry to the study

As shown (Fig 1), cases were entered into the study by BSG members in a variety of centres, the 'trigger' for entry into the study being a pathological report of either early gastric cancer, or gastric dysplasia, or 'worrying mucosal appearances'. Such a report could only be initiated by a pathologist in the referring centre; though it might arise as a result of examination of either biopsy material after endoscopy or histopathological examination of a resected surgical specimen.

Once it was decided to enter a patient, the relevant 'dossier' of information concerning basic, symptomatic, endoscopic and histopathological data was sent to the coordinating centre in Leeds, using a predefined and common proforma. Methods of (computer based) analysis have been described elsewhere.[10 11]

Pathological material

In addition on entry to the study, relevant slides were forwarded to the co-ordinating centre and thence onwards for additional examination by survey histopathologists.

The flow diagram in Figure 1 stylises what was in practice rather a complex arrangement. Each set of material was reviewed by a panel of three pathologists. Initially each pathologist reviewed the material independently; and at a regular series of meetings these independent findings were compared. As a result for each case a 'final' diagnosis was produced; this being the consensus view of the panel of three pathologists.

In this way the project aimed to compare the diagnosis made by the centre pathologists and the consensus view of the panel – although in practice it should be noted that the panel only had access to sections submitted by the referring pathologist, and not the entire relevant specimen.

Criteria

The panel pathologists in this study used the criteria of the Japanese Society to define early gastric cancer as carcinoma that is confined to the mucosa or submucosa, irrespective of the presence of lymph node metastases. The term 'early gastric cancer' has been the subject of criticism and the lesion in question might be better labelled stage T1 gastric cancer (N0 or N1, M0) as defined by the international TNM classification.[12]

Dysplasia was defined as histological abnormalities of cytology and/or architecture which were considered to be neoplastic but which did not amount to unequivocal carcinoma, divided into high grade and low grade dysplasia depending upon the severity of the abnormalities.[13]

Follow up

Once the case was entered into the trial follow up was obtained on a yearly basis, *via* a predefined and pre-agreed proforma. This took place for all cases, whether defined as being early gastric cancer or not, until five years had elapsed after the initial diagnosis and entry into the trial.

Patients

Table I shows the patients, according to final panel diagnosis, provided from the referring centres. In all, a total of 77 consultants in 41 hospitals referred some 319 cases.

Of the 319 cases entered into the survey, a total of 132 patients (41·4%) were finally classified as having early gastric cancer. A further 63 patients (19·7%) were classified as having dysplasia, and no less than 55 patients (17·2%) were ultimately

TABLE I *Breakdown by 'final' panel diagnosis of case material provided*

Diagnostic category	*Cases (n)*	*% of total*
Early gastric cancer	132	41·4%
Dysplasia	63	19·7%
Advanced gastric cancer	55	17·2%
Other	50	15·7%
Unknown	19	6·0%
Total	319	100%

TABLE II *Comparison between original 'centre' diagnosis and 'panel' diagnosis for 319 cases on survey*

			Centre diagnosis			
Panel diagnosis	*EGC*	*Dysplasia*	*AGC*	*Other*	*'Worrying'†*	*Total*
EGC	119	4	1	–	8	132
Dysplasia	7	40	–	4	12	63
Advanced gastric cancer	39	1	9	–	6	55
Other	3	18	–	7	22	50
?/unknown	5	5	–	2	7	19
Total	173	68	10	13	55	319

Agreement: EGC *v* dysplasia 159/170=93·5% Kappa*=0·87; EGC *v* AGC 128/168=76·2% Kappa=0·52. *Kappa statistic[14,15]; †See text.

TABLE III *Agreement between panel pathologists on identical material. Total of 286 'interpathologist' comparisons*

*Outcome of comparison**	*Observations (n)*	*% of total*	
Both agreed cancer	107	37·4%	88·1%
Both agreed dysplasia	145	50·7%	
Disagreed	34	11·9%	

*Kappa value 0·76.

