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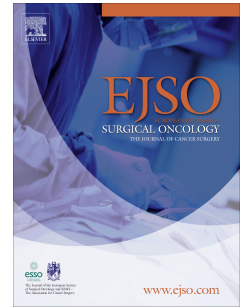
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ORIGINAL ARTICLE

**THE “TWO WEEK WAIT” REFERRAL PATHWAY ALLOWS PROMPT
TREATMENT BUT DOES NOT IMPROVE OUTCOME FOR PATIENTS
WITH OESOPHAGOGASTRIC CANCER**

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ABSTRACT

Introduction: The Two Week Wait Referral Service (2WW) has been implemented as a means of fast-tracking patients with suspected upper gastrointestinal cancers for endoscopy. Whether or not it impacts on the outcome of these patients is unclear. The aim of this study was to compare the outcome of patients referred through 2WW with that of patients with oesophago-gastric cancer identified through alternate referral pathways (routine, emergency).

Methods: The study population was 340 patients with oesophago-gastric carcinoma (gastric 154) diagnosed during the time period 01/2006-12/2007 at University Hospitals of Leicester NHS Trust. Data were collected prospectively by the MDT co-ordinator and analysed retrospectively.

Results: 135 of the 340 patients with oesophago-gastric cancer were diagnosed through the 2WW, 115 patients through routine referral pathways, and 90 patients were admitted on an emergency basis. Patients referred through 2WW had a median referral to 1st treatment time of 47 days (routine 79, emergency 28, $p < 0.001$ all group comparisons). The number of patients treated with potentially curative intent was 37 of 135 for the 2WW, 42 of 115 for the routine referrals and 10 of 90 for patients admitted as emergencies. The corresponding median survivals for the groups were 239 days (2WW), 405 days (routine) and 121 days (emergency), $p < 0.001$ (log rank).

Conclusions: Referral by 2WW resulted in more rapid treatment than routine referral but this did not translate into an improvement in survival. This suggests that the targeting of endoscopy to patients with alarm symptoms is flawed and a less selective approach should be promoted if curable cancers are to be detected.

Keywords: esophageal neoplasms; stomach neoplasms; survival; two-week wait

ACCEPTED MANUSCRIPT

INTRODUCTION

The Two Week Wait Referral Pathway was introduced into the United Kingdom in 2000 in order to fast-track patients with “alarm symptoms” to the appropriate diagnostic investigation.[1] This referral pathway ensures that patients with suspected cancers are seen by a specialist within two weeks of primary care consultation. The premise underpinning this referral system was two-fold, firstly, the assertion that earlier diagnosis would result in the diagnosis of earlier stage disease and secondly, that patient anxiety would be lessened. In spite of its nationwide application, surprisingly little has been reported supporting its use. The National Cancer Plan further stipulated targets of 31 days from decision to treat cancer to commencement of definitive treatment, and 62 days from primary care referral to commencement of definitive treatment.

The aim of the current study was to compare the outcome of patients with oesophago-gastric carcinoma in relation to their route of referral. This would either confirm or refute the hypothesis that the two week wait referral leads to an improved outcome for patients with oesophago-gastric carcinoma.

PATIENTS AND METHODS

Study population

The study population was 340 patients (222 male, 118 female) with gastric (n=154) or oesophageal cancer (n=186) referred through the gastro-oesophageal multi-disciplinary meeting at University Hospitals of Leicester NHS Trust between 1st January 2006 and 31st December 2007. Siewert type 1 and 2 adenocarcinomas of the gastro-oesophageal junction were classified as oesophageal in origin, while Siewert type 3 junctional adenocarcinomas were classified as gastric in origin. Patients with non-epithelial malignancy were excluded. Patients were categorised into one of the following three groups according to their route of referral to the hospital: emergency admission, routine referral (outpatient or open access endoscopy), or two-week wait referral.

Referral criteria

Referral criteria for the two-week wait pathway were according to the National Institute of Health and Clinical Excellence guidelines.[9] This advocates endoscopy for the “alarm symptoms” of dyspepsia, dysphagia, progressive unintentional weight loss, nausea and vomiting, epigastric mass in patients over the age of 55. Patients not satisfying these criteria are initially treated in primary care empirically with anti-secretory medication or *Helicobacter pylori* eradication therapy. Endoscopy is reserved for those with uncontrolled or progressive symptoms after two months of therapy.

