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Impact of route to diagnosis on treatment intent and 1-year survival in patients diagnosed with oesophago-gastric cancer in England

Short title: Routes to diagnosis for oesophago-gastric cancer patients

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Abstract

OBJECTIVE: To investigate the relationship between the route to diagnosis, patient characteristics, treatment intent and one-year survival among patients with oesophago-gastric (O-G) cancer.

SETTING: Cohort study in 142 English NHS trusts and 30 cancer networks.

PARTICIPANTS: Patients diagnosed with O-G cancer between October 2007 and June 2009.

DESIGN: Prospective cohort study. Route to diagnosis defined as general practitioner (GP) referral - urgent or non-urgent, hospital consultant referral, or after an emergency admission. Logistic regression was used to estimate associations and adjust for differences in casemix.

MAIN OUTCOME MEASURES: Proportion of patients diagnosed by route of diagnosis; proportion of patients selected for curative treatment; one-year survival.

RESULTS: Among 14,102 cancer patients, 66.3% were diagnosed after a GP referral, 16.4% after an emergency admission, and 17.4% after hospital consultant referral. Of the 9,351 GP referrals, 68.8% were urgent. Compared to urgent GP referrals, a markedly lower proportion of patients diagnosed after emergency admission had a curative treatment plan (36% v 16%; adjusted odds ratio (OR) = 0.62, 95% CI: 0.52 to 0.74) and a lower proportion of survived one year (43% v 27%; OR = 0.78; 0.68 to 0.89). Urgency of GP referral didn't affect treatment intent or survival. Routes to diagnosis varied across cancer networks, with the adjusted proportion of patients diagnosed after emergency admission ranging from 8.7% to 32.3%.

CONCLUSION: Outcomes for cancer patients are worse if diagnosed after emergency admission. Primary care and hospital services should work together to reduce rates of diagnosis after emergency admission and the variation across cancer networks.

ARTICLE SUMMARY

Article focus

- To investigate the relationship between the route to diagnosis, patient characteristics, treatment intent, and one-year survival.
- To examine whether the routes to diagnosis varied between regional cancer networks.

Key messages

- Two thirds of patients diagnosed with O-G cancer were referred by their general practitioner (GP), of which around two-thirds were referred urgently. Patients referred urgently by their GP did not have better survival rates than non-urgent GP referrals
- One in six patients were diagnosed after an emergency admission, and these patients were less likely to have a curative treatment plan compared to urgent GP referrals. One-year survival was also worse.
- There was significant variation between cancer networks in the rates of emergency admission, which persisted after adjusting for patient factors.

Strengths and limitations of the study

- The study uses data from the large, prospective sample of patients diagnosed in almost all English NHS trusts. 1-year survival was known for all patients.
- Limitations stem from the exclusion of patients due to missing data on route to diagnosis and treatment intent.

INTRODUCTION

Oesophago-gastric (O-G) cancer is the fourth most common cause of cancer death in the United Kingdom resulting in approximately 12,500 deaths per year [1]. The majority of patients are diagnosed with advanced disease and only 20–30% are suitable for curative treatment [2,3]. Consequently, the prognosis is often poor, with 5-year relative survival being approximately 15% [4].

An objective of the UK Cancer Reform Strategy has been to increase the proportion of patients diagnosed with early cancer [5]. Meeting this objective represents a considerable challenge for oesophago-gastric (O-G) cancer services and general practitioners (GP). Many of the symptoms and signs of O-G cancer are non-specific and are present in large numbers of individuals without cancer [6]. For example, uncomplicated dyspepsia constitutes 3-4% of a general practitioner's workload [7,8] but an average general practice will only see four or five O-G cancer patients per year [6]. Guidelines recommend that GPs refer urgently to a specialist team only if patients present with "alarm symptoms" (eg, weight loss, vomiting dysphagia) or have persistent dyspepsia and are over 55 years [9-11]. However, these alarm symptoms are typically associated with advanced disease [12,13].

Across all cancer types, the number of patients diagnosed after an urgent GP referral increased from 80,000 in 2007 to 98,000 in 2009 [14]. But, for O-G cancer patients, information about patients' route to diagnosis and how this affects outcomes is limited [15]. Figures from routine data suggest that a substantial minority of O-G cancer patients are diagnosed following an

emergency presentation and these patients have worse survival [16,17]. One-year relative survival among all patients with oesophageal cancer was 39% but it was only 21% for those diagnosed after an emergency presentation. Among patients with stomach cancer, the corresponding survival figures were 38% and 22%. However, evidence about these relationships is sparse, and there is a need to understand how route to diagnosis contributes with patient characteristics and treatment decisions to influence survival.

This study used a prospectively collected national clinical dataset of patients with O-G cancer in England to investigate the relationship between the route to diagnosis, patient characteristics, treatment intent, and one-year survival. We also examined whether the routes to diagnosis varied between regional cancer networks.

MATERIALS AND METHODS

Data were collected prospectively by English NHS trusts as part of the national oesophago-gastric cancer audit. All adult patients diagnosed in England with invasive, epithelial cancer of the oesophagus or stomach between 1 October 2007 and 30 June 2009 were eligible for inclusion. The audit method and dataset have been published elsewhere [3,18].

The study distinguished between three routes to diagnosis: referral from a GP, referral after an emergency admission, and an "other hospital referral" (patients referred by a hospital consultant from a non-emergency setting). GP referrals were subdivided into urgent (for suspected cancer) and non-urgent referrals. Information was also collected on the patient's age at diagnosis, sex, social deprivation, tumour site and TNM stage (version 6) [19], number of co-morbidities, ECOG

functional performance and treatment intent. Date of death was obtained from the Office for National Statistics death certificate register, which gave full follow-up for a minimum of 380 days from date of diagnosis. Tumour site was categorised as oesophageal (including Siewert 1-3 junctional tumours) or stomach. Treatment intent (curative or palliative) reflected the decision of the multi-disciplinary team meeting after pre-treatment staging was completed. Social deprivation was measured using the UK Index of Multiple Deprivation [20] with patients being grouped into quintiles from least deprived (=1) to most deprived (=5).

Statistical analysis

We calculated the proportion of patients diagnosed via the different routes for all England and the 30 cancer networks that existed on 1 October 2007. Patients were grouped into networks by their NHS trust of diagnosis. The relationship between two variables was examined using the chi-squared test. The association between route to diagnosis and the proportion of patients having a curative treatment plan and one-year survival was examined using logistic regression to control for the influence of age at diagnosis, sex, regional deprivation, tumour site, pre-treatment stage, comorbidities and performance status.

Multinomial logistic regression was used to adjust the proportion of patients diagnosed via each route in each cancer network for patient characteristics [21]. Funnel plots were used to test whether network rates differed significantly from the overall English rate [22]. These graphs show the network rates together with the English rate and two sets of control limits that indicate the ranges within which 95% or 99.8% of the network rates would be expected to fall if differences from the English rate arose from random variation alone.

The analysis was performed in STATA v10. All p-values are two-sided and those lower than 0.05 were considered to show a statistically significant result. Two variables used in the regression models, performance status and pre-treatment stage, were known for 72% and 61% of patients, respectively. Missing data values for these two variables were imputed using multiple imputation by chained equations [23]. The imputation model included age at diagnosis, sex, tumour site, deprivation, number of co-morbidities, referral source, and one-year survival. Twenty-five imputations were created. Missing values were assumed to be "missing at random" (see additional file for details of missing and imputed values).

RESULTS

Information was collected on 16,264 patients from 152 English NHS trusts. Ten trusts were excluded (1196 patients) because the route to diagnosis was entered for less than half of their patients. Patient records that lacked route to diagnosis (n=956) or age at diagnosis (n=10) were also excluded. This left 14,102 patients in the analysis. Their median age was 73 years, two-thirds were male, and 69% had an oesophageal tumour. Patients with stomach tumours were slightly older on average (mean 73.6 v 70.4 years, $p<0.001$) and fewer were aged under 55 years (7.1% v 9.3%, $p<0.001$). Among patients with known pre-treatment stage, 44% had stage 4 (metastatic) disease.

Patterns of route to diagnosis

Overall, 66.3% of patients were referred by their general practitioner, 16.4% were referred following an emergency hospital admission and 17.3% were referred from another hospital consultant. The proportion of GP referrals was lower among patients with stomach tumours compared to oesophageal tumours, which reflected a greater proportion of stomach cancers being

diagnosed after an emergency admission (see Table 1). Diagnosis after emergency admission was least common among patients aged 55-64 years but increased among older and younger patients. This route to diagnosis was also more common among patients as their performance status got worse.

Among the 9,351 GP referrals, 6,438 patients (68.8%) were labelled as urgent (suspected cancer). For oesophageal tumours, 64.4% of patients aged less than 55 years (the guideline threshold) were referred urgently compared to 71.8% for older patients. For stomach tumours, the proportions were 50.6% v 63.5%, respectively.

Association between route to diagnosis, treatment intent and one-year survival

There was a strong association between the route to diagnosis and the likelihood of a patient having a curative treatment plan (Table 2). The differences in the unadjusted proportions partly reflected the characteristics of the patients. For example, the proportions of patients with metastatic disease (stage 4) were greatest amongst emergency admissions and least among other consultant referrals (Table 1). There was also a greater proportion of patients with metastatic disease among urgent GP referrals compared to non-urgent referrals (44.9% v 39.4%, respectively). The difference in the unadjusted rates of curative treatment intent among urgent and non-urgent GP referrals was removed after risk-adjustment. However, diagnosis after emergency admission remained an independent predictor of treatment intent. Differences in one-year survival, consistent with the differences observed in treatment intent, were also found for the various routes to diagnosis (Table 2).

The routes to diagnosis varied distinctly between cancer networks. Adjusted rates of diagnosis after emergency admission ranged from 8.7% to 32.3%, and six networks fell outside the 99.8% funnel limits (Figure 1). There was also substantial variation between the networks in the adjusted rates of urgent referral among patients diagnosed after any GP referral. Five networks had adjusted rates above 80%, while four had rates below 60%.

