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Prognostic Significance of Diagnostic Delay and Deprivation in the Management of Upper Gastrointestinal Cancer

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Abstract

To examine the time taken to diagnose upper gastrointestinal (UGI) cancer, identify sources of delay, and assess its prognostic significance.

Methods: Prospective study of 150 consecutive upper GI cancer patients presenting to a UK cancer network. Outcome measures were times from onset of symptoms to histological diagnosis, radiological-staging steps, decision to treatment, and whether potentially curative therapy was possible.

Results: Total delay consisted of the following components: patient delay (median 12 weeks, 76%); practitioner delay (median 1 day, 1%) and hospital delay (median 25 days, 23%). Overall median delay from onset of symptoms to diagnosis was 15.5 (1-142) weeks. On multivariate analysis the factors influencing patient delay were; gender (HR 1.463, 95% CI 1.038-2.063, p=0.030) and overall deprivation rank (HR 1.000, 95% CI 1.000-1.001, p=0.005). Urgent Suspected Cancer referrals consisted of 94 patients (63%) and were more likely to receive curative treatment (43%) than the 56 patients (37%) referred via Non Urgent Suspected Cancer pathway (25%, p=0.017). Survival was significantly related to overall delay (R=0.210, p=0.010), patients with the shortest delays survived a median 6 (0.25 to 30) months compared with patients with the longest delays who survived for a median 12.5 (0.5 to 32) months.

Conclusions: Patient delay accounted for over three quarters of total delay, and deprivation was an important and independent factor in this regard. Improved public awareness and doctor education, with lower thresholds for referral in deprived geographical areas allied to streamlined diagnostic pathways, are required if earlier diagnosis of UGI cancer is to be achieved.

Keywords: Diagnostic delay; Oesophago-gastric cancer; Deprivation; Outcome

Introduction

The most important prognostic factor in patients diagnosed with oesophageal or gastric cancer is the stage of disease at presentation, yet despite advances in information technology and therapies incurable metastatic disease is still diagnosed in as many as 50% of patients at first presentation [1]. In the absence of a national UK screening programme, and given that tumour doubling time can be as little as 2 months for advanced gastric cancer [2,3] and less than 7 months for oesophageal cancer [4] avoidable delay may potentially allow tumours to upstage significantly.

British Society of Gastroenterology (BSG) guidelines recommend that all patients over 55 years of age with recent onset dyspepsia, and all patients with alarm symptoms suggestive of UGI cancer irrespective of age, should be referred for rapid access endoscopy and biopsy [5]. Moreover, the UK Department of Health has specified that urgent investigations be performed within two weeks of referral [6]. Nevertheless, the potential for delay along the patient's journey are many, and delay may arise at any of three junctures from the initial onset of symptoms to diagnosis; the interval between first noticing symptoms and first consulting a doctor (patient delay); the interval between primary consultation and the subsequent time taken for referral for further investigations (practitioner delay); and finally the time between receipt of referral and diagnosis (hospital delay) [7].

Deprivation is a broad concept which includes limited access to the opportunities and resources which society might expect such as good health, a clean and safe living environment, and protection from crime. Eight types of deprivation, or domains, have been described, including; employment, income, education, health, community, geographical access to services, housing, and physical environment [8]. Multiple deprivations refer to the different types that might occur, and represents a far more profound notion than poverty alone. According to the Welsh Government Cancer Delivery Plan Annual Report (2014) [9] considerable differences remain in cancer incidence, mortality and survival between the least and most deprived geographical areas of the country whereby there is a 21% higher incidence in the most deprived areas compared with the least. Furthermore, one year survival rate is 17% lower in the most deprived areas compared with the least deprived areas, and five year survival difference is even greater, with 28% fewer patients in the

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most deprived areas surviving to 5 years compared with patients in the least deprived areas [9].

