

GASTROINTESTINAL CANCER

Predictive value of alarm features in a rapid access upper gastrointestinal cancer service

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Aims: (i) To determine the value of individual alarm features for predicting cancer in subjects referred to a rapid access upper gastrointestinal cancer service; and (ii) to develop a clinical prediction model for cancer and to prospectively validate this model in a further patient cohort.

Methods: Patient demographics, referral indications, and subsequent diagnosis were recorded prospectively. Logistic regression analyses were employed to determine the predictive value of individual alarm features in an evaluation cohort of 1852 consecutive cases. The potential impact of applying a modified set of referral criteria was then examined in a validation cohort of 1785 patients.

Results: Evaluation cohort: mean age was 59 years; cancer prevalence 3.8%; and serious benign pathology 12.8%. Dysphagia (odds ratio (OR) 3.1), weight loss (OR 2.6), and age >55 years (OR 9.5) were found to be significant predictive factors for cancer but the value of other accepted alarm features was more limited. In particular, uncomplicated dyspepsia in those over 55 years was a negative predictive factor for cancer within this high risk cohort (OR 0.1). Validation cohort: the clinical prediction model would have selected 92% of cancer patients for fast track investigation while reducing the "two week rule" workload by 572 cases (31%).

Conclusions: Fast track endoscopy in subjects fulfilling current criteria for suspected upper gastrointestinal malignancy results in a significant yield of cancer (~4%) and serious benign diseases such as peptic ulceration, strictures, and severe oesophagitis (13%). However, the predictive value of individual features for cancer varies widely. Uncomplicated dyspepsia in older subjects was a poor predictor of cancer. Application of narrower referral criteria for accessing fast track services may reduce pressures while retaining high sensitivity for cancer.

Gastric and oesophageal tumours are leading causes of cancer mortality, accounting for over 14 000 deaths per year in the UK.¹ Clinical diagnosis is notoriously unreliable in diagnosing the underlying cause of dyspepsia^{2 3} but a number of alarm features have been suggested as indicating patients at higher risk for serious disease.^{4 5} These features include the recent onset of dyspepsia in an older subject, occurrence at any age of so-called alarm symptoms (for example, dysphagia, vomiting, or weight loss), or the onset of dyspepsia in a patient known to have a predisposing condition for cancer (for example, Barrett's oesophagus, pernicious anaemia, previous peptic ulcer surgery). There is some evidence to suggest that delays in cancer diagnosis occur as a result of failure to investigate patients with such alarm features.^{6 7}

In the UK, recent Department of Health (DoH) guidelines have specified the "at risk" symptoms that a general practitioner should use to identify patients in need of specialist investigation (table 1).⁸ National guidelines from the British Society of Gastroenterology have reinforced these recommendations.⁴ The DoH has specified a two week waiting time standard for high risk patients to undergo diagnostic evaluation. Complying with the so-called "two week rule" for cancer is regarded as an important performance indicator for individual hospital trusts.

Data from the UK⁹ and elsewhere in Europe¹⁰ suggest that approximately 10% of dyspeptic patients consulting in primary care have alarm symptoms. Hence the potential workload involved in promptly evaluating all "at risk" patients is significant. While there is broad consensus as to the clinical features that should alert clinicians to the possibility of oesophageal or gastric cancer, the relative

predictive values of individual alarm features for cancer are unclear.^{11 12} Previous studies have examined the value of specific symptoms in predicting "significant pathology" (that is, acid peptic disease or cancer) in cohorts of patients referred routinely for endoscopic investigation.² However, there has been no systematic study of the relative value of individual alarm features for predicting cancer diagnosis per se among high risk subjects referred for urgent investigation.

In the present study, we aimed to determine the predictive value of alarm features for cancer in a cohort of high risk subjects referred from primary care to a rapid access upper gastrointestinal cancer service under the UK NHS "two week rule". These data were to be used to develop a clinical prediction model for cancer based only on the most significant predictive alarm features, and the potential impact of this model validated prospectively on a further patient cohort.

METHODS

Setting

The present study was undertaken at a single teaching centre (University Hospital Aintree, Liverpool, UK) serving a target population of approximately 330 000 residents. Prior to the introduction of the new service, the unit was performing approximately 2000 open access gastroscopies per annum and waiting times for investigation were consistently below six weeks.

