3. CLINICAL PROGNOSTIC FACTORS IN OESOPHAGEAL CANCER

3.1 INTRODUCTION

There is a need for accurate methods of determining prognosis in patients with oesophageal cancer; for the selection of patients for surgery, neo-adjuvant therapies, post-operative oncological therapies and non-operative intervention. Tumour length and circumferential resection margin (CRM) involvement may be useful markers of prognosis in oesophageal cancer.

3.1.1 Tumour length as a prognostic marker

It is a widely held belief amongst upper gastrointestinal specialists that long oesophageal tumours are likely to be more advanced and carry a worse prognosis than shorter lesions. Previous studies have shown that longer oesophageal squamous cell carcinomas have a worse prognosis when treated by radical radiotherapy (Slevin et al. 1989; Yamakawa et al. 1994), probably due to the presence of tumour outside the radiotherapy field. A large study recently showed that tumour length was a strong independent predictor of prognosis in oesophageal cancer (Eloubeidi et al. 2002). However, this was an epidemiological based study which used a wide variety of investigation modalities for determining tumour length measurements and involved multiple treatment modalities. Therefore, the prognostic significance of tumour length in surgically treated patients remains uncertain, especially in the context of increasing numbers of tumours occurring around the gastro-oesophageal junction. Of note, the current UICC TNM system for oesophageal cancer does not consider tumour length to be a factor in staging (Sobin 2002).

Currently endoscopic ultrasound (EUS) is one of the most accurate modalities used to define depth of tumour invasion and lymph node metastases pre-operatively. The accuracy of determining T stage ranges between 85% and 90%, whereas nodal staging accuracy approximates 70% to 90% (Reed et al. 1999; Vazquez-Sequeiros et al. 2001). Preliminary studies have been performed assessing tumour length by EUS and correlating this with other pathological variables or prognosis but they have used small patient numbers (Bhutani et al. 2002; Shinkai et al. 2000). Before investigating the prognostic effect of tumour length measured pre-operatively, the aim was to confirm the

prognostic value of tumour length measurements using the gold standard method of careful histological measurement of the pathological specimen after surgical resection (Mapstone 1998). If these post-operative findings can be shown to correlate with prognosis, then it justifies renewed efforts to measure tumour length accurately pre-operatively. Moreover, the relationship between tumour length and other important prognostic histological variables (such as T stage and N stage) need to be clarified and may help in selecting patients for appropriate treatment options.

3.1.2 Circumferential resection margin (CRM) as a prognostic marker

Involvement of the longitudinal resection margin is well known to be a poor prognostic factor (Law et al. 1998; Mulligan et al. 2004). However, the situation is less clear regarding the importance of the CRM. Studies in rectal cancer established that the pathological reporting of the CRM is important since involvement is associated with increased risk of local disease recurrence and reduced survival (Adam et al. 1994; Wibe et al. 2002). However, only a few studies have assessed the outcome of CRM involvement in oesophageal cancer (Table 3.1). Sagar et al studied a small number of patients who had a short post-operative follow up (Sagar et al. 1993). They observed that involvement of the CRM was associated with increased risk of local disease recurrence and reduced survival. It was on the basis of this evidence that the Royal College of Pathologists included CRM status as a required data item in the 1998 Oesophageal Cancer Minimum Dataset (Mapstone 1998). Audits of oesophageal cancer pathology reporting have revealed that CRM status is poorly reported (Burroughs et al. 1999; King et al. 2004). Subsequently only two further studies have assessed the effect of CRM status on patient survival and have revealed conflicting results (Dexter et al. 2001; Khan et al. 2003).

Table 3.1 Previous studies assessing the prognostic impact of CRM status in oesophageal cancer

Ref	Years involved	No.	Type	CRM Pos (%)	Univariate survival	Multivariate survival
(Sagar et al. 1993)	1984–89	50	Retro	40%	p<0.05	N/A
(Dexter et al. 2001)	1990–97	135	Prosp	47%	p<0.015	p=0.013
(Khan et al. 2003)	1982–96	329	Retro	20%	p=0.57	N/A

N/A = Not applicable, Retro = retrospective, Prosp = prospective

3.1.3 Aims

- To investigate the relationship between histologically determined length and CRM and histopathological aspects of the tumour together with survival in patients with surgically treated oesophageal malignancy.

3.2 RESULTS

3.2.1 Patient characteristics

Three hundred and nine patients (242 men and 67 women) were identified who underwent resection of oesophageal malignancy between January 1994 and December 2003. The median age was 64.5 years (range 24-84). Clinicopathological characteristics of the patients and tumour specimens are detailed in Chapter 2 (Table 2.3). Two hundred and twenty five adenocarcinomas (72.8%) and 72 (23.3%) squamous cell carcinomas were included in the study. Other histological types included ten patients with mixed (adenocarcinoma and SCC) tumours, one patient had a small cell tumour and the remaining patient had an undifferentiated carcinoma. Tumour locations were gastro-oesophageal junction (144 patients), lower third of the oesophagus (103 patients), middle to lower (47 patients), middle third (13 patients) and upper third of the oesophagus (2 patients). The operative treatments are described in Chapter 2 (Table 2.2). Neo-adjuvant chemotherapy was given to 39 patients. The regime used was principally 2 cycles pre-operative of cisplatin and 5-fluorouracil as in the OEO2 trial (MRC 2002).

3.2.2 Tumour length as a prognostic marker

Association of tumour length with other clinicopathological variables

The median tumour length was 3.5 cm (range 0.5-14). Table 3.2 shows the correlation between tumour length stratified by the median and other clinico-pathological variables. Tumour length >3.5 cm was associated with increasing T stage ($p<0.001$), worse N stage ($p=0.032$), and increasing overall TNM stage ($p=0.003$). Tumour length >3.5 cm was associated with an increased rate of involvement of the longitudinal resection margin ($p=0.02$) and a trend towards increased rate of involvement of the CRM ($p=0.054$). Patients who received neo-adjuvant therapy were subsequently more likely to have tumours measuring ≤3.5 cm ($p=0.008$). There was no statistical association between tumour length and patient gender, age, M stage or tumour differentiation.

Tumour length measurements as a continuous variable were correlated with other continuous data using the Spearman's rank test. Weak but statistically significant correlations were observed when tumour length was compared with the total number of lymph nodes examined ($r=0.15$, $p=0.01$), number of metastatic lymph nodes ($r=0.15$, $p=0.01$), percentage of metastatic lymph nodes ($r=0.12$, $p=0.04$), T stage ($r=0.19$, $p=0.001$) and overall TNM stage ($r=0.18$, $p=0.01$) (Figures 3.1 and 3.2).

Table 3.2 The distribution of 309 patients with oesophageal cancer according to their tumour length and clinicopathological features

Factor		Tumour length ≤ 3.5 cm (%) n=159		Tumour length > 3.5 cm (%) n=150		χ^2*	p*
Gender	Male	128	(80.5)	114	(76.0)		
	Female	31	(19.5)	36	(24.0)	0.92	0.34
Age	< 65	85	(53.5)	69	(46.0)		
	≥ 65	74	(46.5)	81	(54.0)	1.72	0.19
Neo-adjuvant therapy	No	130	(81.8)	138	(92.0)		
	Yes	29	(18.2)	12	(8.0)	7.03	0.008**
T stage	in-situ/1	26	(15.7)	4	(3.3)		
	2	56	(35.2)	44	(29.3)		
	3/4	78	(49.1)	101	(67.3)	17.48	<0.001**
N stage	0	72	(45.3)	50	(33.3)		
	1	87	(54.7)	100	(66.7)	4.61	0.032**
M stage	0	155	(97.5)	142	(94.7)		
	1	4	(2.5)	8	(5.3)	1.64	0.2
Overall stage	0/1	16	(10.1)	4	(2.7)		
	2a/2b	84	(52.8)	67	(44.7)		
	3/4	59	(37.1)	79	(52.7)	11.76	0.003**
Differentiation†	Well	21	(14.3)	22	(15.6)		
	Moderate	72	(49.0)	60	(42.6)		
	Poor	54	(36.7)	59	(41.8)	1.21	0.55
LRM	No	139	(87.4)	116	(77.3)		
	Yes	20	(12.6)	34	(22.7)	5.45	0.02**
CRM	No	108	(67.9)	86	(57.3)		
	Yes	51	(32.1)	64	(42.7)	3.70	0.054

* Chi-square test statistic and p value; ** statistically significant ($p \leq 0.05$); † 21 had unknown differentiation; LRM=longitudinal margin involvement; CRM=circumferential margin involvement; values in brackets are percentages