DISCUSSION

This national study of 14,102 patients with O-G cancer adds to the limited evidence on patterns of referral and how route to diagnosis is related to treatment outcomes. We found that only 45% of patients were diagnosed after an urgent GP referral. Around 21% of patients were referred non-urgently by their GP which suggests the pattern of symptoms were not suggestive of cancer. The remaining third were split evenly between diagnosis after an emergency admission and after referral by another hospital consultant. There was, however, substantial variation between cancer networks in the proportion of patients diagnosed via each route.

The importance of route to diagnosis is highlighted by its relationship to treatment intent and one-year survival. We found the proportion of patients planned to have curative treatment was considerably lower among patients diagnosed after an emergency admission (16%) compared to urgent GP referrals (36%). This was partly due to differences in the characteristics of patients diagnosed via these routes, with more patients diagnosed after an emergency admission having advanced disease. This suggests that diagnosis after emergency admission is a marker for late diagnosis. In addition, this route to diagnostic occurred more frequently among patients with stomach rather than oesophageal (including junctional) cancer, and was also associated with increasing age, more co-morbidity and worse performance status.

The proportion of urgent GP referrals was significantly lower among patients aged under 55 years and this may reflect the age criterion for urgent referral in the guideline on dyspepsia [9]. We also observed that the proportion of patients with curative treatment plans was lower among urgent GP referrals compared to non-urgent referrals. This is probably due to the alarm symptoms which form the basis of the referral guidelines being associated with more advanced disease [12,13].

Strengths and limitations

The study was based on a large, prospective sample of patients diagnosed in 142 English NHS trusts, 92% of all trusts providing O-G cancer care. Route to diagnosis was a pre-defined data item and 1-year survival was known for all patients. The overall audit included 71% of all patients diagnosed in England during the audit period. A limitation of the study was the exclusion of patients and NHS trusts due to missing data meant this study had an estimated case-ascertainment of 62%. Excluded patients tended to be younger (69.7 v 71.4 years, $p<0.001$) although differences in patient sex or location of tumour were not statistically significant. Estimated case ascertainment varied between networks, with five networks submitting less than 45% of cases. Network-based comparisons would be biased if hospitals with the networks were selective in the patients submitted to the Audit. However, the referral patterns within networks with high, medium and low case ascertainment were not noticeably different and selection bias is unlikely to explain the variation between networks.

A second limitation is that treatment intent was missing for 5% of the 14,102 patients. This might introduce bias in the estimated relationship between referral source and treatment intent but this is likely to be small compared to the size of the observed association.

Another limitation concerns the information available for risk-adjustment. Many factors can influence decisions about treatment intent and one-year survival, and there may be residual confounding caused by unmeasured variables such as the symptoms experienced at diagnosis [24]. However, the analysis included important prognostic factors such as age, comorbidity, performance status and stage of disease, and residual confounding is unlikely to explain the association between the outcomes and referral source. To incorporate performance status and stage, the analysis used multiple imputation, which relies on the assumption that the data were "missing at random". This assumption seems plausible given the range of variables in the imputation model (see additional document). Finally, the effect of the risk-adjustment on the estimated network rates was comparatively small and it seems unlikely that the observed network variation was due to inadequate risk-adjustment.

Comparison with other studies

Few studies have examined the effect of the routes to diagnosis on outcomes for O-G cancer patients. The results of our study are consistent with the evidence that patients diagnosed after emergency have worse survival rates studies [16,25] but we are unaware of any previous study that found, for patients diagnosed after referral by another consultant or non-urgent GP referral, their prognosis was not adversely affected. Compared to the results derived from routine national data [16], we found a higher proportion of diagnoses after urgent GP referral, and a lower proportion after emergency admissions. These differences could stem from the distinct

methodologies. In deriving the results from the routine data, the researchers created eight routes to diagnosis by grouping 269 individual pathways for patients diagnosed in 2007 [26]. Our study distinguished between four pre-defined categories prospectively captured by hospital staff.

The reasons for patients being diagnosed after emergency admission are currently unclear. Various explanations have been proposed [25]. One suggestion is that these patients have more aggressive forms of cancer than patients referred by GPs, or they were asymptomatic prior to presenting at A&E. Other explanations are linked to factors delaying diagnosis. Such delays might be patient related (because the patients ignored their symptoms, did not wish to seek care or did not recognise the seriousness of their symptoms) or might be practitioner related (due to acid suppression treatment, previous negative tests, or initial mis-diagnosis) [27].

Implications for clinical practice and future research

Recent government policy in England has focussed attention on the importance of an efficient pathway to diagnosis by highlighting the worse survival rates for patients diagnosed after emergency presentation [17]. This study provides additional insight into this relationship. That patients diagnosed via this route are less likely to have a curative treatment plan compared to urgent GP referrals arises in part because more patients have advanced disease. Higher rates of diagnosis after emergency admission were also associated with older patients, greater frailty, and more co-morbidity.

Further work is required to determine how the risk of emergency admission can be lowered for patients with these characteristics. That the risk can be modified is implied by the variation between cancer networks in the proportion of patients diagnosed after emergency admission. The

variation suggests the organisation of services and practices within some networks makes this less likely. The lessons to be learnt from these networks require investigation at a local level so that appropriate strategies can be devised.

This study also provides new information on outcomes for patients diagnosed after urgent and non-urgent GP referrals. The comparatively worse outcomes for patients referred urgently is consistent with fact that the alarm symptoms used by current referral guidelines are associated with more advanced disease [12,13]. There was considerable variation between cancer networks in the proportion of patients referred urgently among all GP referrals. The reasons for this variation remain unknown but it may reflect the clinical uncertainty and debate about the utility of these alarm symptoms as criteria for referral. Further research is required on the symptom profiles of patients referred by GPs as well as causes of delays in diagnosis among O-G cancer patients.

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Author contributions

TP, DC, RH, SR conceived the study; TP, DC, RH, SR, JG, JvdM designed the study; TP and DC conducted the statistical analyses; TP and DC wrote the manuscript; RH, SR, JG, JvdM commented on and revised drafts; DC is guarantor.

Ethical approval

Under UK National Research Ethics Service guidance, this study constituted service evaluation and did not require ethics approval.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: support from Healthcare Quality Improvement Partnership (HQIP) for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work."

Data Sharing Statement

No additional information is available.

Table 1: Proportions of patients with oesophago-gastric cancer by the route to diagnosis.

				Route to diagnosis (%)			
		Patients	(%)	GP Referral	Emergency admission	Other hospital	p-value
All patients		14,102		66	16	17	
Tumour	Oesophagus	9,755	(69)	71	13	16	p<0.01
	Stomach	4,347	(31)	56	24	19	
Gender	Female	4,631	(33)	66	18	17	p=0.02
	Male	9,471	(67)	67	16	18	
Age (years)	Under 55	1,215	(9)	66	14	20	p<0.01
	55 to 64	2,567	(18)	72	11	17	
	65 to 74	4,093	(29)	69	13	19	
	75 to 84	4,465	(32)	65	18	17	
	85 & over	1,762	(12)	58	30	12	
Index of Multiple Deprivation	1 (Least)	2,498	(18)	70	14	16	p<0.01
	2	2,814	(20)	68	16	16	
	3	2,969	(21)	68	15	17	
	4	2,879	(20)	64	19	17	
	5 (Most)	2,942	(21)	62	18	20	
Comorbidities	0	7,870	(56)	70	14	16	p<0.01
	1	3,829	(27)	65	17	18	
	2	1,676	(12)	59	21	19	
	3 or more	727	(5)	54	25	21	
Performance Status	0	3,541	(25)	74	8	19	p<0.01
	1	2,838	(20)	70	12	18	
	2	1,926	(14)	63	20	18	
	3 or 4	1,812	(13)	48	36	16	
	Missing	3,985	(28)	67	16	16	
Pre-treatment Stage	1 or 2	2,543	(18)	64	13	22	p<0.01
	3	2,296	(16)	74	11	16	
	4	3,804	(27)	67	20	14	
	Unknown / missing	5,459	(39)	64	18	18	

Table 2: Relationship between route to diagnosis, curative treatment intent and 1-year survival among patients diagnosed with O-G cancer in English NHS trusts.

Referral Source	Patients	Patients with outcome (%)		Unadjusted odds ratio*	Adjusted odds ratio‡ (95%CI)	
Patients with curative intent						
GP referral: urgent	6,084	2,167	(36)	1	1	
GP referral: non-urgent	2,759	1,096	(40)	1.19	1.02	0.90 to 1.15
Emergency admission	2,178	359	(16)	0.36	0.62	0.52 to 0.74
Other hospital referral	2,326	1,059	(46)	1.51	1.38	1.21 to 1.58
All patients	13,347	4,681	(35)			
Patients who survive 1 year (%)						
GP referral: urgent	6,438	2,763	(43)	1	1	
GP referral: non-urgent	2,913	1,413	(49)	1.25	1.11	1.00 to 1.24
Emergency admission	2,311	617	(27)	0.48	0.78	0.68 to 0.89
Other hospital referral	2,440	1,288	(53)	1.49	1.33	1.18 to 1.50
All patients	14,102	6,081	(43)			

*Odds ratio with GP referral: urgent as the baseline category.

‡ Adjusted odds ratio estimated using multiple logistic regression, adjusting for patients' age group, sex, tumour site, stage, number of comorbidities, performance status and regional deprivation.

