4. CLINICAL PROGNOSTIC FACTORS IN GASTRIC AND GASTRO-OESOPHAGEAL CANCER

4.1 INTRODUCTION

National audits of upper gastrointestinal cancer surgery and outcome have been performed in Scotland (SAGOC 2002) and Wales (Pye et al. 2001). The Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland have recently published their second database report summarising operative treatment in 19 hospitals in the UK over a 12 month period (AUGIS 2004). In addition, the ASCOT (Assessment of Stomach and Oesophageal Cancer Outcomes and Treatment) group have also published details of mortality and morbidity following oesophagogastric surgery (McCulloch et al. 2003). The main aims of these studies were to:

- provide a global overview of patient volume and to gather information about local referral patterns to aid future service provision
- assess the changes in tumour location and histological diagnosis to compare with other epidemiological studies showing an alteration in disease site location
- measure outcome factors, such as post-operative mortality, complication rates and to assess prognostic factors for survival
- provide educational benefit by discussing the outcome, activity and audit process and to aid in local clinician appraisal
- provide firm evidence for planning appropriate service configuration and resource allocation with the overall aim to of securing and improving the quality of care of upper gastrointestinal cancer patients
- form a strong foundation for successful clinical research

It is important to perform audits of upper gastrointestinal cancer service provision for the reasons highlighted above. Although institutional audits may have inherent biases that reflect patient referral patterns, diagnostic imaging resources, treatment availability and consultant preferences, they also provide useful information. This may be of value

not only to clinicians, but also to managers, patients and other people involved in cancer care provision.

Table 4.1 Aims of several recent institutional or regional audits of upper gastrointestinal cancer performed in the UK.

Institution	Cancer type	Aim	Reference
Western Infirmary, Glasgow	Gastric cancer	Should general surgeons treat gastric cancer?	(McCulloch 1994)
Fazakerley Hospital, UK	Gastric cancer	Assess the learning curve for D2 gastrectomy in a UK hospital	(Parikh et al. 1996)
Worthing & Southlands Hospitals NHS Trust	Oesophageal cancer	Audit results of oesophageal surgery in a district general hospital	(Dickson et al. 2001)
Royal Gwent Hospital	Gastric and oesophageal cancer	To assess the volume of work generated by one consultant managing all the upper gastrointestinal malignancy in a district general hospital	(Edwards et al. 2001)
South and West England	Gastric and oesophageal cancer	To evaluate specialization in NHS cancer care, volume-outcome relationships were examined	(Bachmann et al. 2002)
West Midlands	Oesophageal and gastro-oesophageal cancer	To explore the relationship between annual workload and outcome following resection for carcinoma of the oesophagus and cardia	(Gillison et al. 2002)
Royal Bournemouth Hospital	Oesophageal cancer	To assess the early impact of centralisation of oesophageal cancer surgery services	(Branagan et al. 2004)
Queen Elizabeth Hospital, Birmingham	Gastric cancer	To examine trends in the treatment of gastric cancer over 20 years in a UK hospital	(Desai et al. 2004)

Several institutional and regional studies have also been performed in the UK; generally with more specific aims (Table 4.1). Although the goals of this Chapter were roughly similar to other audits, the principal aim was to establish a large database of

patients with gastric and GOJ adenocarcinoma treated with surgery which would provide the framework to assess molecular markers of prognosis. Although there are a wide variety of potential molecular markers of prognosis (Table 1.13), none have entered routine clinical practice. To be established as clinically useful, molecular markers need to be evaluated within the context of established clinico-pathological prognostic parameters (McShane et al. 2005). Ideally, they should be independent predictors of prognosis on a multivariate analysis.

Many authors consider gastric and GOJ adenocarcinoma represent different disease entities. They appear to have differing clinico-pathological, survival and molecular characteristics. However, very few comparative studies have been carried out in the UK. Therefore, an additional aim of this chapter was to assess the differences in clinico-pathological characteristics and survival between gastric and gastro-oesophageal junctional tumours. To achieve these aims a large database of patients with gastric and GOJ adenocarcinoma was constructed and the results analysed.

4.2 Aims

- To set up a large retrospective database of patients with gastric and GOJ adenocarcinoma who were treated with primary surgical resection at the South Manchester University Hospitals NHS Trust.
- To audit the patients' presenting symptoms, diagnostic investigations, surgical and oncology treatment, pathological details, morbidity and mortality.
- To analyse relevant clinico-pathological prognostic factors as a preliminary exercise prior to using the database for further immunohistochemical prognostic factor analysis.
- To compare the clinico-pathological and survival differences between gastric and GOJ tumours.

4.3 Results

4.3.1 Summary of patients

This chapter details 251 patients who underwent surgery for gastric or gastro-oesophageal adenocarcinoma at the South Manchester University Hospitals NHS Trust. The inclusion and exclusion criteria for this cohort are detailed in Chapter 2 (Section 2.4). Most patients were male and there was a strong predominance of GOJ tumours (Figure 4.1). Table 4.2 details the clinico-pathological characteristics of the patients. There were 186 males and 65 females. There were 151 GOJ adenocarcinomas and 100 gastric adenocarcinomas. The majority of junctional tumours were Siewert Type 2 tumours (n=103). Most patients had relatively advanced tumour characteristics: the majority had T3 tumours, lymph node metastases, high overall TNM stages and moderate-poorly differentiated histology.

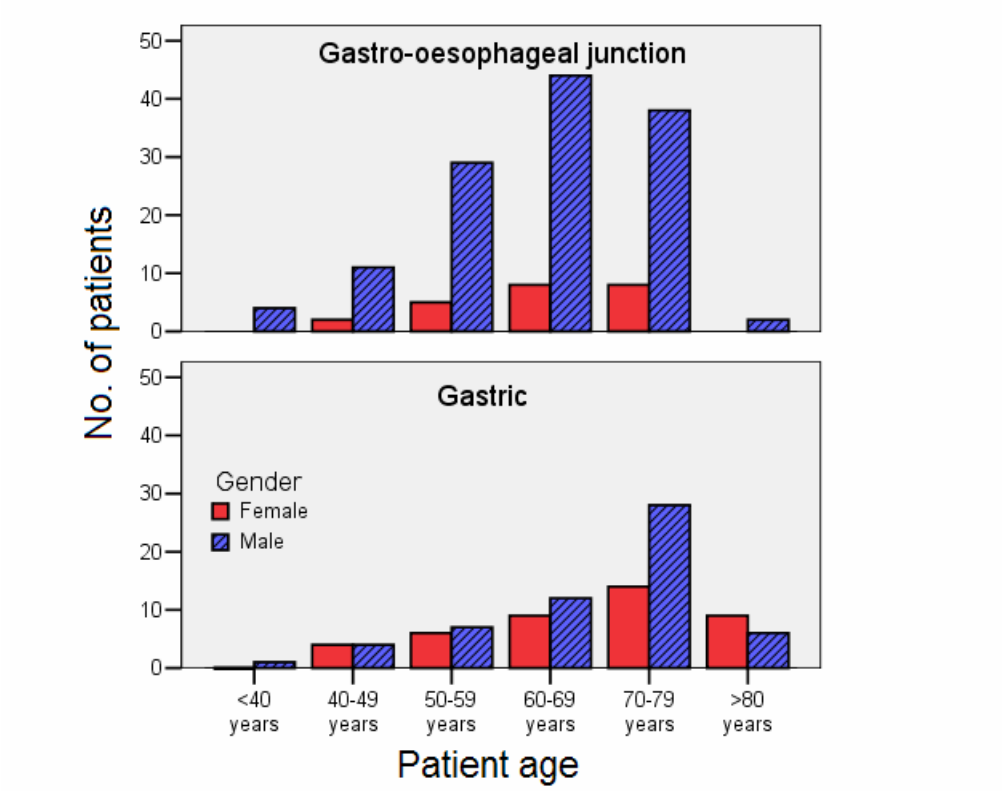

Figure 4.1 Distribution of patient age and gender by tumour sub-site

Table 4.2 Clinico-pathological characteristics of 251 patients with gastric or GOJ adenocarcinoma

Characteristic		**N**	**%**
Gender	Male	186	74.1
	Female	65	25.9
Age	<68 yrs	127	50.6
	≥68 yrs	124	49.4
Tumour location	Siewert Type I	22	14.6
	Siewert Type II	103	68.2
	Siewert Type III	26	17.2
	Total gastro-oesophageal junction	151	60.2
	Non-cardia gastric adenocarcinoma	100	39.8
T Stage	T0 (in-situ)	3	1.2
	T1	23	9.2
	T2	84	33.5
	T3	135	53.8
	T4	6	2.4
N Stage*	N0	77	30.9
	N1	136	54.6
	N2	29	11.6
	N3	7	2.8
M Stage	M0	247	98.4
	M1	4	1.6
Overall TNM Stage	Stage 0	3	1.2
	Stage 1	52	20.7
	Stage 2	75	29.9
	Stage 3	107	42.6
	Stage 4	14	5.6
Differentiation*	Well	23	9.2
	Moderate	103	41.2
	Poor	124	49.6
Lauren type*	Diffuse	111	46.3
	Intestinal	112	46.7
	Mixed	17	7.1

*Missing values: differentiation (n=1), Lauren category (n=11) and N stage (n=2)

4.3.2 Presenting symptoms and diagnosis

The presenting symptoms of patients with gastric and GOJ tumours are detailed in Figures 4.2 and 4.3. As expected most patients with GOJ tumours presented with dysphagia. Other common symptoms were weight loss, dyspepsia and GORD. Only one patient was diagnosed during surveillance for Barrett's oesophagus in this group. Patients with gastric cancer commonly presented with dyspepsia, anaemia, weight loss or epigastric pain. The vast majority of patients underwent upper gastrointestinal endoscopy as their first line diagnostic investigation (Table 4.3); some after initial barium examination. A minority of patients only had a barium meal (n=9).