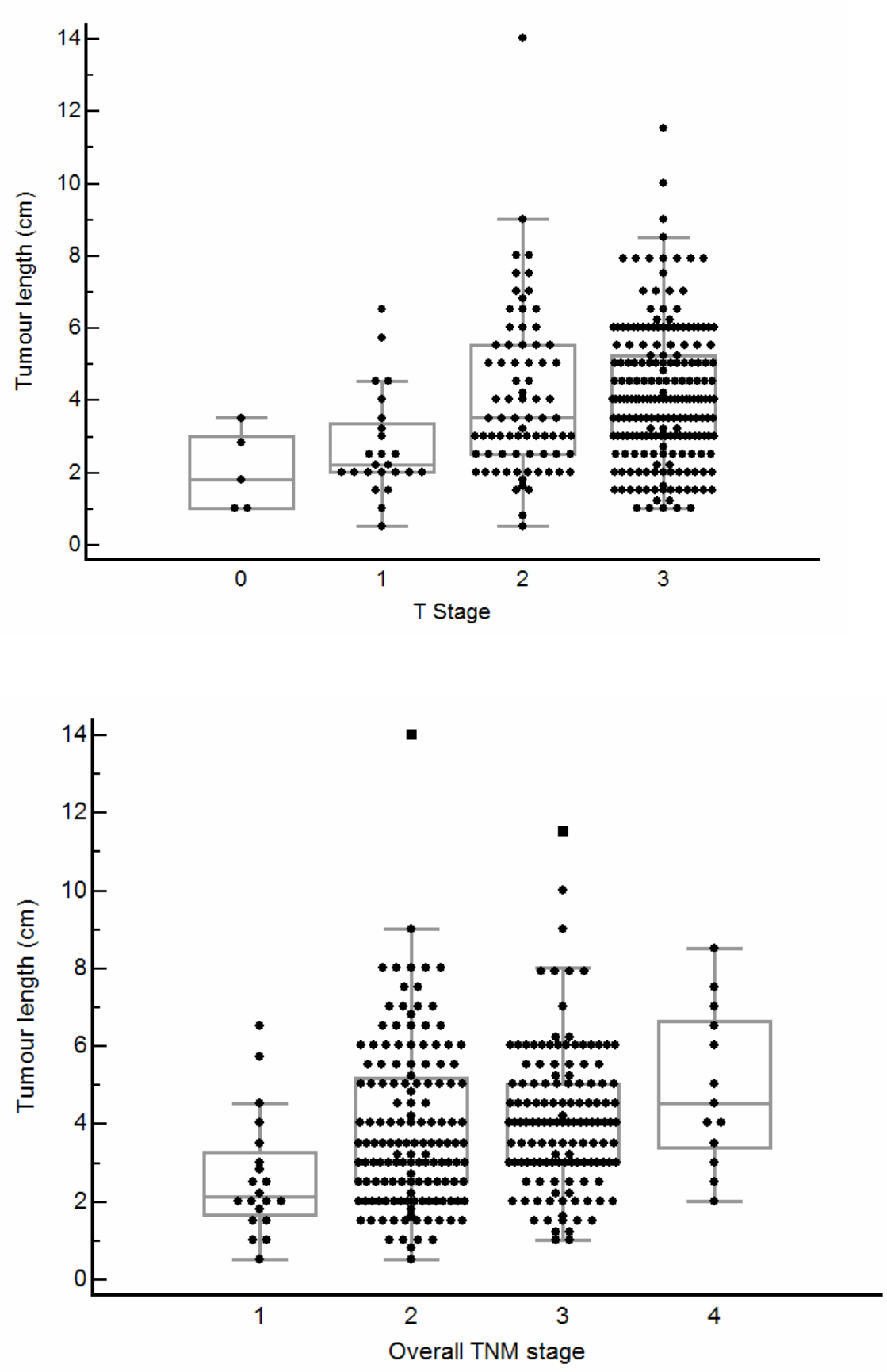

Figure 3.1. Box and whisker distribution of tumour length (cm) versus T stage and overall TNM stage in 309 patients with oesophageal cancer.

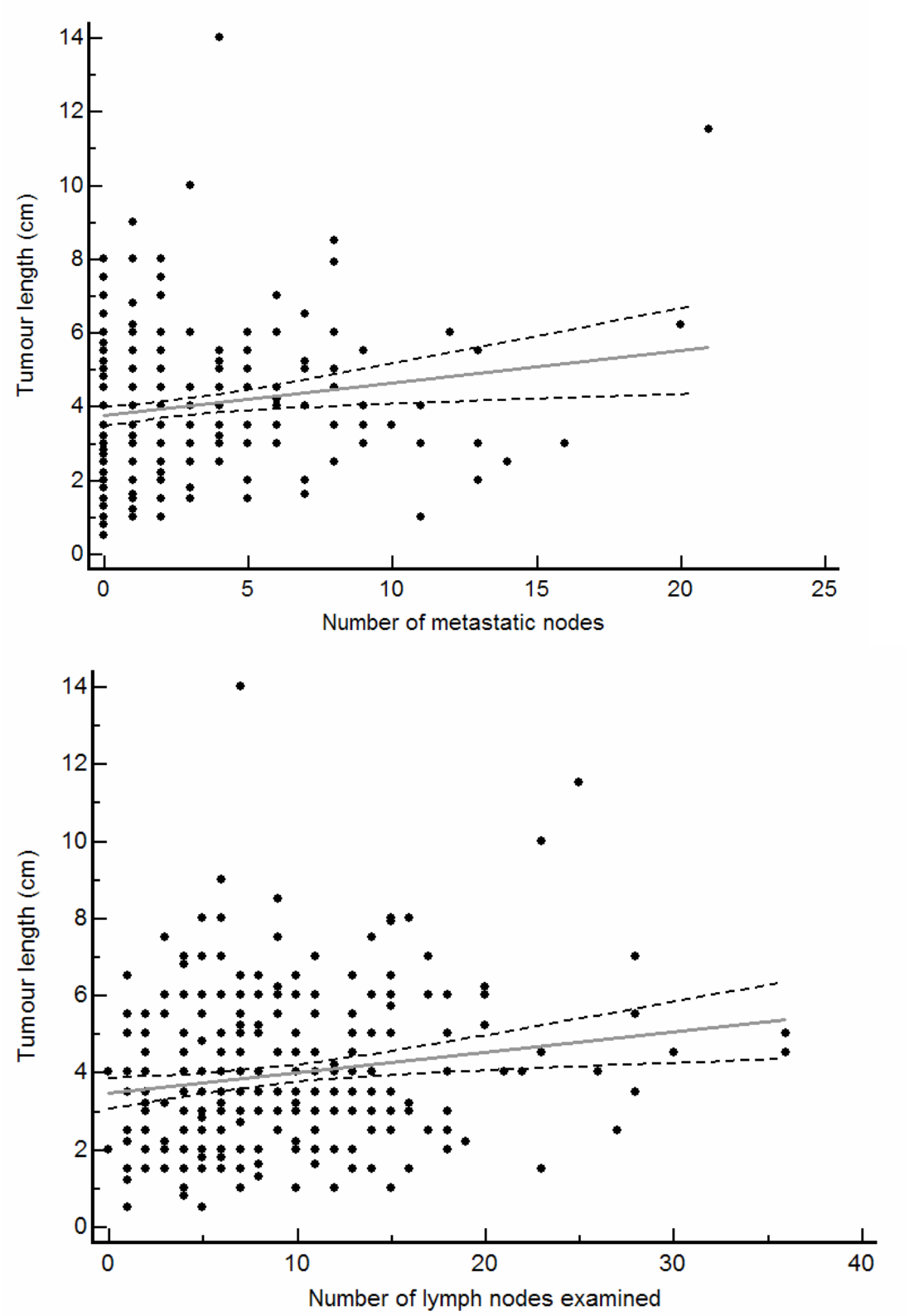

Figure 3.2. Relationships of tumour length (cm) with total number of metastatic lymph nodes and total number of lymph nodes examined in 309 patients with oesophageal cancer. Regression line with 95% confidence interval are shown.

Patient follow-up details and overall survival in the group

The 30-day mortality was 8.7% (27 patients) and these patients were excluded from the survival analysis. At the time of analysis 62.5% (193 patients) were dead (excluding post-operative deaths) and 28.8% (89 patients) alive. The median time to death was 13 months, while the median time to last follow-up in the surviving patients was 53 months.