Treatment protocols

Treatment protocols were as previously reported.[10] In short, the standard of care for physiologically fit patients with operable cancers was surgical resection alone for T1-2 N0 disease or neoadjuvant chemotherapy followed by surgical resection for T3 N0-1 disease. Patients with T3 N0-1 squamous carcinoma of the oesophagus suitable for radical therapy were given the choice of neoadjuvant chemotherapy and surgical resection or radical chemoradiotherapy.

Data collection and statistical methods

Patient information was retrieved from the prospectively maintained electronic database and analysed retrospectively, reporting outcome according to follow-up to 1st March 2010. Comparison of proportions was by χ^2 test and comparison of continuous data by the Mann-Whitney U-test or the Kruskal-Wallis test. Actuarial survival was estimated using the Kaplan-Meier method, with the log rank test for comparison. Significance was assumed at the 5% level.

RESULTS

Referral pathway and influence on survival

One hundred and thirty-five of the 340 patients with oesophago-gastric cancer were diagnosed through the two-week wait system, 115 patients were diagnosed through routine outpatient or open access endoscopy referral, and 90 patients were admitted on an emergency basis.

Table 1 summarises the demographic characteristics of these three groups of patients and their outcome. The overall median survival was 251 days (95% confidence interval 209-293). The median survival for the 251 patients treated with palliative intent was 178 days (95% confidence interval 135-221), compared to a median survival time of 736 days (95% confidence interval 537-935) for the 89 patients treated with curative intent (Figure 1), $X^2=69.3$, $p<0.001$.

Table 1 shows that patients referred through the two-week wait system had outcomes intermediate between those of patients referred routinely and those admitted as emergencies. This last group had the worst outcome of the three groups. They were older, had a higher frequency of metastatic disease, and had the poorest prognosis (Figure 2). Further, there was a higher proportion of gastric cancers and a lower proportion of UICC stages 1 and 2 disease among patients presenting as emergencies compared to the other groups.

31 day mortality

The 31 day mortality after endoscopic stenting was six of 56 patients, while among the 89 patients treated with curative intent (surgery +/- chemotherapy - 68 patients, chemoradiotherapy - 19 patients, endoscopic mucosal resection - two patients), there was one postoperative death.

Delays in the patient journey

Table 2 summarises the time intervals for each point of the patient journey. Patients referred through the two week wait pathway had significantly shorter delays compared to those referred through routine channels.

DISCUSSION

The principal study findings were that patients referred through the two week wait referral pathway were treated more promptly than those referred for routine outpatient clinic or open access endoscopy appointments, although this did not translate into an improved cancer survival.

Literature reporting on two-week wait referral pathway

Table 3 summarises the published literature on the two-week wait referral pathway for all cancer sites. There is surprisingly little information on patients with oesophago-gastric cancer. The table indicates that the cancer yield is low, a median of 10% and that the proportion of cancers identified by this pathway is likewise small, a median of 33%. Our data are in broad agreement with this, with 40% of cancers being identified via this route. The current study has not addressed the cancer detection rate of the two-week wait system, but the authors have previously reported this to be 3% in an analogous, but different cohort.[11] A large primary care study likewise reported a 3% prevalence of oesophagogastric cancer among those with alarm symptoms.[12]

Delays in diagnosis

Patients with cancer diagnosed through “routine” referral pathways experienced significantly longer delays than the other groups of patients, on average three months from initial referral to diagnosis. In spite of this, they had a better prognosis. These patients presented with symptoms indistinguishable from benign upper gastrointestinal pathology. In sharp contrast to this, patients presenting as emergencies fared poorly. This has been noted in previous reports.[13] This group of patients had a lower frequency of UICC stages 1 and 2 disease (15%) compared to the

other two groups (31-32%) and the high early cancer mortality in this group was striking. Further, gastric cancer more frequently presented on the emergency intake. This broadly reflected admission with the complications of upper gastrointestinal haemorrhage or the presence of an abdominal mass.

