

Outcome of oesophagogastric carcinoma in young patients

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Summary

The survival of young patients (≤ 50 years of age) with carcinoma of the oesophagus or stomach has been reported to be poorer than that of their older counterparts. The aim of the current study was to review the outcome of such young patients with oesophagogastric cancer and to compare the outcome in patients with carcinoma of the oesophagus/cardia with patients with carcinoma of the more distal stomach. The study population was 50 patients. Tumour location was oesophagus/cardia ($n=33$) and gastric body/antrum ($n=17$). The most common presenting symptoms were weight loss (66%), epigastric pain (54%), dysphagia (50%), and heartburn (40%). Seventeen patients had experienced foregut symptoms for a period of ≥ 6 months. These patients were more likely to have symptoms of gastro-oesophageal reflux disease and to have received acid suppression therapy than patients with shorter symptom durations. Only 20 patients underwent a potentially curative resection, while 10 underwent open and close laparotomy. The overall median survival was 7 months and the 5-year survival was 8%. Multivariate analysis revealed that surgical resection and UICC stage were the only factors that significantly influenced survival. There was no difference in the survival of patients with proximally situated tumours compared to those with distally located tumours. Wide variations in clinical practice were seen between different surgeons. Consequently, a multidisciplinary team designed to manage all patients with oesophagogastric cancer according to nationally agreed protocols has been established in our hospital. Earlier diagnosis of these tumours is to be encouraged, even if this necessitates the more liberal use of endoscopy in the evaluation of young patients with persistent foregut symptoms.

Keywords: oesophagus; stomach; carcinoma; surgery; age-factors

In recent years, the incidence of adenocarcinoma of the oesophagus and cardia has increased in the Western hemisphere.^{1,2} Approximately 5% of patients with these cancers are aged 50 years or younger.³ Thus, the absolute number of young patients with oesoph-

agoastric carcinoma can be expected to increase. It has been reported that the survival of young patients with these tumours is poorer than that of their older counterparts,^{4,11} possibly because they have a more biologically aggressive disease.

The purpose of this study was to review the outcome of young patients (aged 50 years or less) with carcinoma of the oesophagus or stomach. Similarly, we wished to compare the outcome for patients with cancers of the oesophagus and cardia to the outcome for patients with carcinoma of the more distal stomach.

Patients and methods

The study population consisted of all patients aged 50 years or less at the time of diagnosis of carcinoma of the oesophagus or stomach at hospitals in the former region of South Glamorgan Health Authority, Wales, UK (now Bro-Taf Health Authority) during the period 1989-96. These comprised a University teaching hospital, two affiliated district general hospitals, and the regional oncology centre. Patients were identified from the Hospital Patient Episode Database which is a computerised registry of all hospital attendances that lists patient age and diagnosis according to the diagnostic coding of the International Classification of Diseases (ICD). During the first part of the study period classification was according to ICD-9 and during the remainder ICD-10. The case notes of those patients with the ICD-9 codes 150.1 to 151.9, and ICD-10 codes C15.1 to C16.9 were reviewed retrospectively. The following information was extracted: age, gender, presenting features, radiological imaging, endoscopy findings, surgical treatment and complications. Tumour location was determined from either the surgical resection specimen or from the endoscopy report. Outcome data for all patients was obtained from the Bro-Taf Death Registration Department.

Clinicopathologic staging was according to the American Joint Committee on Cancer/International Union Against Cancer (AJCC/UICC) classifications^{12,13} which utilise the TNM classification of oesophageal and gastric cancer (table 1). The TNM staging for both cancers are similar, with the T and M stages being identical. However, the N stage differs in that oesophageal carcinoma is classified simply as N0 (lymph node metastases absent) or N1 (lymph node metastases present), whilst for

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Table 1 AJCC/UICC classification of oesophago-gastric cancer^{12 13}

	Gastric cancer	Oesophageal cancer
Stage I	T1-2 N0 M0 or T1 N1 M0	T1 N0 M0
Stage II	T1 N2 M0 or T2 N1 M0 or T3 N0 M0	T2-3 N0 M0 or T1-2 N1 M0
Stage III	T2 N2 M0 or T3 N1-2 M0 or T4 N0-1 M0	T3 N1 M0 or T4 Any N M0
Stage IV	T4 N2 M0 or Any T Any N M1	Any T Any N M1

Table 2 Patient characteristics according to tumour location

	Oesophagus (n=17)	Cardia (n=16)	Stomach (n=17)
Male:female	15:2	15:1	8:9*
Weight loss	10 (59%)	13 (81%)	10 (59%)
Dysphagia	13 (76%)	9 (56%)	3 (17%)**
Epigastric pain	5 (29%)	9 (56%)	13 (76%)***
Heartburn	10 (59%)	6 (37%)	4 (24%)
Symptom duration ≥6 months	5 (29%)	6 (37%)	6 (35%)
Acid suppression therapy >1 month	6 (35%)	4 (25%)	7 (41%)
Poorly differentiated tumour	8 (47%)	9 (56%)	13 (76%)