Univariate survival analysis

The results of the Kaplan-Meier univariate survival analysis are shown in Table 3.3 and Figure 3.3. For all tumour types (Figure 3.4), tumour length >3.5 cm was a significant adverse prognostic factor (p=0.0002). The median survival time for patients whose tumours were ≤3.5 cm was 30 months (95% CI 19–41 months), whereas those with tumours >3.5 cm had a median survival of 14 months (95% CI 12–16 months). When patients who received neo-adjuvant treatment were excluded, tumour length remained highly statistically significant (p=0.0001). However, in the 41 patients who received neo-adjuvant therapy, tumour length was not a prognostic factor (p=0.96). When the different histological tumour types were assessed individually the prognostic significance of tumour length remained significant for adenocarcinomas (Figure 3.4) but not for squamous cell carcinomas (Figure 3.4). When tumour length was stratified by lymph node status it remained prognostic in N1 tumours (p=0.017) but only marginally significant in N0 tumours (p=0.057).

The strongest adverse prognostic factors in univariate analysis were high overall TNM stage (p=0.0001), advanced T stage (p=0.0001) and the presence of lymph node metastases (p=0.0001). Other statistically significant poor prognostic factors were age greater than 65 years (p=0.0015), LRM involvement (p=0.001), CRM involvement (p=0.0002), and tumour differentiation (p=0.0003) (Figure 3.3).

Table 3.3 Univariate survival analysis of clinico-pathological variables in 282 patients with oesophageal cancer treated by surgical resection*

Factor		n (events/total)	Median survival			
			Months	SE	95% CI	p
Age	< 65 yrs	89/144	30	4.0	22.1–37.9	0.002
	≥ 65 yrs	104/138	14	2.5	9.1–18.9	
Gender	Male	152/221	23	2.9	17.4–28.6	
	Female	41/61	23	4.7	13.9–32.1	0.8
Neo-adjuvant treatment	No	173/268	21	2.2	16.6–25.4	
	Yes	20/41	27	7.0	13.4–40.6	0.22
LRM	Clear	147/229	26	3.1	20.0–32.0	
	Involved	46/53	14	1.8	10.5–17.5	0.0001
CRM	Clear	105/177	30	5.2	19.7–40.3	
	Involved	88/105	15	1.1	12.9–17.1	0.0001
Differentiation**	Well	20/42	78	-	-	
	Moderate	80/116	24	2.4	19.3–28.7	
	Poor	81/105	14	1.2	11.7–16.3	0.0001
Tumour length	≤ 3.5 cm	83/142	30	5.4	19.4–40.6	
	> 3.5 cm	110/140	14	1.2	11.7–16.3	0.0001
T stage	T0/1	13/29	105	40.8	25.1–184.9	
	T2	38/68	38	8.2	21.9–54.0	
	T3/4	142/185	15	2.1	10.8–19.1	0.0001
N stage	N0	52/109	65	19.1	27.6–102.4	
	N1	141/173	15	1.0	13.0–17.0	0.0001
M stage	M0	184/273	23	2.9	17.2–28.8	
	M1	7/9	23	6.6	10.0–35.9	0.55
Overall TNM Stage	Stage 0/1	8/19	105	29.8	48.5–163.5	
	Stage 2a	44/90	41	18.0	5.6–76.4	
	Stage 2b	25/37	26	6.3	13.6–38.4	
	Stage 3/4	116/136	14	1.1	11.9–16.1	0.0001
Histological subtype	Adeno	145/208	23	2.3	18.5–27.5	
	SCC	40/63	21	8.3	4.8–37.2	
	Other	8/11	10	4.4	1.4–18.6	0.3

*Patients who died post-operatively (n=27) were excluded from the survival analysis; ** 19 had unknown differentiation

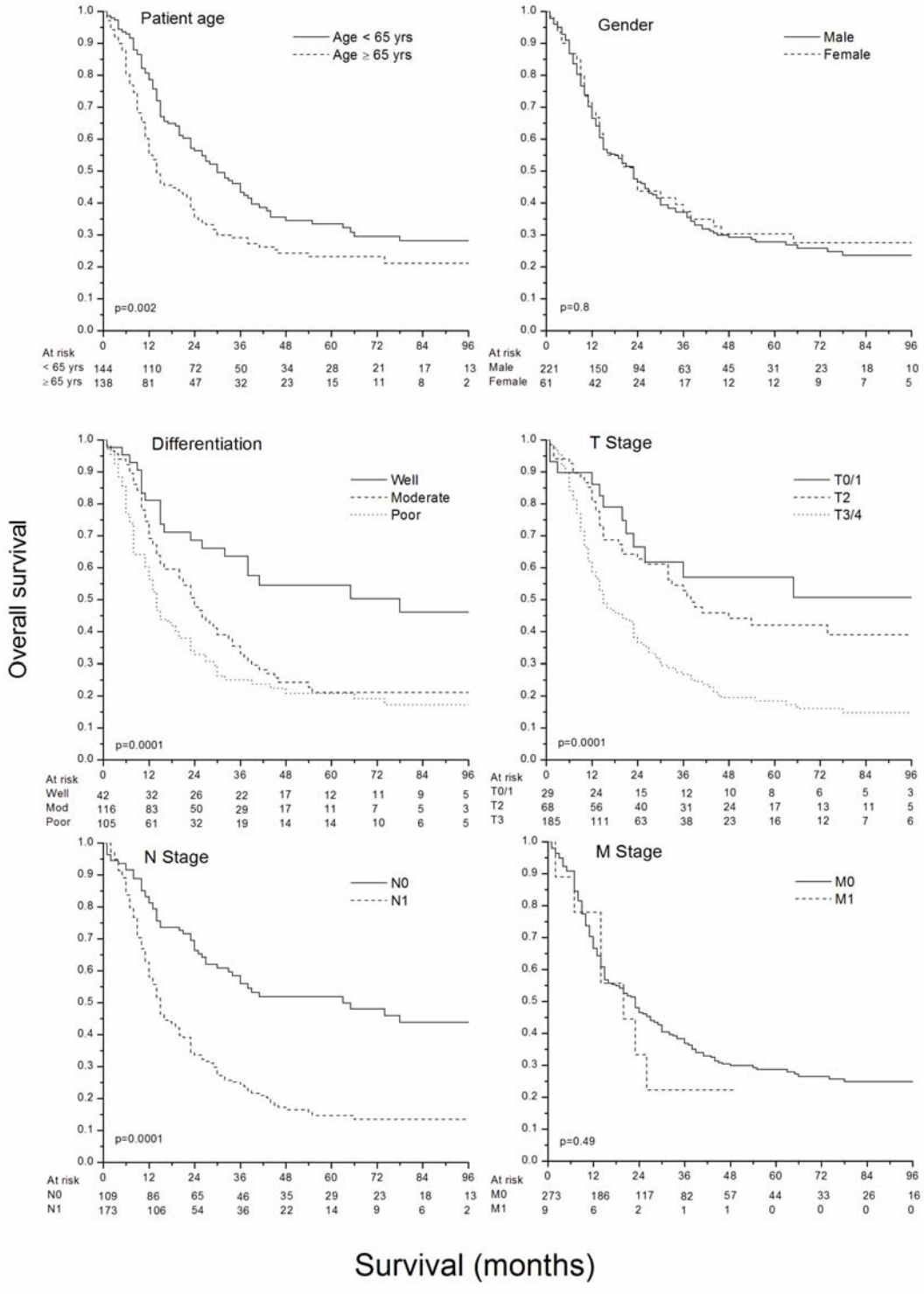

Figure 3.3 Overall survival in relation to clinico-pathological variables in 282 patients with oesophageal cancer treated by surgical resection.