Abbreviations: DoH, Department of Health; RAUGICS, rapid access upper gastrointestinal cancer service; OAE, open access endoscopy; OR, odds ratio

Table 1 Criteria for urgent investigation of suspected upper gastrointestinal cancer under the National Health Service "two week rule"

Uncomplicated dyspepsia	>55 y old with onset of dyspepsia within the last year or continuous symptoms since onset
Or	
Alarm symptoms at any age	Any of the following: Dysphagia Anorexia Vomiting Weight loss Anaemia
Or	
Dyspepsia with high risk features at any age	Any of the following: Family history of upper gastrointestinal cancer in >2 first degree relatives Barrett's oesophagus Pernicious anaemia Peptic ulcer surgery >20 y previously Known dysplasia, intestinal metaplasia or atrophic gastritis

The rapid access upper gastrointestinal cancer service (RAUGICS)

The new direct access service allowed general practitioners to select between either fast track investigations via the RAUGICS (for cases of suspected cancer, under the "two week rule") or standard open access endoscopy (OAE).

Referral to the RAUGICS arm of the direct access service required the presence of predetermined alarm features, as specified in the NHS guidelines (table 1). A standardised referral proforma required general practitioners to stipulate the presence or absence of each of the designated alarm features. Patients referred to the RAUGICS were all subject to gastroscopy within two weeks of referral and then subsequently reviewed in clinic. Those diagnosed with cancer had further fast track staging investigations and treatment.

Prospective data collection

Details of all patients referred to RAUGICS were recorded prospectively on a computerised database. In addition to demographic details, information was recorded relating to referral indications (as provided by the general practitioner on the standardised referral form), the subsequent endoscopic diagnosis, histology, and (in cases of cancer) relevant tumour staging investigations.

Evaluation group

Data relating to a cohort of 1852 consecutive patients were collected between July 2000 and February 2002, designated the *evaluation group*. We used both single and multiple regression analysis to examine the predictive value of individual alarm features (as specified by the referring doctor) for malignant or serious disease within this population using SPSS 10.1 software. Prediction models for predicting cancer and serious pathology were constructed using forward multivariable logistic regression analysis with an entry criteria of $p < 0.05$ and a removal criteria of $p < 0.1$. A simplified clinically applicable prediction model was subsequently constructed using the variables identified as significant. This model allowed the definition of a modified set of criteria for fast track referral, based on a more restrictive set of referral indications.

Validation group

The prediction model derived from the evaluation group was then prospectively validated against a further consecutive

cohort of 1785 patients referred to the service over the subsequent 12 months. This second cohort of patients was designated the *validation group*. We determined the theoretical impact of applying our more restrictive referral criteria to this second cohort of patients.

Verifying the accuracy of referral information

The present study relied on clinical information provided by individual general practitioners using a standard referral proforma. In order to verify the presence of alarm symptoms stipulated by the general practitioner on the referral form, we performed a questionnaire survey in a consecutive series of patients referred to the service ($n = 100$). This self administered seven item questionnaire asked about the presence of symptoms such as dysphagia, weight loss, vomiting, etc. Using this instrument, alarm symptoms were elicited in 97% of subjects.

Impact on the diagnostic profile of "routine" direct access endoscopy

In order to assess the impact of introducing the RAUGICS on the standard direct access endoscopy service, we retrieved retrospective historical control data relating to the pre-existing routine direct access endoscopy service from the unit's endoscopic reporting database (Endoscribe). We compared diagnostic data for a six month time period (before the RAUGICS service was launched) with a comparable time period after establishment of the new fast track service.

RESULTS

Patient characteristics

Between July 2000 and February 2002, 1852 patients were referred directly by their general practitioner to the RAUGICS and underwent rapid evaluation under the "two week rule". All were assessed within the stipulated two week period. Mean age of patients was 59.4 years (range 17–96) with 1164 (63%) above the age of 55 years. There were a total of 2652 individual referral criteria recorded within the 1852 patients from a combination of seven variables (fig 1, upper panel).

Dysphagia (34%), weight loss (29%), and vomiting (28%) were the commonest referral symptoms overall. Vomiting was found to be a more frequent referral indication among the younger age group (38% v 28%; $p < 0.05$). There were 286 patients with "uncomplicated dyspepsia" over the age of 55 years (defined as dyspepsia in the over 55s that either had onset within the last year or had been continuously present since onset). Thirty nine younger patients (<55 years) were referred with uncomplicated dyspepsia alone (that is, no other alarm features present in a young dyspeptic patient) and were therefore classed as inappropriate referrals to the cancer service.