* $\chi^2=12.0$, $p<0.01$; ** $\chi^2=12.1$, $p<0.01$; *** $\chi^2=7.6$, $p<0.05$.

gastric carcinoma, two node positive categories are specified. N1 defines lymph node metastases within 3 cm of the primary tumour whilst N2 defines lymph node metastases more than 3 cm from the primary tumour or the involvement of nodes along the left gastric, common hepatic, splenic or coeliac arteries. Patients undergoing surgery were staged by histological examination of the resected specimen or, in cases where resection was not undertaken, from the operative findings. In those patients who did not undergo surgery, staging was based upon computed tomography findings or upon abdominal ultrasonography. For the majority of these patients, M1 disease was identified by the presence of hepatic metastases or ascites.

Statistical analysis was performed by the chi-square test and Fisher's exact test for comparison of proportions, and the Mann-Whitney U-test for comparison of non-parametric data. Survival was estimated by the Kaplan-Meier method with univariate analysis by the log-rank test and multi-variate comparison by Cox's

proportional hazards model using forward variable selection. Significance was taken at the 5% level.

Results

STUDY POPULATION

Between 1 January 1989 and 31 December 1996, 901 patients were diagnosed with carcinoma of the oesophagus or stomach, 55 of whom (6%) were aged 50 years or less at the time of diagnosis. Complete data were available for 50 patients (38 men, 12 women) of median age 44 years (range 28–50). Primary tumour by site was as follows: oesophagus and gastric cardia: 33 patients (66%); gastric body and antrum: 17 patients (34%). Six patients with oesophageal cancer and one patient with carcinoma of the cardia had squamous cell carcinoma, while the remaining patients had adenocarcinoma. Thirty patients (60%) had poorly differentiated tumours (table 2).

PATIENT CHARACTERISTICS

The commonest presenting symptoms were weight loss ($n=33$, 66%), epigastric pain ($n=27$, 54%), dysphagia ($n=25$, 50%) and heartburn ($n=20$, 40%). The median duration of symptoms at presentation was 3 months (inter-quartile range 2–16 months). Seventeen patients (34%) had experienced foregut symptoms for a period of 6 months or more. These 17 patients had a median symptom duration of 30 months (9–162); none had undergone gastroscopy in the 12 months preceding diagnosis. Two patients were known to have Barrett's oesophagus, neither were in a surveillance programme. Seventeen patients (34%) had received acid suppression therapy, either H2-receptor blockers or proton-pump inhibitors, in the months preceding diagnosis (table 2).

Patients with symptoms of gastro-oesophageal reflux disease (heartburn or regurgitation) were symptomatic for significantly longer than those free of these symptoms (14 months (3–168) vs 3 months (2–5), $p<0.05$). Further, patients that had received acid suppression therapy were symptomatic for significantly longer than patients not receiving these medications (10.0 months (3.0–180.0) vs 3.0 months (2.0–6.7), $p<0.05$).

PRE-OPERATIVE IMAGING

Figure 1 shows the imaging which was performed pre-operatively and its relationship to the surgery performed.

SURGERY

The patients were treated by a total of 10 surgeons, most of whom would not consider themselves to be specialist upper gastrointestinal surgeons. Overall, only 20 patients (40%) underwent a potentially curative resection (table 3). Ten patients with oesophageal carcinoma underwent resection (8 R0, 2 R1) as follows: Ivor-Lewis procedure ($n=4$), left thoraco-abdominal resection ($n=4$) and three-stage oesophagectomy ($n=2$). Six patients with cardia carcinoma underwent left thoraco-