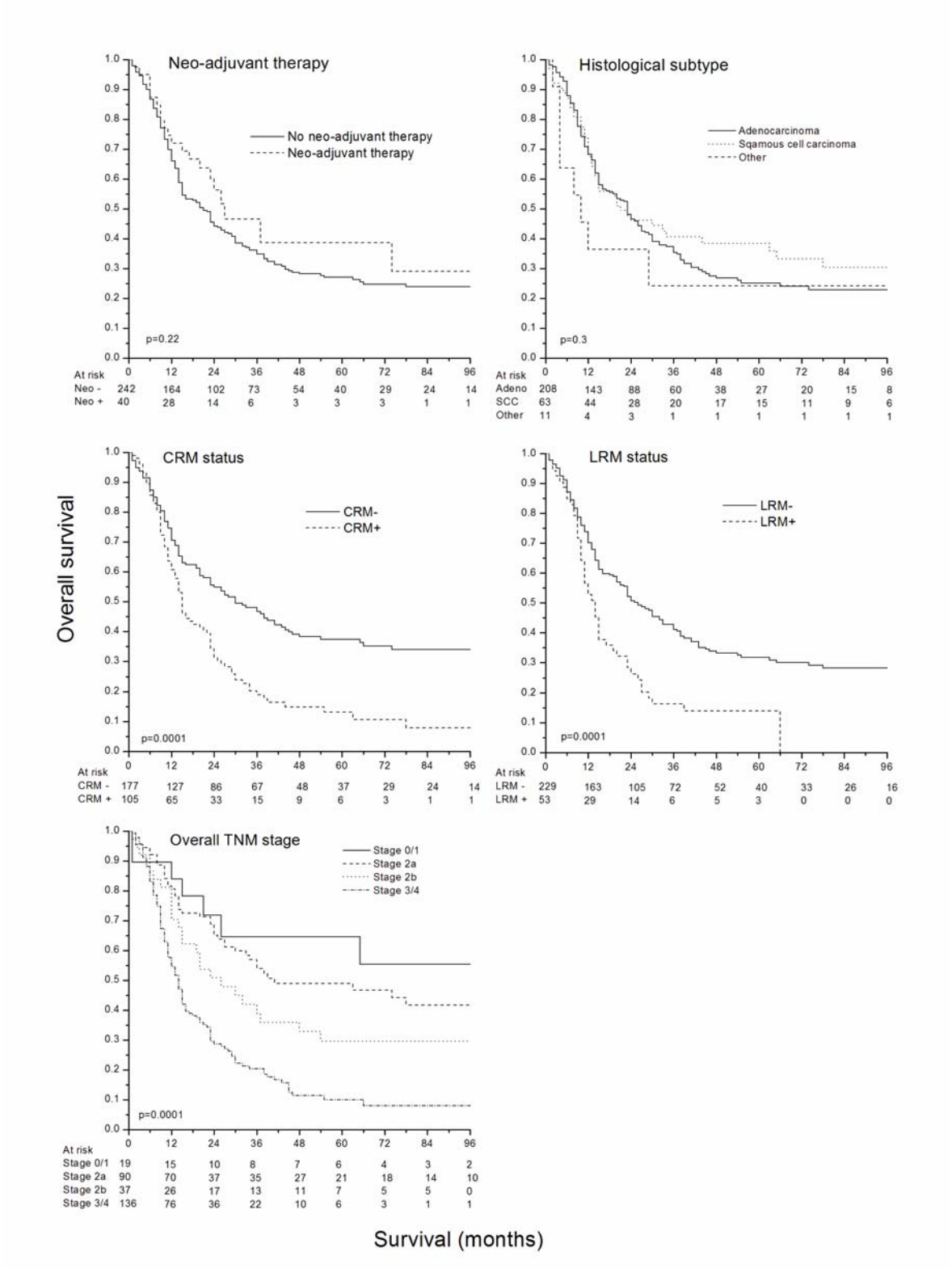

Figure 3.3 (cont) Overall survival in relation to clinico-pathological variables in 282 patients with oesophageal cancer treated by surgical resection.

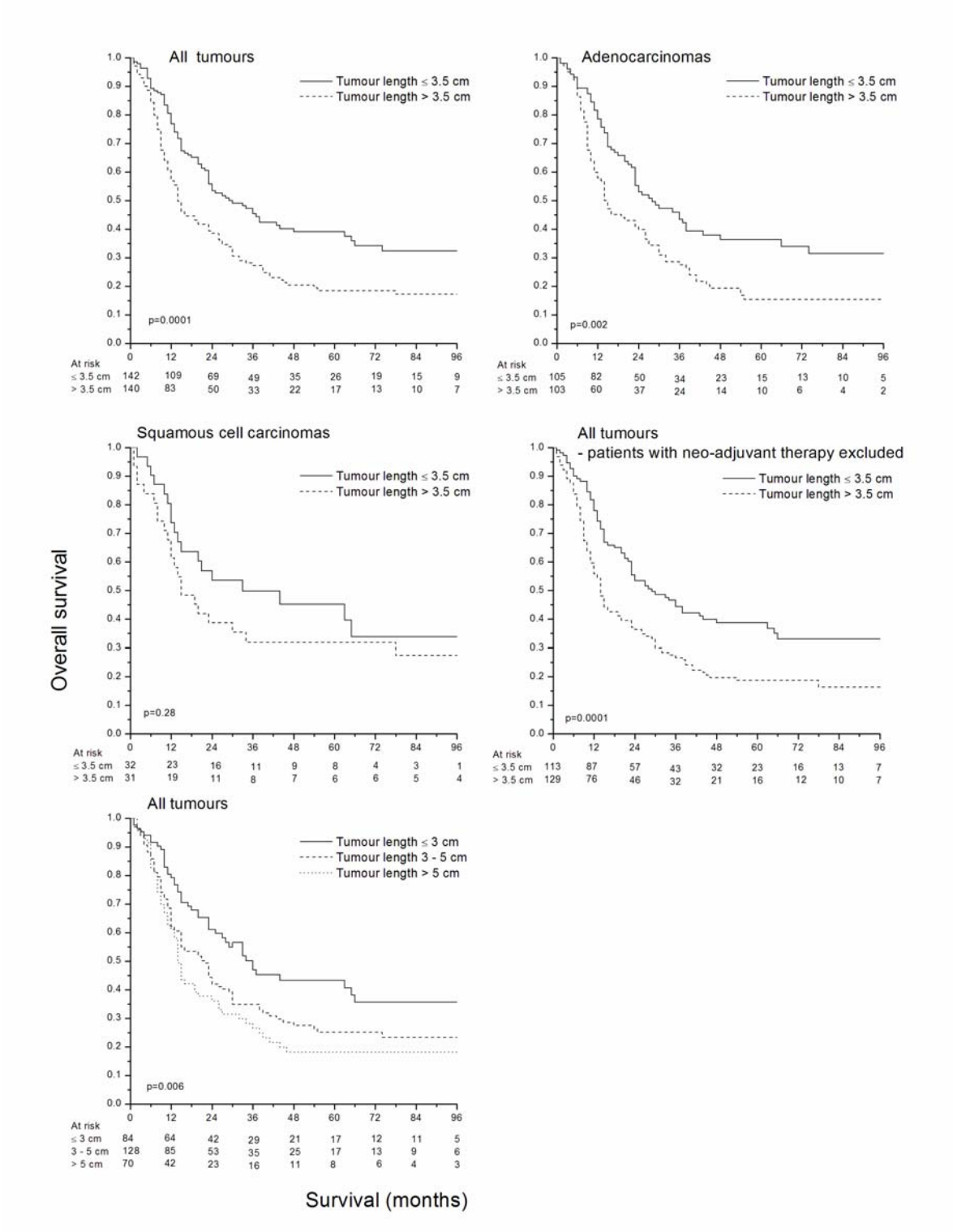

Figure 3.4 Overall survival in relation to tumour length in patients with oesophageal cancer treated by surgical resection.

Multivariate survival analysis

All statistically significant variables found on univariate analysis were entered into a Cox proportional hazards model. Multivariate analysis indicated that tumour length, patient age, tumour differentiation, N stage, LRM and CRM were significant independent prognostic factors for overall survival (Table 3.4). Patients who had tumours >3.5 cm had a 1.4 (95% CI 1.04–1.90, p=0.027) increased risk of death compared with patients with tumours ≤3.5 cm Tumour length was also significant when analysed as a continuous variable in the multivariate model (Hazard Ratio 1.12 [95% CI 1.04–1.20]; p=0.002). In other words, the risk of death increased by 12% for each centimetre increase in tumour length.

Table 3.4. Multivariate analysis of prognostic factors for overall survival using Cox's proportional hazards model.

Parameter	**Coefficient**	**HR**	**95% CI**	**p**
Age (continuous variable)	0.03	1.03	1.01–1.04	0.0001
LRM involvement	0.42	1.53	1.07–2.18	0.021
CRM involvement	0.32	1.38	1.01–1.88	0.042
Differentiation				
Well (reference)	-	-	-	-
Moderate	0.65	1.91	1.16–3.14	0.011
Poor	0.78	2.17	1.32–3.59	0.002
Tumour length (≤ 3.5 vs > 3.5 cm)	0.34	1.41	1.04–1.90	0.027
N Stage	0.88	2.42	1.71–3.42	0.0001

HR: hazard ratio, CI: confidence interval; LRM= longitudinal resection margin; CRM = circumferential resection margin

3.2.3 CRM as a prognostic marker

Patient characteristics

The 249 patients studied were a subgroup of the previous cohort of patients who underwent a potentially curative oesophagogastrectomy. Patients with metastatic (M1a or M1b) disease at surgery; involvement of the LRM; T4 tumours and other palliative surgical resections were excluded from this group.

