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Ten years experience of managing the primary tumours in patients with stage IV colorectal cancers

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ABSTRACT

Introduction: Approximately 20% of patients with colorectal cancer have metastases at the time of presentation. Such patients are often offered systemic chemotherapy but debate continues as to whether these patients benefit from resection of the primary tumour. We describe our ten years experience of managing the primary tumours in patients with stage IV colorectal cancer. The aim of this study was to describe the overall survival of patients undergoing surgery in these circumstances and to determine whether any prognostic indicators could be identified.

Patients & methods: 920 consecutive patients presenting with stage IV colorectal cancer disease were identified from the Leicester Colorectal Cancer database. Patients undergoing resection of the primary tumour (Resection Group) with the residual metastatic disease were compared to those patients who had not their primary tumour excised (Non-Resection Group). Various different variables in two groups were compared by using Mann-Whitney U test. Kaplan–Meier survival analysis and log-rank test were used to compare the overall survivals. Univariate analysis was performed for each group to elicit the significant prognostic factors whereas Cox regression model was used to identify the independent predictors of overall survival.

Results: The Kaplan–Meier survival analysis of two groups showed prolonged survival for Resection Group compared to the Non-Resection Group (median; 14.5 Vs 5.83 months, $p = <0.005$). The multivariate analysis of different survival predicting variables, revealed the resection of the primary tumour as an independent predictor of overall survival ($p < 0.001$). The univariate analysis of resection group identified age at presentation, tumour site, tumour stage (pT), lymph nodal stage (pN), complete histological resection, tumour fixity, ASA grade, mode of surgery, post-operative chemotherapy and sites of metastasis as significant factors ($p < 0.05$) for survival prediction. When these factors were used in Cox-Regression model, only the age at presentation ($p = 0.001$), tumour fixity ($p = 0.012$) and lymph nodal involvement ($p = 0.042$) were independent predictors for overall survival. Treatment with post-operative chemotherapy and a smaller volume of liver metastases were associated with prolonged survival ($p < 0.05$).

Conclusions: Surgical resection of primary tumour for stage IV colorectal cancers is associated with prolonged survival for selected patients. Age at presentation, extent of liver involvement, tumour fixity and ASA grade can help to decide the patients who will benefit from surgery.

1. Introduction

Colorectal cancer (CRC) is the third most common malignant neoplasm worldwide[1] and the fourth leading cause of cancer-related deaths worldwide (World Health Organization, 2008). It is a significant health problem in the UK, accounting for 28.3 deaths per 100,000 in men and 24.2 deaths per 100,000 in women in 2007.[2] Around 100 new cases of colorectal cancer are diagnosed each day in the UK; around two-thirds in the colon and one-third in the rectum. The survival and prognosis of CRC depends on the stage of the tumour at the time of detection and unfortunately more than 20% of patients with cancer have distant spread of their disease (stage IV) at the time of diagnosis.[3,4] Despite significant investment and advances in the management of cancer, the overall survival for

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Table 1
Comparison of demographics, clinical and tumour characteristics of patients in the colorectal cancer Resection and Non-Resection Groups.

Demographics	Characteristics	Resection *n* (%)	Non-resection *n* (%)	*p*-values
Patient (*n*)	Number of patients	366	281	NS
Age	Median (range) years	70 (27–92)	72 (31–96)	NS
Gender	Male	198 (54.1)	219 (78.0)	<0.05
	Female	168 (45.9)	62 (22.0)	
Site of tumour	Right colonic	144 (39.3)	65 (23.2)	<0.05
	Left colonic	114 (31.1)	97 (34.5)	
	Rectal	108 (29.5)	119 (42.3)	
Tumour fixity	Fixed	34 (9.2)	25 (8.9)	<0.05
	Mobile	135 (36.9)	02 (0.7)	
	Tethered	73 (19.9)	09 (3.2)	
	Unknown	124 (33.9)	245 (87.1)	
Detection of metastasis	Radiology imaging	232 (63.4)	242 (86.1)	<0.05
	Radiology imaging & histology	10 (2.7)	11 (3.9)	
	Radiology imaging & surgery	16 (4.4)	05 (1.8)	
	Surgery ± histology	108 (29.5)	23 (8.2)	
Distant metastasis site	Liver – solitary	55 (15.0)	12 (4.8)	<0.05
	Liver – multiple unilobar	56 (15.3)	13 (4.6)	
	Liver – multiple unilobar and lungs	05 (1.4)	02 (0.7)	
	Liver – multiple bi-lobar	130 (35.5)	111 (39.5)	
	Liver – multiple bilobar and lungs	16 (4.4)	42 (14.9)	
	Multi-organ excluding lungs	19 (5.2)	15 (5.3)	
	Lungs only	12 (3.8)	20 (7.1)	
	Peritoneal spread	49 (13.4)	44 (15.6)	
	Extra-mesenteric lymph nodes	37 (10.1)	13 (4.6)	
Oncology treatment	Radiotherapy	20 (5.5)[a]	25 (8.9)	NS
	Chemotherapy	21 (5.7)[b]	101 (35.9)	<0.05
		231 (63.1)[c]		
ASA score	ASA – II	213 (58.2)	47 (16.7)	<0.05
	ASA – III	101 (27.6)	37 (13.2)	
	ASA – IV	19 (5.2)	12 (4.3)	
	Unknown	33 (9.0)	185 (65.8)	
Mode of surgery	Urgent	112 (30.6)	N/A	N/A
	Not recorded	14 (3.8)		
	Routine	240 (66.5)		