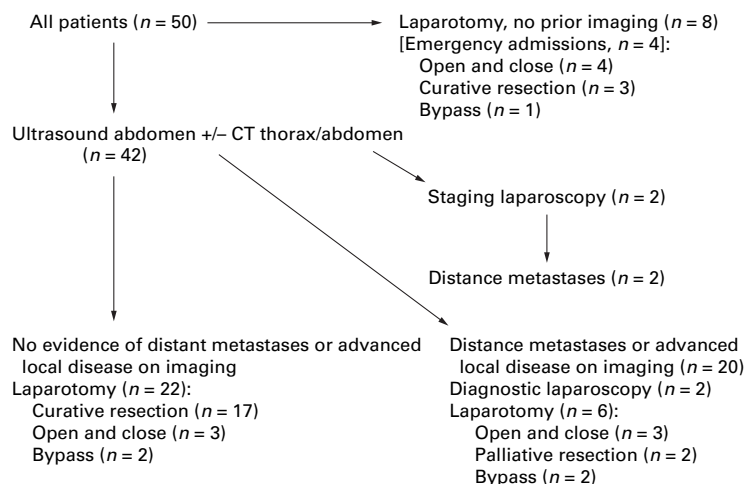


Figure 1 Schedule of patient management

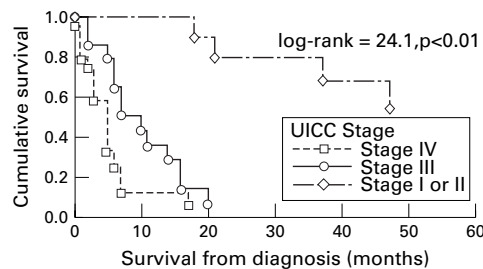
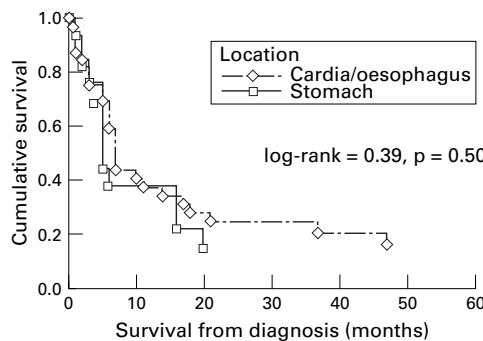
Table 3 Patient treatment according to tumour location

	Oesophagus (n=17)	Cardia (n=16)	Stomach (n=17)
R0/R1 resection	10	5	5
R2 resection or bypass procedure	0	3	3
Exploratory surgery. No resection	2	2	6
No operation	5	6	3

Table 4 Clinicopathologic stage according to tumour location

	Oesophagus & cardia (n=33)	Stomach (n=17)
Stages I & II	8 (24%)	3 (18%)
Stage III	11 (33%)	4 (24%)
Stage IV	14 (42%)	10 (59%)

abdominal resection (4 R0, 1 R1, 1 R2). Six patients with gastric carcinoma underwent resection (4 R0, 1 R1, 1 R2) as follows: Billroth I ($n=1$), Billroth II ($n=4$) and total gastrectomy ($n=1$). D2 lymphadenectomy was employed in only one patient in this series. Overall, 10/50 patients (20%) underwent an exploratory laparotomy without any surgical procedure being performed, seven of whom had peritoneal metastases and three had extensive local nodal disease. Of these 10 patients, four had not had any prior imaging of their tumour. Patients who were staged pre-operatively were less likely to undergo exploratory surgery without resection than patients who had no pre-operative staging (14% *vs* 50%, $p<0.05$, Fisher's exact test).

**Figure 2** Survival by UICC stage. Stage I&II *vs* III log-rank=16.4, $p<0.01$; stage I&II *vs* IV log-rank=17.9, $p<0.01$; stage III *vs* IV log-rank=4.1, $p<0.05$ **Figure 3** Survival by tumour location

STAGING

There was no significant difference between patients with carcinoma of the cardia/oesophagus and patients with carcinoma of the more distal stomach with respect to clinicopathologic stage (table 4). The duration of symptoms at the time of presentation showed no correlation with clinicopathologic stage, ie, patients who had been symptomatic for longer time periods were not more likely to have more advanced disease.

RADIOCHEMOTHERAPY

Six patients with carcinoma of the oesophagus and five patients with carcinoma of the cardia received pre-operative chemotherapy with epirubicin, cisplatin and 5-fluorouracil. Three of these patients also received pre-operative radiotherapy. Twelve patients received post-operative chemotherapy with regimens that included the agents epirubicin, cisplatin, 5-fluorouracil and mitomycin.

SURVIVAL

The overall median survival was 7 months (5.0–20.0) and the overall 1-year, 2-year and 5-year survivals were 34%, 20% and 8%, respectively. The influence of the following factors on patient survival was investigated: degree of tumour differentiation, histologic type (squamous cell carcinoma *vs* adenocarcinoma), administration of pre-operative or post-operative radiochemotherapy, surgical resection, gender, UICC stage, symptom duration, tumour location (cardia and oesophagus *vs* stomach) and prior use of acid suppression therapy. Univariate and multivariate analysis revealed that only surgical resection ($p<0.05$) and UICC stage ($p<0.05$) significantly influenced survival. Figure 2 shows patient survival according to UICC stage. The median survival of patients with stage III disease was 10.0 months (5.2–14.8) and for stage IV disease, it was 5.0 months (3.5–6.5). Patients with stage I and II disease had not reached their median survival at a median follow-up time of 37 months (21–89) with 7/11 patients alive. For these young patients, there was no significant difference in survival between patients with carcinoma of the cardia/oesophagus and patients with carcinoma of the gastric body/antrum, 7.0 months (5.9–8.1) *vs* 5.0 months (3.5–6.5), see figure 3.