Figure 1: Proportion of patients referred after an emergency admission for the 30 English cancer networks, adjusted for patient age, sex, tumour site, comorbidities, performance status and regional deprivation

[Figure 1]

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SUPPLEMENTARY INFORMATION

Appendix 1: Information about patient characteristics and missing values and the effect of multiple-imputation on the estimates of logistic regression models

Table A1: Performance status at diagnosis across patient characteristics, before and after imputation

Patient characteristic		Performance status 0	1	2	3	4	Unknown
Tumour	Oesophagus	27%	20%	13%	9%	2%	29%
	Stomach	21%	20%	15%	14%	3%	27%
Gender	Female	21%	20%	15%	12%	3%	29%
	Male	27%	20%	13%	10%	2%	28%
Age (years)	Under 55	46%	17%	7%	4%	1%	26%
	55 to 64	42%	20%	8%	4%	1%	26%
	65 to 74	28%	24%	13%	8%	1%	27%
	75 to 84	15%	21%	18%	13%	3%	30%
	85 & over	6%	12%	17%	25%	6%	33%
Index of Multiple Deprivation	1 (Least)	28%	18%	11%	9%	2%	32%
	2	27%	19%	12%	9%	3%	30%
	3	26%	20%	13%	10%	2%	29%
	4	23%	22%	15%	11%	2%	26%
	5 (Most)	22%	21%	17%	13%	3%	25%
Comorbidities	0	28%	16%	9%	7%	1%	38%
	1	25%	26%	17%	12%	3%	17%
	2	17%	24%	22%	18%	4%	15%
	3 or more	9%	23%	25%	24%	4%	15%
Performance status distribution							
Before imputation (all)		25%	20%	14%	11%	2%	28%
Before imputation (known)		35%	28%	19%	15%	3%	.
Imputed values		35%	28%	19%	14%	3%	

Table A2: Pre-treatment (clinical) stage across patient characteristics, before and after imputation

Patient characteristic		Pre-treatment stage 1	2	3	4	Unknown
Tumour	Oesophagus	3%	14%	19%	26%	37%
	Stomach	11%	8%	11%	29%	42%
Gender	Female	6%	12%	15%	25%	42%
	Male	5%	13%	17%	28%	37%
Age (years)	Under 55	7%	11%	18%	33%	31%
	55 to 64	5%	14%	20%	29%	32%
	65 to 74	6%	14%	18%	27%	35%
	75 to 84	6%	12%	14%	27%	41%
	85 & over	5%	8%	10%	19%	57%
Index of Multiple Deprivation	1 (Least)	5%	12%	16%	28%	39%
	2	6%	13%	16%	26%	38%
	3	6%	13%	16%	26%	40%
	4	6%	13%	15%	27%	39%
	5 (Most)	6%	11%	17%	28%	38%
Comorbidities	0	5%	11%	15%	27%	42%
	1	6%	14%	19%	28%	34%
	2	7%	17%	17%	25%	34%
	3 or more	11%	15%	16%	24%	34%
Performance Status	0	8%	17%	24%	22%	29%
	1	6%	16%	19%	29%	30%
	2	5%	12%	16%	33%	34%
	3	5%	9%	10%	35%	41%
	4	4%	8%	5%	35%	47%
	Unknown	4%	8%	11%	23%	54%
Pre-treatment Stage distribution						
Before imputation (all)		6%	12%	16%	27%	39%
Before imputation (known)		9%	20%	27%	44%	
Imputed values		9%	20%	26%	45%	

Table A3: Results of logistic regression models for association between patient characteristics and odds of patients having a curative treatment plan

		Odds ratios of coefficients in regression model			
		Unadjusted	Basic model	Model with imputed data	Complete case analysis
Route to Diagnosis	Urgent GP referral	1	1	1	1
	Non-urgent GP referral	1.19	1.16	1.02	1.00
	Emergency admission	0.36	0.43	0.62	0.68
	Other hospital referral	1.51	1.53	1.38	1.30
Tumour	Oesophagus		1	1	1
	Stomach		1.19	1.34	1.63
Gender	Female		1	1	1
	Male		1.16	1.19	1.31
Age (years)	Under 55		1.21	1.14	1.37
	55 to 64		1.34	1.25	1.48
	65 to 74		1	1	1
	75 to 84		0.41	0.43	0.34
	85 & over		0.07	0.08	0.08
Index of Multiple Deprivation	1 (Least)		1	1	1
	2		1.10	1.09	1.12
	3		0.93	0.92	0.90
	4		0.96	0.98	1.06
	5 (Most)		0.82	0.91	0.93
No. of comorbidities			0.92	0.92	0.82
Performance Status	0			1	1
	1			0.56	0.49
	2			0.28	0.18
	3 or 4			0.10	0.03
Pre-treatment Stage	1			2.01	3.22
	2			1.62	2.23
	3			1	1
	4			0.15	0.04
Area under the curve			0.72	0.86	0.92

Table A4: Results of logistic regression models for association between patient characteristics and odds of patients surviving one year

		Odds ratios of coefficients in regression model			
		Unadjusted	Basic model	Model with imputed data	Complete case analysis
Route to Diagnosis	Urgent GP referral	1	1	1	1
	Non-urgent GP referral	1.25	1.23	1.11	1.12
	Emergency admission	0.48	0.55	0.78	0.85
	Other hospital referral	1.49	1.48	1.33	1.48
Tumour	Oesophagus		1	1	1
	Stomach		1.09	1.11	1.11
Gender	Female		1	1	1
	Male		1.03	1.01	0.98
Age (years)	Under 55		1.24	1.14	1.12
	55 to 64		1.29	1.18	1.16
	65 to 74		1	1	1
	75 to 84		0.58	0.68	0.66
	85 & over		0.34	0.47	0.53
Index of Multiple Deprivation	1 (Least)		1	1	1
	2		1.10	1.10	1.19
	3		1.06	1.10	1.11
	4		0.98	1.02	1.14
	5 (Most)		0.88	0.99	1.02
No. of comorbidities			1.01	1.03	1.02
Performance Status	0			1	1
	1			0.58	0.59
	2			0.34	0.33
	3 or 4			0.18	0.14
Pre-treatment Stage	1			2.92	3.37
	2			1.70	1.64
	3			1	1
	4			0.31	0.30
Area under the curve			0.65	0.79	0.80

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Cohort design in abstract.
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5-6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	n/a
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers.	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5*
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	Aimed to collect all cases in England
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-7
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	7
		(*d*) If applicable, explain how loss to follow-up was addressed	n/a
		(*e*) Describe any sensitivity analyses	n/a

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	n/a
		(c) Consider use of a flow diagram	Not warranted
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1 and appendix
		(b) Indicate number of participants with missing data for each variable of interest	Appendix
		(c) Summarise follow-up time (eg, average and total amount)	Table 2
Outcome data	15*	Report numbers of outcome events or summary measures over time	n/a
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Tables 1 and 2
		(*b*) Report category boundaries when continuous variables were categorized	Table 1
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Appendix
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-11
Generalisability	21	Discuss the generalisability (external validity) of the study results	11-13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Impact of route to diagnosis on treatment intent and 1-year survival in patients diagnosed with oesophago-gastric cancer in England

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Impact of route to diagnosis on treatment intent and 1-year survival in patients diagnosed with oesophago-gastric cancer in England

Short title: Routes to diagnosis for oesophago-gastric cancer patients

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Abstract

OBJECTIVE: To investigate the relationship between the route to diagnosis, patient characteristics, treatment intent and one-year survival among patients with oesophago-gastric (O-G) cancer.

SETTING: Cohort study in 142 English NHS trusts and 30 cancer networks.

PARTICIPANTS: Patients diagnosed with O-G cancer between October 2007 and June 2009.

DESIGN: Prospective cohort study. Route to diagnosis defined as general practitioner (GP) referral - urgent (suspected cancer) or non-urgent, hospital consultant referral, or after an emergency admission. Logistic regression was used to estimate associations and adjust for differences in casemix.

MAIN OUTCOME MEASURES: Proportion of patients diagnosed by route of diagnosis; proportion of patients selected for curative treatment; one-year survival.

RESULTS: Among 14,102 cancer patients, 66.3% were diagnosed after a GP referral, 16.4% after an emergency admission, and 17.4% after hospital consultant referral. Of the 9,351 GP referrals, 68.8% were urgent. Compared to urgent GP referrals, a markedly lower proportion of patients diagnosed after emergency admission had a curative treatment plan (36% v 16%; adjusted odds ratio (OR) = 0.62, 95% CI: 0.52 to 0.74) and a lower proportion survived one year (43% v 27%; OR = 0.78; 0.68 to 0.89). Urgency of GP referral didn't affect treatment intent or survival. Routes to diagnosis varied across cancer networks, with the adjusted proportion of patients diagnosed after emergency admission ranging from 8.7% to 32.3%.

CONCLUSION: Outcomes for cancer patients are worse if diagnosed after emergency admission. Primary care and hospital services should work together to reduce rates of diagnosis after emergency admission and the variation across cancer networks.

ARTICLE SUMMARY

Article focus

- To investigate the relationship between the route to diagnosis, patient characteristics, treatment intent, and one-year survival.
- To examine whether the routes to diagnosis varied between regional cancer networks.

Key messages

- Two thirds of patients diagnosed with O-G cancer were referred by their general practitioner (GP), of which around two-thirds were referred urgently. Patients referred as an urgent (two-week wait) referral by their GP did not have better survival rates than non-urgent GP referrals
- One in six patients were diagnosed after an emergency admission, and these patients were less likely to have a curative treatment plan compared to urgent GP referrals. One-year survival was also worse.
- There was significant variation between cancer networks in the rates of emergency admission, which persisted after adjusting for patient factors.

Strengths and limitations of the study

- The study uses data from the large, prospective sample of patients diagnosed in almost all English NHS trusts. 1-year survival was known for all patients.
- Limitations stem from the study capturing only 62% of all patients eligible for the study and from the exclusion of patients due to missing data on route to diagnosis and treatment intent.

INTRODUCTION

Oesophago-gastric (O-G) cancer is the fourth most common cause of cancer death in the United Kingdom resulting in approximately 12,500 deaths per year [1]. The majority of patients are diagnosed with advanced disease and only 20–30% are suitable for curative treatment [2,3]. Consequently, the prognosis is often poor, with 5-year relative survival being approximately 15% [4].

An objective of the UK Cancer Reform Strategy has been to increase the proportion of patients diagnosed with early cancer [5]. Meeting this objective represents a considerable challenge for oesophago-gastric (O-G) cancer services and general practitioners (GP). Many of the symptoms and signs of O-G cancer are non-specific and are present in large numbers of individuals without cancer [6]. For example, uncomplicated dyspepsia constitutes 3-4% of a general practitioner's workload [7,8] but an average general practice will only see four or five O-G cancer patients per year [6]. Guidelines recommend that GPs refer urgently to a specialist team only if patients present with "alarm symptoms" (eg, weight loss, vomiting dysphagia) or have persistent dyspepsia and are over 55 years [9-11]. However, these alarm symptoms are typically associated with advanced disease [12,13].