TABLE IV *Modality by which EGC was diagnosed in 132 cases*

Modality	*Cases (n)*	*% of total*
Firm diagnosis on clinical picture	?	?*
Radiology confirmed by endoscopy	5	
No endoscopy	2	
Total	7	5·3%
Endoscopy, confirmed by biopsy	24	18·2%
Biopsy (endoscopy appearances negative, uncertain)	74	56·1%
Found at operation	13	9·8%
Unknown/unrecorded	14	10·6%
Total	132	100·0%

*One firm diagnosis of early gastric cancer. Several cases diagnosed as 'suspicious'.

TABLE V *Radiologists findings and opinions in 33 EGC cases*

		Cases (n)	*% of total*	
A: Appearances reported	Typical cancer seen	7	21·2%	
	? filling defect	2	6·1%	
	Gastric ulcer	12	36.4%	
	Irregular mucosa	2	6·1%	
	Polyp	1	3·0%	
	Pyloric deformity	1	3·0%	
	? Polyp ? ulcer	1	3·0%	
	No abnormality in stomach	7	21·2%	
B: Radiologist opinion	Cancer	7	21·2%	36·4%
	Possible cancer	5	15·2%	
	Benign gastric ulcer	12	36·4%	42·5%
	Other benign appearance	2	6·1%	
	Stomach normal	7	21·2%	

classified by the panel as having gastric cancer which had progressed beyond an early stage; whilst a further 50 patients (15·7%) had a variety of other diagnoses established.

The great majority of cases submitted which were not classified by the panel as dysplasia were considered to represent reactive hyperplasia consequent upon either active gastritis or peptic ulceration. The condition which caused the greatest difficulty was undoubtedly faveolar hyperplasia which, in the opinion of the panel pathologists, was often misdiagnosed as low grade dysplasia. A number of cases of intestinal metaplasia were also submitted which were not considered to show dysplasia by the panel.

Finally, in 19 patients (6·0% of the total) the final diagnosis had not been agreed at the time of the writing of this report.

Results

OBSERVER RELIABILITY

Table II shows a comparison between the original diagnosis made by the pathologist in the referring centre and the consensus diagnosis of the panel for each of the 319 cases entered into the survey.

A high degree of agreement was reached between the centre pathologists and the pathologists panel in respect of classification of patients where the distinction concerned dysplasia *v* early gastric cancer. There were 170 patients where this (centre *v* panel) comparison was relevant, and agreement was reached in 159 (93·5%).

There was, however, less agreement where 'early' and 'advanced' gastric cancer was concerned. Out of 168 cases where this question was relevant, there was agreement in only 128 (76·2%). Some 39 cases referred by the centre pathologists as 'early gastric cancer' were concluded by the pathologists panel to have more advanced disease.

One possible reason for disagreement between centre and panel pathologists might of course be that they were examining different material (*vide supra*). For this reason further study was carried out in which each of the panel pathologists studied identical material from 41 cases ultimately classified as early gastric cancer and 63 cases classified as dysplasia. The results (Table III) confirmed a high accuracy of match in a total of 286 'inter-pathologist' comparisons – that is, comparisons between each pair of pathologists for each case.

MODE OF DETECTION

Table IV indicates the mode by which early gastric cancer was diagnosed in each of the 132 cases agreed by the panel to have that category of disease. In practice, the diagnosis was almost never made on the clinical picture alone, though several cases were described as 'suspicious' in the clinical records.

The data, however, confirm the extent to which endoscopy and biopsy, dominate the diagnosis of early gastric cancer. (Endoscopy with biopsy and cytology seems to be the preferred investigation in most United Kingdom centres – possibly because it provides a tissue diagnosis with maximum rapidity.)