The characteristics of patients included in the analysis are described in Chapter 2 (Table 2.3). There were 195 males and 54 females, with a median age of 64 (range 24–84) years. A total of 178 adenocarcinomas and 61 squamous cell carcinomas were included in the study. The remaining ten carcinomas were of mixed adenosquamous type. The gastro-oesophageal junction (n=117) and lower third of the oesophagus (n=82) were the predominant carcinoma locations. The remainder were located in the middle third (n=48) and upper third (n=2) of the oesophagus. Neo-adjuvant chemotherapy was given to 34 patients. The regime used was principally cisplatin and 5-fluorouracil given for 2 cycles pre-operatively as in the OEO2 trial (MRC 2002).

CRM involvement

CRM was involved in 79 of 249 (32%) of patients. Table 3.5 summarises the clinicopathological characteristics of the patients according to CRM status. Only patients with T3 tumours had CRM involvement. Patients with CRM involvement were more likely to have lymph node metastases, longer tumours and more advanced overall TNM stage (Table 3.5).

Patient follow-up details and overall survival of the group

Twenty four patients died within 30 days of surgery and were excluded from the survival analysis. At the time of analysis 157 patients had died (excluding post-operative deaths) and 68 patients were alive. The median time to death was 14 months, while the median time to last follow-up in the surviving patients was 70 months.

Table 3.5 Clinicopathological features of patients in relation to CRM involvement (n= 249)

Factor		CRM involvement		
		Not involved	Involved	χ^2 p value *
Gender	Male	135	60	
	Female	35	19	0.54
Age	< 65 yrs	84	44	
	≥ 65 yrs	86	35	0.36
Neo-adjuvant treatment	No	148	69	
	Yes	22	10	0.95
Differentiation ‡	Well	32	6	
	Moderate	73	36	
	Poor	57	30	0.09
Tumour length (cms)	≤ 3.5 cm	100	35	
	>3.5 cm	70	44	0.032 †
T stage	T in-situ/T1	27	0	
	T2	67	0	
	T3	76	79	0.0001 †
N Stage	N0	87	22	
	N1	83	57	0.001 †
Overall stage	Stage 0/1	19	0	
	Stage 2a	68	22	
	Stage 2b	36	0	
	Stage 3	47	57	0.0001 †
Histological subtype	Adeno	117	61	
	SCC	46	15	
	Others	7	3	0.37
Operative approach	LTA[¥]	106	50	
	Ivor-Lewis	52	23	
	Other	6	4	
	Unknown	6	2	0.91

* Chi-squared test; † statistically significant; ‡ 15 cases had unknown tumour differentiation; [¥] LTA = left thoracoabdominal approach.

Univariate survival analysis

Table 3.6 shows the details of the univariate survival analysis. The median survival of patients without CRM involvement was 37 months (95% CI 27–47 months) compared with only 18 months (95% CI 13–23 months) if the CRM was involved (p=0.0001) (Figure 3.5a).

Since only T3 tumours in this study had evidence of CRM involvement these tumours were assessed in more detail. Figure 3.5b shows the effect of CRM on survival in T3 tumours. There was a trend for T3CRM+ tumours to be associated with a worse prognosis than T3CRM- tumours (p=0.074). However, when sub-stratified by lymph node burden CRM status had prognostic value in T3 tumours with low metastatic lymph node ratio (≤25% nodes affected) (Figure 3.5c) compared with T3 tumours with a high metastatic lymph node ratio (>25% nodes affected) (Figure 3.5d).

Multivariate survival analysis

All statistically significant prognostic factors on univariate analysis were entered into a Cox proportional hazards multivariate analysis. CRM status, patient age and overall TNM stage were independent predictors of outcome (Table 3.7). The HR for risk of death with CRM involvement was 1.69 (95% CI 1.16–2.48). Age was an independent prognostic factor as a continuous variable; the HR for risk of death increased by 3% (95% CI 1.0–5.0%) for every yearly increase in a patient's age.

Table 3.6 Treatment outcome analysis for patients who had potentially curative surgery (n=225)

Factor				Median survival			
		n (events/total)	%	Months	SE	95% CI	p
Age	< 65 yrs	76/118	64	35	4.5	26.2 – 43.8	
	≥ 65 yrs	81/107	76	18	3.4	11.4 – 24.6	0.011†
Gender	Male	122/176	69	28	3.6	20.9 – 35.1	
	Female	35/49	71	24	9.1	6.1 – 41.8	0.97
Neo-adjuvant treatment	No	139/192	72	25	3.2	18.6 – 31.4	
	Yes	18/33	55	37	12.0	13.5 – 60.5	0.36
CRM	Clear	94/153	61	37	4.9	27.5 – 46.5	
	Involved	63/72	88	18	2.4	13.3 – 22.7	0.0001†
Diff*	Well	20/37	54	65	33.3	0 – 130.3	
	Moderate	68/96	71	28	4.5	19.2 – 36.8	
	Poor	61/79	77	15	3.0	7.3 – 22.7	0.005†
Tumour length	≤ 3.5 cm	74/120	62	35	6.3	22.7 – 47.3	
	> 3.5 cm	83/105	79	20	5.0	10.1 – 29.9	0.004†
T Stage	T0/1	13/26	50	73	32.1	10.0 – 136.0	
	T2	32/57	56	48	21.7	5.5 – 90.5	
	T3	112/142	79	21	2.6	15.8 – 26.2	0.0001†
N Stage	N0	48/96	50	73	14.9	43.8 – 102.2	
	N1	109/129	84	15	2.2	10.4 – 19.6	0.0001†
% lymph node metastases**	≤25%	94/155	61	35	4.5	26.1 – 43.9	
	>25%	62/68	91	15	2.9	9.4 – 20.6	0.0001†
Overall TNM Stage	Stage 0/1/2a	48/96	50	73	14.9	43.8 – 102.2	
		24/32	72	22	6.8	8,6 – 35.4	
	Stage 2b Stage 3	85/97	88	15	1.3	12.4 – 17.6	0.0001†
Histological subtype	Adeno	116/163	71	28	3,5	21.1 – 34.9	
	SCC	35/53	66	32	9.6	13.2 – 50.8	
	Other	6/9	66	10	3.3	1.2 – 18.8	0.64

*13 cases had unknown tumour differentiation, ** in 2 cases the percentage of lymph node metastases could not be calculated, † statistically significant, SCC = squamous cell carcinoma