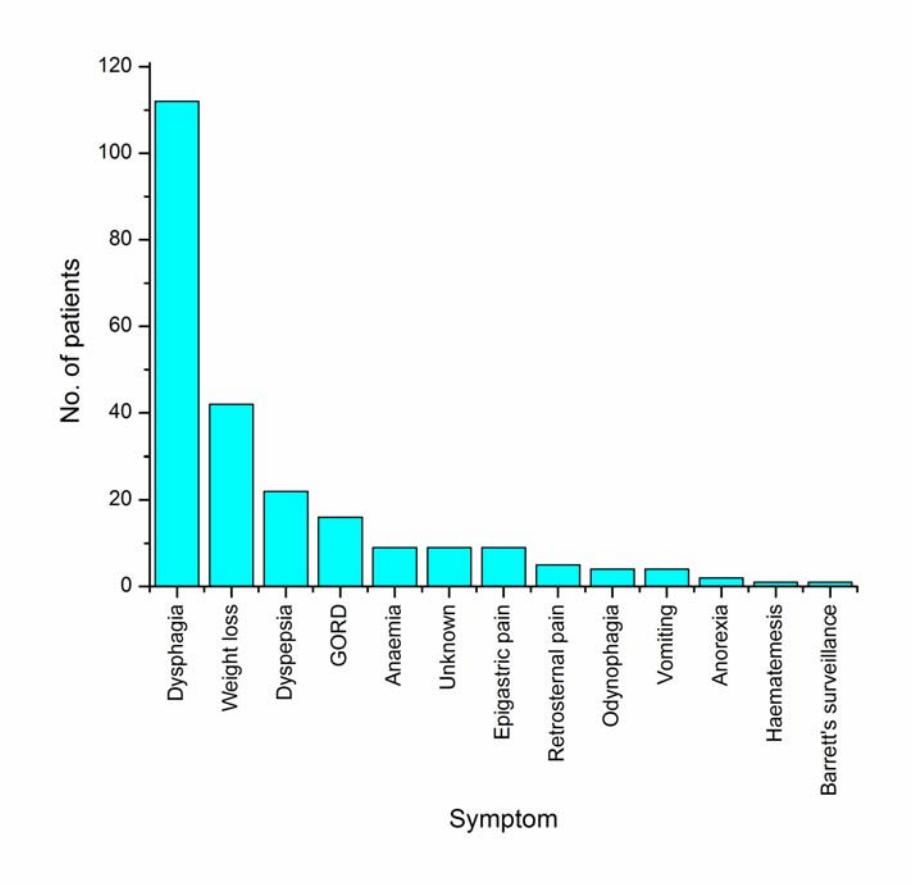

Figure 4.2 Presenting symptoms of 151 patients with gastro-oesophageal junction adenocarcinoma

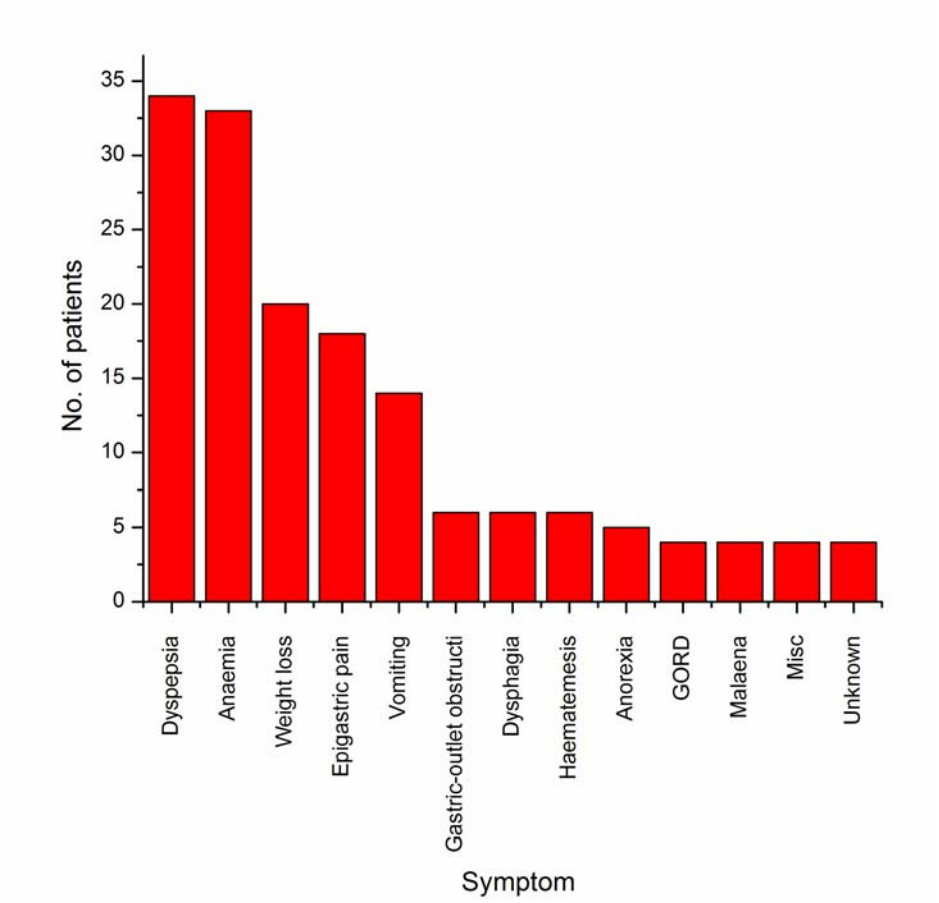

Figure 4.3 Presenting symptoms of 100 patients with gastric adenocarcinoma

Table 4.3 Method of diagnosis

Method of diagnosis	No.	%
OGD and biopsy	223	88.1
Barium meal	9	3.6
Both	6	2.4
Unknown	13	5.2

OGD = oesophago-gastro-duodenoscopy

4.3.3 Treatment

Trends in the surgical speciality treating patients with oesophagogastric cancer at SMUHT

Table 4.4 details the surgical speciality of the consultant surgeon performing the surgical resection according to tumour location.

Table 4.4 Surgical specialty of the consultant surgeon performing resection for patients with gastric and GOJ adenocarcinoma

Tumour location	Surgeon specialty	n	%
GOJ (n=151)	Cardiothoracic	91	60.3
	General surgery with upper GI interest	50	33.1
	General surgery	10	6.6
Gastric (n=100)	General surgery with upper GI interest	68	68
	General surgery	32	32

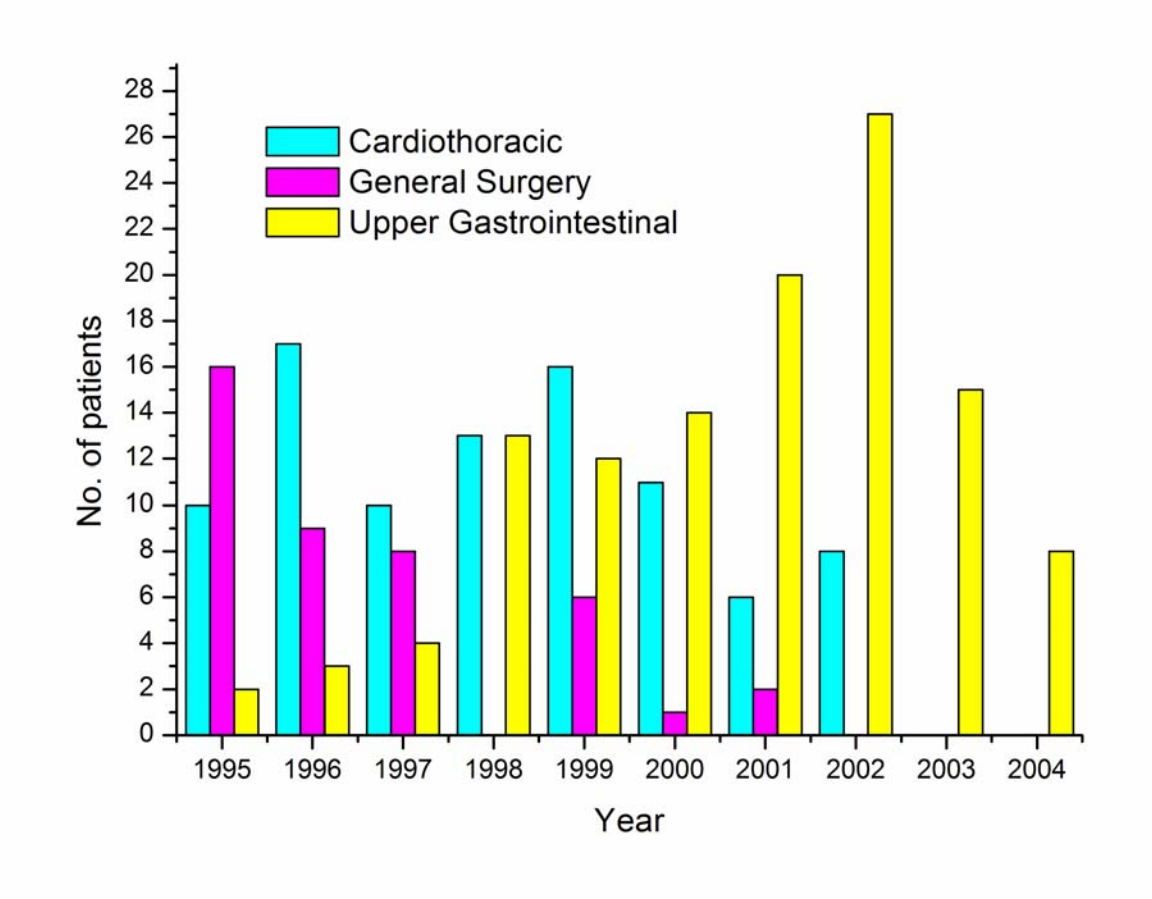

Figure 4.4 Consultant surgeon speciality operating on 251 patients with gastro-oesophageal junction and gastric adenocarcinoma at South Manchester University Hospitals NHS Trust between 1995 and 2004

Seventeen surgeons performed the surgical resections in this cohort of patients. The operations performed per surgeon ranged from one to 52, with a median of eight resections. The surgical specialities performing these resections changed over time (Figure 4.4). From 1995 to 2001 general surgeons performed less upper gastrointestinal surgery (this was mainly gastric surgery). In 2002 the cardiothoracic surgeons stopped performing oesophagogastric surgery at the SMUHT. Since 1998 there has been an increasing trend for specialist upper gastrointestinal surgeons to perform oesophagogastric surgery (Figure 4.4).

Details of neo-adjuvant treatment

No patient with gastric adenocarcinoma received neo-adjuvant therapy. Thirty-one patients with GOJ adenocarcinoma received neo-adjuvant therapy (Table 4.5); this mainly consisted of 5-flurouracil and cisplatin given for 2 cycles pre-operatively as performed in the MRC OEO2 trial (MRC 2002). Other regimes that were occasionally used are detailed in Table 4.5. Two of the patients received novel palliative chemotherapy for laparoscopically identified metastatic disease. Although it is not standard management to resect these patients, they had an almost complete regression of disease at re-staging after completing treatment and were therefore offered surgical resection.

Table 4.5 The types of neo-adjuvant therapy given to patients with gastro-oesophageal junctional adenocarcinoma

Regime	Treatment	No. of patients	Reference
MRC OEO2*	5-flurouracil and cisplatin	24	(MRC 2002)
MRC MAGIC	Epirubicin, cisplatin and 5-flurouracil	4	(Cunningham et al. 2005a)
REAL 2†	Epirubicin, oxaliplatin and capectitabine	1	(Sumpter et al. 2005)
SP1049C†	Doxorubicin and two non-ionic pluronic block copolymers	1	(Danson et al. 2004)
Other‡	Radiotherapy and CDDP/FU	1	(Herskovic et al. 1992)
Total	**-**	**31**	**-**

*16 were treated within the confines of the trial; the rest had the same regime but outside the trial; 23 patients completed all 2 cycles.
†These two patients had advanced disease with peritoneal and omental metastases but after a complete regression of disease on restaging were put forward for surgery.
‡This patient commenced treatment abroad.