A total of 70 upper gastrointestinal cancers (45 oesophageal and 25 gastric) were identified in the RAUGICS patients (3.8% prevalence; mean age 69.8 years) with 65/70 (93%) occurring in subjects over 55 years of age. In the younger age group, four cancers presented with dysphagia and one with a combination of dyspepsia with vomiting and anorexia. Only one cancer patient, aged 68 years, presented with uncomplicated dyspepsia.

Fifty six tumours were adenocarcinomas, 12 were squamous cell carcinomas, and two were lymphomas. Staging was not undertaken in 14/70 (20%) patients due to age and/or comorbidity. Tumour staging (computed tomography scanning with or without endoscopic ultrasound) demonstrated that 42 patients (60%) had at least a TNM stage T3 tumour and/or evidence of metastases. Eleven subjects (15.7%) underwent surgical resection (six oesophageal and five gastric tumours). The findings for other significant pathologies stratified according to age are summarised in

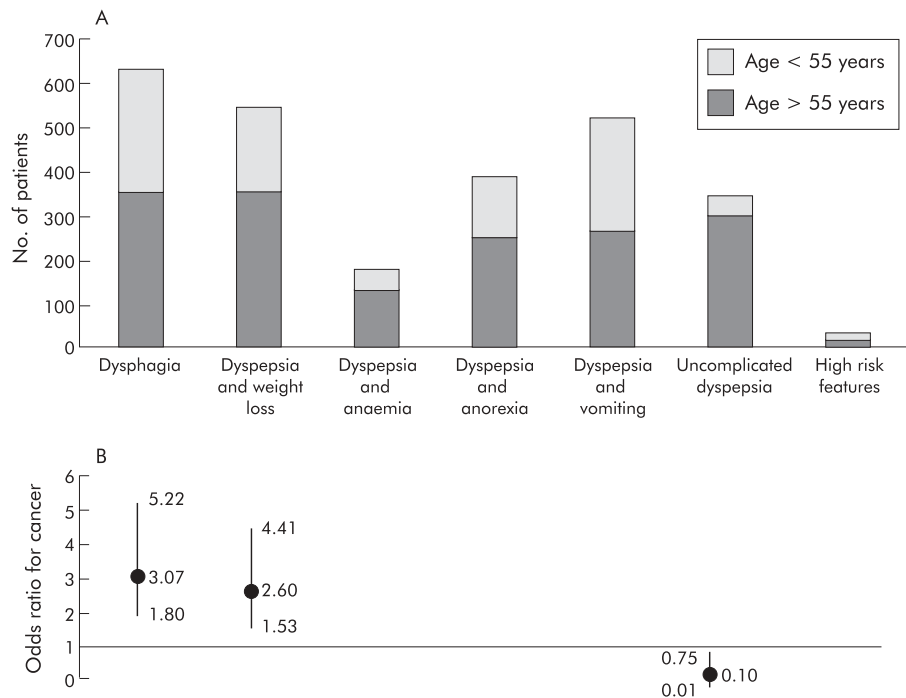


Figure 1 (A) Prevalence of individual alarm features among 1852 patients referred under the “two week rule” for investigation of suspected upper gastrointestinal cancer. (B). Odds ratio of individual alarm features for predicting cancer (only significant values are shown, based on multiple linear regression analysis).

table 2, which also compares the diagnostic profile of the standard OAE service before and after the launch of the RAUGICS.

Predictive value of alarm features within a high risk population

Using forward multivariable logistic regression analysis, dysphagia (odds ratio (OR) 3.1 (95% confidence interval (CI) 1.80–5.22)), weight loss (OR 2.6 (95% CI 1.53–4.41)), and age >55 years (OR 9.5 (95% CI 3.80–23.93)) were found to be significant positive predictive factors for cancer. Figure 1A illustrates the odds ratios for cancer diagnosis for those factors found to be significant in the regression analysis. Uncomplicated dyspepsia was actually found to be a negative predictor of cancer within this cohort of patients referred under the “two week rule” (OR 0.1 (95% CI 0.01–0.75)). The analysis was repeated excluding the 39 young patients with uncomplicated dyspepsia and produced identical results. Addition of the other variables such as anaemia (p = 0.267), anorexia (p = 0.685), vomiting (p = 0.329), or

high risk features (p = 0.44) to the model did not result in any additional benefit in predicting malignancy.

Regression analysis was repeated using different parameters, including detecting cancer in those over 55 years alone or detecting cancer plus benign oesophageal strictures at any age. In both cases, the same factors (age, weight loss, and dysphagia) were identified as significant. However, if the detection of any significant pathology (cancer, peptic ulcer disease, strictures, and oesophagitis) was stipulated, then age (OR 1.3), dysphagia (OR 2.0), and high risk features (OR 2.4) became the only significant predictors.