[a] Pre-operative radiotherapy.
[b] Pre-operative chemotherapy.
[c] Post-operative chemotherapy.

advanced and metastatic disease has changed little over the past 20 years with 5-year survival at almost 90% for stage I cancers to 5%–15% for stage IV disease.[2,5,6] Approximately 10–25% of patients with stage IV cancer present with metastatic disease that can be resected surgically.[7] Such low rates of resectability are attributed to the heterogeneous nature of metastasis, severity of presenting symptoms, general health of persons and well-defined indications for resection of metastasis in liver and lungs.[8,9] The management of patients with stage IV colorectal cancer is a matter of ongoing controversy, which is further complicated by the introduction of effective chemotherapy and targeted therapy regimens that have been proven to result in resectable metastatic disease in many patients. This paper aims to describe the outcomes of such surgery in a population of patients presenting with metastatic (stage IV) colorectal cancers. To help in the decision making process for individual patients, this study aims to identify different variables predicting overall survival for patients undergoing resection of their primary tumours without the resection of their metastases.

2. Patients & methods

The University Hospitals of Leicester (UHL) Colorectal Cancer Database, a prospective audit of patient outcomes, was examined for all patients diagnosed with stage IV colorectal cancer at presentation between January 1998 and December 2007.

Table 2
Comparison of mean and median survivals of Resection and Non-Resection Groups.

Operation	Mean survival time (months)				Median survival time (months)			
	Survival (months)	Std. error	95% Confidence interval		Survival (months)	Std. error	95% Confidence interval	
			Lower bound	Upper bound			Lower bound	Upper bound
Resection	24.6	1.780	21.05	28.11	14.53	0.77	13.01	16.06
Non-Resection	9.3	0.56	8.52	10.37	5.83	0.55	4.74	6.92
Overall	21.5	1.50	18.55	24.41	12.400	0.801	10.82	13.98

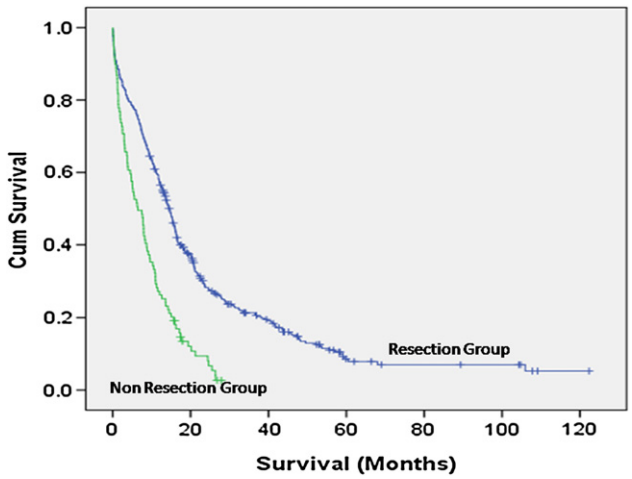

Fig. 1. Kaplan–Meier survival curves comparing the overall survival of Resection and Non-Resection Groups ($p < 0.001$).