Surgical treatment

The surgical treatment according to tumour location is shown in Table 4.6. Most patients with gastric cancer underwent either partial or total gastrectomy. Six patients had undergone previous partial gastrectomy many years ago for benign gastric ulcers and these patients underwent completion or stump gastrectomy.

The surgical resection favoured by the cardiothoracic surgeons for gastro-oesophageal tumours was a left thoraco-abdominal oesophagogastrectomy. As they preformed most of the surgery prior to 2002, this was the most common resectional operation for these tumours. A right sided oesophagogastrectomy (Ivor-Lewis) was the preferred technique for upper gastrointestinal surgeons and for patients with tumours extending high into the oesophagus. Patients with GOJ tumours were treated using a range of operative approaches, including proximal gastrectomy, total gastrectomy and distal oesophagectomy and oesophagogastrectomy. Twenty-nine patients underwent additional splenectomy and seven patients had combined distal pancreatectomy and splenectomy.

Table 4.6 Primary operative procedure performed together with any additional surgical resection (n=251)

Operation type	Siewert type (n=151)			Non-cardia (n=100)	Total (n=251)
	I (n=22)	II (n=103)	III (n=26)		
Completion gastrectomy	-	-	-	6	6
Proximal gastrectomy	-	-	4	-	4
Partial or subtotal gastrectomy	-	-	-	53	53
Total gastrectomy ± distal oesophagectomy	-	2	10	41	53
Ivor-lewis oesophagogastrectomy	10	28	-	-	38
Left thoraco-abdominal oesophago-gastrectomy	12	73	12	-	97
No additional resection	21	95	18	81	215
Additional splenectomy*	1	6	7	15	29
Distal pancreatectomy and splenectomy	0	2	1	4	7

*10 cases were for iatrogenic splenic injury

Adjuvant treatment

Adjuvant therapy was given to 16 patients. This was principally for resection margin involvement or extensive lymph node metastases. Seven of these patients were given MAYO style post-operative chemo-radiotherapy (Macdonald et al. 2001). Three patients completed the MAGIC protocol of 3 additional cycles of ECF (Cunningham et al. 2005a). Two patients were treated with other forms of chemotherapy: MCF (mitomycin, cisplatin and 5-fluorouracil) or cisplatin and 5-fluorouracil. In addition, three patients were given post-operative radical radiotherapy.

4.3.4 Involvement of the surgical resection margins

Table 4.7 summarises the details regarding involvement of the surgical resection margins. There was proximal resection margin involvement in 14% of cases and distal resection margin involvement in 8% of cases. CRM status was only available for Type 1 and 2 GOJ tumours and was found in 38%.

Table 4.7 Involvement of the each surgical resection margin in each specimen

	GOJ tumours (n=151)		**Gastric tumours (n=100)**	
	Involved*	**Not involved**	**Involved***	**Not involved**
PRM	20 (13.2)	131 (86.8)	14 (14)	86 (86)
DRM	11 (7.2)	140 (92.8)	9 (9)	91 (91)
CRM†	48 (37.8)	79 (62.2)	N/A	N/A

*Involvement was defined as microscopic tumour cells within 1 mm of the margin; †Does not apply to Siewert type III (n=24) GOJ tumours; PRM = proximal resection margin; DRM = distal resection margin; CRM = circumferential resection margin; Values in parenthesis are percentages; N/A = not applicable

4.3.5 Adverse post-operative events

Twenty five patients died post-operatively (defined as inpatient mortality) following surgical resection. Table 4.8 shows the number of post-operative deaths for each operation type and additional surgical resection performed. Patients who had Ivor-Lewis oesophagogastrectomy, partial or subtotal gastectomy, or additional resection of the spleen or distal pancreas had the highest post-operative mortalities.

The demographic details, operative procedure performed, ASA grade and presumed cause of death in individual patients are detailed in Table 4.9. The most

common cause of post-operative mortality was respiratory complications, such as pneumonia or adult respiratory distress syndrome (ARDS). There were four anastomosis leaks leading to death.

Post-operative complications which did not result in death are detailed in Tables 4.10 and 4.11. These are arbitrarily separated into 'surgical' and 'medical' complications following surgical resections. The complications are further categorised by the operative approach. Approaches involving abdominal access only (completion, partial, subtotal or total gastrectomy) are detailed separately from those which required access to the thoracic cavity (Ivor-Lewis or left thoraco-abdominal approach). Table 4.11 details the post-operative surgical complications. The medical post-operative complication rate was high; but included minor, non-life threatening conditions such as urinary tract infections and erratic blood sugars (Table 4.10). More serious post-operative complications included respiratory failure (often requiring re-intubation), pulmonary embolism and cerebrovascular accident.

Table 4.8 Post-operative mortality by operative procedure

	Post-operative mortality	
Operative procedure	**No.**	**%**
Completion gastrectomy (n=6)	0	0
Partial or subtotal gastrectomy (n=53)	7	13.2
Proximal gastrectomy (n=4)	0	0
Total gastrectomy (n=53)	5	9.4
Sub-Total (n=116)	**12**	**10.3**
Left thoracoabdominal oesophagogastrectomy (n=97)	7	7.2
Ivor-lewis oesophagogastrectomy (n=38)	6	15.8
Sub-Total (n=135)	**13**	**9.6**
No addition splenectomy or pancreatectomy (n=215)	18	8.4
Additional splenectomy (n=29)*	5	17.1
Additional distal pancreatectomy (n=7)	1	14.2
Total (n=251)	**25**	**9.9**

*10 cases were for iatrogenic splenic injury

Table 4.9 Details of the 25 patients who died after surgical resection

Gender	Age	Tumour location	ASA Grade	Operation	Cause of post-operative death
F	75	Gastric	3	Partial gastrectomy	Unknown
F	72	Junctional	2	Ivor-lewis oesophagogastrectomy	Pneumonia
M	71	Gastric	N/A	Total gastrectomy	Pneumonia
F	61	Junctional	2	Total gastrectomy	ARDS and multi-organ failure
F	59	Gastric	N/A	Partial gastrectomy	Pneumonia
F	74	Junctional	2	LTA oesophagogastrectomy	Anastomosis leak, bronchopneumonia
M	69	Junctional	3	LTA oesophagogastrectomy	Anastomosis leak, septicaemia
M	64	Junctional	2	Ivor-lewis oesophagogastrectomy	Anastomosis leak, tracheo-oesophageal fistula, ARDS
M	55	Junctional	2	Ivor-lewis oesophagogastrectomy	ARDS and multi-organ failure
M	69	Junctional	3	Ivor-lewis oesophagogastrectomy	ARDS and multi-organ failure
M	70	Junctional	3	Total gastrectomy	ARDS and multi-organ failure
M	73	Junctional	2	Ivor-lewis oesophagogastrectomy	Aspergillus pneumonia
M	58	Junctional	2	LTA oesophagogastrectomy	ARDS and multi-organ failure
M	78	Junctional	3	Ivor-lewis oesophagogastrectomy	Severe post op pneumonia
M	76	Gastric	3	Total gastrectomy	Large CVA
M	73	Junctional	2	LTA oesophagogastrectomy	Myocardial infarction
M	68	Junctional	3	LTA oesophagogastrectomy	Multi-organ failure
M	79	Gastric	2	Partial gastrectomy	Multi-organ failure, pancreatitis
M	76	Gastric	2	Partial gastrectomy	Pneumonia
F	83	Gastric	2	Partial gastrectomy	Pneumonia
M	71	Junctional	3	LTA oesophagogastrectomy	Pneumonia
M	78	Junctional	2	LTA oesophagogastrectomy	Anastomosis leak, septicaemia
F	77	Gastric	4	Subtotal gastrectomy	Pneumonia
F	70	Gastric	3	Partial gastrectomy	Pneumonia
M	54	Gastric	2	Total gastrectomy	Pneumonia

N/A = not available; LTA = left thoracoabdominal, ARDS = adult respiratory distress syndrome, CVA = cerebrovascular accident

Table 4.10 Post-operative medical complications.

Medical complication	Abdominal approaches (n=105)		Approaches involving thoracotomy (n=122)	
	No.	**%**	**No.**	**%**
Cardio-Respiratory				
Chest infection	7	6.6	12	10
LVF	2	1.9	1	0.8
AF	4	3.8	12	10
Respiratory failure	7	6.6	3	2.5
PE	2	1.9	2	1.6
Other				
UTI	2	1.9	2	1.6
Urinary retention	2	1.9	2	1.6
CVA	1	1.0	1	0.8
DVT	1	1.0	0	0
Psychiatric	4	3.8	3	2.5
C. difficile diarrhoea	1	1.0	0	0
Severe reflux oesophagitis	1	1.0	0	0
Upper GI bleeding	0	0	1	0.8
Erratic blood sugars	0	0	1	0.8
Gout	0	0	1	0.8
Renal impairment	0	0	1	0.8
None	66	62.9	87	71.3
Unknown	5	4.8	2	0.2
Total No. of complications	34	32.4	42	34.4
No. of patients experiencing one or more complications	34	32.4	33	27.0

LVF = left ventricular failure; AF = atrial fibrillation; PE = pulmonary embolism; UTI = urinary tract infection; CVA = cerebrovascular accident; GI = gastrointestinal.

Table 4.11 Post-operative surgical complications

Surgical complications	Abdominal approaches (n=105)		Approaches involving thoracotomy (n=122)	
	No.	**%**	**No.**	**%**
Return to theatre				
Anastomosis leak	1	0.9	0	0
Chyle leak	1	0.9	3	2.5
Small bowel obstruction / or ileus	2	1.9	0	0
Air leak	0	0	1	0.8
Removal of NGT	0	0	1	0.8
Bleeding	0	0	1	0.8
Abdominal or thoracic collections				
Subphrenic	2	1.9	0	0
Pleural effusion	4	3.8	7	5.7
Left upper quadrant	3	2.9	0	0
Other				
Bile leak	1	0.9	0	0
Wound infection	5	4.8	8	6.6
Herniation of roux loop	1	0.9	0	0
Duodenal stump leak	1	0.9	0	0
Anastomosis leak*	4	3.8	4	3.3
Pancreatitis	0	0	1	0.8
Pneumothorax	0	0	1	0.8
Left recurrent laryngeal nerve injury	0	0	1	0.8
Empyema	0	0	1	0.8
Minor chyle leak	0	0	1	0.8
Prolapse of stomach into right chest	0	0	1	0.8
None	79	75.2	89	73.0
Unknown	5	4.8	4	3.3
Total complications	25	23.8	31	26.2
No. of patients experiencing one or more complications	21	20.0	29	23.8

*Small radiologically defined anastomosis leaks which were treated conservatively
NGT = nasogastric tube

4.3.6 Prognostic factors

Table 4.12 summarises the outcome of all the patients included in the database. Approximately a third of patients were alive at the time of the survival analysis; three of these patients had evidence of disease recurrence. The minium follow-up period in the surviving patients was 13 months. The majority of patients who were dead died from gastric or gastro-oesophageal adenocarcinoma (disease-specific deaths). A minority of patients died from other cancers and a few of causes other than cancer. Ten percent of patients died in the post-operative period (defined as in-hospital mortality) and these patients were excluded from the survival analysis.