Across all cancer types, the number of patients diagnosed after an urgent GP referral increased from 80,000 in 2007 to 98,000 in 2009 [14]. But, for O-G cancer patients, information about patients' route to diagnosis and how this affects outcomes is limited [15]. Figures from routine data suggest that a substantial minority of O-G cancer patients are diagnosed following an

emergency presentation and these patients have worse survival [16-18]. One-year relative survival among all patients with oesophageal cancer was 40% but it was only 18% for those diagnosed after an emergency presentation; among patients with stomach cancer, the corresponding survival figures were 41% and 23% [18]. However, evidence about these relationships is sparse, and there is a need to understand how route to diagnosis contributes with patient characteristics and treatment decisions to influence survival.

This study used a prospectively collected national clinical dataset of patients with O-G cancer in England to investigate the relationship between the route to diagnosis, patient characteristics, treatment intent, and one-year survival. We also examined whether the routes to diagnosis varied between regional cancer networks.

MATERIALS AND METHODS

Data were collected prospectively by English NHS trusts as part of the national oesophago-gastric cancer audit. All adult patients diagnosed in England with invasive, epithelial cancer of the oesophagus or stomach between 1 October 2007 and 30 June 2009 were eligible for inclusion. The audit method and dataset have been published elsewhere [3,19].

The study captured route to diagnosis by adopting the "source of referral" and "cancer referral priority" data items from the National Cancer Dataset [20]. Source of referral to the cancer specialist / team differentiated between: referral from a GP (non-emergency, to outpatient clinics), referral after an emergency admission (via Accident & Emergency, Medical Admissions Unit, etc) and an "other hospital referral" (patients referred by a hospital consultant from a non-

emergency setting). Patients referred by GPs under the urgent "2-week wait" (2WW) referral system were classified as "urgent (for suspected cancer)". All other GP referrals to the cancer team via outpatients were grouped as "non-urgent". Information was also collected on the patient's age at diagnosis, sex, social deprivation, tumour site and TNM stage (version 6) [21], number of co-morbidities, ECOG functional performance and treatment intent. Date of death was obtained from the Office for National Statistics death certificate register, which gave full follow-up for a minimum of 380 days from date of diagnosis. Tumour site was categorised as oesophageal (including Siewert 1-3 junctional tumours) or stomach. Treatment intent (curative or palliative) reflected the decision of the multi-disciplinary team meeting after pre-treatment staging was completed. Social deprivation was measured using the UK Index of Multiple Deprivation [22] with patients being grouped into quintiles from least deprived (=1) to most deprived (=5).

Statistical analysis

We calculated the proportion of patients diagnosed via the different routes for all England and the 30 cancer networks that existed on 1 October 2007. Patients were grouped into networks by their NHS trust of diagnosis. The relationship between two variables was examined using the chi-squared test. The association between route to diagnosis and the proportion of patients having a curative treatment plan and one-year survival was examined using logistic regression to control for the influence of age at diagnosis, sex, regional deprivation, tumour site, pre-treatment stage, comorbidities and performance status.

Multinomial logistic regression was used to adjust the proportion of patients diagnosed via each route in each cancer network for patient characteristics [23]. Funnel plots were used to test

whether network rates differed significantly from the overall English rate [24]. These graphs show the network rates together with the English rate and two sets of control limits that indicate the ranges within which 95% or 99.8% of the network rates would be expected to fall if differences from the English rate arose from random variation alone.

The analysis was performed in STATA v10. All p-values are two-sided and those lower than 0.05 were considered to show a statistically significant result. Two variables used in the regression models, performance status and pre-treatment stage, were known for 72% and 61% of patients, respectively. Missing data values for these two variables were imputed using multiple imputation by chained equations [25]. The imputation model included age at diagnosis, sex, tumour site, deprivation, number of co-morbidities, referral source, and one-year survival. Twenty-five imputations were created. Missing values were assumed to be "missing at random" (see additional file for details of missing and imputed values).

RESULTS

Information was collected on 16,264 patients from 152 English NHS trusts. Ten NHS trusts were excluded (1196 patients) because the route to diagnosis was entered for less than half of their patients. Six of these trusts had this information on less than 10% of their patients. Other patient records that lacked route to diagnosis (n=956) or age at diagnosis (n=10) were also excluded. This left 14,102 patients in the analysis. Their median age was 73 years, two-thirds were male, and 69% had an oesophageal tumour. Patients with stomach tumours were slightly older on average (mean 73.6 v 70.4 years, $p<0.001$) and fewer were aged under 55 years (7.1% v 9.3%, $p<0.001$). Among patients with known pre-treatment stage, 44% had stage 4 (metastatic) disease.

Patterns of route to diagnosis

Overall, 66.3% of patients were referred by their general practitioner, 16.4% were referred following an emergency hospital admission and 17.3% were referred from another hospital consultant. The proportion of GP referrals was lower among patients with stomach tumours compared to oesophageal tumours, which reflected a greater proportion of stomach cancers being diagnosed after an emergency admission (see Table 1). Diagnosis after emergency admission was least common among patients aged 55-64 years but increased among older and younger patients. This route to diagnosis was also more common among patients as their performance status got worse.

In terms of the overall routes to diagnosis, the proportions of patients with oesophageal and stomach tumours who were referred as urgent (2WW) were 50.3% and 35.3%, respectively. In relation to GP referrals only, 71.1% of oesophageal cancer patients and 62.6% of gastric cancer patients were labelled as urgent (2WW). These proportions were lower for patients whose age was below the guideline threshold. For oesophageal tumours, 64.4% of patients aged less than 55 years were referred urgently (2WW) by GPs compared to 71.8% for older patients. For stomach tumours, the proportions were 50.6% and 63.5%, respectively.

Association between route to diagnosis, treatment intent and one-year survival

There was a strong association between the route to diagnosis and the likelihood of a patient having a curative treatment plan (Table 2). The differences in the unadjusted proportions partly reflected the characteristics of the patients. For example, the proportions of patients with metastatic disease (stage 4) were greatest amongst emergency admissions and least among other

consultant referrals (Table 1). There was also a greater proportion of patients with metastatic disease among urgent (2WW) GP referrals compared to non-urgent referrals (44.9% v 39.4%, respectively). The difference in the unadjusted rates of curative treatment intent among urgent (2WW) and non-urgent GP referrals was removed after risk-adjustment. However, diagnosis after emergency admission remained an independent predictor of treatment intent. Differences in one-year survival, consistent with the differences observed in treatment intent, were also found for the various routes to diagnosis (Table 2).

The routes to diagnosis varied distinctly between cancer networks. Adjusted rates of diagnosis after emergency admission ranged from 8.7% to 32.3%, and six networks fell outside the 99.8% funnel limits (Figure 1). There was also substantial variation between the networks in the adjusted rates of urgent (2WW) referral among patients diagnosed after any GP referral. Five networks had adjusted rates above 80%, while four had rates below 60%.

DISCUSSION

This national study of 14,102 patients with O-G cancer adds to the limited evidence how routes to diagnosis are related to treatment outcomes. We found that only 45% of patients were diagnosed after an urgent (2WW) GP referral. Around 21% of patients were referred non-urgently by their GP which suggests their pattern of symptoms were not suggestive of cancer. The remaining third were split evenly between diagnosis after an emergency admission and after referral by another hospital consultant. There was, however, substantial variation between cancer networks in the proportion of patients diagnosed via each route.

The importance of route to diagnosis is highlighted by its relationship to treatment intent and one-year survival. We found the proportion of patients planned to have curative treatment was considerably lower among patients diagnosed after an emergency admission (16%) compared to urgent (2WW) GP referrals (36%). This was partly due to differences in the characteristics of patients diagnosed via these routes, with more patients diagnosed after an emergency admission having advanced disease. This suggests that diagnosis after emergency admission is a marker for late diagnosis. In addition, this route to diagnostic occurred more frequently among patients with stomach rather than oesophageal (including junctional) cancer, and was also associated with increasing age, more co-morbidity and worse performance status.

The proportion of urgent (2WW) GP referrals was significantly lower among patients aged under 55 years and this may reflect the age criterion for urgent referral in the guideline on dyspepsia [9]. We also observed that the proportion of patients with curative treatment plans was lower among urgent (2WW) GP referrals compared to non-urgent referrals. This is probably due to the alarm symptoms which form the basis of the referral guidelines being associated with more advanced disease [12,13].

Strengths and limitations

The study was based on a large, prospective sample of patients diagnosed in 142 English NHS trusts, 92% of all trusts providing O-G cancer care. Route to diagnosis was defined using items from the English national cancer dataset and 1-year survival was known for all patients.

The study suffers from various limitations. First, using data from the routine Hospital Episode Statistics (HES) database, the overall audit was estimated to include 71% of patients diagnosed in

England during the data collection period [3]. Further excluding patient records and NHS trusts with missing data meant this analysis included 62% of all potential cases. The analysed Audit data and HES dataset showed similar demographic characteristics (average age was 71.4 and 71.3 years, respectively, while the proportion of male patients was 67.2% and 66.3% respectively). The differences between the analysed and excluded audit patients were also small. Excluded audit patients were slightly younger on average (69.7 v 71.4 years, $p<0.001$) but did not differ by a statistically significant amount in terms of patient sex (male 69.2% v 67.2%, $p=0.06$) or location of tumour (stomach 29.6% v 30.8%, $p=0.27$).

Another limitation was the variation in estimated case ascertainment between networks. Sixteen networks submitted data on over 70% of expected cases, while two submitted less than 40% of cases. Excluding records due to poor data quality produced marginal changes in case-ascertainment for most networks, with it being reduced by less than 5% for 19 networks. Excluding the 10 NHS trusts because of poor route to diagnosis data affected six networks and reduced their case-ascertainment by between 11% and 42%. These exclusions could have biased the individual network rates if hospitals were selective in the patients submitted to the Audit and/or data completeness was related to particular patient characteristics. However, the routes to diagnosis within networks with high, medium and low case-ascertainment were not noticeably different, and selection bias is unlikely to explain the variation observed between networks. Among the nine networks that submitted over 80% of estimated cases and that had less than 5% of records excluded for incomplete data, the adjusted proportion of patients diagnosed after a GP referral ranged from 52% to 71%, while the adjusted proportion of patients diagnosed after emergency admission ranged from 9% to 30%.