The Cancer Plan was set up with the premise that earlier diagnosis of cancer would lead to an improved outcome.[1] However, the evidence supporting a link between delay in diagnosis and poorer cancer outcome is weak.[14-25] The greatest number of studies examining diagnostic delays have been in patients with breast cancer. The majority of these studies have failed to identify an association between delay in diagnosis and prognosis. Further, these studies have shown that the majority of the delay occurs before the patient accesses the healthcare system rather than afterwards. Nonetheless, on ethical and humanistic grounds, there are compelling arguments to facilitate early diagnosis.

What this audit has not addressed nor have most of previous reports is the impact on quality of life of the two-week wait referral system. Intuitively, one would expect shorter diagnostic delays to cause less emotional and psychological distress to patients. Further studies should focus on these domains.

Conclusions

In conclusion, although it has provided prompt access to specialist services, the two-week wait referral pathway has not resulted in an improved survival compared to routine referral pathways. Further, the majority of oesophago-gastric cancers (60%) at our institution were diagnosed through other referral pathways. More liberal use of unselected endoscopy or screening, targeting the younger population, such as those aged 70 years or less, is likely the only way in which earlier diagnosis of oesophago-

gastric cancer and an improved outcome will be achieved. Although this will incur additional costs, these could be offset by a more pragmatic approach to investigation in patients not suitable for radical therapy. The median age of patients referred through the two-week wait system in our population was 75 years. Many of these patients would only be suitable for palliative treatments, irrespective of the cancer stage.

Table 1: Outcome according to route of patient referral

Referral pathway	Routine (n=115)	Two-week wait (n=135)	Emergency (n=90)
Median age in years (range)	71 (37-88) ^a	75 (40-96)	77 (36-97)
Younger than age 55: <i>n</i>	12	9	11
Sex (male:female)	77:38	83:52	62:28
Cancer site (oesophagus:stomach)	67:48	81:54	38:52 ^b
UICC stage (1:2:3:4) : <i>n</i>	11:25:40:36	6:35:53:37	2:10:32:37 ^c
Treated with curative intent: <i>n</i>	42	37	10 ^d
Death < 31 days of referral: <i>n</i>	6	6	23 ^e
Median survival in days (95% CI) ^f	405 (305-505)	239 (188-289)	121 (58-184)

For 16 bed bound patients treated palliatively, it was considered that staging investigations would not influence treatment and no cross-sectional imaging and formal UICC staging was obtained.

^dNote that in the results section, the median survival of these 89 patients (referral pathway: routine, 42; two-week wait, 37; emergency 10) treated with potentially curative intent was compared to the outcome of the remaining 251 patients treated with palliative intent (referral pathway: routine, 73; two-week wait, 98; emergency, 80).

^ap=0.002 vs. emergency & p=0.007 vs. 2WW; ^bp=0.03 vs. routine & p=0.01 vs. 2WW; ^cp=0.03 vs. routine & p=0.02 vs. 2WW; ^dp<0.001 vs. routine & p=0.005 vs. 2WW; ^ep<0.001 vs. routine & 2WW; ^fp<0.001

Table 2: Time intervals in days for each stage of the Care Pathway

^a Referral pathway	Routine (n=115)	Two-week wait (n=135)	Emergency (n=90)
<i>Department of Health Cancer Wait Targets</i>			
Referral to 1 st hospital visit	19 (0-76)	12 (5-20)	0 (0-5)
Referral to 1 st treatment	79 (19-160)	47 (20-88)	28 (9-117)
Decision to treat to 1 st treatment	9 (0-26)	6 (0-16)	2 (0-19)

Values shown are medians and 95% confidence intervals

^ap<0.001 for all comparisons, except 2WW decision to treat to 1st treatment time, p=0.001 vs. emergency & p=0.05 vs. routine

Note that those values shown are the unadjusted absolute time intervals. For the purposes of compliance with the cancer target waits, the time intervals are adjusted if the patient cancels or reschedules an appointment, defers admission to hospital, wishes to have a period of time to consider treatment options, or if the patient is unfit for treatment until additional intervention has been received (eg. nutritional supplementation).