Only seven cases (5·3% of the total) were diagnosed on radiology and five of those underwent confirmatory endoscopy. Perhaps more surprisingly, only 24 cases were diagnosed on endoscopy by visual appearances; the vast majority of cases being diagnosed on histopathological examination often in the face of negative or uncertain visual appearances at endoscopy. Finally, 13 cases came to light at operation (usually after the surgical removal of

TABLE VI *Endoscopists findings and opinions in 114 EGC cases*

		Cases (n)	% of total
A: Appearances reported	Gastric ulceration	69	60·5%
	Abnormal mucosa	10	8·8%
	Plaque	9	7·9%
	Polyp	8	7·0%
	Erosion	3	2·6%
	Gastritis	2	1·8%
	Miscellaneous	13	11·4%
B: Endoscopist opinion*	Malignant	24	21·1%
	Suspicious	22	19·3%
	Benign	46	40·4%
	Not sure/not stated	22	19·3%

*On visual appearances.

TABLE VII *Can computer-aided analysis* identify EGC cases from symptoms alone?*

	'Correct diagnosis'†		
Computer prediction	*'Functional' (50 cases)*	*'Dysplasia' (57 cases)*	*'Early gastric cancer' (104 cases)*
Functional/hiatus hernia	22	9	5
Duodenal ulcer	10	1	7
Gastric ulcer	5	5	6
Cholecystitis	4	1	6
Early gastric cancer	6	21	64
Advanced gastric cancer	3	20	16
% diagnosed as cancer	18%	71·9%	76·9%
% placed in 'high risk' band*	28%	91·2%	91·3%
% placed in 'low risk' band*	40%	8·8%	1·9%

*For methodology see Davenport *et al.*[11] High risk band is where computer predicts greater than 10% chance of gastric cancer or EGC. Low risk band is where computer predicts either functional or hiatus hernia, with less than 10% chance of cancer; †'Correct diagnosis' is that of the panel, as regards either dysplasia or early gastric cancer. 'Functional' cases are from the Leeds Primary Health Care Study;[10] all followed for at least three years after negative investigation without organic disease being established or further symptoms.

an apparently benign gastric ulcer) and in around 10% of cases it was not possible from the case records to assign a patient to one of the above categories.

RADIOLOGICAL AND ENDOSCOPY APPEARANCES

Tables V and VI illustrate the radiological and endoscopic findings and opinions reported, from 33 cases undergoing upper GI radiology and 114 cases undergoing endoscopy.

Although the radiological data are scanty, they are disquieting. In only 21% of cases (seven of 33) was a typical cancer seen and though cancer was mentioned in about one third of patients, in 14 patients (42·5%) the appearances were thought to be benign by the radiologist and in seven patients (21·2%) the stomach was said to be completely normal.

The visual findings on endoscopy and the endoscopist's predictions from 114 cases of early gastric cancer are shown in Table VI. Once again the proportion of patients in whom a firm diagnosis of malignancy was made is somewhat low (24 cases, 21·1%). In a further 19·3% of cases malignancy was questioned, but 46 patients' visual endoscopic features were described as 'benign'.

SYMPTOMATIC ANALYSIS

As almost none of the early gastric cancer cases were diagnosed firmly on symptomatic grounds it became relevant to enquire as to whether there were any 'clues' which could be utilised to improve early diagnosis. Accordingly the symptomatic data from the cases concerned were analysed using a desk top computer as described previously by Clamp and Wenham 1984[10] and Davenport *et al* 1985.[11] In all, 104 cases of early gastric cancer from the present series, 57 cases with dysplasia from the series and a further 50 functional cases from the Leeds Primary Health Care Study – that is, patients with non-ulcer dyspepsia all followed for at least three years after negative investigations without organic disease being established – were analysed as previously described by comparison with a reference series of just under 1000 cases[10 11] (Table VII).

Of the early gastric cancer cases just under 77% were diagnosed as cancer by the computer predictive system, but an almost equal number of 'dysplasia' cases were also diagnosed as cancer by the system. Nevertheless, both early gastric cancer and dysplasia (each of which warrant further urgent investigation) were separated reasonably well from patients with non-organic dyspepsia. The computer placed over 91% of each group (early gastric cancer and dysplasia) in a high risk category as regards cancer, and only two patients with early gastric cancer out of 104 were placed in the 'low risk' category.