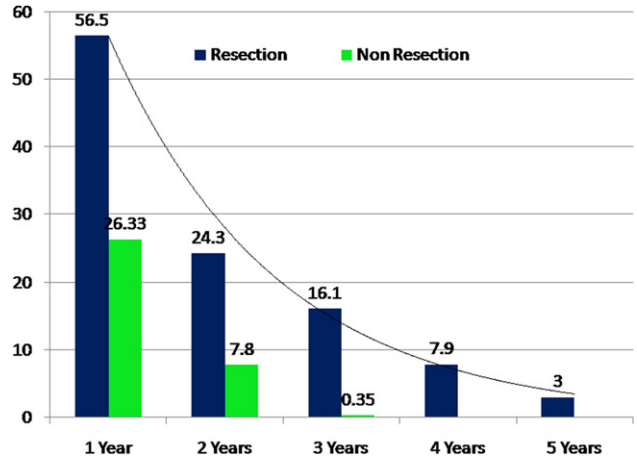

Fig. 2. Comparison of yearly survivals associated with Resection and Non-Resection Groups ($p < 0.05$).

This database is prospectively updated and maintained by the consultant surgeons, colorectal MDT (multidisciplinary team) co-ordinators and the gastrointestinal cancer audit data analyst. Those patients who had resection of their primary tumour with the residual metastatic disease (Resection group) and those who had not their primary tumour excised (Non-Resection Group) were included in the study. Patients presenting with intractable bleeding, malignant ascites, malignant pleural effusion, bowel fistulation, obstructive jaundice, intra-abdominal abscess, bowel obstruction and/or bowel perforation were excluded from the study. For the patients included in the study, the following parameters were studied; age at presentation, gender, site of primary tumour, fixity of primary tumour, site of metastasis, mode of detection of metastasis, ASA grade, mode of surgery and oncological treatment. In the Resection group following additional parameters were also studied; pre resection oncological treatment, post resection oncological treatment, histo-pathological characteristics of resected tumour, post-operative complications, 30 day post-operative mortality and 90 day post-operative mortality.

Table 3
Clinical and tumour characteristics used for univariate and multivariate analysis of Non-Resection Group. Median survivals are tabulated with 95% confidence intervals of survival ranges.

Criterion	Characteristics	*n*	Median survival (months)	95% Confidence interval		Univariate *p*-value	Multivariate *p*-value
				Lower bound	Upper bound		
Gender	Male	219	5.46	4.29	6.63	0.027	0.65
	Female	62	8.23	3.66	12.79		
Age at presentation (years)	<50	27	8.23	5.23	11.23	0.002	0.01
	51–60	39	11.23	8.78	13.68		
	61–70	61	6.33	3.56	9.1		
	71–80	84	4.33	2.72	5.94		
	>80	70	3.13	2.51	3.78		
Tumour site	Right colonic	65	6.36	3.08	9.64	0.005	0.045
	Left colonic	97	7.86	5.38	10.35		
	Rectal	119	3.30	1.64	4.95		
Tumour fixity	Fixed	25	10.90	8.74	13.06	0.105	N/A
	Tethered	02	9.90	0.00	25.7		
	Mobile	09	10.33	3.41	17.24		
	Not recorded	245	6.68	2.52	10.10		
ASA grade	ASA II	47	12.167	9.70	14.63	0.002	0.041
	ASA III	37	5.83	2.57	9.09		
	ASA IV	12	4.93	0.00	9.96		
	Not recorded	185	4.66	3.47	5.86		
Chemotherapy	No	180	3.53	2.65	4.41	0.046	0.058
	Yes	101	7.70	5.52	9.87		
Metastasis site	Liver – solitary	12	13.96	6.74	17.19	0.029	0.12
	Lungs only	20	16.80	14.17	19.43		
	Solitary liver & solitary lung	13	15.06	8.25	31.88		
	Liver – multiple unilobar	13	3.73	0.68	6.78		
	Liver – multiple bi-lobar	111	4.93	3.45	6.41		
	Liver – multiple bilobar & lungs	42	5.63	3.62	7.64		
	Multi-organ excluding lungs	15	3.66	0.33	7.83		

Table 4
Clinical and tumour characteristics used for univariate and multivariate analysis of Resection Group. Median survivals are tabulated with 95% confidence intervals of survival ranges.