Table 3: Summary of literature reporting on cancer detection rates among patients referred through two-week wait (2WW) pathway

	Cancer site	Time period	% of cancers diagnosed via 2WW	Prevalence of cancer in 2WW cohort
Khawaja[2]	Breast	1998-9		20%
Chohan[3]	Colon	2000-1	33%	14%
Glancy[4]	Colon	2000-1		10%
Shah[5]	Head & neck	2001-3	33%	6%
Spahos[6]	Oesophagogastric	2000-2	15%	6%
John[7]	Colon	2004-5	34%	2%
Potter[8]	Breast	1999-2005	73%	10%

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LEGEND FOR FIGURES

Figure 1: Plot of overall survival from date of diagnosis for patients treated according to curative (n=89) or palliative (n=251) intent.

Figure 2: Plot of overall survival from date of diagnosis for patients stratified by referral pathway into routine (n=115), open access (n=135) or emergency (n=90).

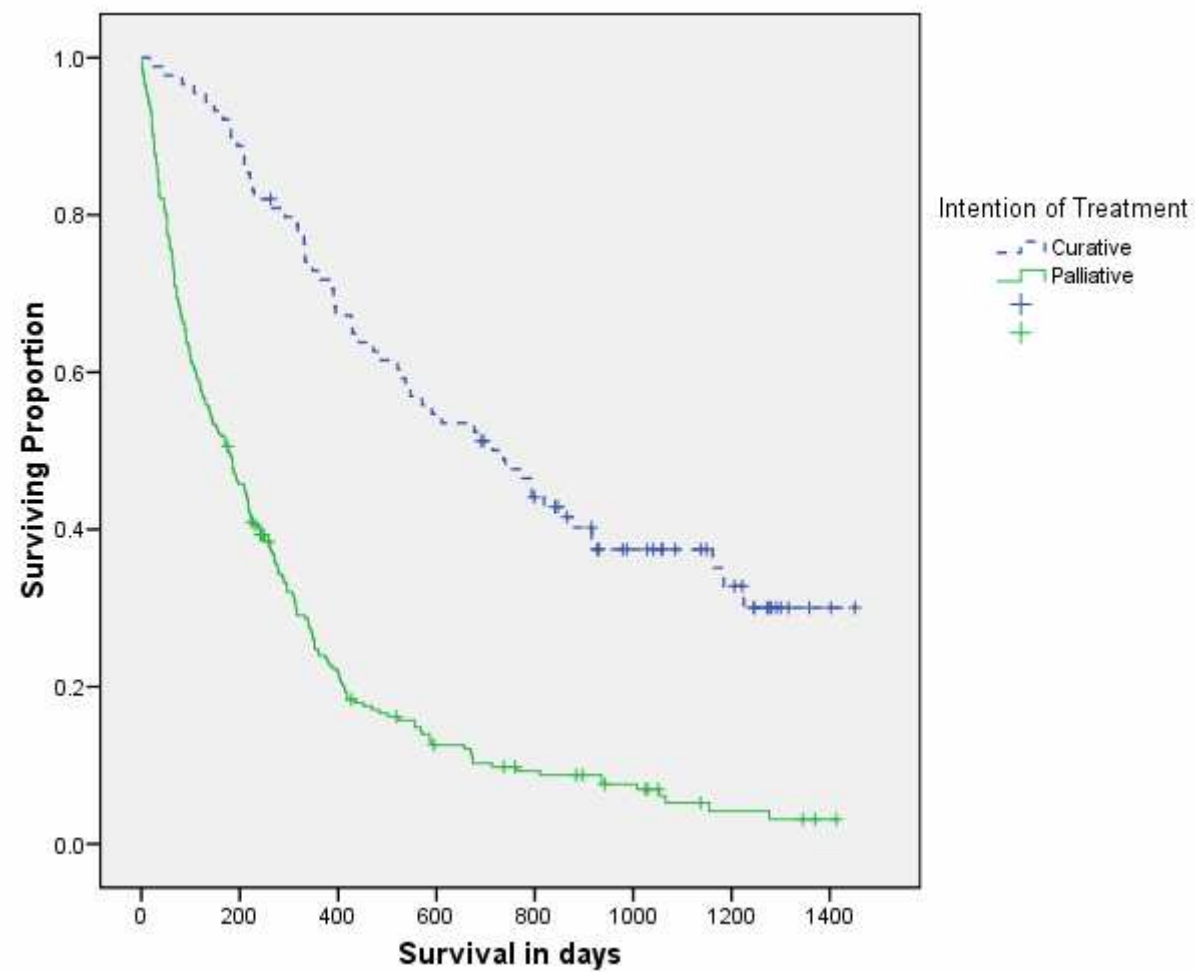


Figure 1

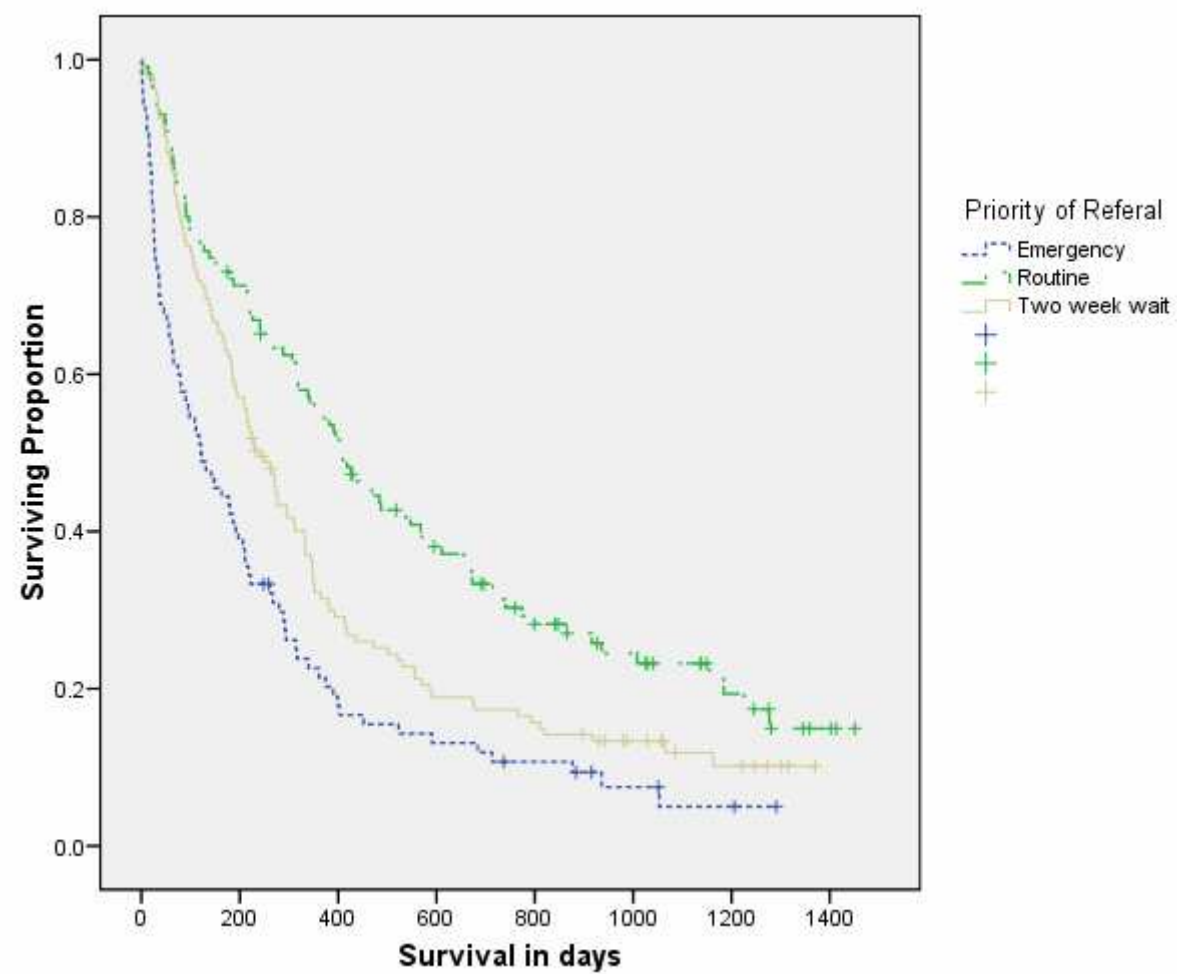


Figure 2