PROGRESSION OF SYMPTOMS

Since computer aided prediction can to some extent separate patients at high risk of early gastric cancer, it becomes relevant to ask why this is not currently done. Part of the answer is illustrated in Table VIII. This further analysis compares the symptoms of the 'classical cancer syndrome' in groups of patients with increasingly progressive disease – 63 cases of dysplasia from the present series, 132 cases of early gastric cancer, 55 cases registered into the series with early gastric cancer but found to have slightly more extensive disease (tumour just involving the innermost fibres of circular muscle) and finally 100 cases of advanced gastric cancer from earlier Leeds studies.[10]

The data indicate that although the classical cancer syndrome is present in almost all of the patients who present routinely in the conventional manner to hospital with advanced gastric cancer, these features are present in only half of the cases with early gastric cancer, and in far less than half of the cases with dysplasia.

FOLLOW UP

Of necessity the data concerning follow up are less complete than those concerning the initial presentation. Some preliminary actuarial data, however, are shown in Figure 2.

Several aspects are worth comment. First, the five year survival rate (around 90%) of the 132 early gastric cancer cases (calculated on an actuarial basis using the patient year concept) is not dissimilar from that shown in several Japanese series, and rather higher than the age adjusted survival of T1 cases from the Birmingham series.[1]

When the patients are further subdivided, however, according to the 'panel' consensus diagnosis some important differences are seen. The five year survival rate in cases agreed by the panel to have early gastric cancer is high (around

TABLE VIII *Progression of symptoms v progression of disease*

Symptom	*Dysplasia (63 cases)*	*EGC (132 cases)*	*AGC* (55 cases)*	*AGC† (100 cases)*
Nausea	42%	50%	56%	77%
Vomiting	24%	40%	56%	66%
Anorexia	43%	53%	59%	90%
Dysphagia	7%	9%	13%	19%
Wt loss	27%	53%	67%	85%

*Data from present series, cases eventually said by panel to have some evidence of advanced gastric cancer;
†Data from earlier Leeds studies,[10] from more advanced cases.

95%). By contrast, the four year survival rate (numbers thereafter being too small for analysis) of patients registered as 'early gastric cancer' (but said by the panel to have somewhat more extensive disease) is considerably different – being around 70% after only four years. Finally, the handful of cases entered into the study which were agreed by all concerned to have advanced gastric cancer fared (unsurprisingly) poorly; one quarter died within a year of entry.

It is difficult to provide any reliable form of actuarial analysis on the dysplasia cases for two reasons. First, the numbers are relatively small. Second, when carcinoma is diagnosed during the follow up of dysplasia it is impossible to be sure whether there has been progression of dysplasia to carcinoma or whether the two conditions coexisted at the time of the original biopsy but the carcinoma was missed by sampling error. Although approximately 20% of dysplasia cases have undergone surgery for gastric cancer within two years, the vast majority of these carcinomas were diagnosed within one year of the original biopsy and it is felt more likely that they represent association of dysplasia with cancer than true progression. Longer follow up of the remaining dysplasia cases should help to clarify this.

Discussion

It is important in assessing the results of this survey to emphasise that the survey makes no claim whatsoever to be a rigorous, comprehensive assessment of the international picture – namely, early gastric cancer in the United Kingdom. It needs to be re-emphasised that entry into this survey was at the discretion of individual BSG members and the survey can thus provide no evidence at all concerning incidence figures or even the proportion of patients with cancer who have early gastric cancer.

Nevertheless, the study has three features which commend it. First, the number of patients overall (319 *in toto*, 132 with early gastric cancer) is quite large. Second, the patient details provided concerning symptomatic presentation, mode of detection of cancer and so on – are unusually full. Finally, the series is probably unique in that every patient has had histopathological material examined by at least four pathologists and the decision to classify the 132 patients as early gastric cancer has been made in the light of discussions after these independent examinations.

Particularly relevant in this respect is the finding that in 39 cases the original diagnosis of early gastric cancer was not confirmed by the pathologist panel, but after detailed examination, agreed amongst themselves there was evidence of more extensive disease. This finding may go some way to explain (when taken in conjunction with the data in Figure 2), the not inconsiderable difference in survival between various series of early gastric cancer around the world – for if the death rate amongst 'pure' early gastric cancer cases is low, and their numbers small, it takes only a few 'contaminating' cases radically to alter apparent survival data.