A third limitation is that treatment intent was missing for 5% of the 14,102 patients. This might introduce bias in the estimated relationship between referral source and treatment intent but this is likely to be small compared to the size of the observed association.

Another limitation concerns the information available for risk-adjustment. Many factors can influence decisions about treatment intent and one-year survival, and there may be residual confounding caused by unmeasured variables such as the symptoms experienced at diagnosis [26]. However, the analysis included important prognostic factors such as age, comorbidity, performance status and stage of disease and residual confounding is unlikely to explain the association between the outcomes and referral source. To incorporate performance status and stage, the analysis used multiple imputation, which relies on the assumption that the data were "missing at random". This assumption seems plausible given the range of variables in the imputation model (see additional document). Finally, the effect of the risk-adjustment on the estimated network rates was comparatively small and it seems unlikely that the observed network variation was due to inadequate risk-adjustment.

Comparison with other studies

Various studies have examined the pathway to diagnosis, with many focusing on patients diagnosed after an urgent (2WW) GP referral. In a systematic review, Thorne et al [27] derived pooled data on 498 patients from seven studies conducted between 2003 and 2008, and estimated that 34% of patients with upper gastro-intestinal cancer were diagnosed after urgent (2WW) GP referral. An audit of cancer diagnosis in English primary care in 2009/10 [28] reported that the proportion of patients with oesophageal cancer (n=596) diagnosed after an urgent (2WW) GP referral and emergency presentation was 58% and 10% respectively; for stomach cancers

(n=319), the proportions were 40% and 21%, respectively. The national study using English Cancer Registry and routine health data [18] reported higher rates of emergency presentation (22% for oesophageal and 33% for stomach) and lower rates of urgent (2WW) GP referrals (34% for oesophageal and 23% for stomach).

Our results are generally comparable to these estimates. Compared to the results derived from routine national data [18], we found a higher proportion of diagnoses after urgent (2WW) GP referral, and a lower proportion after emergency admission. These differences could arise for various reasons. First, the audit may have suffered from potential under-reporting of patients diagnosed via particular pathways. Second, the two studies used different pathway categories and the "emergency admission" definition from the National Cancer dataset and the NCIN definition of emergency presentation may not entirely overlap. Finally, the studies had distinct methodologies. In deriving the results from the routine data, the researchers created eight routes to diagnosis by grouping 71 distinct combinations [18].

Few studies have examined the effect of the routes to diagnosis on outcomes for O-G cancer patients. The results of our study are consistent with the evidence that patients diagnosed after emergency have worse survival rates [16,18,29] but we are unaware of any previous study that found, for patients diagnosed after referral by another consultant or non-urgent GP referral, their risk-adjusted prognosis was not adversely affected.

The reasons for patients being diagnosed after emergency admission are currently unclear. Various explanations have been proposed [29-32]. One suggestion is that these patients have more aggressive forms of cancer than patients referred by GPs, or they were asymptomatic prior

to presenting at A&E. Other explanations are linked to factors delaying diagnosis. Such delays might be patient related (because the patients ignored their symptoms, did not wish to seek care or did not recognise the seriousness of their symptoms) or might be practitioner related (due to acid suppression treatment, previous negative tests, or initial mis-diagnosis) [32].

Implications for clinical practice and future research

Recent government policy in England has focussed attention on the importance of an efficient pathway to diagnosis by highlighting the worse survival rates for patients diagnosed after emergency presentation [17]. This study provides additional insight into this relationship. That patients diagnosed via this route are less likely to have a curative treatment plan compared to urgent (2WW) GP referrals arises in part because more patients have advanced disease. Higher rates of diagnosis after emergency admission were also associated with older patients, greater frailty, and more co-morbidity.

Further work is required to determine how the risk of emergency admission can be lowered for patients with these characteristics [30]. That the risk can be modified is implied by the variation between cancer networks in the proportion of patients diagnosed after emergency admission. The variation suggests the organisation of services and practices within some networks makes this less likely. The lessons to be learnt from these networks require investigation at a local level so that appropriate strategies can be devised.

This study also provides new information on outcomes for patients diagnosed after urgent (2WW) and non-urgent GP referrals The comparatively worse outcomes for patients referred urgently is consistent with fact that the alarm symptoms used by current referral guidelines are

associated with more advanced disease [12,13]. There was considerable variation between cancer networks in the proportion of patients referred urgently among all GP referrals. The reasons for this variation remain unknown but it may reflect the clinical uncertainty and debate about the utility of these alarm symptoms as criteria for referral. Further research is required on the symptom profiles of patients referred by GPs as well as causes of delays in diagnosis among O-G cancer patients.

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Author contributions

TP, DC, RH, SR conceived the study; TP, DC, RH, SR, JG, JvdM designed the study; TP and DC conducted the statistical analyses; TP and DC wrote the manuscript; RH, SR, JG, JvdM commented on and revised drafts; DC is guarantor.

Ethical approval

Under UK National Research Ethics Service guidance, this study constituted service evaluation and did not require ethics approval.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: support from Healthcare Quality Improvement Partnership (HQIP) for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work."

Table 1: Proportions of patients with oesophago-gastric cancer by the route to diagnosis.

				Route to diagnosis (%)			
		Patients	(%)	GP Referral	Emergency admission	Other hospital	p-value
All patients		14,102		66	16	17	
Tumour	Oesophagus	9,755	(69)	71	13	16	p<0.01
	Stomach	4,347	(31)	56	24	19	
Gender	Female	4,631	(33)	66	18	17	p=0.02
	Male	9,471	(67)	67	16	18	
Age (years)	Under 55	1,215	(9)	66	14	20	p<0.01
	55 to 64	2,567	(18)	72	11	17	
	65 to 74	4,093	(29)	69	13	19	
	75 to 84	4,465	(32)	65	18	17	
	85 & over	1,762	(12)	58	30	12	
Index of Multiple Deprivation	1 (Least)	2,498	(18)	70	14	16	p<0.01
	2	2,814	(20)	68	16	16	
	3	2,969	(21)	68	15	17	
	4	2,879	(20)	64	19	17	
	5 (Most)	2,942	(21)	62	18	20	
Comorbidities	0	7,870	(56)	70	14	16	p<0.01
	1	3,829	(27)	65	17	18	
	2	1,676	(12)	59	21	19	
	3 or more	727	(5)	54	25	21	
Performance Status	0	3,541	(25)	74	8	19	p<0.01
	1	2,838	(20)	70	12	18	
	2	1,926	(14)	63	20	18	
	3 or 4	1,812	(13)	48	36	16	
	Missing	3,985	(28)	67	16	16	
Pre-treatment Stage	1 or 2	2,543	(18)	64	13	22	p<0.01
	3	2,296	(16)	74	11	16	
	4	3,804	(27)	67	20	14	
	Unknown / missing	5,459	(39)	64	18	18	

Table 2: Relationship between route to diagnosis, curative treatment intent and 1-year survival among patients diagnosed with O-G cancer in English NHS trusts.

Referral Source	Patients	Patients with outcome (%)		Unadjusted odds ratio*	Adjusted odds ratio‡ (95%CI)	
Patients with curative intent						
GP referral: urgent	6,084	2,167	(36)	1	1	
GP referral: non-urgent	2,759	1,096	(40)	1.19	1.02	0.90 to 1.15
Emergency admission	2,178	359	(16)	0.36	0.62	0.52 to 0.74
Other hospital referral	2,326	1,059	(46)	1.51	1.38	1.21 to 1.58
All patients	13,347	4,681	(35)			
Patients who survive 1 year (%)						
GP referral: urgent	6,438	2,763	(43)	1	1	
GP referral: non-urgent	2,913	1,413	(49)	1.25	1.11	1.00 to 1.24
Emergency admission	2,311	617	(27)	0.48	0.78	0.68 to 0.89
Other hospital referral	2,440	1,288	(53)	1.49	1.33	1.18 to 1.50
All patients	14,102	6,081	(43)			

*Odds ratio with GP referral: urgent as the baseline category.

‡ Adjusted odds ratio estimated using multiple logistic regression, adjusting for patients' age group, sex, tumour site, stage, number of comorbidities, performance status and regional deprivation.

Figure 1: Proportion of patients referred after an emergency admission for the 30 English cancer networks, adjusted for patient age, sex, tumour site, comorbidities, performance status and regional deprivation

[Figure 1]

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Impact of route to diagnosis on treatment intent and 1-year survival in patients diagnosed with oesophago-gastric cancer in England

Short title: Routes to diagnosis for oesophago-gastric cancer patients

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Abstract

OBJECTIVE: To investigate the relationship between the route to diagnosis, patient characteristics, treatment intent and one-year survival among patients with oesophago-gastric (O-G) cancer.

SETTING: Cohort study in 142 English NHS trusts and 30 cancer networks.

PARTICIPANTS: Patients diagnosed with O-G cancer between October 2007 and June 2009.

DESIGN: Prospective cohort study. Route to diagnosis defined as general practitioner (GP) referral - urgent (suspected cancer) or non-urgent, hospital consultant referral, or after an emergency admission. Logistic regression was used to estimate associations and adjust for differences in casemix.

MAIN OUTCOME MEASURES: Proportion of patients diagnosed by route of diagnosis; proportion of patients selected for curative treatment; one-year survival.

RESULTS: Among 14,102 cancer patients, 66.3% were diagnosed after a GP referral, 16.4% after an emergency admission, and 17.4% after hospital consultant referral. Of the 9,351 GP referrals, 68.8% were urgent. Compared to urgent GP referrals, a markedly lower proportion of patients diagnosed after emergency admission had a curative treatment plan (36% v 16%; adjusted odds ratio (OR) = 0.62, 95% CI: 0.52 to 0.74) and a lower proportion survived one year (43% v 27%; OR = 0.78; 0.68 to 0.89). Urgency of GP referral didn't affect treatment intent or survival. Routes to diagnosis varied across cancer networks, with the adjusted proportion of patients diagnosed after emergency admission ranging from 8.7% to 32.3%.