Table 4.12 Outcome status of the 251 patients with gastro-oesophageal and gastric adenocarcinoma

Status	No.	%	Median Survival (months)	Range Survival (months)
Alive and well	72	28.7	45	13 - 123
Alive with progressive disease	3	1.2	25	14 - 34
Alive with stable disease	1	0.4	27	n/a
Death from disease	132	52.6	14	2 - 74
Death from other cancer cause[†]	3	1.2	9	7 - 27
Death from other cause[‡]	15	6	23	2 - 111
Post-operative death[*]	25	10	0	0 - 3

[†]Deaths from other cancer causes: lung cancer (n=1); squamous cell cancer of the tonsil (n=1); adenocarcinoma of the gallbladder (n=1)
[‡]Deaths from other causes: cerebrovascular accident (n=2); pneumonia (n=7); ischaemic heart disease/myocardial infarction (n=5); renal disease (n=1)
[*]Defined as in-hospital mortality

4.3.7 Univariate survival analysis

Table 4.13 shows the results of the univariate survival analysis for 226 patients with GOJ and gastric adenocarcinoma. Overall and disease-specific survival details are shown. Significant predictors of adverse post-operative survival were: high ASA

grade, additional resection of the spleen or pancreas, residual-disease classification, poor tumour differentiation, diffuse or mixed Lauren type, advance T stage, lymph node metastases (N stage), distant metastases (M stage), advanced overall TNM stage and proximal or distal resection margin involvement (Table 4.13). The corresponding Kaplan-Meier disease-specific survival graphs are shown in Figure 4.5. Separate graphs are shown for all tumour types combined, GOJ only and gastric only. Patient gender, age, year of surgery, surgical operation and the use of adjuvant therapy had no effect on survival (Table 4.13 and Figure 4.5).

Table 4.13 Univariate survival analyses of clinico-patholoigcal factors for all gastro-oesophageal and gastric adenocarcinomas (n=226)*

Factor		Overall survival (months)			Disease-specific survival (months)		
		Median	**Range**	**p**	**Median**	**Range**	**p**
Gender	Female	32	23-41		33	23-43	
	Male	23	17-29	0.59	30	19-41	0.72
Age	< 68 yrs	31	22-40		32	22-42	
	≥ 68 yrs	22	16-28	0.47	25	12-38	0.97
Year of surgery	<2000	22	15-29		26	18-34	
	≥2000	28	19-38	0.26	35	24-46	0.39
ASA	1	37	16-58		37	16-58	
	2	36	27-46		39	31-47	
	3	14	8-20		17	11-23	
	4	14	8-20	0.001	14	8-20	0.004
Neo-adjuvant treatment	No	25	20-30		27	19-35	
	Yes	40	8-72	0.60	40	8-72	0.77
Operation	Stump	27	12-42		27	-	
	LTA	27	15-39		30	17-43	
	Part/S G	32	11-53		74	20-129	
	PG	13	0-41		13	0-41	
	Ivor-lewis	17	10-25		17	9-25	
	TG	22	14-31	0.61	25	14-36	0.36
Additional resection	None	27	19-35		35	27-43	
	Spleen	22	18-27		22	18-27	
	S&P	7	4-11	0.0001	7	4-11	0.0001
Adjuvant therapy	No	25	20-29		27	19-35	
	Yes	-	-	0.30	-	-	0.47
R Class	R0	42	32-52		48	22-74	
	R1	15	12-18		15	12-18	
	R2	9	2-17	0.0001	9	2-17	0.0001

*Patients who died post-operatively are excluded; LTA = left thoracoabdominal; Part/S G = partial or subtotal gastrectomy; PG = proximal gastrectomy; TG = total gastrectomy; S&P = spleen and pancreas

Table 4.13 continued Univariate survival analyses of clinico-patholoigcal factors for all gastro-oesophageal and gastric adenocarcinomas (n=226)*

Factor		Overall survival (months)			Disease-specific survival (months)		
		Median	**Range**	**p**	**Median**	**Range**	**P**
Diff	Well	111	46-175		-		
	Mod	26	20-33		35	25-45	
	Poor	19	14-24	0.001	19	14-24	0.0001
Lauren type	Diffuse	19	14-25		19	13-25	
	Intestinal	36	24-49		41	33-49	
	Mixed	20	7-33	0.037	25	7-43	0.001
T Stage	T0	32	-		-	-	
	T1	111	56-165		-	-	
	T2	37	30-44		40	32-48	
	T3	17	12-22		18	13-23	
	T3	7	5-9	0.0001	7	5-9	0.0001
N Stage	N0	70	34-106		-	-	
	N1	20	15-25		22	16-29	
	N2	14	9-19		14	9-19	
	N3	13	0-26	0.0001	13	0-26	0.0001
N Stage (grouped)	N0	70	35-105		-	-	
	N1/2/3	18	14-22	0.0001	19	15-23	0.0001
M Stage	M0	26	20-32		31	23-39	
	M1	4	0-20	0.038	4	0-20	0.021
Overall TNM Stage	Stage 0	-	-		-	-	
	Stage 1	-	-		-	-	
	Stage 2	40	28-52		44	20-69	
	Stage 3	15	13-18		15	12-18	
	Stage 4	7	5-10	0.0001	7	5-10	0.0001
PRM	Clear	31	24-39		36	29-43	
	Involved	12	8-16	0.0001	12	7-17	0.0001
DRM	Clear	27	20-34		35	27-43	
	Involved	11	7-15	0.007	11	7-15	0.001

*Patients who died post-operatively are excluded; PRM = proximal resection margin; DRM = distal resection margin