Staging protocols for oesophago-gastric cancer are now complex including endoscopy, CT, CT PET and Endoscopic Ultrasonography (EUS), all of which carry their own potential for further delay. As prognosis for patients diagnosed with UGI cancer is often poor, the potential benefit from understanding and addressing reversible factors is substantial. The aim of this study is to identify the source and magnitude of such delays, determine the prognostic significance, and examine whether delays are related to deprivation.

Materials and Methods

Data was collected on 150 consecutive patients [median age 70 years (range 26 to 95), 96 male, 54 female, 102 oesophageal, 48 gastric cancer, 125 adenocarcinoma (ACA), 25 squamous cell carcinoma (SCC), diagnosed between 1st August 2012 and 31st July 2013 within 2 South East Wales Health Boards (Aneurin Bevan and Cardiff and Vale). All patients were managed by the South East Wales UGI Cancer network multidisciplinary team (MDT).

The time interval (weeks) between the patient first noticing symptoms and presenting to their general practitioner (GP) was recorded according to the patient's personal recollection of events and cross-referenced with the GP urgent suspected cancer (USC) referral letter. For emergency admissions the delay between first noticing a symptom and presentation to hospital was recorded. Practitioner delays (days) were recorded from the Welsh National Cancer Network Information System (CANISC) database and patient notes. Hospital delays were also recorded contemporaneously from CANISC. For hospital delays, intervals were recorded between date of GP referral to the date of upper gastrointestinal endoscopy (OGD), to date of CT (days), from date of OGD to CT (days), from CT to EUS (weeks), from CT to CT PET (weeks), from referral to diagnosis (days), from referral to the decision to treat date at the regional MDT (weeks), and from the decision to treat date to the commencement of treatment (weeks). The overall delay between initial onset of symptoms and the date a decision to treat was made was also recorded. Date of diagnosis was the day on which a histological diagnosis of malignancy was confirmed. In the case of patients who did not undergo OGD date of diagnosis was recorded as the day the patient underwent radiological imaging.

Deprivation rankings were designated for each patient using the Welsh Index of Multiple Deprivation (WIMD) 2011, [8]. This index gives the official measure of multiple deprivation for every postcode in Wales and is based on eight described forms of deprivation including employment, income, education, health, community, geographical access to services, housing, and physical environment. The country is divided into 1,896 areas of approximately 1,500 people with the most deprived geographical area ranked 1 and the least deprived area ranked 1,896. The WIMD for all areas was also sub-classified into equally sized socio-economic quintiles; the most deprived group was labelled quintile 1, and the least deprived quintile 5. Health deprivation (HD) was also examined, the indicators for which are cancer incidence, all-cause death rate, percentage of live single births <2.5kg, and the number of inhabitants with limiting long-term illness per 100,000 of the population [8]. HD was similarly sub-classified into equally sized quintiles.

Staging investigations

Patients deemed to have potentially curable tumours underwent diagnostic gastroscopy with histopathological confirmation of oesophageal or gastric cancer and computed tomography (CT) of the thorax and upper abdomen. Patients selected for radical treatment also underwent EUS, CT Positron Emission Tomography (CT-PET) and laparoscopy, if appropriate. Tumours were staged according to the unified TNM classification of UGI cancer, edition 7 [10].

Multidisciplinary management

Patients were initially discussed at one of three local multidisciplinary team (MDT) meetings and if deemed potentially curative they were then discussed at the regional South East Wales UGI MDT meeting. Patients were selected for appropriate radical treatment based on histopathological stage, co-morbidity, the technical feasibility of surgery and patient choice according to an algorithm described previously [11]. Patients unsuitable or who declined radical therapy were offered specialist palliative care.

Statistical analysis

Statistical analysis appropriate for non-parametric data was used. Grouped data were presented as median (range), and quintiles were grouped to allow Cox regression analysis. Bivariate correlations were calculated using Spearman`s correlation test. Differences were deemed statistically significant when $p<0.05$. Data analysis was carried out with the Statistical Package for Social Sciences (SPSS) version 20 package (IBM Corporation, New York).