CONCLUSION: Outcomes for cancer patients are worse if diagnosed after emergency admission. Primary care and hospital services should work together to reduce rates of diagnosis after emergency admission and the variation across cancer networks.

ARTICLE SUMMARY

Article focus

- To investigate the relationship between the route to diagnosis, patient characteristics, treatment intent, and one-year survival.
- To examine whether the routes to diagnosis varied between regional cancer networks.

Key messages

- Two thirds of patients diagnosed with O-G cancer were referred by their general practitioner (GP), of which around two-thirds were referred urgently. Patients referred as an urgent (two-week wait) referral by their GP did not have better survival rates than non-urgent GP referrals
- One in six patients were diagnosed after an emergency admission, and these patients were less likely to have a curative treatment plan compared to urgent GP referrals. One-year survival was also worse.
- There was significant variation between cancer networks in the rates of emergency admission, which persisted after adjusting for patient factors.

Strengths and limitations of the study

- The study uses data from the large, prospective sample of patients diagnosed in almost all English NHS trusts. 1-year survival was known for all patients.
- Limitations stem from the study capturing only 62% of all patients eligible for the study and from the exclusion of patients due to missing data on route to diagnosis and treatment intent.

INTRODUCTION

Oesophago-gastric (O-G) cancer is the fourth most common cause of cancer death in the United Kingdom resulting in approximately 12,500 deaths per year [1]. The majority of patients are diagnosed with advanced disease and only 20–30% are suitable for curative treatment [2,3]. Consequently, the prognosis is often poor, with 5-year relative survival being approximately 15% [4].

An objective of the UK Cancer Reform Strategy has been to increase the proportion of patients diagnosed with early cancer [5]. Meeting this objective represents a considerable challenge for oesophago-gastric (O-G) cancer services and general practitioners (GP). Many of the symptoms and signs of O-G cancer are non-specific and are present in large numbers of individuals without cancer [6]. For example, uncomplicated dyspepsia constitutes 3-4% of a general practitioner's workload [7,8] but an average general practice will only see four or five O-G cancer patients per year [6]. Guidelines recommend that GPs refer urgently to a specialist team only if patients present with "alarm symptoms" (eg, weight loss, vomiting dysphagia) or have persistent dyspepsia and are over 55 years [9-11]. However, these alarm symptoms are typically associated with advanced disease [12,13].

Across all cancer types, the number of patients diagnosed after an urgent GP referral increased from 80,000 in 2007 to 98,000 in 2009 [14]. But, for O-G cancer patients, information about patients' route to diagnosis and how this affects outcomes is limited [15]. Figures from routine data suggest that a substantial minority of O-G cancer patients are diagnosed following an

emergency presentation and these patients have worse survival [16-18]. One-year relative survival among all patients with oesophageal cancer was 40% but it was only 18% for those diagnosed after an emergency presentation; among patients with stomach cancer, the corresponding survival figures were 41% and 23% [18]. However, evidence about these relationships is sparse, and there is a need to understand how route to diagnosis contributes with patient characteristics and treatment decisions to influence survival.

This study used a prospectively collected national clinical dataset of patients with O-G cancer in England to investigate the relationship between the route to diagnosis, patient characteristics, treatment intent, and one-year survival. We also examined whether the routes to diagnosis varied between regional cancer networks.

MATERIALS AND METHODS

Data were collected prospectively by English NHS trusts as part of the national oesophago-gastric cancer audit. All adult patients diagnosed in England with invasive, epithelial cancer of the oesophagus or stomach between 1 October 2007 and 30 June 2009 were eligible for inclusion. The audit method and dataset have been published elsewhere [3,19].

The study captured route to diagnosis by adopting the "source of referral" and "cancer referral priority" data items from the National Cancer Dataset [20]. Source of referral to the cancer specialist / team differentiated between: referral from a GP (non-emergency, to outpatient clinics), referral after an emergency admission (via Accident & Emergency, Medical Admissions Unit, etc) and an "other hospital referral" (patients referred by a hospital consultant from a non-

emergency setting). Patients referred by GPs under the urgent "2-week wait" (2WW) referral system were classified as "urgent (for suspected cancer)". All other GP referrals to the cancer team via outpatients were grouped as "non-urgent". Information was also collected on the patient's age at diagnosis, sex, social deprivation, tumour site and TNM stage (version 6) [21], number of co-morbidities, ECOG functional performance and treatment intent. Date of death was obtained from the Office for National Statistics death certificate register, which gave full follow-up for a minimum of 380 days from date of diagnosis. Tumour site was categorised as oesophageal (including Siewert 1-3 junctional tumours) or stomach. Treatment intent (curative or palliative) reflected the decision of the multi-disciplinary team meeting after pre-treatment staging was completed. Social deprivation was measured using the UK Index of Multiple Deprivation [22] with patients being grouped into quintiles from least deprived (=1) to most deprived (=5).

Statistical analysis

We calculated the proportion of patients diagnosed via the different routes for all England and the 30 cancer networks that existed on 1 October 2007. Patients were grouped into networks by their NHS trust of diagnosis. The relationship between two variables was examined using the chi-squared test. The association between route to diagnosis and the proportion of patients having a curative treatment plan and one-year survival was examined using logistic regression to control for the influence of age at diagnosis, sex, regional deprivation, tumour site, pre-treatment stage, comorbidities and performance status.

Multinomial logistic regression was used to adjust the proportion of patients diagnosed via each route in each cancer network for patient characteristics [23]. Funnel plots were used to test

whether network rates differed significantly from the overall English rate [24]. These graphs show the network rates together with the English rate and two sets of control limits that indicate the ranges within which 95% or 99.8% of the network rates would be expected to fall if differences from the English rate arose from random variation alone.

The analysis was performed in STATA v10. All p-values are two-sided and those lower than 0.05 were considered to show a statistically significant result. Two variables used in the regression models, performance status and pre-treatment stage, were known for 72% and 61% of patients, respectively. Missing data values for these two variables were imputed using multiple imputation by chained equations [25]. The imputation model included age at diagnosis, sex, tumour site, deprivation, number of co-morbidities, referral source, and one-year survival. Twenty-five imputations were created. Missing values were assumed to be "missing at random" (see additional file for details of missing and imputed values).

RESULTS

Information was collected on 16,264 patients from 152 English NHS trusts. Ten NHS trusts were excluded (1196 patients) because the route to diagnosis was entered for less than half of their patients. Six of these trusts had this information on less than 10% of their patients. Other patient records that lacked route to diagnosis (n=956) or age at diagnosis (n=10) were also excluded. This left 14,102 patients in the analysis. Their median age was 73 years, two-thirds were male, and 69% had an oesophageal tumour. Patients with stomach tumours were slightly older on average (mean 73.6 v 70.4 years, p<0.001) and fewer were aged under 55 years (7.1% v 9.3%, p<0.001). Among patients with known pre-treatment stage, 44% had stage 4 (metastatic) disease.

Patterns of route to diagnosis

Overall, 66.3% of patients were referred by their general practitioner, 16.4% were referred following an emergency hospital admission and 17.3% were referred from another hospital consultant. The proportion of GP referrals was lower among patients with stomach tumours compared to oesophageal tumours, which reflected a greater proportion of stomach cancers being diagnosed after an emergency admission (see Table 1). Diagnosis after emergency admission was least common among patients aged 55-64 years but increased among older and younger patients. This route to diagnosis was also more common among patients as their performance status got worse.

In terms of the overall routes to diagnosis, the proportions of patients with oesophageal and stomach tumours who were referred as urgent (2WW) were 50.3% and 35.3%, respectively. In relation to GP referrals only, 71.1% of oesophageal cancer patients and 62.6% of gastric cancer patients were labelled as urgent (2WW). These proportions were lower for patients whose age was below the guideline threshold. For oesophageal tumours, 64.4% of patients aged less than 55 years were referred urgently (2WW) by GPs compared to 71.8% for older patients. For stomach tumours, the proportions were 50.6% and 63.5%, respectively.

Association between route to diagnosis, treatment intent and one-year survival

There was a strong association between the route to diagnosis and the likelihood of a patient having a curative treatment plan (Table 2). The differences in the unadjusted proportions partly reflected the characteristics of the patients. For example, the proportions of patients with metastatic disease (stage 4) were greatest amongst emergency admissions and least among other

consultant referrals (Table 1). There was also a greater proportion of patients with metastatic disease among urgent (2WW) GP referrals compared to non-urgent referrals (44.9% v 39.4%, respectively). The difference in the unadjusted rates of curative treatment intent among urgent (2WW) and non-urgent GP referrals was removed after risk-adjustment. However, diagnosis after emergency admission remained an independent predictor of treatment intent. Differences in one-year survival, consistent with the differences observed in treatment intent, were also found for the various routes to diagnosis (Table 2).

The routes to diagnosis varied distinctly between cancer networks. Adjusted rates of diagnosis after emergency admission ranged from 8.7% to 32.3%, and six networks fell outside the 99.8% funnel limits (Figure 1). There was also substantial variation between the networks in the adjusted rates of urgent (2WW) referral among patients diagnosed after any GP referral. Five networks had adjusted rates above 80%, while four had rates below 60%.

DISCUSSION

This national study of 14,102 patients with O-G cancer adds to the limited evidence how routes to diagnosis are related to treatment outcomes. We found that only 45% of patients were diagnosed after an urgent (2WW) GP referral. Around 21% of patients were referred non-urgently by their GP which suggests their pattern of symptoms were not suggestive of cancer. The remaining third were split evenly between diagnosis after an emergency admission and after referral by another hospital consultant. There was, however, substantial variation between cancer networks in the proportion of patients diagnosed via each route.