The findings of the regression analysis were used to produce a simpler and more clinically applicable prediction model based on theoretical changes that might be made to the selection criteria for referral of suspected cancer under the “two week rule”. Referrals with at least one positive predictive referral criteria were included in the new model but referrals with factors identified as negative predictors for malignancy were excluded.

Table 2 Endoscopic diagnoses in patients referred from primary care to a rapid access upper gastrointestinal cancer service

Diagnosis	Evaluation cohort		Validation cohort	
	All ages	<55 y	All ages	<55 y
Cancer	70 (3.8%)	5 (0.7%)	52 (2.9%)	1 (0.2%)
Benign peptic stricture	37 (2.0%)	16 (2.3%)	24 (1.3%)	7 (1.2%)
Severe oesophagitis	111 (6.0%)	36 (5.2%)	46 (2.6%)	12 (2%)
Mild oesophagitis	201 (11%)	91 (13%)	199 (11.1%)	79 (13.1%)
Peptic ulcer	89 (4.8%)	24 (3.5%)	85 (4.8%)	29 (4.8%)
Normal or minor disease*	1344 (73%)	516 (75%)	1379 (77.3%)	476 (78.8%)
Total	1852 (100%)	688 (100%)	1785 (100%)	604 (100%)

*Includes hiatus hernia, gastritis, and duodenitis.

The new criteria specified:

Dysphagia or weight loss at any age
OR
Dyspepsia aged >55 years with any alarm feature*
(anaemia, anorexia, vomiting, dysphagia, weight loss, or
high risk features)
(*This does not include isolated/uncomplicated dyspepsia
alone.)

Age was the most powerful independent predictive factor for cancer. We therefore included all older patients in our new model provided they did not have uncomplicated (simple) dyspepsia alone. This would seem valid as our analysis suggested that older subjects who lacked any of the traditional alarm features (anaemia, anorexia, vomiting, dysphagia, weight loss, or high risk features) were at reduced risk of cancer within this patient population. Recognising that our regression analysis identified both dysphagia and weight loss as independent predictors for cancer, we concluded that these symptoms would trigger urgent investigation regardless of age.

These more stringent referral criteria identified a higher risk group of 1307/1852 patients (71%). The theoretical sensitivity, specificity, and positive and negative predictive values of these criteria for detecting cancer were 98.6% (69/70), 30.5% (544/1782), 5.3% (69/1307), and 99.8% (544/545), respectively. Applying these criteria would have resulted in re-allocation of 545 patients to a less urgent ("low risk") group. Such patients might be investigated by standard OAE and would not require formal outpatient follow up in our current system. The predictive model would have identified 99% of cancers and 76% (223/293) of "significant" pathology (cancer, benign stricture, oesophageal ulcers, and peptic ulcer disease combined).

Validation of the model

The proposed model was subsequently validated prospectively on a further cohort of 1785 consecutive patients referred directly to the RAUGICS via their general practitioner. There were no changes in referral criteria, waiting times, or setting of endoscopy activity over this period. The diagnostic profile of the validation group remained unchanged with a malignancy yield of 52 (3%) and yield of significant pathology of 207 (12%). The average age of patients with malignancy was 70.2 years (range 55–92). There were 33 oesophageal and 19 gastric, of which 20 underwent surgery. There were 45 adenocarcinoma and seven squamous cancers.

Implementation of our predictive model in this second cohort of patients would have resulted in re-allocation of 570 of 1785 patients (31.2%) to routine OAE. Within this re-allocated group of 570 patients, four cancers were diagnosed at endoscopy of which two have undergone potentially curative surgery. If we had applied our prediction model in practice, these patients would not have been fast tracked to the upper gastrointestinal cancer service at referral although they would have still undergone gastroscopy as part of the open access service. The cancer yield in this so-called low risk group would be 0.7%. This figure is in keeping with the yield of cancer in traditional open access services investigating unselected dyspeptic populations (~1%). Conversely, the yield of cancer within the high risk group, selected on the basis of more restrictive criteria for fast track investigation, would have been 4.0%. The sensitivity, specificity, and positive and negative predictive values of these criteria for detecting cancer in the validation cohort are 92.3% (48/52), 32.7% (566/1733), 4.0% (48/1215), and 99.3% (566/570), respectively.