Results

Patient delay

The median time interval between patients first experiencing symptoms and initial presentation to a medical practitioner was 12 (1 -104) weeks and accounted for 76% of the delay from initial onset of symptoms until the decision to treat date. Patient delay correlated with gender [females 13 (2-104) weeks compared with males 8 (1-78) weeks (R =-0.179, p=0.030)], level of deprivation (R=-0.214, p=0.009), and health deprivation (R=-0.214, p=0.009). When analysed by quintile, the median delay for patients in the most deprived quintile was 13 (2-78) weeks compared with 8 (1-26) weeks for those in the least deprived quintile (R=-0.210, p=0.010). With regard to HD, the median delay for patients in the most deprived HD quintile was 15 (4-78) weeks compared with 8 (1-26) weeks for those in the least deprived quintile (R=-0.210, p=0.010) (Table 1).

Patients with oesophageal cancer had a median delay of 9 (1-78) weeks and patients with gastric cancer 13 (1-104) weeks (R=0.041, p=0.620). No correlation was found between longer patient delays and advanced radiological (r) TNM staging (R=-0.063, p=0.477) or with radiologically defined metastatic disease (R=0.058, p=0.509). For patients who underwent radiological staging, stage I disease was diagnosed in 11%, stage II in 17%, stage III in 27% and stage IV in 45%.

Univariable analysis of factors associated with length of patient delay: The factors associated with patient delay are shown in Table 2.

Multivariable analysis of factors associated with length of

Table 1: Details of diagnostic delay related to diagnosis.

Delay Intervals	Oesophagus	Gastric	All
Symptoms to GP (weeks)	9 (1-78)	13 (1-104)	12 (1-104)
GP to referral (days)	1 (1-5)	1 (1-546)	1 (1-546)
Referral to OGD (days)	25 (1-201)	25.5 (1-262)	25 (1-262)
Referral to CT (days)	33.5 (1-212)	35.5 (1-268)	34 (1-268)
Symptoms to diagnosis (weeks)	13 (1-64)	17 (2-142)	15.5 (1-142)
CT to EUS (weeks)	4 (2-10)	3 (2-4)	4 (2-10)
CT to CT PET (weeks)	3 (0.5-11.5)	2.5 (1.5-3.5)	3 (0.5-11.5)
Referral to decision to treat (weeks)	6 (1-33)	5.5 (0.5-39)	6 (0.5-39)
Total delay from symptom onset to decision to treat (weeks)	16 (3-69)	20 (3-143)	18 (3-143)

Figures are median (range).

Table 2: Univariable analysis of factors associated with length of patient delay.

Factor	Log rank	DF	p-value
Age	57.513	45	p=0.100
Age (per decade)	8.883	4	p=0.064
Gender	4.822	1	p=0.028
Deprivation Rank	416.39	136	p<0.0001
Health Deprivation Rank	416.39	136	p<0.0001

Table 3: Multivariable analysis of factors associated with length of patient delay.

Factor	HR	Confidence Interval (95%)	p-value
Gender	1.463	1.038-2.063	p=0.030
Deprivation Rank	1	1.000-1.001	p=0.005

patient delay: Factors found to be associated with patient delay (p<0.10) on univariable analysis were entered into a multivariable analysis using Cox's proportional hazards model shown in Table 3. Gender (HR 1.463, 95% CI 1.038-2.063, p=0.030) and overall deprivation rank (HR 1.000, 95% CI 1.000-1.001, p=0.005) were found to be independently associated with patient delay.

Practitioner delay

The median delay between a patient consulting their GP and referral for further investigation was 1 day (range 1 day to 18 months) and accounted for 1.25% of the total delay from the onset of symptoms to the decision to treat date.