The importance of route to diagnosis is highlighted by its relationship to treatment intent and one-year survival. We found the proportion of patients planned to have curative treatment was considerably lower among patients diagnosed after an emergency admission (16%) compared to urgent (2WW) GP referrals (36%). This was partly due to differences in the characteristics of patients diagnosed via these routes, with more patients diagnosed after an emergency admission having advanced disease. This suggests that diagnosis after emergency admission is a marker for late diagnosis. In addition, this route to diagnostic occurred more frequently among patients with stomach rather than oesophageal (including junctional) cancer, and was also associated with increasing age, more co-morbidity and worse performance status.

The proportion of urgent (2WW) GP referrals was significantly lower among patients aged under 55 years and this may reflect the age criterion for urgent referral in the guideline on dyspepsia [9]. We also observed that the proportion of patients with curative treatment plans was lower among urgent (2WW) GP referrals compared to non-urgent referrals. This is probably due to the alarm symptoms which form the basis of the referral guidelines being associated with more advanced disease [12,13].

Strengths and limitations

The study was based on a large, prospective sample of patients diagnosed in 142 English NHS trusts, 92% of all trusts providing O-G cancer care. Route to diagnosis was defined using items from the English national cancer dataset and 1-year survival was known for all patients.

The study suffers from various limitations. First, using data from the routine Hospital Episode Statistics (HES) database, the overall audit was estimated to include 71% of patients diagnosed in

England during the data collection period [3]. Further excluding patient records and NHS trusts with missing data meant this analysis included 62% of all potential cases. The analysed Audit data and HES dataset showed similar demographic characteristics (average age was 71.4 and 71.3 years, respectively, while the proportion of male patients was 67.2% and 66.3% respectively). The differences between the analysed and excluded audit patients were also small. Excluded audit patients were slightly younger on average (69.7 v 71.4 years, $p<0.001$) but did not differ by a statistically significant amount in terms of patient sex (male 69.2% v 67.2%, $p=0.06$) or location of tumour (stomach 29.6% v 30.8%, $p=0.27$).

Another limitation was the variation in estimated case ascertainment between networks. Sixteen networks submitted data on over 70% of expected cases, while two submitted less than 40% of cases. Excluding records due to poor data quality produced marginal changes in case-ascertainment for most networks, with it being reduced by less than 5% for 19 networks. Excluding the 10 NHS trusts because of poor route to diagnosis data affected six networks and reduced their case-ascertainment by between 11% and 42%. These exclusions could have biased the individual network rates if hospitals were selective in the patients submitted to the Audit and/or data completeness was related to particular patient characteristics. However, the routes to diagnosis within networks with high, medium and low case-ascertainment were not noticeably different, and selection bias is unlikely to explain the variation observed between networks. Among the nine networks that submitted over 80% of estimated cases and that had less than 5% of records excluded for incomplete data, the adjusted proportion of patients diagnosed after a GP referral ranged from 52% to 71%, while the adjusted proportion of patients diagnosed after emergency admission ranged from 9% to 30%.

A third limitation is that treatment intent was missing for 5% of the 14,102 patients. This might introduce bias in the estimated relationship between referral source and treatment intent but this is likely to be small compared to the size of the observed association.

Another limitation concerns the information available for risk-adjustment. Many factors can influence decisions about treatment intent and one-year survival, and there may be residual confounding caused by unmeasured variables such as the symptoms experienced at diagnosis [26]. However, the analysis included important prognostic factors such as age, comorbidity, performance status and stage of disease and residual confounding is unlikely to explain the association between the outcomes and referral source. To incorporate performance status and stage, the analysis used multiple imputation, which relies on the assumption that the data were "missing at random". This assumption seems plausible given the range of variables in the imputation model (see additional document). Finally, the effect of the risk-adjustment on the estimated network rates was comparatively small and it seems unlikely that the observed network variation was due to inadequate risk-adjustment.

Comparison with other studies

Various studies have examined the pathway to diagnosis, with many focusing on patients diagnosed after an urgent (2WW) GP referral. In a systematic review, Thorne et al [27] derived pooled data on 498 patients from seven studies conducted between 2003 and 2008, and estimated that 34% of patients with upper gastro-intestinal cancer were diagnosed after urgent (2WW) GP referral. An audit of cancer diagnosis in English primary care in 2009/10 [28] reported that the proportion of patients with oesophageal cancer (n=596) diagnosed after an urgent (2WW) GP referral and emergency presentation was 58% and 10% respectively; for stomach cancers

(n=319), the proportions were 40% and 21%, respectively. The national study using English Cancer Registry and routine health data [18] reported higher rates of emergency presentation (22% for oesophageal and 33% for stomach) and lower rates of urgent (2WW) GP referrals (34% for oesophageal and 23% for stomach).

Our results are generally comparable to these estimates. Compared to the results derived from routine national data [18], we found a higher proportion of diagnoses after urgent (2WW) GP referral, and a lower proportion after emergency admission. These differences could arise for various reasons. First, the audit may have suffered from potential under-reporting of patients diagnosed via particular pathways. Second, the two studies used different pathway categories and the "emergency admission" definition from the National Cancer dataset and the NCIN definition of emergency presentation may not entirely overlap. Finally, the studies had distinct methodologies. In deriving the results from the routine data, the researchers created eight routes to diagnosis by grouping 71 distinct combinations [18].

Few studies have examined the effect of the routes to diagnosis on outcomes for O-G cancer patients. The results of our study are consistent with the evidence that patients diagnosed after emergency have worse survival rates [16,18,29] but we are unaware of any previous study that found, for patients diagnosed after referral by another consultant or non-urgent GP referral, their risk-adjusted prognosis was not adversely affected.

The reasons for patients being diagnosed after emergency admission are currently unclear. Various explanations have been proposed [29-32]. One suggestion is that these patients have more aggressive forms of cancer than patients referred by GPs, or they were asymptomatic prior

to presenting at A&E. Other explanations are linked to factors delaying diagnosis. Such delays might be patient related (because the patients ignored their symptoms, did not wish to seek care or did not recognise the seriousness of their symptoms) or might be practitioner related (due to acid suppression treatment, previous negative tests, or initial mis-diagnosis) [32].

Implications for clinical practice and future research

Recent government policy in England has focussed attention on the importance of an efficient pathway to diagnosis by highlighting the worse survival rates for patients diagnosed after emergency presentation [17]. This study provides additional insight into this relationship. That patients diagnosed via this route are less likely to have a curative treatment plan compared to urgent (2WW) GP referrals arises in part because more patients have advanced disease. Higher rates of diagnosis after emergency admission were also associated with older patients, greater frailty, and more co-morbidity.

Further work is required to determine how the risk of emergency admission can be lowered for patients with these characteristics [30]. That the risk can be modified is implied by the variation between cancer networks in the proportion of patients diagnosed after emergency admission. The variation suggests the organisation of services and practices within some networks makes this less likely. The lessons to be learnt from these networks require investigation at a local level so that appropriate strategies can be devised.

This study also provides new information on outcomes for patients diagnosed after urgent (2WW) and non-urgent GP referrals The comparatively worse outcomes for patients referred urgently is consistent with fact that the alarm symptoms used by current referral guidelines are

associated with more advanced disease [12,13]. There was considerable variation between cancer networks in the proportion of patients referred urgently among all GP referrals. The reasons for this variation remain unknown but it may reflect the clinical uncertainty and debate about the utility of these alarm symptoms as criteria for referral. Further research is required on the symptom profiles of patients referred by GPs as well as causes of delays in diagnosis among O-G cancer patients.

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Author contributions

TP, DC, RH, SR conceived the study; TP, DC, RH, SR, JG, JvdM designed the study; TP and DC conducted the statistical analyses; TP and DC wrote the manuscript; RH, SR, JG, JvdM commented on and revised drafts; DC is guarantor.

Ethical approval

Under UK National Research Ethics Service guidance, this study constituted service evaluation and did not require ethics approval.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: support from Healthcare Quality Improvement Partnership (HQIP) for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work."

Table 1: Proportions of patients with oesophago-gastric cancer by the route to diagnosis.

				Route to diagnosis (%)			
		Patients	(%)	GP Referral	Emergency admission	Other hospital	p-value
All patients		14,102		66	16	17	
Tumour	Oesophagus	9,755	(69)	71	13	16	p<0.01
	Stomach	4,347	(31)	56	24	19	
Gender	Female	4,631	(33)	66	18	17	p=0.02
	Male	9,471	(67)	67	16	18	
Age (years)	Under 55	1,215	(9)	66	14	20	p<0.01
	55 to 64	2,567	(18)	72	11	17	
	65 to 74	4,093	(29)	69	13	19	
	75 to 84	4,465	(32)	65	18	17	
	85 & over	1,762	(12)	58	30	12	
Index of Multiple Deprivation	1 (Least)	2,498	(18)	70	14	16	p<0.01
	2	2,814	(20)	68	16	16	
	3	2,969	(21)	68	15	17	
	4	2,879	(20)	64	19	17	
	5 (Most)	2,942	(21)	62	18	20	
Comorbidities	0	7,870	(56)	70	14	16	p<0.01
	1	3,829	(27)	65	17	18	
	2	1,676	(12)	59	21	19	
	3 or more	727	(5)	54	25	21	
Performance Status	0	3,541	(25)	74	8	19	p<0.01
	1	2,838	(20)	70	12	18	
	2	1,926	(14)	63	20	18	
	3 or 4	1,812	(13)	48	36	16	
	Missing	3,985	(28)	67	16	16	
Pre-treatment Stage	1 or 2	2,543	(18)	64	13	22	p<0.01
	3	2,296	(16)	74	11	16	
	4	3,804	(27)	67	20	14	
	Unknown / missing	5,459	(39)	64	18	18	

Table 2: Relationship between route to diagnosis, curative treatment intent and 1-year survival among patients diagnosed with O-G cancer in English NHS trusts.

Referral Source	Patients	Patients with outcome (%)		Unadjusted odds ratio*	Adjusted odds ratio‡ (95%CI)	
Patients with curative intent						
GP referral: urgent	6,084	2,167	(36)	1	1	
GP referral: non-urgent	2,759	1,096	(40)	1.19	1.02	0.90 to 1.15
Emergency admission	2,178	359	(16)	0.36	0.62	0.52 to 0.74
Other hospital referral	2,326	1,059	(46)	1.51	1.38	1.21 to 1.58
All patients	13,347	4,681	(35)			
Patients who survive 1 year (%)						
GP referral: urgent	6,438	2,763	(43)	1	1	
GP referral: non-urgent	2,913	1,413	(49)	1.25	1.11	1.00 to 1.24
Emergency admission	2,311	617	(27)	0.48	0.78	0.68 to 0.89
Other hospital referral	2,440	1,288	(53)	1.49	1.33	1.18 to 1.50
All patients	14,102	6,081	(43)			

*Odds ratio with GP referral: urgent as the baseline category.