Criterion	Characteristics	Number (*n*)	Median survival (months)	95% Confidence interval		Univariate *p*-value	Multivariate *p*-value
				Lower bound	Upper bound		
Gender	Male	198	15.53	13.7	17.3	0.126	N/A
	Female	168	13.33	11.0	15.7		
Age at presentation (years)	<50	30	28.9	14.2	43.7	<0.001	0.001
	51–60	62	20.3	13.5	27.1		
	61–70	100	15.7	14.3	17.1		
	71–80	119	11.9	9.0	14.8		
	>80	55	6.76	2.5	11.0		
Tumour site	Right colonic	144	12.00	9.8	14.2	0.034	0.142
	Left colonic	113	15.70	13.7	17 6		
	Rectal	108	16.63	12.2	21.1		
Tumour stage (pT)	T2	9	59.13	27.2	91.1	0.005	0.108
	T3	128	16.56	14.4	18.7		
	T4	200	12.60	10.3	14.9		
Nodal stage (pN)	N0	61	20.6	15.5	25.7	0.05	0.042
	N1	99	15.4	10.6	20.1		
	N2	176	13.7	12.0	15.4		
	N3	2	9.1				
	Unknown	28	10.3	2.8	17.9		
Complete histological resection	No	64	13.3	9.0	17.7	0.027	0.504
	Yes	166	16.0	13.1	18.9		
Tumour fixity	Fixed	34	10.26	2.9	17.6	0.01	0.012
	Tethered	135	11.9	8.0	15.7		
	Mobile	73	16.5	12.9	20.0		
	Not recorded	124	14.4	10.7	18.1		
ASA grade	ASA II	213	16.36	14.1	18.6	<0.001	0.24
	ASA III	101	9.36	5.5	13.3		
	ASA IV	19	1.60	0.0	04.2		
	Not recorded	33	12.10	9.3	14.9		
Mode of surgery	Routine	240	16.6	14.6	18.5	<0.001	0.058
	Urgent	112	9.16	6.6	11.7		
	Not recorded	14	13.0	11.6	14.3		
Post-operative chemotherapy	No	135	3.7	1.2	06.1	<0.001	0.120
	Yes	231	16.6	13.9	19.3		
Peritoneal spread	Yes	49	13.7	10.5	16.9	0.246	N/A
	No	317	15.0	13.3	16.7		
Distant metastasis site	Liver – solitary	55	20.4	17.1	23.6	0.007	0.969
	Liver – multiple unilobar	56	20.2	10.2	30.2		
	Liver – multiple unilobar & lungs	05	15.9	0.00	14.2		
	Liver –multiple bilobar	130	11.76	9.2	14.3		
	Liver – multiple bilobar & lungs	16	13.33	5.1	21.6		
	Multi-organ excluding lungs	19	13.63	7.4	19.8		
	Lungs only	12	20.96	14.4	27.5		
	Extra-mesenteric lymph nodes	37	10.60	4.6	16.6		

Patient survival was determined by either data entered on the UHL Hospital Information and Support System (HISS), from the Trent Cancer Registry or by contacting the patient's general practitioner.

3. Statistical analysis

The statistical evaluations were based on the date of the patient's death or the date of last follow-up. The inter-group comparisons were made for the following parameters; age at presentation, gender, site of primary tumour, fixity of primary tumour, site of metastasis, mode of detection of metastasis, ASA grade and oncological treatment.

The two groups (Resection & Non-Resection) were compared by using Mann–Whitney U test. Survival curves were generated by using Kaplan–Meier survival analysis and the curves were compared with the log-rank test. Univariate analyses were performed for each group to identify the significant prognostic factors whereas Cox-regression model for survival analysis was used to identify the independent predictors of survival. Differences were considered statistically significant at $p < 0.05$. All the statistical tests were performed by using the SPSS 16.0 statistical software.

4. Results

Nine hundred and twenty patients registered in the database with the diagnosis of stage IV colorectal cancer disease were studied. 273 patients with malignant ascites ($n = 13$), malignant pleural effusion ($n = 3$), bowel fistulation ($n = 2$), obstructive jaundice ($n = 14$), intra-abdominal abscess ($n = 4$), intractable bleeding ($n = 8$), symptomatic bowel obstruction ($n = 156$) and

Table 5
Peri-operative complications in 366 patients undergoing resection of primary colorectal tumour. The post-operative complications were counted for each complication type. 93 different major and 43 minor post-operative complications were recorded for 118 (32%) patients.

