Original article

Adenocarcinomas of the distal oesophagus and gastric cardia are one clinical entity

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Background: Adenocarcinomas of the distal third of the oesophagus and the gastric cardia have similar characteristics but different staging criteria are being used. In the present study the question is addressed whether these tumours should be regarded and staged as one clinical entity.

Methods: From January 1987 to January 1997, 252 patients with an adenocarcinoma of the oesophagus (n = 111) or gastric cardia (n = 141) underwent transhiatal resection. Pathology, pathological tumour node metastasis (pTNM) stage and survival were analysed retrospectively, and a comparison was made between tumours of the oesophagus and gastric cardia.

Results: Barrett's epithelium was diagnosed in 54 per cent of oesophageal adenocarcinomas compared with 13 per cent of adenocarcinomas of the gastric cardia (P < 0·001). Oesophageal carcinomas had a more favourable pT stage, fewer positive locoregional lymph nodes ($pN_{1–2}$ 56 *versus* 62 per cent; P = 0·3), but more distant metastases accounted for by positive lymph nodes around the coeliac axis (pM_1 19 *versus* 4 per cent; P < 0·001). Five-year overall survival (26 *versus* 27 per cent; P = 0·9) and survival according to tumour stage were no different between the groups. Multivariate analysis showed that the location of the primary tumour was not an independent prognostic factor.

Conclusion: Adenocarcinomas of the distal oesophagus and gastric cardia should be regarded as one clinical entity. Uniform staging criteria for both malignancies are recommended.

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Introduction

According to the pathological tumour node metastasis (pTNM) criteria established by the Union Internacional Contra la Cancrum (UICC) and the American Joint Committee on Cancer, carcinoma of the gastric cardia is classified as gastric cancer; carcinoma of the distal 8 cm of the oesophagus, including the intra-abdominal oesophagus, is classified as oesophageal cancer[1,2]. However, several studies suggest common risk factors and a similar phenotype for adenocarcinomas arising from the distal oesophagus and gastric cardia[3–8]. Therefore, the distinction in classification seems rather artificial.

The present study questioned whether these tumours should be regarded and staged as two separate entities. Pathology, TNM stage and survival were studied in 252 patients who underwent resection for adenocarcinoma of the distal oesophagus or gastric cardia.

Patients and methods

From 1 January 1987 to 1 January 1997, 499 patients with an adenocarcinoma of the distal oesophagus or gastric cardia were evaluated at this hospital. After preoperative analysis 391 patients were operated on with curative intent. In 59 (15 per cent) of these, resection was not possible because of metastatic spread or local irresectability. Patients who received preoperative radiation and/or chemotherapy (n = 43), and those who underwent oesophageal resection and total gastrectomy reconstructed by colonic interposition (n = 25) or a transthoracic approach with two-field lymph node dissection (n = 12), were excluded from the study.

The remaining 252 patients underwent transhiatal oesophageal resection and the continuity of the gastrointestinal tract was restored by a gastric tube with cervical anastomosis. In all patients a standard dissection of the

perigastric, left gastric and coeliac nodes was performed. Macroscopic tumour clearance was aimed at in all cases but no extended lymph node dissection was done.

Pathology

The pathology records of all patients were reviewed. A tumour was considered to arise from the distal oesophagus when the epicentre of the mass was located in the tubular oesophagus extending from the tracheal bifurcation to the gastro-oesophageal junction including the intra-abdominal oesophagus, according to the TNM classification (International Classification of Diseases for Oncology C15·5). The tumour was considered to be cardiac when the epicentre was at the gastric cardia, defined as the area at and immediately below the gastro-oesophageal junction, extending approximately 2 cm downwards. It was preferable to rely on the muscular wall rather than on the mucosal Z-line to define the transition between oesophagus and stomach, because many tumours destroyed the cardiac mucosa. Tumours arising from the fundus or corpus of the stomach and infiltrating the gastric cardia or distal oesophagus were excluded.

Gross specimens were processed according to a standard laboratory protocol. Multiple 4-μm sections of the tumour and surrounding mucosa were taken and stained with haematoxylin and eosin. Barrett's epithelium was diagnosed when specific evidence of intestinal metaplasia was present. Lymph nodes were identified in the formalin-fixed specimens by the pathologist and subsequently evaluated for metastases.