Discussion

The high frequency of tumours occurring at the gastro-oesophageal junction and the high male:female ratio are in keeping with publications from other investigators reporting on patients of all ages.^{1,2} Blot *et al*² stated that, for the time period 1976–87, the rate of increase in incidence of adenocarcinoma of the oesophagus and gastric cardia had “surpassed that of any other cancer, outpacing increases in the incidence of skin melanoma, non-Hodgkin’s lymphoma, and cancers of the lung”.

One of the principal study findings was that survival of young patients with oesophageal or gastric carcinoma was highly dependent upon

Table 5 Literature review of oesophagogastric carcinoma in young patients

Reference	Time period	Country	Patient age (years)	Patients (n)	M/F ratio	5-yr survival (%)	Unselected or surgical bias
<i>Carcinoma stomach</i>							
15	1944-74	US	<40	73	0.92	20	Unselected
16	1946-76	US	≤35	37	0.4	5	Unselected
11	1970-79	Canada	≤40	31	1.24	22	Unselected
17	1948-83	US	≤35	38	1.0	3	Unselected
18	1980-85	South Africa	≤35	37	0.95	3	Unselected
5	1965-85	Japan	<30	38	0.9	33	Surgical
10	1965-83	Japan	<50	140 M 122 F	1.1	45 32	Surgical
<i>Carcinoma oesophagus</i>							
19	1965-88	Japan	<50	28	6.1	9.5	Surgical
9	1980-89	India	<50	87 M 69 F	1.3	16 35	Surgical
6	1968-78	China	≤35	76	3.2	27	Surgical
20	1983-92	UK	<50	47	1.8	16	Surgical
<i>Carcinoma oesophagus & stomach</i>							
Current series	1989-96	UK	≤50	50	3.2	8	Unselected

the clinicopathologic stage at presentation. Tumour stage and the performance of surgical resection were the only two factors that correlated with survival on multivariate analysis. Patients with stages I and II disease had yet to attain their median survival at a follow-up time of 37 months. This underscores the importance of an early diagnosis for these patients. In an attempt to promote the earlier diagnosis of upper gastrointestinal cancer, open access gastroscopy¹⁴ has been introduced into the UK. However, many units, including our own, impose age guidelines on the provision of open access gastroscopy to general practitioners, targeting specifically those over the age of 45 years. Thirty-two of the study patients (64%) were aged 45 years or less. Of concern, 17 (34%) of these young patients had experienced foregut symptoms for long periods of time at the time of diagnosis. In particular, the symptoms of gastro-oesophageal reflux disease were associated with significantly longer symptom durations at the time of diagnosis.

Review of the literature (table 5) reveals that the overall 5-year survival of 8% is in keeping with that reported by other investigators describing unselected series.^{11-15,18} Higher survivals were published by centres reporting only surgical patients.^{5,6,9,10,19,20}

This paper highlights several management issues. Firstly, some 10 surgeons were involved in the care of these patients, most of whom would not consider themselves specialist upper gastrointestinal surgeons. Further, 20% of patients underwent exploratory laparotomy, at which no resection was performed. This was a particular problem in patients who had not been staged pre-operatively. The high exploratory laparotomy rate in these young patients could be justified by the surgeons' intentions to do everything possible for the patient and their family. However, clearly open and close laparotomies do the patient no service.

One way forward under these circumstances is the establishment of a Calman style cancer unit²¹ for the treatment of these patients. In our own region we have established a multi-disciplinary team^{22,23} to manage all patients with oesophagogastric cancer. Since 1996 all patients with foregut cancers have been managed according to locally agreed protocols based on best clinical practice²⁴ in an attempt to optimise patient management.

In conclusion, up to a third of young patients with oesophagogastric cancer were symptomatic for long periods of time before a diagnosis was reached; this was especially so for those with a history of gastro-oesophageal reflux disease. In young patients there was a high frequency of cancers affecting the oesophagus and gastro-oesophageal junction, similar to the trend observed in older patients. Survival was highly correlated with clinicopathologic stage and the performance of a complete surgical resection. Earlier diagnosis of these tumours is to be encouraged even if this necessitates the more liberal use of endoscopic evaluation of young patients with persistent foregut symptoms. Management of young patients with oesophageal or gastric cancer should be according to established protocols in order to improve outcomes and avoid inappropriate exploratory surgery.

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