Post-operative complications	Number of patients (n)	Patient (%)
Major complications		
Full thickness wound dehiscence	11	3
Intra-abdominal collections	11	3
Anastomotic leak	11	3
Intra-abdominal sepsis	08	2.2
Multi-organ failure	07	1.9
Arrthymia	07	1.9
Clostridium difficle infection	05	1.4
Aspiration pneumonia & respiratory failure	05	1.4
Haemorrhage	05	1.4
Post-operative ileus	04	1.1
Broncho-pneumonia & respiratory failure	04	1.1
Acute renal failure	04	1.1
Myocardial infarction	03	0.8
MRSA infection	03	0.8
Left ventricular failure	03	0.8
Deep vein thrombosis	01	0.3
Splenic tear	01	0.3
Inter-loop fistula	00	0.0
Minor complications		
Chest infection	12	3.3
Wound infections without dehiscence	11	3
Urinary infection	06	1.6
Superficial wound dehiscence	04	1.1
Complications of stoma	02	0.6
Urinary incontinence	02	0.6
Pleural effusion	02	0.6
Post-operative confusion	02	0.6
Urinary retention	01	0.3
Pressure sore	01	0.3

bowel perforation ($n = 93$) were excluded from the study. 366 patients (median age 70 years; M:F = 1.17:1) underwent resection of their primary colorectal tumour without the resection of their synchronous metastases. A total of 281 (median age 72 years; M:F = 1.38:1) patients with stage IV colorectal cancer disease were included in the Non-Resection Group. This group included patients who received symptomatic and supportive treatment ($n = 168$) or chemotherapy ($n = 101$). 45.55% ($n = 128$) of the patients in this group required surgical intervention [diverging stoma formation ($n = 101$), colonic bypass ($n = 7$), colonic stent insertion ($n = 20$)] to relieve the obstructing symptoms, they developed during the course of their treatment for stage IV colorectal tumours. The decision as to which treatment strategy used was made by the multi-disciplinary team, based on the individual patient circumstances. The patient and tumour characteristics for these two groups of patients are summarized in Table 1.

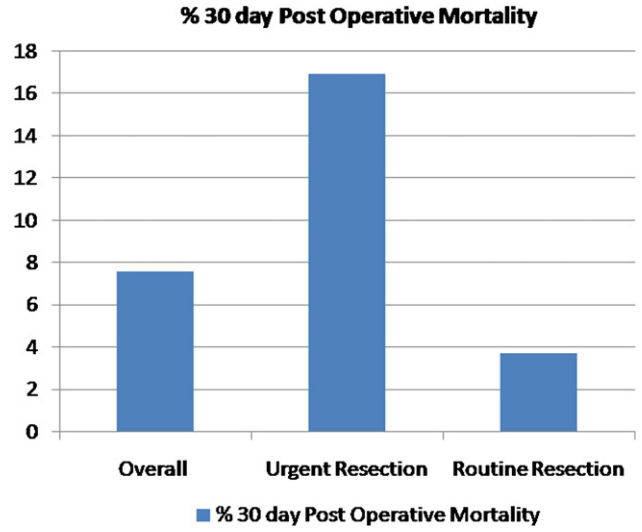

Fig. 3. Percentage 30 day mortalities associated with Resection of Primary tumours in patients with stage IV Colorectal Cancers. Figure also shows the comparison of 30-day post-operative mortality for routine and urgent surgical procedures.

4.1. Overall survival & five-year survivals

The median follow-up for 647 patients was 34 (10–122) months. The multivariate analysis showed that one of the major determinants of outcome was whether the primary tumour had been resected or not ($p < 0.001$). When two groups were compared with the Kaplan–Meier survival analysis (Table 2 and Fig. 1) the Resection group was associated with longer survival (median; 14.5 Vs 5.83 months, $p \leq 0.005$).