Staging

Adenocarcinomas of the oesophagus and gastric cardia were classified according to the pTNM criteria for carcinoma of the oesophagus or stomach, established by the UICC in 1992[1].

Statistical analysis

Differences in patient and tumour characteristics and TNM classifications were assessed with the χ^2 test. Follow-up was until 1 January 1997 or until death if earlier. Overall survival rates were calculated according to the Kaplan–Meier method and included perioperative deaths. For calculation of intercurrent death-corrected survival, patients who died from causes unrelated to carcinoma were considered as withdrawn from the study at the moment of death. Differences in survival rates were assessed with the log rank test. The Cox proportional hazard model was used to evaluate various factors simultaneously. Statistical significance was set at the 5 per cent level.

Results

Some 252 patients who underwent transhiatal resection and stomach tube reconstruction for adenocarcinoma of the oesophagus or gastric cardia were included in the study. The in-hospital mortality rate was 4 per cent ($n = 9$); causes of death were anastomotic leak ($n = 3$), pneumonia and respiratory failure ($n = 3$), thrombosis of the basilar artery ($n = 1$), tracheo-oesophageal fistula ($n = 1$) and stomach tube–aortic fistula ($n = 1$).

In 111 patients the tumour originated from the distal oesophagus and in 141 patients it originated from the gastric cardia. In both groups the median age of the patients was 66 (range 33–82) years. Male : female ratios were 3·1 : 1 for patients with oesophageal tumours and 7·8 : 1 for those with gastric cardia tumours ($P = 0·007$).

Macroscopic appearances

The median diameter of oesophageal and gastric cardia carcinomas was 4 cm. Macroscopically, 53 oesophageal adenocarcinomas (48 per cent) were limited to the distal oesophagus and 58 tumours (52 per cent) involved the cardia with a median length of 1 cm. Thirty gastric cardia tumours (21 per cent) were limited to the cardia and 111 tumours (79 per cent) showed some infiltration of the distal oesophagus (median length 1·5 cm). A mean of 13 lymph nodes was dissected out of each specimen by the pathologist (mean 3·4 nodes positive for tumour microscopically).

Microscopy

Table 1 shows the microscopic characteristics of adenocarcinomas of the oesophagus and gastric cardia. Tumour-free resection margins were achieved in 67–74 per cent of the patients. Most carcinomas were moderately (G_2) or poorly (G_3) differentiated; signet ring cells were detected in 20 per cent of the oesophageal carcinomas and 19 per cent of gastric cardia carcinomas. There was microscopic evidence of Barrett's epithelium in 54 per cent of the oesophageal carcinomas and in 13 per cent of the gastric cardia carcinomas.

Tumour stage

Gastric cardia carcinomas were more likely to be found at an advanced T stage (*Table 2*). The frequency of metastatic locoregional lymph nodes was similar in the two groups.

Table 1 Microscopic characteristics according to location of primary tumour

Microscopic characteristics	Oesophagus (n = 111)	Gastric cardia (n = 141)	P
Residual tumour classification			0·2
R_0 (tumour-free margins)	74 (67)	105 (74)	
$R_{1–2}$ (tumour positive)	37 (33)	36 (26)	
Circumferential	32	30	
Distal plane of resection	1	3	
Proximal plane	3	3	
Both	1	0	
Grade of differentiation			0·6
G_1 (well)	5 (4)	5 (3)	
G_2 (moderate)	63 (57)	70 (50)	
G_3 (poor)	43 (39)	66 (47)	
Signet ring cells			0·9
Yes	22 (20)	27 (19)	
No	89 (80)	114 (81)	
Barrett's epithelium			<0·001
Yes	60 (54)	18 (13)	
No	51 (46)	123 (87)	

Values in parentheses are percentages

Table 2 Tumour node metastasis subclassification according to location of primary tumour

	Oesophagus (n = 111)	Gastric cardia (n = 141)	P
Tumour			0·03
T_{is}/T_1	18 (16)	9 (6)	
T_2	16 (14)	28 (20)	
$T_{3–4}$	77 (70)	104 (74)	
Nodes			0·3
N_0	49 (44)	53 (38)	
$N_{1–2}$	62 (56)	88 (62)	
Metastases			<0·001
M_0	90 (81)	136 (96)	
M_1	21 (19)	5 (4)	

Values in parentheses are percentages

Twenty-one patients (19 per cent) with adenocarcinoma of the oesophagus were classified as having metastatic disease: metastases in distant lymph nodes were detected in 19 patients, whereas two patients had visceral metastases. In 15 of 19 patients these nodes were located around the coeliac axis (N_2 for gastric carcinomas). Only three patients with gastric cardia carcinomas had positive distant nodes and two patients had visceral metastases.