Ninety four patients (63%) were referred via the Urgent Suspected Cancer (USC) pathway or open access gastroscopy pathway, with the remaining 56 patients (37%) admitted to hospital with emergency complications of their tumours. Patients referred via USC pathways had a median 27 day delay (1-262) between the time of GP referral and diagnosis. There was an inverse correlation between age and USC referral (R=-0.233, p=0.004), whereby all patients younger than 50 years were referred via the USC route compared with 11 patients (39.3%) aged 80 years or older (R=-.225, p=0.006). Forty-four percent of the younger cohort were offered curative treatment compared with 14.3% of the older cohort (R=-0.277, p=0.001). There was a strong correlation between referral via USC pathway and the likelihood of potentially curative treatment (R=0.194, p=0.017), with 43% of USC patients offered treatment with curative intent compared with 25% of patients referred via non-USC routes. There was no correlation between gender and USC endoscopy referrals with 72.3% of female and 60% of male patients referred by their GPs via this route (R=-0.091, p=0.269). For USC patients median delay from receipt of GP referral to date treatment started was 85 (1-526) days. Thirty four patients (36.2%) started treatment within 62 days and the median delay for this cohort was 15 (1-59) days. For the remaining 60 patients (63.8%), the median delay was 119 (64-526) days. Among non-USC patients (n=56), median delay from the decision to treat date was made to treatment was 1 (1-253) days, and 51 patients (91.1%) were treated within 31 days. For the remaining 5 patients median delay was 176 (53-253) days.

Hospital delay

Median delay between GP referral and histological diagnosis was 25 (1-262) days and accounted for 23% of the total delay experienced by the patient. For patients referred via USC pathways the median delay from time of receipt of referral to commencing treatment was 91 (3-328) days, for non-USC referrals the delay from the date a decision to treat was made and subsequently commencing treatment was 1 (1-253) days. Regarding USC patients, 18 (24.7%) started treatment within the recommended 62 day guideline from time of receipt of referral, and for non-USC patients 51 (91.1%) had commenced treatment within 31 days.

For patients undergoing surgery the median delay between diagnosis and surgery was 23 (2-46) weeks. Oesophageal cancer patients waited a median 25 (8-46) weeks compared with gastric cancer patients who had a median delay of 8 (4-29) weeks (R=-0.537, p=0.003). A positive correlation was observed between HD and delay to surgery with patients in the most deprived quintile (1), waiting a median 25 (8-46) weeks compared with patients in the least deprived quintile (5) who waited 13 (4.0-31) weeks (R=-0.401, p=0.038). No correlation was observed between the duration of patient delay and subsequent operability (open and close surgery, R=0.088, p=0.684), post-operative morbidity (R=0.180, p=0.474), post-operative mortality (R=0.051, p=0.840), length of hospital stay (R=0.157, p=0.535), pT (R=-0.089, p=0.724), pN (R=-0.012, p=0.963) or pM stage (R=-0.393, p=0.441).

Univariable analysis of factors associated with length of total delay: The factors associated with length of total delay are shown in Table 4.

Multivariable analysis of factors associated with length of total delay: Factors found to be associated with length of total delay (p<0.10)

Table 4: Univariable analysis of factors associated with length of total delay.

Factor	Log rank	DF	p-value
Age	93.935	45	p<0.0001
Deprivation Rank	519.419	136	p<0.0001
Health Deprivation Rank	519.41	136	p<0.0001
Length of Patient Delay	131.871	20	p<0.0001
Practitioner Delay	28.656	3	p<0.0001
Delay Referral to OGD	135.65	54	p<0.0001
Delay Referral to Diagnosis	133.625	56	p<0.0001
Delay Symptoms to Diagnosis	217.472	51	p<0.0001
USC Referral	10.626	1	p=0.001

Table 5: Multivariable analysis of factors associated with length of total delay.

Factor	HR	Confidence Interval (95%)	p-value
Patient Delay	0.924	0.896-0.953	p<0.0001
USC Referral	0.374	0.165-0.849	p=0.019

on univariable analysis were also entered into a multivariable analysis using Cox's proportional hazards model shown in Table 5. Length of patient delay (HR 0.924, 95% CI 0.896-0.953, p<0.0001) and urgent suspected cancer (USC) referrals (HR 0.374, 95% CI 0.165-0.849, p=0.019) were found to be independently associated with total delay.