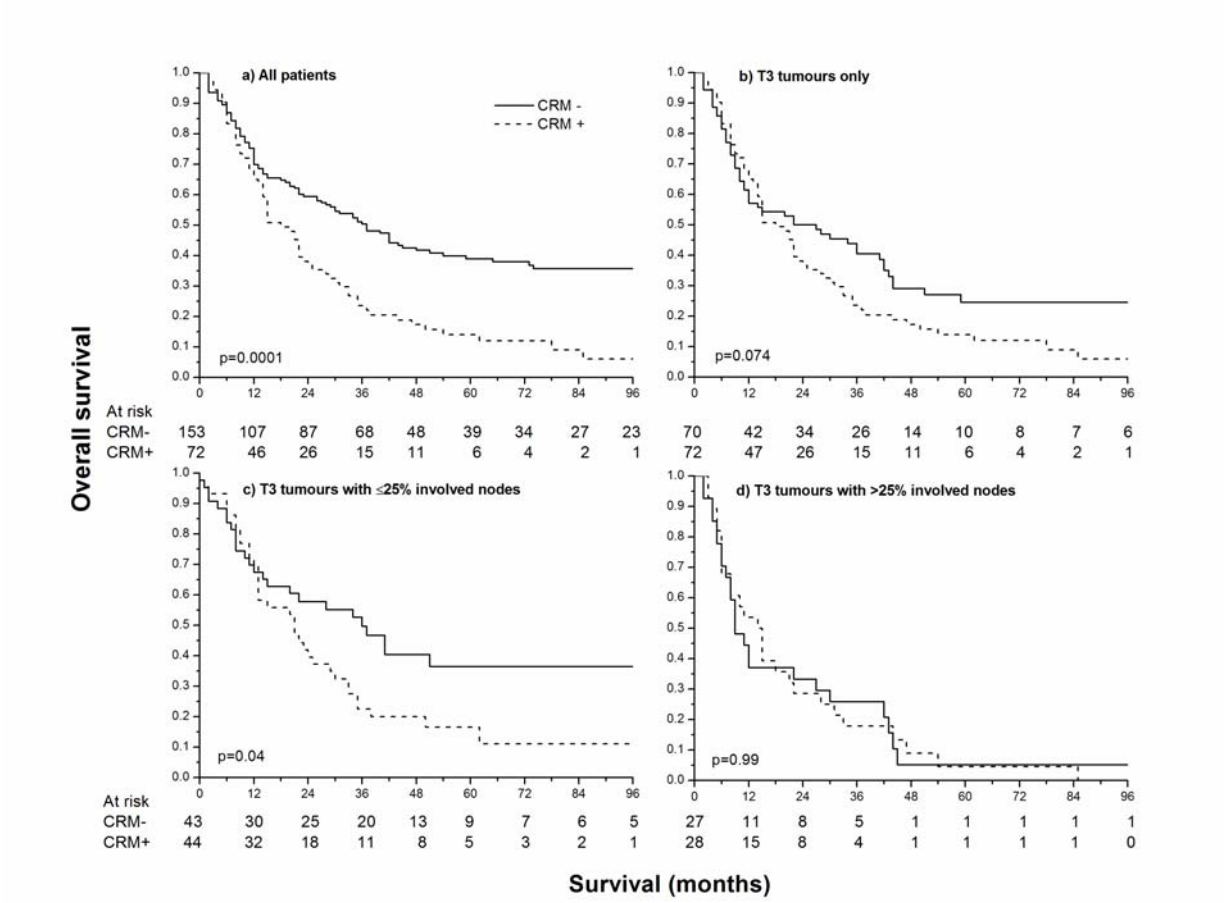

Figure 3.5 Kaplan-Meier survival graphs of overall survival in relation to CRM status for all patients in the study (n=225) (a); CRM status in T3 tumours only (b); CRM status in T3 tumours with a low (≤25%) metastatic lymph node burden (c); and CRM status in T3 tumours with a high (>25%) metastatic lymph node burden (d).

Table 3.7 Multivariate survival analysis

Parameter	HR	95% CI	p Value
CRM status	1.69	1.16 – 2.48	0.007
Age (continuous variable)	1.03	1.01 – 1.05	0.0001
Overall stage 0/1/2a (reference)	-	-	-
Overall stage 2b	2.28	1.37 – 3.82	0.002
Overall stage 3	2.81	1.89 – 4.18	0.0001

HR=hazard ratio, CI = confidence interval

3.3 DISCUSSION

3.3.1 Tumour length as a prognostic factor

Summary

I observed that increasing length of resected oesophageal tumour was associated with several adverse pathological features, including worse T stage, N stage, overall TNM stage and involvement of the surgical resection margins. Tumour length was a significant adverse prognostic factor in univariate survival analysis and remained an independent prognostic factor in multivariate analysis. The risk of death increased by 12% for each centimetre increase in length of the oesophageal tumour.

Comparison with other studies

Few other studies have looked at the relationship between tumour length and patient survival in oesophageal cancer, with only one large study having this as its primary aim (Eloubeidi et al. 2002). This large study was population based and performed in the USA using National Cancer Institute Surveillance, Epidemiology and End Results (SEER) data (Eloubeidi et al. 2002). Although the study involved 10,441 patients, tumour length data were missing from over half. The methods of assessing tumour length were variable and included measurements from pre-operative endoscopy, radiological investigations and histopathology. Furthermore patients were treated using various modalities including surgery. Nonetheless, they also observed that tumour length was an independent prognostic factor. The 2-year survival of patients with tumours measuring 1 cm was 78% compared with 18% for tumours measuring 9-10 cm. They proposed a modification to the TNM staging classification, where the T stage could be suffixed with either an 'a' (≤3 cm length) or a 'b' (>3 cm length), as the most current version of the UICC TNM system does not include tumour length in the classification (Sobin 2002). It is of interest to note that tumour length was used as a part of the staging criteria in the 1983 version of TNM (AJC) staging system for oesophageal tumours (Thompson 1983). Non-circumferential tumours <5 cm in length and causing no obstruction and were classified as T1. Tumours >5 cm in length or that were causing obstruction or were circumferential were designated T2.

In a recent prospective study assessing 219 patients who underwent resection for oesophageal cancer who did not have lymph node metastases, tumour length was not found to be a prognostic factor (p=0.86) (Khan et al. 2004). In this study, patients with

positive surgical resection margins and lymph node metastases were excluded. As tumour length is strongly associated with these adverse factors, so their exclusions might have reduced the prognostic significance of tumour length. Despite these associations, however, tumour length remained an independent prognostic factor in multivariate analysis.

Subgroup analysis showed that tumour length was not statistically significant in the squamous cell carcinoma group. It is likely that the small size of this group may have underestimated the prognostic effect of tumour length; however a biological reason for this cannot be excluded. Although a relationship between tumour length and survival in squamous cell carcinoma was not found, this has been shown before by other authors (Igaki et al. 2001; Tachibana et al. 2002). Tachibana et al reviewed 76 patients who were treated surgically with curative intent and found that tumours >3 cm had a worse survival (p=0.02) (Tachibana et al. 2002). The 6-year survival for 16 patients with tumours <3 cm was 63% compared to 33% for 60 patients with tumours >3 cm. Igaki et al reviewed 116 patients who had squamous cell carcinoma of the lower oesophagus who underwent three-field lymph node dissection (Igaki et al. 2001). Interestingly although they found that tumour length of >5 cm determined histologically was a poor prognostic factor (p=0.03), pre-operative tumour length determined by barium swallow examination was not (p=0.24).

Tumour length as a prognostic factor in patients treated with radiotherapy

Tumour length has been shown to be a prognostic factor in patients who undergo radical radiotherapy for oesophageal cancer (Newaishy et al. 1982; Slevin et al. 1989; Yamakawa et al. 1994; Yang et al. 1983). In these studies the predominant tumour type was squamous cell carcinoma and tumour length was measured either by oesophagoscopy or barium studies. Patients with the best 5-year survival rates had tumours lengths <5 cm in length, upper third oesophageal tumours, good performance status and good response to radiotherapy (Newaishy et al. 1982; Slevin et al. 1989). A study in inoperable locally advanced oesophageal cancer found that the 5-year survival of tumours <5 cm was 18%, 10% in tumours 5-10 cm in length and only 3% for tumours >10 cm (Okawa et al. 1989). In another study, the 5-year survival rates for male patients with tumour length <5 cm was 11% compared with only 3% for those with tumours 5-10 cm long (p<0.05). However, in females the 5-year survival rates were not statistically different when stratified by tumour length: 13% in tumours <5 cm and 11% in tumours 5-10 cm (Newaishy et al. 1982).

Tumour length as a prognostic factor in patients treated with chemo-radiotherapy

In a study of 117 patients with oesophageal cancer treated with chemo-radiotherapy, tumour length was associated with a poor prognosis in multivariate analysis (Gill et al. 1992). The treatment regime consisted of 35-60 Gy over 4 weeks with concurrent fluorouracil and cisplatin administered intravenously. In addition, surgical resection was performed in 44 patients 4-6 weeks after completion of the chemotherapy. Univariate survival analysis showed that patients with tumours <5 cm had a significantly longer survival ($p = 0.016$). Tumour length and a complete response to treatment were the only two factors which were significant in multivariate analysis.

Effect of neo-adjuvant therapy on tumour length

It was observed that patients who were treated with neo-adjuvant chemotherapy had significantly shorter tumours. Although this could have occurred either as a selection bias or by chance, it is likely that pre-operative treatment led to significant tumour shrinkage. As this study was retrospective and pre-operative tumour measurements were unavailable this remains an area for speculation.

Benefits and limitations of this work

In this study, tumour length measurements were obtained by histopathological examination of the fixed (unpinned) resection specimen, which is the most accurate method of assessing tumour length. As the length of the specimen may vary depending on whether it is taken pinned or unpinned, the Royal College of Pathologists Minimum Dataset for the reporting of oesophageal cancer recommended that this information is documented on the pathology report (Mapstone 1998). However, despite the fact that the oesophagus can contract by up to a quarter of its length on removal and fixation (Siu et al. 1986), the tumour portion appears to contract very little. There are accurate correlations between endoscopic ultrasound (EUS) determination of tumour volume and histopathological volume (Shinkai et al. 2000). In that study the tumour dimensions contracted to only 92% of the original area after formalin fixation (Shinkai et al. 2000).