Survival

Follow-up was complete for all 252 patients. Median follow-up was 19 (range 1–118) months. Median follow-up for patients who survived was 31 (range 3–118) months. The overall 3- and 5-year survival rates (n = 252) were 36 and 24 per cent respectively, with a median survival of 22 months. As only 16 patients died without suspected or proven recurrence of disease, the overall survival rate was similar to the intercurrent death-corrected 5-year survival rate (26 per cent). Therefore, only overall survival is considered further.

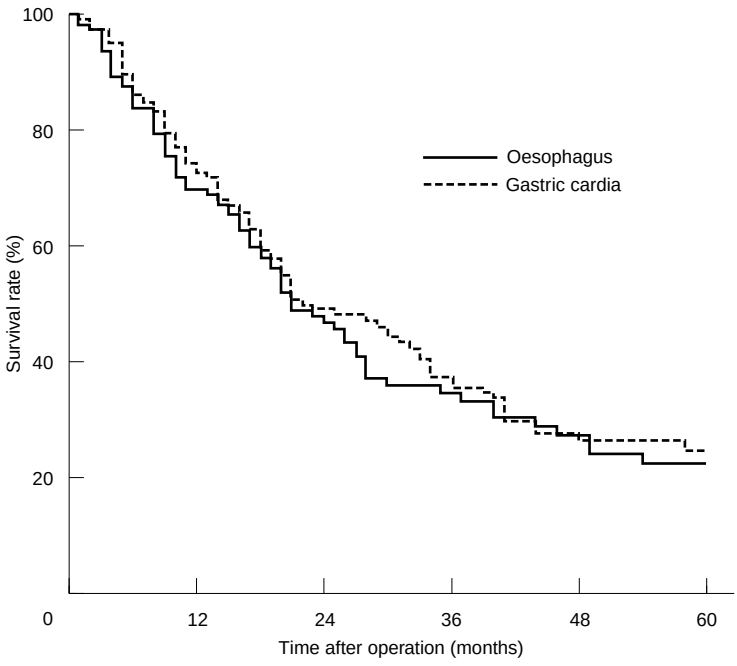
Table 3 Multivariate analysis regarding survival of various factors (Cox's regression)

Factor	No. of patients	Relative death rate	P
Age (years)			
< 50*	33	—	
50–60	47	1·2 (0·6–2·2)	0·6
61–70	109	1·8 (1·0–3·0)	0·03
> 71	63	2·3 (1·3–4·2)	0·004
T category			
$T_{is–1}$*	27	—	
T_2	44	2·1 (0·8–5·2)	0·1
$T_{3–4}$	181	2·4 (1·0–5·8)	0·04
N category			
N_0*	102	—	
$N_{1–2}$	150	2·2 (1·5–3·2)	< 0·001
M category			
M_0*	226	—	
M_1	26	1·7 (1·1–2·8)	0·03
Grade of differentiation			
$G_{1–2}$*	143	—	
G_3	109	1·4 (1·0–1·9)	0·05
Radicality			
R_0*	179	—	
$R_{1–2}$	73	1·8 (1·3–2·5)	0·01
Location of tumour			
Oesophagus*	111	—	
Gastric cardia	141	0·9 (0·7–1·3)	0·8

Values in parentheses are 95 per cent confidence intervals.
*Reference categories

Survival in relation to TNM subclassifications for the whole group was as follows: patients with T_{is}/T_1 tumours had a 5-year survival rate of 70 per cent, compared with 37 per cent for T_2 and 14 per cent for those with $T_{3–4}$ carcinomas. Patients with negative lymph nodes (N_0; n = 102) had a 5-year survival rate of 42 per cent, whereas those with positive lymph nodes (N_1 or N_2; n = 150) had a survival rate of 11 per cent (P < 0·0001). In the gastric cardia group the 5-year survival rate for patients with N_1 lymph nodes was not statistically different from that for patients with N_2 lymph nodes: 11 and 14 per cent respectively (P = 0·4). The 5-year survival rate for patients without metastasis (M_0) was 27 per cent compared with zero in patients with metastasis (M_1) (P < 0·0001).