Survival

Median survival for all patients was 10 (0.25 to 32) months. There was no correlation between survival and length of patient delay (R=0.094, p=0.251), with survival similar irrespective of the delay (quintiles 1 and 5) at 9.5 (0.25 to 30) and 9.5 (1 to 32) months respectively. Survival did however correlate with overall delay (R=0.210, p=0.010), whereby patients with the shortest overall delay (quintile 1) survived for a median 6 (0.25 to 30) months compared with patients with the longest overall delay who survived for a median 12.5 (0.5 to 32) months.

Discussion

The principal findings of this study were that delays in the diagnosis and treatment of UGI cancer remain common, on average approaching four months, little better than the 17 weeks described in a similar study in Leeds, UK some 20 years ago [12]. In contrast to the above report however, where practitioner and hospital delay accounted for the majority, delay on the part of the patient was responsible for over 75% of the time interval between initial onset of symptoms and diagnosis. Deprivation and female gender were significantly and independently associated with longer patient delays, with females and patients residing in the most deprived geographical areas waiting a median of 5 weeks longer before seeking medical advice when compared with males and patients residing in the least deprived areas. Almost two thirds of patients were referred via the open access urgent suspected cancer (USC) endoscopy route, which was associated with younger age, and a higher likelihood of potentially curative treatment. The study also found that those patients with the shortest overall delay time subsequently had the shortest survival time, and on review these patients were, for the majority, emergency admissions with previously undiagnosed stage IV disease.

Several factors have been implicated and reported to be associated with UGI cancer diagnostic delay. Traditionally, with regard to patient delay, the perceived significance of symptoms, the presence of pain or bleeding, and multiple symptoms all influence delay [13]. Pain has been equivocally reported to be associated with both an apparent decreased [14,15] and increased delay [16], and weight loss has also been reported to be associated with increased delay [17]. Factors influencing practitioner delay include initial misdiagnosis of common symptoms and the blind prescription of treatments such as acid suppression for presumed benign conditions in patients subsequently diagnosed with UGI cancer [13]. The influence of deprivation is controversial, with a report by Porta suggesting that lower socioeconomic status was associated with increased delay [18], yet Mikulin reported that patients from lower socio-economic groups, once having presented to their GPs, experienced shorter referral times [19]. Other factors found to reduce practitioner delay include availability of a rapid access endoscopy service [12,20], the introduction of Department of Health cancer referral guidelines [21], male gender [22], and older age [19].

The study has a number of potential limitations. The length of patient delay was a subjective recollection on the part of the patient or their relatives without objective corroboration. Deprivation scores were measured at the area level, i.e. each individual was given a score based on the degree of deprivation of their local community. Area-based deprivation scores, as opposed to individual-based scores, calculated on individuals' incomes or occupations, risks the introduction of potential bias, given that it is unlikely that all residents of a specific postcode will have the attributes of that community (the ecological fallacy) [23]. This was a comparative study, and the definition and analysis of subgroups within a study may lead to bias, while comparisons of groups may prove to be not statistically significant simply because the study has insufficient power to demonstrate real differences. The use of quintiles (as opposed to quartiles or deciles, for example) was arbitrary. In contrast the study has several strengths in that data was prospectively and consecutively collected for unselected patients from a well-defined geographical area, a large proportion of whom reside in areas shown to be amongst the most deprived in the United Kingdom. All patients were managed by a specialist MDT whose clinical outcomes and results are well audited and can stand up to international scrutiny [11]. All dates were initially recorded according to the patient's recollection but were then cross referenced and verified with the patient's notes, the electronic clinical portal and CANISC. This is the first study to correlate diagnostic delay with government designed socioeconomic (SED) and health deprivation (HD) ranking systems, and access to the SED and HD rank for all patients adds further strength. The findings of an association between greater level of deprivation and increased patient delay are in keeping with those of Porta who demonstrated patients of lower socioeconomic status experienced longer diagnostic delay [18]. Regarding other patient demographic factors, the findings are in keeping with previous reports which did not find any association between patient delay and age [15], but contradict further studies which reported little evidence of any association between time to presentation and gender [13]. The principal factor influencing contemporary practitioner delay in South East Wales appeared to be initial misdiagnosis on first presentation, a finding supported