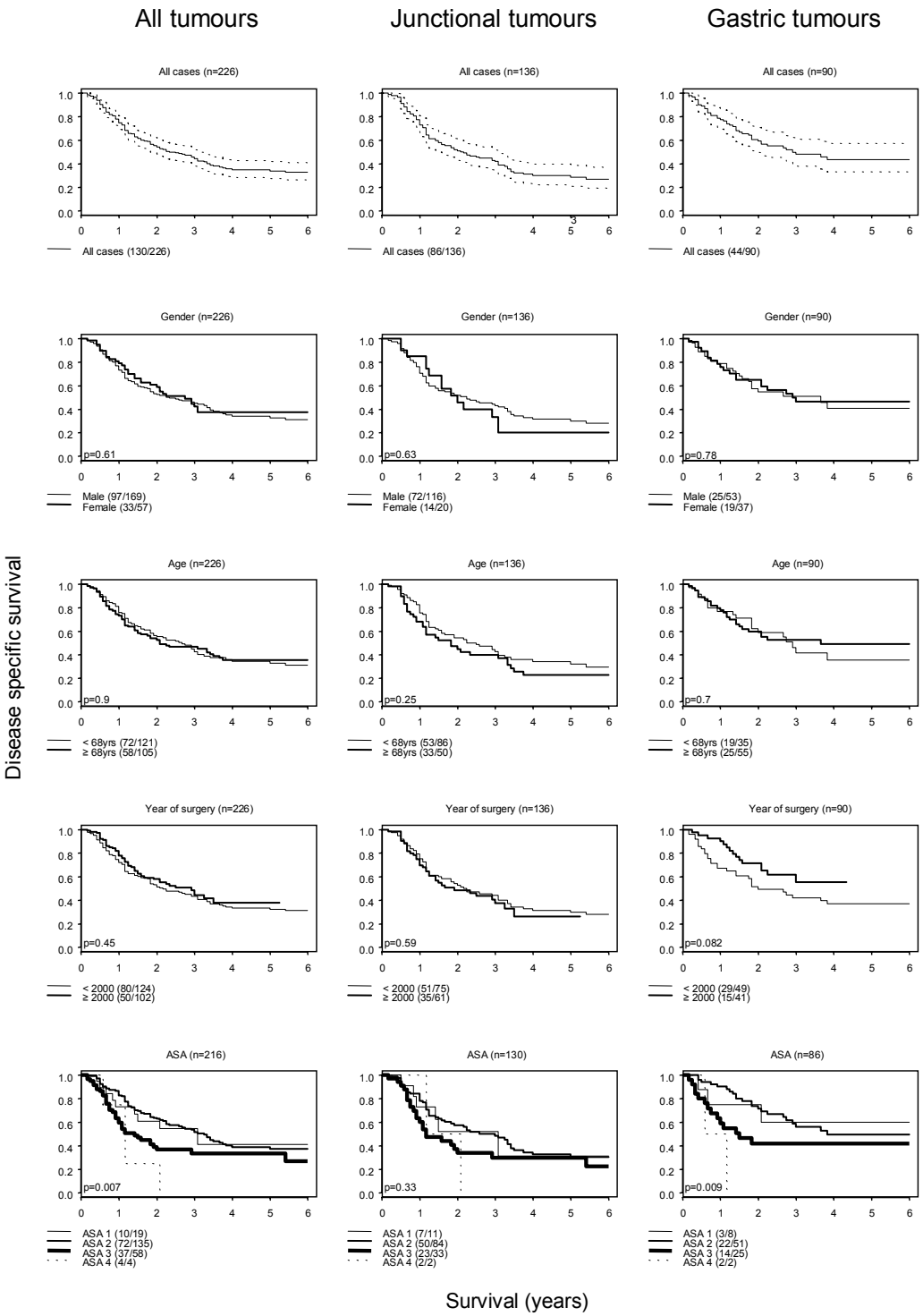

Figure 4.5 Univariate Kaplan-Meier analyses

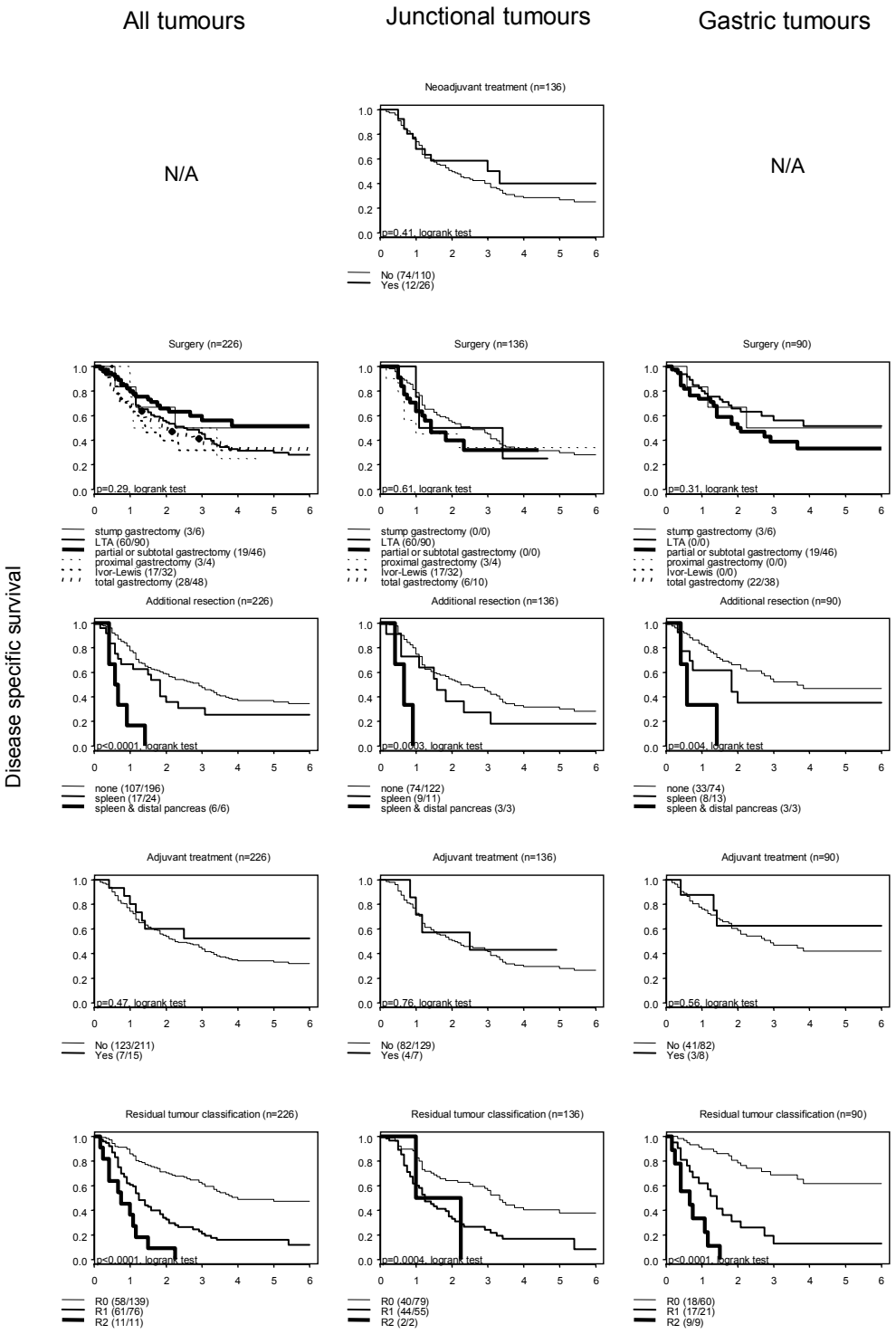

Figure 4.5 Univariate Kaplan-Meier analyses (cont)

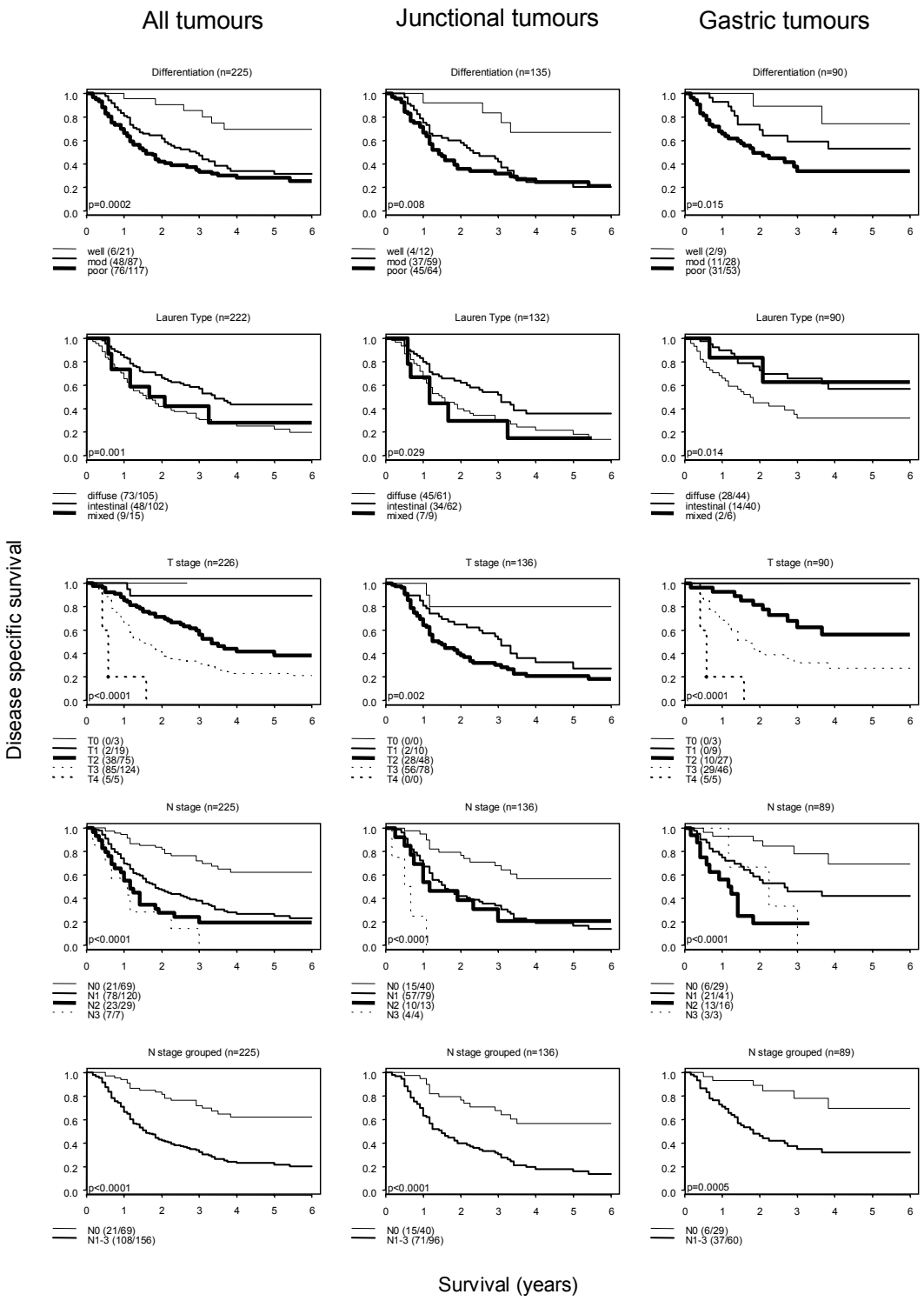

Figure 4.5 Univariate Kaplan-Meier analyses (cont)

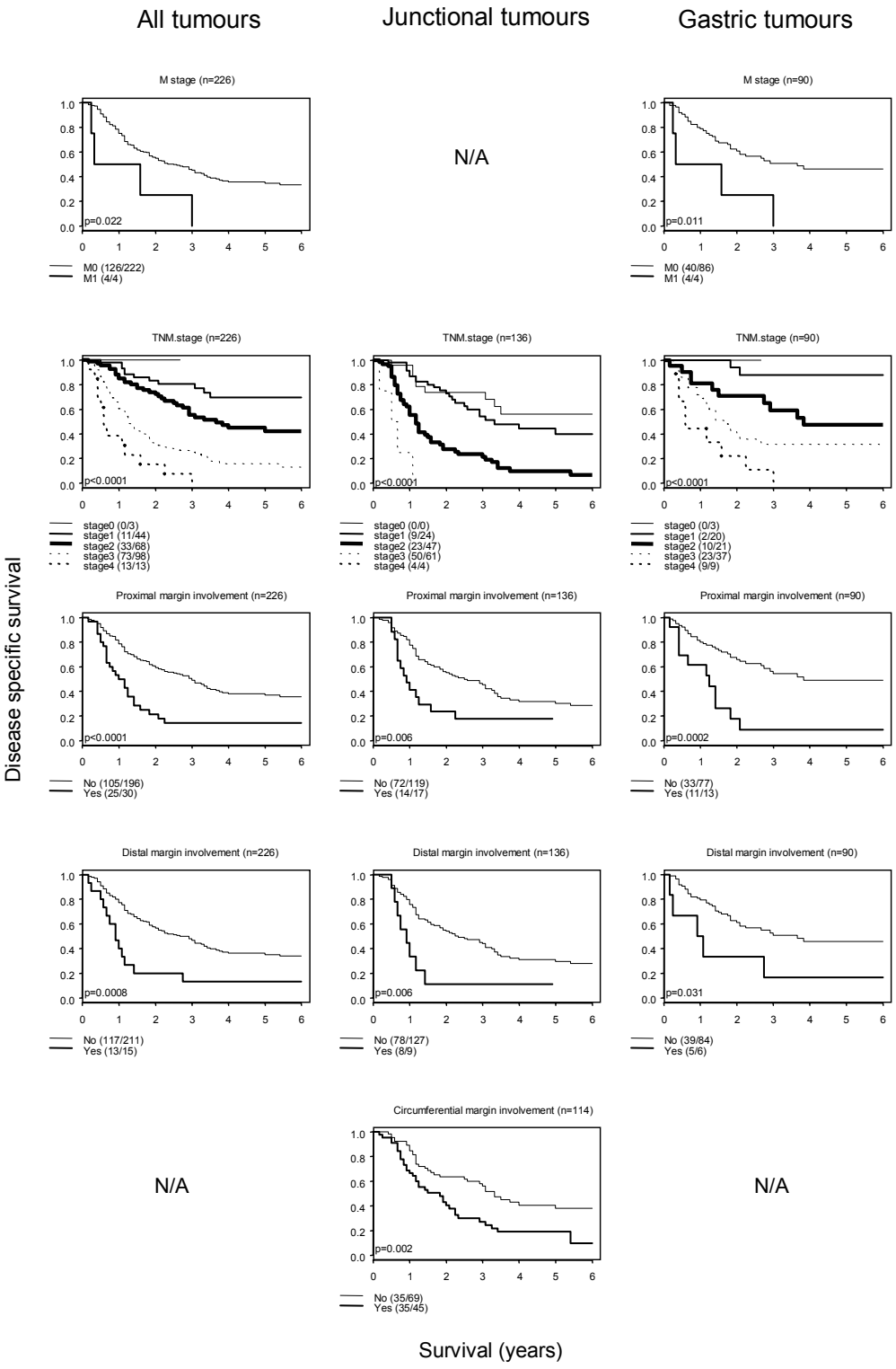

Figure 4.5 Univariate Kaplan-Meier analyses (cont)

4.3.8 Multivariate survival analysis

All significant factors in univariate survival analysis were entered into a Cox proportional hazards model to assess factors of independent significance. Additional resection of the spleen or spleen and distal pancreas together with ASA grade were the only two independent prognostic factors for survival (Table 4.14).

Table 4.14 Multivariate analysis of prognostic factors for survival using the Cox proportional hazards model.