Analysis for survival according to histopathological grading showed that there was a survival advantage for patients with well and moderately differentiated carcinomas ($G_{1–2}$ 31 per cent) over patients with poorly differentiated carcinomas (G_3 18 per cent) (P = 0·004). The 5-year survival rate of patients with positive resection margins



No. at risk

Total	252	175	100	62	42	25
Oesophagus	111	76	43	25	18	12
Gastric cardia	141	99	57	37	24	13

Fig. 1 Kaplan–Meier survival curves for patients with tumours located in the oesophagus and gastric cardia

(R_{1-2}) was 8 per cent and that of patients with tumour-free margins was 33 per cent ($P < 0{\cdot}0001$). When adenocarcinomas were classified as Barrett-related ($n = 78$) and non-Barrett-related ($n = 174$) carcinomas, no significant difference in survival was observed between the groups, with rates of 38 and 27 per cent respectively ($P = 0{\cdot}2$).

The 3- and 5-year survival rates for patients with oesophageal adenocarcinoma were 40 and 26 per cent respectively, and were similar to those for patients with an adenocarcinoma of the gastric cardia (38 and 27 per cent) ($P = 0{\cdot}9$; *Fig. 1*). Survival was also assessed after stratification of patients into the following groups: $T_{is-2}\,N_0\,M_0$, $T_{3-4}\,N_0\,M_0$, $T_{is-2}\,N_1\,M_0$ and $T_{3-4}\,N_1\,M_0$. No significant differences in 5-year survival rates between adenocarcinomas of the oesophagus and gastric cardia were observed within these groups.

Multivariate analysis showed that age, T, N and M category, radicality of resection and grade of differentiation were independent variables predicting survival. Location of the primary tumour was not an independent prognostic factor (*Table 3*).

Discussion

The incidence of adenocarcinomas of the oesophagus and gastric cardia has shown large increases in many populations examined[9,10]. This trend is in contrast to a decrease in the incidence of distal gastric adenocarcinomas and a relative stability of oesophageal squamous cell carcinomas. However, some studies have found only small rises in incidence or stable rates of gastric cardia cancers and non-parallel rates of oesophageal adenocarcinomas[11,12].

The present study showed that patients with gastric cardia carcinomas share characteristics in terms of age, sex distribution (predominance of men) and histological features with patients with adenocarcinomas of the distal oesophagus, as has been reported by others[6,13]. When gastric cardia carcinomas were compared with non-cardiac gastric carcinomas significant differences were found[14–16]. This suggests common risk factors and a similar phenotype for adenocarcinomas arising from the distal oesophagus and gastric cardia, and that gastric cardia tumours are more closely related to oesophageal adenocarcinomas than to distal gastric carcinomas.

It has been postulated that adenocarcinomas of the distal oesophagus arise from the Barrett metaplasia–dysplasia–carcinoma sequence, and that this might be true for all adenocarcinomas arising in the region of the lower oesophagus as well as the gastric cardia[7,17–19]. However, the risk of developing an adenocarcinoma in the intestinal metaplasia of the gastric cardia needs to be determined in

larger prospective studies[20,21]. In general, the length of Barrett's epithelium in patients with an adenocarcinoma of the cardia is shorter than that in patients with oesophageal adenocarcinoma[22,23]. The low incidence of Barrett's epithelium found in the present group of cardiac carcinomas may be explained by the fact that these shorter lengths may be easily overgrown by invasive tumour[24]. These findings are identical to those of Steup *et al.*[25] but contrast with reported incidences of Barrett's metaplasia in adenocarcinomas of the gastro-oesophageal junction and gastric cardia of approximately 40 per cent[23, 26]. A possible explanation involves the difference in definition of the gastric cardia. Furthermore, the specimens were examined for the presence of Barrett's epithelium by several pathologists over the years, based on haematoxylin and eosin staining only. Interobserver variability in diagnosing Barrett's epithelium and failure to use mucin staining, which increases the sensitivity for detection of intestinal metaplasia, could be responsible for the lower prevalence of Barrett's epithelium in the present group.