‡ Adjusted odds ratio estimated using multiple logistic regression, adjusting for patients' age group, sex, tumour site, stage, number of comorbidities, performance status and regional deprivation.

Figure 1: Proportion of patients referred after an emergency admission for the 30 English cancer networks, adjusted for patient age, sex, tumour site, comorbidities, performance status and regional deprivation

[Figure 1]

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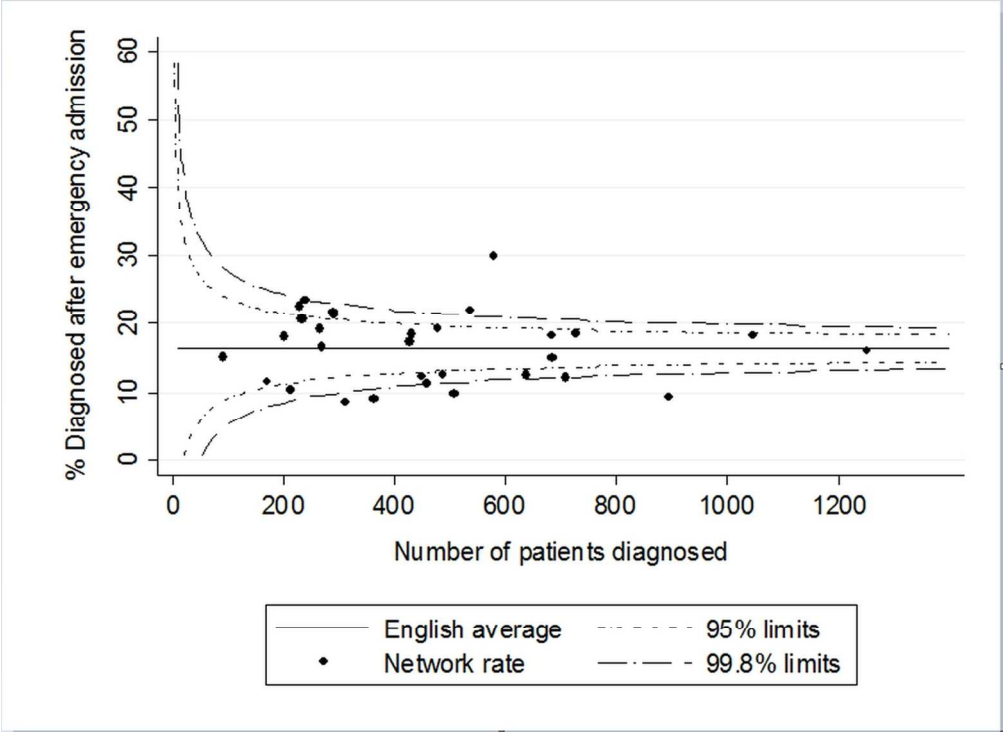

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SUPPLEMENTARY INFORMATION

Appendix 1: Information about patient characteristics and missing values and the effect of multiple-imputation on the estimates of logistic regression models

Table A1: Performance status at diagnosis across patient characteristics, before and after imputation

Patient characteristic		Performance status 0	1	2	3	4	Unknown
Tumour	Oesophagus	27%	20%	13%	9%	2%	29%
	Stomach	21%	20%	15%	14%	3%	27%
Gender	Female	21%	20%	15%	12%	3%	29%
	Male	27%	20%	13%	10%	2%	28%
Age (years)	Under 55	46%	17%	7%	4%	1%	26%
	55 to 64	42%	20%	8%	4%	1%	26%
	65 to 74	28%	24%	13%	8%	1%	27%
	75 to 84	15%	21%	18%	13%	3%	30%
	85 & over	6%	12%	17%	25%	6%	33%
Index of Multiple Deprivation	1 (Least)	28%	18%	11%	9%	2%	32%
	2	27%	19%	12%	9%	3%	30%
	3	26%	20%	13%	10%	2%	29%
	4	23%	22%	15%	11%	2%	26%
	5 (Most)	22%	21%	17%	13%	3%	25%
Comorbidities	0	28%	16%	9%	7%	1%	38%
	1	25%	26%	17%	12%	3%	17%
	2	17%	24%	22%	18%	4%	15%
	3 or more	9%	23%	25%	24%	4%	15%
Performance status distribution							
Before imputation (all)		25%	20%	14%	11%	2%	28%
Before imputation (known)		35%	28%	19%	15%	3%	.
Imputed values		35%	28%	19%	14%	3%	

Table A2: Pre-treatment (clinical) stage across patient characteristics, before and after imputation

Patient characteristic		Pre-treatment stage 1	2	3	4	Unknown
Tumour	Oesophagus	3%	14%	19%	26%	37%
	Stomach	11%	8%	11%	29%	42%
Gender	Female	6%	12%	15%	25%	42%
	Male	5%	13%	17%	28%	37%
Age (years)	Under 55	7%	11%	18%	33%	31%
	55 to 64	5%	14%	20%	29%	32%
	65 to 74	6%	14%	18%	27%	35%
	75 to 84	6%	12%	14%	27%	41%
	85 & over	5%	8%	10%	19%	57%
Index of Multiple Deprivation	1 (Least)	5%	12%	16%	28%	39%
	2	6%	13%	16%	26%	38%
	3	6%	13%	16%	26%	40%
	4	6%	13%	15%	27%	39%
	5 (Most)	6%	11%	17%	28%	38%
Comorbidities	0	5%	11%	15%	27%	42%
	1	6%	14%	19%	28%	34%
	2	7%	17%	17%	25%	34%
	3 or more	11%	15%	16%	24%	34%
Performance Status	0	8%	17%	24%	22%	29%
	1	6%	16%	19%	29%	30%
	2	5%	12%	16%	33%	34%
	3	5%	9%	10%	35%	41%
	4	4%	8%	5%	35%	47%
	Unknown	4%	8%	11%	23%	54%
Pre-treatment Stage distribution						
Before imputation (all)		6%	12%	16%	27%	39%
Before imputation (known)		9%	20%	27%	44%	
Imputed values		9%	20%	26%	45%	

Table A3: Results of logistic regression models for association between patient characteristics and odds of patients having a curative treatment plan

		Odds ratios of coefficients in regression model			
		Unadjusted	Basic model	Model with imputed data	Complete case analysis
Route to Diagnosis	Urgent GP referral	1	1	1	1
	Non-urgent GP referral	1.19	1.16	1.02	1.00
	Emergency admission	0.36	0.43	0.62	0.68
	Other hospital referral	1.51	1.53	1.38	1.30
Tumour	Oesophagus		1	1	1
	Stomach		1.19	1.34	1.63
Gender	Female		1	1	1
	Male		1.16	1.19	1.31
Age (years)	Under 55		1.21	1.14	1.37
	55 to 64		1.34	1.25	1.48
	65 to 74		1	1	1
	75 to 84		0.41	0.43	0.34
	85 & over		0.07	0.08	0.08
Index of Multiple Deprivation	1 (Least)		1	1	1
	2		1.10	1.09	1.12
	3		0.93	0.92	0.90
	4		0.96	0.98	1.06
	5 (Most)		0.82	0.91	0.93
No. of comorbidities			0.92	0.92	0.82
Performance Status	0			1	1
	1			0.56	0.49
	2			0.28	0.18
	3 or 4			0.10	0.03
Pre-treatment Stage	1			2.01	3.22
	2			1.62	2.23
	3			1	1
	4			0.15	0.04
Area under the curve			0.72	0.86	0.92

Table A4: Results of logistic regression models for association between patient characteristics and odds of patients surviving one year

		Odds ratios of coefficients in regression model			
		Unadjusted	Basic model	Model with imputed data	Complete case analysis
Route to Diagnosis	Urgent GP referral	1	1	1	1
	Non-urgent GP referral	1.25	1.23	1.11	1.12
	Emergency admission	0.48	0.55	0.78	0.85
	Other hospital referral	1.49	1.48	1.33	1.48
Tumour	Oesophagus		1	1	1
	Stomach		1.09	1.11	1.11
Gender	Female		1	1	1
	Male		1.03	1.01	0.98
Age (years)	Under 55		1.24	1.14	1.12
	55 to 64		1.29	1.18	1.16
	65 to 74		1	1	1
	75 to 84		0.58	0.68	0.66
	85 & over		0.34	0.47	0.53
Index of Multiple Deprivation	1 (Least)		1	1	1
	2		1.10	1.10	1.19
	3		1.06	1.10	1.11
	4		0.98	1.02	1.14
	5 (Most)		0.88	0.99	1.02
No. of comorbidities			1.01	1.03	1.02
Performance Status	0			1	1
	1			0.58	0.59
	2			0.34	0.33
	3 or 4			0.18	0.14
Pre-treatment Stage	1			2.92	3.37
	2			1.70	1.64
	3			1	1
	4			0.31	0.30
Area under the curve			0.65	0.79	0.80

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Cohort design in abstract.
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5-6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	n/a
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers.	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5*
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	Aimed to collect all cases in England
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-7
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	7
		(*d*) If applicable, explain how loss to follow-up was addressed	n/a
		(*e*) Describe any sensitivity analyses	n/a

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	n/a
		(c) Consider use of a flow diagram	Not warranted
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1 and appendix
		(b) Indicate number of participants with missing data for each variable of interest	Appendix
		(c) Summarise follow-up time (eg, average and total amount)	Table 2
Outcome data	15*	Report numbers of outcome events or summary measures over time	n/a
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Tables 1 and 2
		(*b*) Report category boundaries when continuous variables were categorized	Table 1
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Appendix
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-11
Generalisability	21	Discuss the generalisability (external validity) of the study results	11-13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.