Pre-operative assessment of tumour length

There are many potential methods of assessing tumour length pre-operatively including barium oesophagram, oesophago-gastroscopy, CT, EUS and PET imaging. Routine pre-operative staging at South Manchester University Hospitals NHS Trust included

oesophago-gastroscopy and CT of the thorax and abdomen to exclude the presence of metastatic disease. EUS and PET imaging were used in selected clinical circumstances in a small minority of recently treated patients. As tumour length was not accurately or routinely documented by pre-operative methods and because of the retrospective nature of these results it was not possible to correlate pre-operative tumour length measurements with the final histopathological specimen. Recent studies showed promise in evaluating tumour length by EUS and PET.

Endoscopic assessment of tumour length

Few studies have assessed the clinical utility or accuracy of measuring tumour length by endoscopy. However, a recent study evaluated 213 consecutive patients with oesophageal cancer to assess whether simple clinical and endoscopic criteria could predict early stage disease (T1, N0) prior to surgical treatment (Portale et al. 2005). In patients who did not complain of dysphagia and had a tumour length <2 cm and a non-circumferential lesion, the positive predictive value for early stage disease was 82%. Interestingly, however, even in this group of patients 14% were found to have lymph node metastases in the surgical specimen. The study may have implications for the selection of patients for local treatments of oesophageal cancer, such as endoscopic mucosal resection (EMR).

Endoscopic ultrasound assessment of tumour length

Two small studies have utilised EUS pre-operatively to correlate tumour length with pathological variables or prognosis. Bhutani et al examined 35 patients using EUS and found that tumours with a length >5 cm or that were sufficiently stenotic to prevent passage of the endoscope, were much more likely to be T3 or higher lesions (Bhutani et al. 2002). In addition, they also found that tumours <5 cm in length had a 92% chance of being either T1 or T2. Shinkai et al assessed tumour volume (as calculated from tumour length and cross-sectional area) and prognosis in 113 patients with squamous cell carcinoma of the oesophagus (Shinkai et al. 2000). They found a significant correlation between EUS measurements and pathological measurements (r=0.92). The prognosis of patients decreased with increasing tumour volume; patients with tumours <50 mm^3 had a five-year survival rate of 100%, whereas those with tumours >300 mm^3 had a five-year survival of 29%. However, the EUS measurements of long oesophageal tumours is associated with a decrease in the accuracy of T stage, lymph node metastases, and metastatic disease assessment (Heeren et al. 2004; Rice et al. 2005). The accuracy of EUS was greater in tumours ≤5 cm than in tumours >5 cm (82% vs

52% for the T stage, p<0.05; 88% vs 59% for the N stage, p<0.05; 92% vs 56% for the M stage, p<0.001) (Heeren et al. 2004). In light of these drawbacks, it will be important to assess further tumour length as a prognostic marker in large prospective studies using EUS. The correlation between pre-operatively determined tumour length and important histopathological variables in the surgical specimen as well as prognosis will be of interest.

Positron emission tomography (PET) assessment of tumour length

A preliminary study used PET imaging to assess pre-operative tumour length as a prognostic marker using the uptake of ^{18}F-FDG (Choi et al. 2004). Although they included only 69 patients, tumour length <3, 3-5 and ≥5 cm were associated with an overall survival of 82, 68 and 32 months respectively (p=0.018). They found tumour length to be a significant independent prognostic factor on multivariate analysis (p=0.01). The non-invasive nature of PET imaging and the fact that ^{18}F-FDG PET appears to be more accurate at identifying lymph node and distant metastatic disease than either CT or EUS make this an exciting staging modality (Kato et al. 2002; Wallace et al. 2002).

3.3.2 CRM as a prognostic marker

CRM involvement was associated with advanced T stage, longer tumour length, greater burden of lymph node metastases and worse TNM stage. Overall, the median survival time for patients with CRM involvement was only 18 months compared to 37 months for those without CRM involvement. In multivariate analysis, CRM involvement, patient age and overall TNM stage were independent predictors of survival. As CRM involvement in this study was only found in T3 tumours these were analysed separately. Overall there was a trend for worse prognosis in T3CRM+ compared with T3CRM- tumours. However, in T3 tumours with a low metastatic lymph node burden CRM status was significant at predicting survival. In patients with a high metastatic lymph node burden, CRM status had no statistical prognostic relevance, suggesting that lymph node involvement is a much stronger prognostic marker in this sub-group.

Differences in CRM status between oesophageal and rectal cancer

In rectal cancer, the risk of local recurrence increases 12-fold with involvement of the CRM (Adam et al. 1994). Although the prognostic role of CRM status has been well established in rectal cancer, important differences exist between the two tumour sites

(Figure 3.6). The oesophagus lacks a serosal layer, so that tumours originating in the oesophagus can easily spread into any of several important structures, such as the heart, aorta, trachea and lung. The majority of these adjacent structures cannot be sacrificed and resected en-bloc. In addition, there is no specific fascial boundary equivalent to the mesorectal or Denonvillier's fascia present in the rectum.

CRM involvement in the oesophageal cancer specimen may therefore be much more a consequence of advanced tumour stage than the skill of the surgeon in carrying out a complete resection. Nevertheless, involvement of the CRM may be an indicator of the quality of pre-operative staging. At present most pathologists open oesophagogastric resections longitudinally, with or with out pinning out of the fresh specimen, for fixation. This does not allow good comparison with radiological imaging. In rectal tumours transverse slices through the tumour are advocated to allow comparison with MRI (Figure 3.6). If the quality of oesophagogastric cancer pre-operative staging is to be studied concisely transverse slices through the tumour are recommended.

It is only with further investigation into CRM status that a level of understanding can be achived to equal that in field of rectal cancer. For example studies are needed which directly compare histopathological and pre-operative cross-sectional imaging date in order to try and predict CRM involvement and thus the need for neo-adjuvant therapy prior to resection.

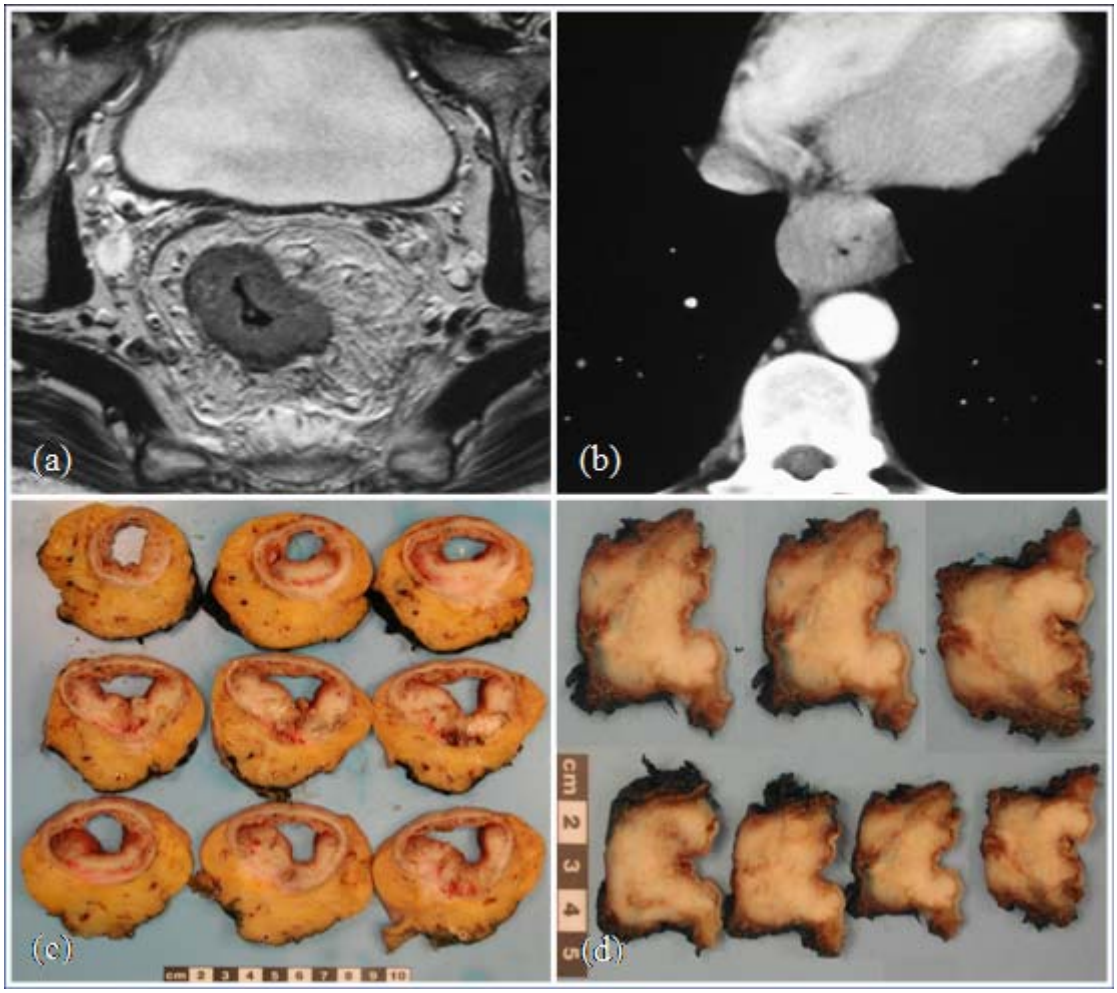

Figure 3.6 Anatomical differences between the rectal and oesophageal tumour locations shown by radiological imaging and pathological specimens