A significantly better survival for patients with adenocarcinomas associated with Barrett's epithelium *versus* non-Barrett-related carcinomas has been reported[27,28]. Significant differences in survival rates were not observed in this study but a tendency towards a better survival rate was noted for the Barrett-related carcinomas. The median diameter of the tumour was 3 cm for Barrett-related carcinomas and 4·5 cm for the non-Barrett-related carcinomas. This may indicate that the so-called non-Barrett-related carcinomas are simply late tumours that have overgrown the Barrett's oesophagus and therefore show a tendency towards a worse prognosis.

Location of the tumour was not an independent prognostic parameter for survival, and 3- and 5-year overall survival rates as well as survival according to tumour stage were similar for adenocarcinomas of the oesophagus and gastric cardia. Similar results have been reported by other groups[23,25,29–31]. However, a more favourable T and N stage was seen in patients with oesophageal carcinoma. This could be explained by the fact that carcinomas of the oesophagus give rise to symptoms of dysphagia earlier and are therefore detected at an earlier stage. Moreover, the higher prevalence of early stage (T_{is}/T_1) tumours in oesophageal cancer might reflect the fact that patients with a known Barrett's oesophagus were under endoscopic surveillance at this or the referring hospital. Ruol *et al.*[32] reported prevalence rates for early cancer (T_1) of the oesophagus and cardia of 27 and 4 per cent respectively, and also found no difference in overall survival between the groups. Apparently, at the time of diagnosis cardiac tumours are at a more advanced stage of disease but this has no impact on survival.

At this institution carcinomas of the gastric cardia and the distal oesophagus are mostly treated as one clinical entity, by subtotal oesophagectomy and proximal gastrectomy. Total gastrectomy with oesophagojejunostomy for 'true' cardiac cancer not infiltrating the oesophagus, as favoured by others[33–35], is not used because of the higher risk of positive resection margins. The majority of the patients with a positive plane of resection showed involvement of the circumferential plane and only five patients (three patients with gastric cardia carcinomas) had involvement of the distal resection margin in this series. Closer analysis of the seven patients with involvement of the proximal resection plane in the neck revealed that these were all poorly differentiated carcinomas with submucosal satellite lesions infiltrating the middle and upper oesophagus.

Adenocarcinomas with their epicentre in the distal oesophagus are regarded as oesophageal carcinoma and regional lymph nodes for these carcinomas are the mediastinal and perigastric nodes, excluding the coeliac nodes. Adenocarcinomas with their epicentre at or just distal to the gastro-oesophageal junction are regarded as gastric carcinomas; regional lymph nodes are the perigastric nodes, nodes along the lesser and greater curvature (N_1 less than 3 cm and N_2 more than 3 cm from the edge of the primary tumour) and the nodes along the left gastric, common hepatic, splenic and coeliac arteries (N_2). In the individual patient assignment of the primary tumour to one of the two locations is artificial, so the analysis of lymph nodes is biased. Steup *et al.*[25] reported that, when carcinomas of the gastro-oesophageal junction were staged as oesophageal carcinomas compared with staging as gastric cancer, no major difference was seen between the two staging modalities either in overall survival or in survival by stage. Another staging system currently proposed for oesophageal carcinomas is the modified Skinner classification based on the wall node metastases (WNM) concept[36,37]. Carcinomas of the cardia are also included in this classification because the surgical approach to such lesions is similar; a comparison of staging criteria for oesophageal and gastric cancer showed no difference in the staging results[29]. In the present study 15 of 21 patients with an adenocarcinoma of the oesophagus had positive lymph nodes around the coeliac axis and were staged as M_1, whereas these would be N_2 nodes in cases of gastric cardia cancer. Therefore, these data support a classification in which involved lymph nodes resected by standard lymphadenectomy are all considered as loco-regional lymph nodes for adenocarcinomas of the distal oesophagus as well the gastric cardia, and both carcinomas are regarded as one entity.

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