The data from Tables IV–VI confirm the dominance of histopathological examination of biopsy specimens in establishing the diagnosis of early gastric cancer. Almost all cases where this diagnosis was established before operation were thus diagnosed. This trend is probably justified, for in the relatively few cases coming to radiological investigation, cancer was only diagnosed or suspected in about one third. Even so, the data from Table VI suggest that the visual appearances at endoscopy are often inadequate to make a firm diagnosis of early gastric cancer. This also implies an important caveat – namely that biopsy must be carried out for safe clinical practice.

How then can earlier diagnosis be made? Computer-aided analysis of the patients' symptoms from the present series indicate that it is almost impossible to distinguish symptomatically between cases of dysplasia and cases of early gastric cancer. Nevertheless, it seems possible to categorise patients as being at 'high risk' and this analysis may prove useful in the future in terms of patient screening.

This is particularly important since 34·1% of the early gastric cancer cases in the present series had in fact been prescribed H_2 blockers for over one month at the time of presentation. Clarification of the natural history and symptomatic presentation of both early gastric cancer and non-ulcer dyspepsia on an international basis are urgently needed. Such studies (under the auspices of the OMGE Research Committee) are under way.

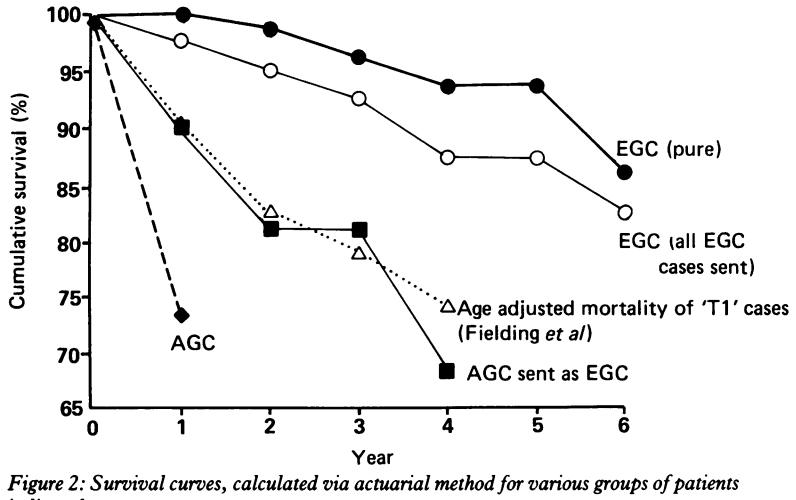

Figure 2: Survival curves, calculated via actuarial method for various groups of patients indicated.

Future studies

In the immediate future, the data presented here

would seem to suggest a variety of further studies. First, there is need to categorise more fully and in greater detail both the histopathological features of 'early gastric cancer' and also the various types of dysplasia. This study is nearing completion and will be presented separately.[12] Next, there is need to increase the pool of patients with 'dysplasia' at least to match the cohort numbers; so that more detailed comparisons can be made between the two, and more detailed study be made between the various types of dysplasia.

Finally, there is need to follow up further this interesting cohort of patients, both those with dysplasia and those with early gastric cancer. As regards 'early gastric cancer' cases, their five year survival has been re-assuringly high particularly where all concerned agreed that the patients had early gastric cancer. Nevertheless, it is important to prolong the survival curve to see whether this excellent prognosis is maintained or whether the related mortality has been merely delayed in these patients for a few years by their relatively early cancer detection.

The survey team acknowledge warmly the support and encouragement of those indicated in the text, notably the Council and Education and Science committee of the BSG during the formative part of the survey. Support is also gratefully acknowledged from Barr and Stroud Ltd and Pilkington Medical Systems Ltd. Finally, and particularly, we thank those of our colleagues who registered cases into the survey and without whose diligent data collection the survey would have been impossible.

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