Parameter	Overall survival			Disease-specific survival		
	HR	**95% CI**	**p**	**HR**	**95% CI**	**p**
Additional surgical resection						
None (ref)	-	-	-	-	-	-
Spleen	9.1	2.2-37.2	0.002	11.7	2.8-48.1	0.001
Spleen & pancreas	412.7	20.2-8450.6	0.0001	325.2	17.5-6059.6	0.0001
ASA Grade						
ASA 1 (ref)	-	-	-	-	-	-
ASA 2	24.5	2.4-255.1	0.007	14.7	1.5-141.1	0.02
ASA 3	66.0	5.5-797.2	0.001	41.4	3.8-455.6	0.002
ASA 4	98.5	4.2-2321.1	0.004	70.3	3.2-1547.0	0.007

HR: hazard ratio, CI: confidence interval; Ref: reference value

4.3.9 Comparison between GOJ and gastric adenocarcinomas

Different clinico-pathological characteristics of GOJ and gastric adenocarcinomas

When different clinico-pathological characteristics were compared between the different tumour locations (classified by Siewert type) using χ^2 test there were significant differences in age, gender and residual disease classification status (Table 4.15). No statistically significant differences were found between ASA grade, differentiation, Lauren type, T stage, N stage, M stage and overall TNM stage. Table 4.16 shows the same comparisons, but with all Siewert type categories combined (I, II and III). In this analysis, there were additional statistically significant differences in T stage, M stage and overall TNM stage.

Table 4.15 Clinicopathological comparison between different Siewert types and non-cardia gastric cancer (n=251)

Characteristic		Siewert type I n=22	II n=103	III n=26	Non-cardia n=100	χ^2 p
Age (years)	**< 68**	12 (55)	64 (62)	14 (54)	37 (37)	
	≥ 68	10 (45)	39 (38)	12 (46)	63 (63)	0.004
Gender	**Female**	2 (9)	13 (13)	8 (31)	42 (42)	
	Male	20 (91)	90 (87)	68 (69)	18 (58)	0.0001
ASA grade*	**I**	2 (9)	7 (7)	2 (8)	8 (8)	
	II	14 (67)	61 (62)	18 (72)	55 (59)	
	III	5 (24)	29 (29)	5 (20)	28 (30)	
	IV	0	2 (2)	0	3 (3)	0.95
Diff*	**Well**	2 (9)	10 (10)	1 (4)	10 (10)	
	Mod	13 (59)	41 (40)	14 (54)	35 (35)	
	Poor	7 (32)	51 (50)	11 (42)	55 (55)	0.33
Lauren type*	**Diffuse**	11 (50)	45 (46)	9 (39)	46 (47)	
	Intestinal	10 (45)	45 (46)	12 (52)	45 (46)	
	Mixed	1 (5)	8 (8)	2 (9)	6 (6)	0.98
T stage	**0**	0	0	0	3 (3)	
	1	3 (14)	8 (8)	2 (8)	10 (10)	
	2	7 (32)	37 (36)	11 (42)	29 (29)	
	3	12 (55)	58 (56)	13 (50)	52 (52)	
	4	0	0	0	6 (6)	0.19
N stage*	**0**	10 (46)	33 (32)	3 (12)	31 (32)	
	1	10 (46)	59 (57)	19 (73)	48 (49)	
	2	2 (9)	9 (9)	2 (8)	16 (16)	
	3	0	2 (2)	2 (8)	2 (3)	0.14
M stage	**0**	22 (100)	103 (100)	26 (100)	96 (96)	
	1	0	0	0	4 (4)	0.1
Overall TNM stage	**0**	0	0	0	3 (3)	
	1	7 (32)	20 (19)	3 (12)	22 (22)	
	2	6 (27)	38 (37)	8 (31)	23 (23)	
	3	9 (41)	43 (42)	13 (50)	42 (42)	
	4	0	2 (2)	2 (8)	10 (10)	0.11
R Class	**R0**	10 (46)	60 (58)	18 (69)	67 (67)	
	R1	12 (54)	40 (39)	7 (27)	24 (24)	
	R2	0	2 (3)	1 (4)	9 (9)	0.032

* Missing values: differentiation (n=1), Lauren type (n=11), N stage (n=3) and ASA grades (n=12); values in parentheses are percentages

Table 4.16 Comparison between GOJ and non-cardia gastric cancers (n=251)

Characteristic		GOJ n=151	Gastric n=100	p
Age (years)	**< 68**	90 (60)	37 (37)	
	≥ 68	61 (40)	63 (63)	0.0001
Gender	**Female**	23 (15)	42 (42)	
	Male	128 (85)	58 (58)	0.0001
ASA grade*	**I**	11 (8)	8 (8)	
	II	93 (63)	55 (58)	
	III	39 (27)	28 (30)	
	IV	2 (2)	2 (3)	0.7
Diff*	**Well**	13 (9)	10 (10)	
	Mod	68 (45)	35 (35)	
	Poor	69 (46)	55 (55)	0.27
Lauren type*	**Diffuse**	65 (45)	46 (47)	
	Intestinal	67 (47)	45 (46)	
	Mixed	11 (8)	6 (6)	0.90
T stage	**0**	0	3 (3)	
	1	13 (9)	10 (10)	
	2	55 (36)	29 (29)	
	3	83 (55)	52 (52)	
	4	0	6 (6)	0.005
N stage*	**0**	46 (30)	31 (32)	
	1	88 (58)	48 (49)	
	2	13 (9)	16 (16)	
	3	4 (3)	3 (3)	0.26
M stage	**0**	151 (100)	96 (96)	
	1	0	4 (4)	0.013
Overall TNM stage	**0**	0	3 (3)	
	1	30 (20)	22 (22)	
	2	52 (34)	23 (23)	
	3	65 (43)	42 (42)	
	4	4 (3)	10 (10)	0.011
R Class	**R0**	88 (58)	67 (67)	
	R1	59 (39)	24 (24)	
	R2	4 (3)	9 (9)	0.008

* Missing values: differentiation (n=1), Lauren type (n=11), N stage (n=2) and ASA grades (n=12); values in parentheses are percentages

Survival analysis

The survival by different tumour locations was analysed using the Kaplan-Meier method (Figure 4.6). First, survival was assessed for all tumours in the database (excluding post-operative deaths) comparing tumour location. There was no statistically significant difference between Siewert types and non-cardia gastric cancer prognosis (p=0.18) (Figure 4.6a); although there was a trend for GOJ to have a worse prognosis than non-cardia gastric cancer (p=0.086) (Figure 4.6b).

A second survival analysis was performed to exclude any potential biases of incomplete surgery or the down-staging effect of neo-adjuvant therapy. Therefore, patients who had an incomplete resection (R1 or R2) or received neo-adjuvant therapy were excluded. In this analysis, there was a trend for patients with Siewert type tumours to have a worse prognosis (p=0.10) (Figure 4.6c). When these categories were grouped, however, gastro-oesophageal junctional tumours had a significantly worse prognosis (p=0.013) (Figure 4.6d).

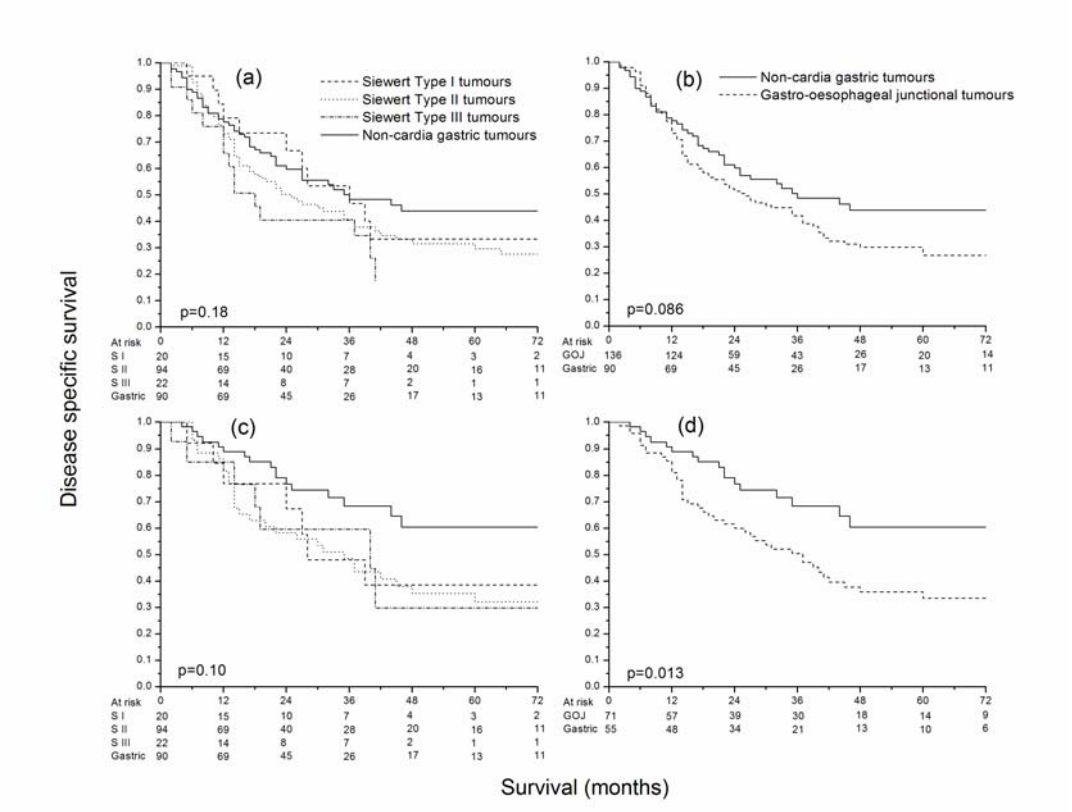

Figure 4.6 Kaplan-Meier survival analyses comparing the disease-specific survival of gastro-oesophageal junctional tumours versus non-cardia gastric cancer. Graphs (a) and (b) show all patients (n=226); excluding post-operative deaths. Graphs (c) and (d) also exclude patients who had an incomplete surgical resection (R1/2) or received neo-adjuvant therapy (n=126).

4.4 Discussion

4.4.1 Presenting symptoms

As expected the majority of the patients with gastric or GOJ cancer in this study presented with alarm symptoms (Figure 4.2 and 4.3). Table 4.17 shows the current NHS urgent referral criteria for suspected upper gastrointestinal cancer.

Table 4.17 Criteria for urgent investigation of suspected upper gastrointestinal cancer under the National Health Service "two week rule"

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

The criteria for urgent referral and the new NICE guidelines for the management of dyspepsia in general practice are controversial (NICE 2004). These guidelines recommend that open access gastroscopy for dyspepsia is not necessary for patients who present without alarm symptoms at any age, the exception being patients over 55 whose symptoms persist despite *H. pylori* testing and treatment with proton pump inhibitors (PPI). Endoscopy is recommended if patients have one or more of the following: previous gastric ulcer or surgery; continuing need for NSAID treatment or raised risk of gastric cancer, or anxiety about cancer. Patients without these exclusions are recommended to receive empirical PPI therapy.