Impact of the RAUGICS on referral rates and diagnostic profiles

In order to assess the impact on total direct access endoscopy activity of introducing the fast track RAUGICS system, we compared two defined six month periods (one before and one after the introduction of the new rapid access service). There was a 33% increase in total gastroscopy referrals received directly from primary care (from 932 to 1236 referrals per six months). Interestingly, just over half (632/1236) of all direct referrals for endoscopy from primary care were designated by their general practitioner as having alarm features fulfilling current recommendations for the fast track arm of the direct access service. The overall prevalence of cancer in the total direct access endoscopy population for the two time periods was similar (1.5% v 1.6%). However, once the new service was established, most cancers (19/20) were diagnosed within the RAUGICS group. Over the six month period of observation, the yield of cancer was 3% in the RAUGICS group and just 0.2% in the "standard" OAE arm of the service. This suggests that the DoH guidelines were highly effective in channelling cancer patients into the fast track arm of our diagnostic service.

DISCUSSION

There are a limited number of ways in which the upper gastrointestinal tract can indicate disquiet and it is well recognised that clinical history is a poor guide to the underlying diagnosis of dyspepsia.^{2 3 13} Approximately 3–4% of the population consult their general practitioner with upper intestinal symptoms each year, of which over 10% will have so-called alarm symptoms.¹⁴ Nevertheless, a typical general practitioner serving approximately 2000 patients will see only one new case of upper gastrointestinal cancer per year.

Unfortunately, the symptoms of early stage cancer may be indistinguishable from benign conditions whereas the presence of established alarm symptoms (for example, dysphagia or weight loss) may signify advanced inoperable disease. This presents a dilemma in terms of setting criteria and priorities for investigating upper intestinal symptoms, particularly in healthcare systems where the potential demand for endoscopy may exceed the level of service provision.

In the UK, the National Health Service has introduced referral guidelines for rapid evaluation within two weeks for patients with symptoms that raise suspicion of cancer.⁸ For oesophageal and gastric cancer, the stipulated criteria for automatic fast track investigation are based on a patient's age and the presence of a number of alarm features. Our study aimed to establish the cancer yield and predictive value of these referral criteria within a large cohort of patients referred to a fast track cancer service under the NHS "two week rule".

The stipulated referral criteria were effective in channelling patients with malignancy into the rapid access arm of a direct access diagnostic service. The cancer prevalence within patients referred to the fast track service (3.8%) was approximately double that generally reported for patients referred for unselected OAE (1–2%). Our analysis of the relative predictive value of individual referral criteria identified dysphagia and weight loss in particular as strong predictors of cancer, consistent with currently held opinion.¹²

It is interesting that uncomplicated dyspepsia in over 55 year olds was a negative predictor of malignancy within this high risk population. The principal of automatic investigation of older subjects with undiagnosed dyspepsia is based on the rising incidence of malignancy with age. However, there is surprisingly little robust evidence on which to support this practice. The Canadian CADET study examined 1021 referrals from primary care (one third older

than 50 years) without alarm features and identified just two cancers, indicating the low frequency of cancer in subjects with simple dyspepsia.² A prospective study of upper gastrointestinal cancer in Scotland over two years showed that only 7% of cancers in those over 55 years presented without alarm features and only 1.7% of patients had no alarm symptoms and survived more than a year.¹⁵ A number of other studies have suggested that the yield of cancer in simple dyspepsia is low and that only a small proportion of those cancers identified are resectable.^{16–18} Dyspeptic symptoms overall are very common in the general population and it is not clear whether the incidence of malignancy in patients with uncomplicated dyspepsia is different from that of the non-dyspeptic population.¹⁹ Early upper gastrointestinal cancer may be asymptomatic and diagnosed by chance in subjects complaining of dyspeptic symptoms that are secondary to a benign or functional cause.²⁰ Previous guidelines have suggested automatic investigation of uncomplicated dyspepsia in older dyspeptic population.^{5, 21} However, more recent guidelines have acknowledged that evidence is lacking for such a policy.^{22, 23}

There are major resource implications in providing fast track evaluation for all individuals who satisfy current UK criteria for the “two week rule” assessment. In our study, automatic investigation of older subjects with uncomplicated dyspepsia accounted for one fifth of the service workload (18%) but the prevalence of cancer within this group was just 0.3%.