by Rothwell who reported delays in referral particularly for young female patients who were instead being blindly treated with acid suppression for a presumed benign condition [24]. This finding was further supported by a report by Bramble [25]. This study supports the findings of Manes who reported patients experienced less delay in referral where a rapid access service was available [20]. The median delay between GP referral and OGD was 25 days (1 day- 37 weeks), falling short of the UK Department of Health recommendation that urgent OGD be performed within 2 weeks of referral [6]. Indeed only a quarter of USC referrals (25.7%) underwent OGD within the 14 day Department of Health cancer referral guidelines. Previous work has reported deprived patients were less likely to accept an invitation to be screened for colorectal cancer [26], but this was not apparent in the current study in that no reluctance was evident on the part of the most deprived patients to undergo OGD. This study found that patient delay did not influence survival, patients with the shortest and longest patient delay times had similar median survival times of 9 and 9.5 months respectively. Overall delay time was however significantly associated with duration of survival, patients with the shortest overall delay survived a median 6 months compared with 12.5 months for patients with longest overall delay. The former patients were however, mostly emergency admissions with complications of their tumours who were treated palliatively and did not undergo extensive radiological investigation involving EUS and CT-PET scans or staging laparoscopies.

Previous reports have suggested that patient referral and hospital assessment be expedited in an attempt to reduce delays in diagnosis and treatment in UGI cancer [12]. This is of particular clinical significance in UGI cancer given a potentially short tumour doubling time and associated poorer prognosis. There has been significant research performed in this arena and specific guidelines issued recommending that primary healthcare professionals should take part in education, peer review and other activities to improve the quality of clinical consulting, reasoning and diagnostic skills [27]. Yet the findings of this study suggest that the majority of diagnostic delay was accounted for by the patients rather than individual practitioners or hospital services. Indeed, previous UK population surveys have shown widespread lack of awareness of cancer symptoms [28,29], and such awareness is poorer among lower socio-economic strata [29]. A further Office for National Statistics survey reported respondents were able to name just two cancer symptoms or signs with the commonest perceived sign of mischief being the presence of an abnormal lump, but fewer than 32% could name any other symptom and 9% knew of none [30].

Conclusion

In conclusion, this study has shown that long delays remain common in the diagnosis and treatment of upper GI cancer, and these delays are strongly associated with deprivation and are therefore likely associated with lack of awareness and poor education. In order to address this lack of understanding, the Cancer Reform Strategy, published in 2007, launched the National Awareness and Early Diagnosis Initiative (NAEDI), a partnership between the Department of Health and Cancer Research UK. The role of NAEDI is to help raise public awareness of cancer signs and symptoms, and reverse the trend towards later diagnosis seen in Great Britain than in other countries with comparable health care systems. Previous campaigns to raise public awareness of cancer such as the UK National Bowel Cancer Awareness Campaign, the US National Breast Cancer Awareness Month and the UK National Lung Cancer Awareness campaign each significantly raised the profile of these specific conditions and led to increased public awareness of the respective red-flag signs and symptoms [31,32,33]. The next challenge for the Department of Health, organisations such as Cancer Research UK, and frontline clinicians is to raise public awareness of the potential significance of dysphagia, dyspepsia and weight loss, often the harbingers of UGI cancer, through efforts such as the UK Northern Oesophago Gastric Unit's "Oesophagoose" annual awareness campaign.

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