The change in the guidelines has caused concern that early cancers may be missed (Griffin et al. 2005). A criticism is that patients presenting with alarm symptoms often have advanced stage disease (Blackshaw et al. 2003; Phull et al. 2006). Therefore, there seems to be less benefit in fast-tracking endoscopy to patients whose disease is only suitable for palliative therapy. A recent study showed that patients with gastric cancer who presented with alarm symptoms had a statistically significant worse prognosis than those without (Stephens et al. 2005). An earlier study by Sue-Ling et al showed that the more widespread use of endoscopy leads to a higher incidence of detection of early stage cancers with subsequent improvement in 5 year survival (Sue-Ling et al. 1993). A meta analysis of symptoms in upper gastrointestinal cancer showed that, although malignancy is rare in the absence of alarm symptoms, a quarter of patients presenting with upper GI cancer do not have alarm symptoms (Fransen et al. 2004). However, even the presence of alarm symptoms are a poor predictor of cancer. Kapoor et al showed that only 4% of patients sent for fast track endoscopy will have a final diagnosis of cancer (Kapoor et al. 2005). Another problem is that PPI are recommended for empirical use in any age group with out alarm symptoms prior to performing gastroscopy. However, it is known that PPIs may mask early changes of malignancy at endoscopy and their use prior to endoscopy should be discouraged (Bramble et al. 2000; Wayman et al. 2000). The consequence of PPI use is that the diagnosis of upper gastrointestinal cancer is delayed by a mean of 17.6 weeks (Panter et al. 2004).

4.4.2 Disease diagnosis

The vast majority of patients were diagnosed by endoscopy and had histologically confirmed malignancy before proceeding to surgery. A minority of patients had a barium study as their sole diagnostic modality; principally in the early years of this study. It must be emphasised that proceeding to surgical resection without a confirmatory tissue diagnosis would be considered bad practice today and reflects the time period of this research.

However, despite the wide spread use of diagnostic upper GI endoscopy, it is not without risk (Thompson et al. 2004). In patients at increased risk of perforation, e.g. those with oesophageal strictures or potential cervical lesions, barium swallow might be the best initial investigation (SAGOC 2002). In addition, up to 7% of oesophagogastric cancer may be missed or misdiagnosed at initial endoscopy (Yalamarthi et al. 2004).

The presumed causes for this were endoscopist (73%) or pathological (27%) error. This study highlights the importance of identifying earlier changes of malignancy and having a low threshold for performing multiple endoscopic biopsies of suspicious lesions.

4.4.3 Surgical treatment

There is an increasing trend to concentrate the treatment of oesophagogastric cancer into centralized hospitals. It is recommended that surgical resection for oesophagogastric cancer is performed in cancer centres containing all necessary multidisciplinary services, and serving a population of at least one million. This change in disease management is readily apparent in this chapters results (Figure 4.4); where previously non-specialist general surgeons and cardiothoracic surgeons performed the resections. Currently all resections for upper gastrointestinal cancer are performed by specialist upper gastrointestinal surgeons. There is a large body of evidence indicating that hospitals which manage large numbers of patients with upper gastrointestinal cancer have better outcomes (Branagan et al. 2004; Lerut et al. 2005; Metzger et al. 2004).

The operative approach in these patients was chosen by the consultant surgeon in charge. The precise procedure was decided by the location of the tumours, stage of disease, fitness of the patient and the individual surgeon's preference. This explains the lack of standardisation in the treatment of these tumours; especially in comparison with other series of surgically treated GOJ tumours (Siewert et al. 2000).

4.4.4 Post-operative morbidity and mortality

Post-operative morbidity and mortality are known to be high after oesophagogastric resectional surgery (Ikeguchi et al. 2001; Jamieson et al. 2004). This is especially true in the UK and other Western countries where patients are generally older, have a high level of co-morbid disease, are more likely to have proximal tumour location and advanced tumour stages (Table 1.3). Table 4.1 shows some regional audits performed in the UK assessing post-operative morbidity and mortality after surgery. The post-operative mortality rate of 10% and morbidity of 48% reported here are similar to other published UK studies for gastric cancer. Similarly, the post-operative mortality rate of 11% and morbidity of 52% are similar to other UK studies for GOJ and oesophageal cancer. The most recent AUGIS database has shown comparably low (5.2-5.6%) post-operative mortality; however, the data were highly selective as it was provided

voluntarily from members of the AUGIS. In addition, the study period was more recent (2002-2003) compared with this chapter's data.

Table 4.18 Other UK studies that have assessed post-operative morbidity and mortality following surgery for oesophagogastric cancer.

Study	Year	Gastric			GOJ			Ref
		No.	Mort%	Morb%	No.	Mort%	Morb%	
Welsh Audit	1995-1996	139	9*	N/A	250	12.8*	N/A	(Pye et al. 2001)
ASCOT	1999-2002	590	10.3	43	365	13.7	60	(McCulloch et al. 2003)
AUGIS	2002-2003	209	5.6	N/A	299	5.2	N/A	(AUGIS 2004)
Summary of this chapters results	1995-2004	100	10	48	151	11	52	n/a

Mort = mortality; Morb = morbidity; *30 day mortality; all other values show in hospital mortality

There is an interest in assessing factors which may predict post-operative complications so that patient selection for surgical resection can be improved. A recent large study analysed 773 patients who were treated by surgical resection for oesophageal and gastro-esophageal junction cancer to assess factors associated with post-operative death (Abunasra et al. 2005). They found three factors that were independently associated with post-operative mortality in multivariate analysis: patient age, impaired pre-operative respiratory function (as measured by FEV1) and upper third tumour location. Other authors have shown that a composite risk score involving scores for general health and cardiac, hepatic and respiratory function may help in the selection of patients for oesophagectomy (Bartels et al. 1998).

Similar studies assessing factors associated with post-operative morbidity and mortality have been performed in patients with gastric adenocarcinoma. Older age, combined resection and Bilroth II reconstruction after radical subtotal gastrectomy were independently associated with a higher level of complications and mortality (Park et al. 2005).

4.4.5 Prognostic factors

A wide variety of clinico-pathological factors are associated with prognosis in oesophagogastric cancer (Table 1.11). In this chapter a wide range of potential prognostic factors were examined. Significant predictors of adverse post-operative survival were high ASA grade, additional resection of the spleen or pancreas, residual disease classification, poor tumour differentiation, diffuse or mixed Lauren type, advance T stage, lymph node metastases (N stage), distant metastases (M stage), advanced overall TNM stage and proximal or distal resection margin involvement. These factors are consistent with other studies (Table 1.11). It is of interest that only additional organ resection and ASA grade were independent factors in multivariate analysis.

Additional resection of the spleen and pancreas

Additional resection of the spleen and pancreas was associated with a higher post-operative mortality. This has also been shown by both the MRC (Cuschieri et al. 1999) and the Dutch Gastric Cancer Group (Bonenkamp et al. 1999). Although both of these studies were designed to compare the extent of lymphadenectomy (D1 versus D2), they revealed that the highest morbidity and mortality rates, irrespective of lymphadenectomy, were in patients who had additional resection of the spleen and distal pancreas. Therefore routine pancreatectomy and should no longer be a requirement for D2 lymphadenectomy. Recent population based data from the SAGOC study provides additional data to reinforce this message (Nanthakumaran et al. 2005).

American Society of Anaesthesiologists (ASA) grade

The ASA grade is a subjective score given to a patient by the anaesthetist prior to surgery that categorises patient fitness (Dripps et al. 1961). The following categories apply: ASA 1, normally fit and healthy; ASA 2, mild systemic disease with no functional limitation; ASA 3, mild systemic disease with some functional limitation; ASA 4, severe systemic disease that poses a constant threat to life; ASA 5, not expected to survive 24 hours. Other studies have shown that perioperative risk increases with ASA grade. For example, in the ASCOT study (McCulloch et al. 2003) the overall mortality rate from resection was 12% (111/955) and mortality increased markedly with

increasing ASA grade: ASA 1, 8% (13/166), ASA 2 9% (44/491); ASA 3, 18% (44/242); ASA 4 27% (3/11). Interestingly, ASA grade was not an independent predictor of postoperative death and complication in the ASCOT study (McCulloch et al. 2003). However, assessment of patient fitness by the surgeon (Grade 1: patient considered fit for surgery, 2: patient potentially fit for major resection, but significant comorbidity problems identified, 3: serious comorbidity problems identified that present considerable risk to survival in postoperative period) and physiological and operative severity score for enumeration of mortality and morbidity (POSSUM) were significant factors in multivariate analysis (McCulloch et al. 2003). The current BSG guidelines recommend that surgical resection is only performed on patients with an ASA grade of less than 3 (Allum et al. 2002).

In this analysis, ASA was an independent predictor of prognosis after surgical resection. This agrees with other studies, such as the Scottish audit (SAGOC 2002). However, it is known to be a subjective measure of patient fitness and as such should probably not guide treatment decisions (Allum et al. 2002).

Extent of tumour invasion (T stage)

The T stage is determined by the maximum extent of spread through the stomach wall and is one of the most important factors determining surgical resectability and survival. Carcinoma restricted to the mucosa and submucosa (early gastric cancer) is associated with excellent survival (Sue-Ling et al. 1993) whereas penetration through the serosa and invasion of adjacent structures has a poor prognosis (Maruyama et al. 1996). Selected patients with locally advanced gastric carcinoma invading adjacent organs (T4 disease) may benefit from aggressive surgical resection as long as R0 resection can be achieved (Carboni et al. 2005). However, operative morbidity and mortality are increased and thoughtful patient selection is essential.

Lymph node metastases and prognosis in gastric cancer

Lymph node involvement is a well-established and consistent prognostic factor and it is often significant on multivariate analysis in other studies. Survival is also related to lymph node involvement with prognosis proportional to the number of lymph node metastases (Noda et al. 1998; Wu et al. 1996). Involvement of lymph nodes metastases has been related to several aspects of the primary tumour, including size, depth of invasion, and histological sub-type according to Lauren's classification (Siewert et al. 1998a).

The 2002 edition of the UICC uses four lymph node groups: pN0 (no lymph node metastases), pN1 (1-6 lymph nodes involved), pN2 (7-15 lymph nodes involved) and pN3 (>15 lymph nodes involved) (Sobin 2002). This method is simple and easily reproducible compared with previous systems which used anatomical location (Hermanek et al. 1998; Roder et al. 1998; Yoo et al. 1999). However, one concern about the new lymph node staging system is that the number of metastatic lymph nodes is likely to be influenced by the number of lymph nodes resected and examined (Lee et al. 2001). Simply examining a small number of lymph nodes can lead to an underestimation of stage, resulting in stage migration (this is also known as the Will Rodgers phenomenon) (Feinstein et al. 1985). This effect can cause substantial differences in stage-specific survival and confound comparison of treatment results (Lee et al. 2001).