We generated a more restrictive set of referral criteria for fast track investigation based on multivariate analysis of symptom data from a large cohort of patients referred to our centre under the “two week rule”. These modified referral criteria reflected two main findings. Firstly, we observed a very low frequency of cancer (1/259) in younger subjects who had so-called alarm symptoms (other than dysphagia and weight loss). Secondly, cancer yield in older subjects with uncomplicated dyspepsia was very low (0.3%). In view of the fact that our analysis indicated that dysphagia and weight loss were strong positive predictors for cancer, we regarded these symptoms as meriting urgent evaluation at any age. In our model, the presence of other alarm features (for example, vomiting, anaemia, “high risk features”) would trigger urgent evaluation only in subjects over the age of 55 years, as age is the strongest independent predictor of malignancy.

Applying these theoretical criteria to an additional cohort of patients would have reduced our urgent service workload by one third while retaining a sensitivity of 92% for malignancy. The management strategy for the low risk group might involve less urgent endoscopy and/or empirical treatment strategies. In the case of uncomplicated dyspepsia in over 55 year olds, our data would support recent guidelines that suggest invasive investigation is not mandatory.^{22, 23} Currently, approximately 450 000 endoscopies are undertaken in England per annum, approximately 1% of the population.²⁴ It was anticipated that the introduction of the “two week rule” would generate a rise in the number of urgent referrals, with the DoH estimating a total of 256 000 urgent referrals per annum for suspected oesophago-gastric malignancy (1020 per 200 000 population per year).⁸ The numbers of patients who were referred as urgent cases within the previous system is unknown but was estimated at between 50% and 90% of eligible cases. The DoH therefore predicted a rise in demand for urgent endoscopy of between 25 000 to 130 000 cases per annum.

There is clearly some potential for primary care doctors to either under- or over-refer patients to fast track diagnostic services, based on interindividual variation in their interpretation of symptoms or their knowledge of referral criteria. Furthermore, patient sociodemographic factors may

influence consultation behaviour in different localities. In the present study, we found little evidence for inappropriate referrals to the service based on our symptom questionnaire survey. We are currently examining the contribution of general practice characteristics (for example, partner number, training status, deprivation score of practice population) to variation in referral volume and diagnostic outcomes. Preliminary data suggest that despite variation in total referrals per capita of practice population between different practices, the pick up rate for significant disease is not significantly different between high or low referring doctors.²⁵ This implies a reasonably uniform uptake of the guidelines in our locality.

Several centres have presented initial data of their yield of malignancy in high risk patients referred under the “two week rule”, reporting values of 4%,²⁶ 5.5%,²⁷ 6.3%,²⁸ and 15%.²⁹ However, the numbers of patients referred per six months in these centres appears low (79, 85, 149, and 112, respectively) suggesting either poor local uptake of rapid assessment services or possible differences in local interpretation of the criteria laid down by the DoH for the designation of urgent referrals. Review of the DoH website for cancer shows that these data reflect a national pattern (www.doh.gov.uk/cancer/gastro.htm). Nearly two years after the introduction of the “two week rule”, referral numbers remained at only 13% of that predicted. Despite the large number of RAUGICS referrals seen at our centre, this remains only three quarters of that predicted by DoH estimates for our target population. These data suggest that current referral numbers represent only a fraction of the potential dyspeptic patients in the community who meet the currently stated criteria for rapid assessment. The NHS cancer plan encourages education in primary care in order to promote full compliance with referral recommendations.

It is clearly highly desirable to be able to provide rapid diagnosis for all cancer patients, irrespective of tumour stage or prognosis. The DoH recommendations should undoubtedly improve the patient journey for cancer sufferers, although it is unclear whether this strategy will alter national mortality figures for upper gastrointestinal malignancy. Achieving improved survival rates for these diseases may require a number of initiatives, including public education and possibly some form of targeted population screening. Whereas endoscopic screening programmes for colorectal cancer are of proven benefit, few studies have established whether current strategies for detecting upper gastrointestinal tumours are cost effective.³⁰ Research is needed to evaluate whether our current emphasis in the UK on improving fast track evaluation of symptomatic patients is effective in improving patient outcomes. Our experience in North Liverpool confirms initial concerns about the potentially high workload generated by a well publicised fast track diagnostic service.

Widespread implementation of our model for fast track upper gastrointestinal cancer services would have significant resource implications for the NHS. If full compliance with DoH guidelines is to be actively encouraged, referral numbers are likely to increase substantially in many centres. We suggest that modification of the stipulated referral criteria for suspected upper gastrointestinal malignancy may facilitate this process while maintaining sensitivity for cancer detection. In particular, routine investigation of uncomplicated dyspepsia in older subjects appears to be the weakest of the alarm symptoms for cancer detection.

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