(a) MRI of the pelvis showing the ample surrounding mesorectal tissue and fascia, in comparison with (b) which shows a CT image of the mediastinum demonstrating how little tissue separates the oesophagus from important unresectable structures such as the aorta and heart. (c) Transverse cut sections of anterior resection specimen for rectal cancer; this method of sectioning allows direct comparison with the pre-operative MRI staging. (d) Oesophageal tumours are often cut longitudinally; this does not allow direct comparison with pre-operative radiological staging.

Comparison with previous studies assessing CRM status and prognosis in oesophageal cancer

Few studies have assessed the impact of CRM margin status in oesophageal cancer (Table 3.1). Sagar et al assessed 50 patients undergoing oesophagectomy and showed that involvement of the CRM was associated with increased risk of local disease recurrence and reduced 2-year survival (Sagar et al. 1993). The results in this chapter are comparable to those of Dexter et al who prospectively studied 135 patients undergoing potentially curative oesophagogastrectomy (Dexter et al. 2001). CRM involvement in their study was 47%, compared with 33% found in this chapter study.

They showed that survival was significantly reduced in patients with CRM involvement and it was an independent predictor of survival. The findings in this chapter are comparable with their data, as when they stratified patients into low and high nodal metastatic burden, the effect of CRM status on survival was more pronounced in patients with low metastatic lymph node burden (≤25% involved).

CRM involvement is often considered to be representative of advanced tumour spread and the results presented in this chapter would support this notion. Other studies have shown that CRM involved tumours have a higher incidence of poor prognostic features, such as tumour budding (Roh et al. 2004) and bone marrow metastases (Spence et al. 2004).

The influence of surgical technique and extent of surgical resection on CRM status

There is limited information on the effect of surgical technique on CRM status. The Scottish Audit of Gastric and Oesophageal Cancer (SAGOC) compared CRM status in 371 patients treated surgically for oesophageal cancer (SAGOC 2002). CRM involvement was common; in 68% of patients with an incomplete resection an involved CRM was the cause. Rates of CRM involvement (excluding multiple margin involvement) were 36% in transhiatal resections, 24% in left thoracoabdominal resections and 15% in Ivor-Lewis procedures (SAGOC 2002).

Khan et al found no difference in survival between patients with or without CRM involvement (Khan et al. 2003). There is a suggestion from this study that the more aggressive surgical resection may lessen the prognostic impact of CRM status. In support of this hypothesis, the surgical technique favoured extensive mediastinal dissection with en-bloc oesophagogastrectomy performed by one dedicated team of thoracic surgeons. In this chapters results and that of Khan et al only T3 tumours (tumour invading the adventitia) had evidence of CRM involvement. Whereas in the study by Dexter et al there were cases of T2 tumours (tumours invading muscularis propria) with CRM involvement (Dexter et al. 2001). In addition, Khan et al reported the lowest rate of CRM involvement (20%). It would therefore appear that the prognostic impact of CRM status is related to how radical the resection is. This has been shown to occur in rectal cancer surgery where the prognostic effect of CRM involvement is lessened with a more radical approach (Merchant et al. 1999).

Several studies have shown that radical en-bloc oesophagectomy appears to improve survival even in patients with transmural tumours and lymph node metastases

(Clark et al. 1994; Johansson et al. 2004; Nigro et al. 1999) . However, this is only true if a small number of metastatic lymph nodes are present. These studies may be biased by the effect of stage migration, but they support the main findings of this chapter; namely that patients with T3 tumours and a negative CRM can achieve a better survival if a low percentage (≤25%) of lymph node metastases is found.

Patient age as a prognostic factor in oesophageal cancer

Patient age was a strong prognostic factor on univariate and multivariate analysis. Numerous studies have found that age alone should not be a barrier to surgical treatment and that with careful patient selection morbidity, post-operative mortality and subsequent 5-year survival rates are not significantly different compared with younger patients (Bonavina et al. 2003; Johansson et al. 2000; Sabel et al. 2002). In a study assessing the prognosis of elderly patients following oesophageal surgery (Poon et al. 1998), younger patients had a better overall outcome compared to patients aged greater than 70 years, however there was no difference in survival when deaths from unrelated medical conditions were excluded.

Limitations and benefits of this work

Although the results presented in this chapter were retrospective and involved both thoracic and upper gastrointestinal surgeons, a major benefit is the long follow-up period. As specific cause of death data were unavailable, all-cause mortality was chosen as an end point. This study assessed CRM status with regard to patient survival; it did not specifically examine modes of tumour recurrence following surgery. Unfortunately loco-regional tumour recurrence affects between 12% and 27% of patients even following an apparently curative procedure (Dresner et al. 2000; Mariette et al. 2003). Sagar et al showed that CRM involvement was associated with increased rates of local tumour recurrence (Sagar et al. 1993). In their work eleven out of the 20 patients (55%) with involved CRM developed histologically proven local recurrence, compared with only four of the 30 patients (13%) without CRM involvement ($p<0.01$).

Neo-adjuvant chemotherapy and CRM status

Pre-operative chemotherapy appeared to have no effect on the rate of CRM involvement, however, only a small percentage of patients were treated in this way. The use of multimodal therapy significantly reduced resection margin involvement in a study by Mulligan et al (Mulligan et al. 2004) who randomised 212 patients to receive either surgery alone or multimodal therapy. The multimodal group had a significant reduction in resection margin involvement, locoregional tumour recurrence and a survival advantage compared with the surgery alone group. They hypothesised that the survival advantage observed resulted from a decreased rate of resection margin involvement. However, the MRC's recent OEO2 trial showed no apparent difference in CRM status between the surgery only and pre-operative chemotherapy arms despite showing a significant survival advantage (MRC 2002). However, surgical treatment was not standardised in the OEO2 study as individual surgeons chose their own preferred technique. Prescriptive surgical protocols have been designed for future MRC studies to ensure that surgical treatment is standardised.

3.4 CONCLUSIONS

3.4.1 Tumour length as a prognostic marker

Tumour length >3.5 cm determined histologically is significantly associated with adverse pathological features, advanced TNM stage and poor overall patient survival in both univariate and multivariate analyses. The risk of cancer related death increases by 12% for each centimetre increase in oesophageal tumour length as measured by histopathology. Well designed prospective studies assessing the pre-operatively determined tumour length and correlation with histopathological variables are required. Preliminary work using endoscopic ultrasound and PET imaging, although expensive and not widely available, have shown encouraging results. If preoperative tumour length results prove to have similar as those observed in this chapter, this may ultimately assist in patient selection for appropriate treatments. Future revisions of the TNM classification system for patients with oesophageal adenocarcinoma should include tumour length. Adequate knowledge of simple clinico-pathological measurements which correlate highly with prognosis are required before embarking on studies to assess potential molecular prognostic factors.

3.4.2 CRM as a prognostic marker

Following a potentially curative oesophagogastrectomy, the presence of microscopic tumour either at or within 1 mm of the CRM is a statistically significant adverse prognostic factor in univariate and multivariate analysis. CRM involvement reflects advanced disease and occurred in T3 tumours only. The prognostic impact of CRM status appears to depend on the degree of lymphatic nodal burden and the extent of surgical en-bloc resection. However, even with T3 tumours an improved prognosis can be achieved with a radical resection and a clear CRM, but only in patients with a low percentage of lymph node metastases. CRM involvement should be reported in surgical and oncological trials as it reflects the extent of tumour resection and may be useful in comparing different surgical techniques. It should continue to be routine to comment on this variable in histopathology reports of resected specimens.