For accurate staging, however, at least 15 lymph nodes must be examined (Roder et al. 1998; Wu et al. 1996). Mullaney et al demonstrated that only 31% of surgically resected gastric cancer in the UK had accurate lymph node staging (more than 15 lymph nodes examined) (Mullaney et al. 2002). Some authors have suggested that in stage IIIB tumours (which is defined as between 7 to 15 involved lymph nodes) more than 35 lymph nodes should be examined for optimal staging to reduce the effect of stage migration (Lee et al. 2001).

Several authors found a relationship between the total number of lymph nodes removed and the number of metastatic nodes. It is interesting to note that a low number of total non-metastatic nodes examined was shown to be a poor prognostic factor (Kattan et al. 2003; Lee et al. 2001; Siewert et al. 1996). In a study by Kattan et al, patients who had 0-10 non-metastatic lymph nodes had a significantly worse prognosis than those with 30 negative nodes (Kattan et al. 2003). This result was confirmed by Lee et al who showed that both the number of metastatic lymph nodes identified and survival increased significantly when 15 or more lymph nodes were examined (Lee et al. 2001). This is perhaps further indirect evidence that an extended lymphadenectomy may result in an improved prognosis; however it may just represent improved lymphatic staging (i.e. reduced stage migration). To correct for this, the lymph node ratio may be a better indicator of prognosis (Rodriguez Santiago et al. 2005).

Metastatic disease and prognosis

Distant metastatic disease in gastric cancer is an ominous sign. On rare occasions patients present with isolated metastases that may be suitable for surgical excision. In women, for example, isolated metastases may occur to the ovaries (Krukenburg tumours). Recently a survival advantage has been shown for patients who underwent surgical resection of their ovaries in the absence of other metastatic disease (Cheong et al. 2004).

4.4.6 Limitations and benefits of this study

This study details the outcome of patients who underwent surgical resection for gastric and GOJ adenocarcinoma. As such, limitations of this study include its retrospective data collection, single institution bias and non-standardised surgical management for GOJ tumours. Data collection has unfortunately included a time period of change within the Trust. The bias of the move away from general surgeons and cardiothoracic surgeons performing surgery for this tumour group and the move towards specialist accredited surgeons is unknown. The benefits of this study are the large number of patients included and the length of the follow-up obtained. Surviving patients were followed for a minimum of 13 months (median was 45 months). In this analysis, in-hospital mortality (which is known to be more accurate than the 30 day mortality used in many studies) was reported.

4.4.7 Differences between GOJ and gastric adenocarcinomas

As mentioned in the Introduction, there has been a dramatic increase in the incidence of GOJ adenocarcinomas in the Western world, including the UK. This has predominantly been among Caucasian males between the ages of 50 and 70 years. Although no incidence data was available, there are remarkable differences in patient age and gender between patients with GOJ and non-cardia gastric adenocarcinoma. Patients with GOJ adenocarcinomas were more likely to male and are of a younger age. These differing characteristics have been shown in other studies (Siewert et al. 2005; Siewert et al. 2000; Siewert et al. 1998b). It was also observed that patients with GOJ tumours were more likely to undergo a R1 resection (residual microscopic tumour) than non-cardia gastric cancer patients. This was principally due to involvement of the CRM, as there were no apparent differences between the percentages of involvement of the proximal or

distal resection margins. CRM involvement has been extensively discussed in the previous chapter.

The findings that R2 (residual macroscopic tumour) were more common in non-cardia gastric cancer patients can be explained by the fact that these patients were more likely to undergo palliative surgery. There is currently no role for palliative surgery in patients with GOJ tumours as post-operative morbidity and mortality in this setting is extremely high. There are also a range of safer alternatives to surgery for the palliation of malignant dysphagia, such as self-expanding metal stents, argon beam coagulation, photodynamic therapy and palliative chemoradiotherapy. However, these treatments are of limited use in the palliation of gastric cancer, especially if bleeding is the main problem. Therefore, palliative surgical resection still has a role in the treatment of gastric cancer.

No statistically significant differences in survival between different GOJ tumours when classified into Siewert types were found (Figure 4.6). This is in keeping with other studies (Wijnhoven et al. 1999). However, other authors who have analysed larger datasets have found survival differences between the different Siewert categories. Siewert has recently shown that the 5 and 10 year survival rates for Type I GOJ tumours were significantly better compared with Type III tumours, whereas the survival rate for Type II tumours was somewhere in between (Siewert et al. 2005). Also shown in this study was an increase in the percentage of diffuse tumour type, poor differentiation and lymph node metastases from Type I to Type III categories. Other hypothesized reasons for the better prognosis of Type I (Barrett's) tumours is earlier presentation with dysphagia or that patients were enrolled in surveillance programmes.

Why do GOJ cancers have a worse prognosis than non-cardia gastric cancer?

Other studies have shown differences in survival between GOJ and non-cardia gastric cancers (Kajiyama et al. 1997; Kim et al. 2005; Pinheiro et al. 1999). Although, there was a trend in the analysis for a worse survival in patients with GOJ tumours compared with gastric cancers (p=0.086), it was only when patients treated with neo-adjuvant therapy and those that underwent a non-curative resection (R1/2) were excluded that the poorer prognosis of GOJ tumours can be fully appreciated (p=0.013) (Figure 4.6). Table 4.19 outlines the reasons and theories surrounding why GOJ tumours have a poorer prognosis than non-cardia gastric cancers.

Table 4.19 Reasons or theories why GOJ tumours have a worse prognosis than gastric tumours

Reason or theory	Ref
Increased propensity to metastasize to lymph nodes	(Siewert et al. 2005)
Potential for lymph node metastases to three different compartments (mediastinal, retroperitoneal and abdominal)	(Dresner et al. 2001) (Lagarde et al. 2005)
More aggressive pathological characteristics, such as deeper T stage, lympho-vascular invasion and poorly differentiated tumours	(Siewert et al. 2005) (Kajiyama et al. 1997)
Anatomical reasons including thinness of the muscularis layer and lack of serosal covering at the gastro-oesophageal junction	(Ichikura et al. 2003)
Late presentation with dysphagia (in particular Siewert type III tumours)	(Ichikura et al. 2003)
Potential molecular or biological differences	(Kim et al. 2005)

Problems with the classification of GOJ tumour location

The confusion over where the oesophagus ends and the stomach begins has caused problems with data collection in numerous similar studies (Byrne et al. 2002; SAGOC 2002). Indeed studies have shown that the classification of tumours around the gastro-oesophageal junction have been notoriously inaccurate (Byrne et al. 2002; Dolan et al. 1999; Ekstrom et al. 1999). To overcome this, some authors have deliberatively adopted a pragmatic definition of GOJ cancers. This has involved classifying all cancers which have evidence of GOJ involvement as GOJ tumours without sub-classifying them by the bulk of tumour location (Byrne et al. 2002; Dolan et al. 1999; SAGOC 2002).

To ensure the correct classification of GOJ tumours in this analysis, the pre-operative endoscopy report, radiological imaging report, operative details and histopathology report were reviewed. Using these data, the Siewert classification was assigned retrospectively. Therefore the results using Siewert classification should be treated with some degree of circumspection as they may not be completely accurate. In recognition of these sub-classification limitations, a pragmatic definition of the GOJ as used in other studies was also applied to the analyses in this chapter (Byrne et al. 2002; Dolan et al. 1999; SAGOC 2002).

The Liverpool sub-site classification for upper gastrointestinal cancer provides a simple system to classify oesophagogastric tumours (Table 4.20. It is unfortunate that it has not been widely adopted as it provides a pragmatic and easily applicable system to classify these tumours. The use of this system would have the potential to standardise research in this area. Its benefits are that further sub-classification of the GOJ group with the Siewert classification system is possible and that patients treated non-operatively can be easily classified.

Table 4.20 The 'Liverpool' classification of oesophagogastric cancer location

Site	Subsite	Definition
Oesophagus	Upper third	Cricopharyngeal sphincter to thoracic inlet
	Middle third	Thoracic inlet to 8th thoracic vertebra
	Lower third	Below 8th thoracic vertebra and above the GOJ
GOJ	GOJ	Involves the GOJ, either from above or below
Stomach	Proximal	Proximal to incisura angularis
	Distal	Distal to incisura angularis
	Overlapping	Involves more than 50% of each subsite

Information taken from (Dolan et al. 1999)

Possible molecular differences between GOJ and non-cardia gastric tumour locations

Few studies have assessed the molecular differences between GOJ and non-cardia gastric cancers. Kim et al showed that the immunohistochemical expression of several proteins, including p16, smad4, CEA, CD44, MUC1 and MUC5AC were statistically different in cardia versus non-cardia gastric cancer (Kim et al. 2005). Another study showed there were differences in p16 and pRb expression between cardia and antral gastric tumours (Gulmann et al. 2004). Therefore, these studies support the hypothesis that tumours of these two locations are genetically different and may account for some of the observed epidemiological, clinicopathological and survival differences found in previous studies.

However, against this hypothesis other studies have found similar molecular profiles between cardia and non-cardia gastric cancer locations. For example, telomerase activity (hTERT expression) was similar in cardia and antral tumours (Gulmann et al. 2005). The same group also showed no differences in the expression of

adenomatous polyposis coli gene, β-catenin and E-cadherin expression between the tumour subsites (Gulmann et al. 2003).

Other studies have assessed molecular differences between different precise tumour locations. For example, in a study assessing whether the expression profiles of cytokeratins (CK7, CK20) and mucins (MUC1, MUC2, MUC5AC) could be useful in distinguishing between tumour location, similar expression was found in adenocarcinomas of the distal oesophagus, GOJ and the proximal stomach (Flucke et al. 2003). The expression of cytokeratins (CK7, CK20) was also found to be identical in oesophageal and gastric cardia tumour locations in another study (Driessen et al. 2004). A small study showed similar levels of microsatellite instability and loss of heterozygosity in tumours around the GOJ (Dolan et al. 2004), classified either by the Siewert or Liverpool classification. Whereas in a study assessing chromosomal aberrations by genomic hybridization in different GOJ tumours, loss of 14q31-32.1 occurred significantly more frequently in Barrett's related adenocarcinomas compared with gastric cardia cancers (van Dekken et al. 1999).

Therefore, it appears that no firm conclusions can be made about the molecular differences between various oesophagogastric tumour locations. Studies in this area are hampered by a lack of a universal classification system for these cancer types. Future research in this area would be strengthened by the strict application of a universally accepted disease site classification system.

4.5 Conclusions

Although the primary aim of this chapter was a preliminary analysis prior to using data for future molecular prognostic studies, it contains useful clinical audit material. Despite the study period representing a transition phase in the surgical treatment of oesophagogastric cancer within the Trust, its value is its comprehensive nature and size. Standard clinico-pathological survival factors have been comprehensively explored using both univariate and multivariate techniques. The clinico-pathological and survival differences between GOJ and gastric adenocarcinomas have also been explored. Chapter 5 will detail the use of the database to analyse potential molecular predictors of prognosis.