4.1.1. Survival analysis for Non-Resection Group

Only one patient in Non-Resection Group was alive at three years after the diagnosis. For this group one and two-year survivals were 26.33% and 7.8% respectively. The univariate analysis of different variables predicting the survival in the Non-Resection Group identified the gender ($p = 0.027$), ASA grade ($p = 0.002$), increasing age ($p < 0.002$), chemotherapy ($p = 0.046$), tumour site ($p = 0.05$) and the metastasis site ($p = 0.029$) as statistically significant factors. When used for Cox-Regression risk modelling the increasing age ($p = 0.01$), tumour site ($p = 0.045$) and ASA grade ($p = 0.041$) were found to be the independent predictors of the overall survival (Table 3). 36% of the patients in the Non-Resection Group received chemotherapy. These patients benefited from higher survival when compared with those who did not receive chemotherapy (median; 7.70 Vs 3.53 months, $p = 0.046$). Patients who received chemotherapy, those with ASA-grade 2 benefited with longer survivals when compared with those with ASA-grades 3 & 4 (median; 13.5 Vs 5.86 months, $p < 0.05$). However, patients who did not receive chemotherapy, those with ASA-grade 2 still benefited with the longer survivals when compared with those with ASA-grades 3 & 4. (Median; 11.9 Vs 3.96 months, $p < 0.05$)

4.1.2. Survival analysis for Resection group

The median time interval from detection of metastatic disease to resection of primary tumour was 28 (0–482) days. For the Resection group the yearly survivals were: 56.5% (1 year); 24.3% (2 years); 16.1% (3 years); 7.9% (4 years) and 3% (5 years). Fig. 2 compares the yearly survivals for Resection & Non-Resection Groups. The Kaplan–Meier analysis with log-rank test and the univariate analysis of different variables in the Resection group identified the age at presentation, primary tumour site, ASA grades, mode of surgery, post-operative chemotherapy, sites of metastasis, tumour stage (pT), lymph nodes stage (pN), histological completeness of resection, fixity of tumour, as significant ($p < 0.05$) factors for survival prediction (Table 4, Figs. 4 and 5). When these factors were used in Cox-Regression model, only age at presentation ($p = 0.001$), tumour fixity ($p = 0.012$) and nodal stage (pN) ($p = 0.042$) were independent predictors for overall survival. Table 4 shows the median survivals and ranges of survivals (95% confidence interval) for different variables. Table 4 also shows the p-values for variables identified in univariate and multivariate analysis of survival.

Patients ($n = 49$) with peritoneal metastasis had no significant differences ($p = 0.246$) in the overall survival (median survival: 13.7 Vs 15.0 months) when compared with the patients ($n = 317$) who

had no peritoneal involvement. In patients with multiple unilobar liver metastasis the median survival was significantly longer when compared for patients with multiple bilobar liver metastasis (median; 17.46 Vs 11.76 months, $p < 0.05$) (Table 5). This confirms the findings of previous studies reporting that the extent of the liver involvement determines the overall survival of stage IV colorectal cancers. The comparisons were made for the patients where pathological findings for the primary tumour were available. The Table 4 compares the overall survival by TN stage of the primary, tumour fixity and histological completeness of excision of the primary. The median survival (28.9 months) was significantly prolonged for patients under the age of 50 years, continued to drop with each decade, and reached 6.7 months for patients over the age of 80 years. 237 (63%) of patients who underwent resection of the primary tumour received post-operative chemotherapy. Patients who received systemic therapy showed a survival advantage when compared with patients who did not receive chemotherapy (median; 16.6 Vs 3.7 months, $p = 0.001$).

4.2. Post-operative morbidity

93 different major and 43 minor post-operative complications were recorded for 118 (32%) patients in the Resection group. In the Resection group, anastomotic leak, intra-abdominal collections, full thickness wound dehiscence, chest infections and superficial wound dehiscence contributed to nearly half of the post-operative morbidities. The Table 5 further elaborates the frequencies of major and minor complications.

4.3. Thirty day and ninety day post-operative mortality

This study reports the 30 days and 90 days post-operative mortalities for Resection group as 7.6% and 15% respectively. Thirty-day mortality for elective resection of the primary tumour (3.75%) was significantly lower ($p < 0.05$) when compared with the 30-day mortality associated with the resections performed urgently (16.96%) The Fig. 3 shows the comparison of 30-day post-operative mortalities for urgent and routinely performed two surgical procedures.

5. Discussion

In this selected group of patients these data have shown that significant survival can be obtained for patients undergoing surgery in the presence of metastatic disease. Patients who underwent surgical resection of primary tumour had clear survival advantage (One year survival; 56.5% Vs 26.33%, two year survival; 24.3% Vs 7.86%) over those patients who did not have their tumours resected

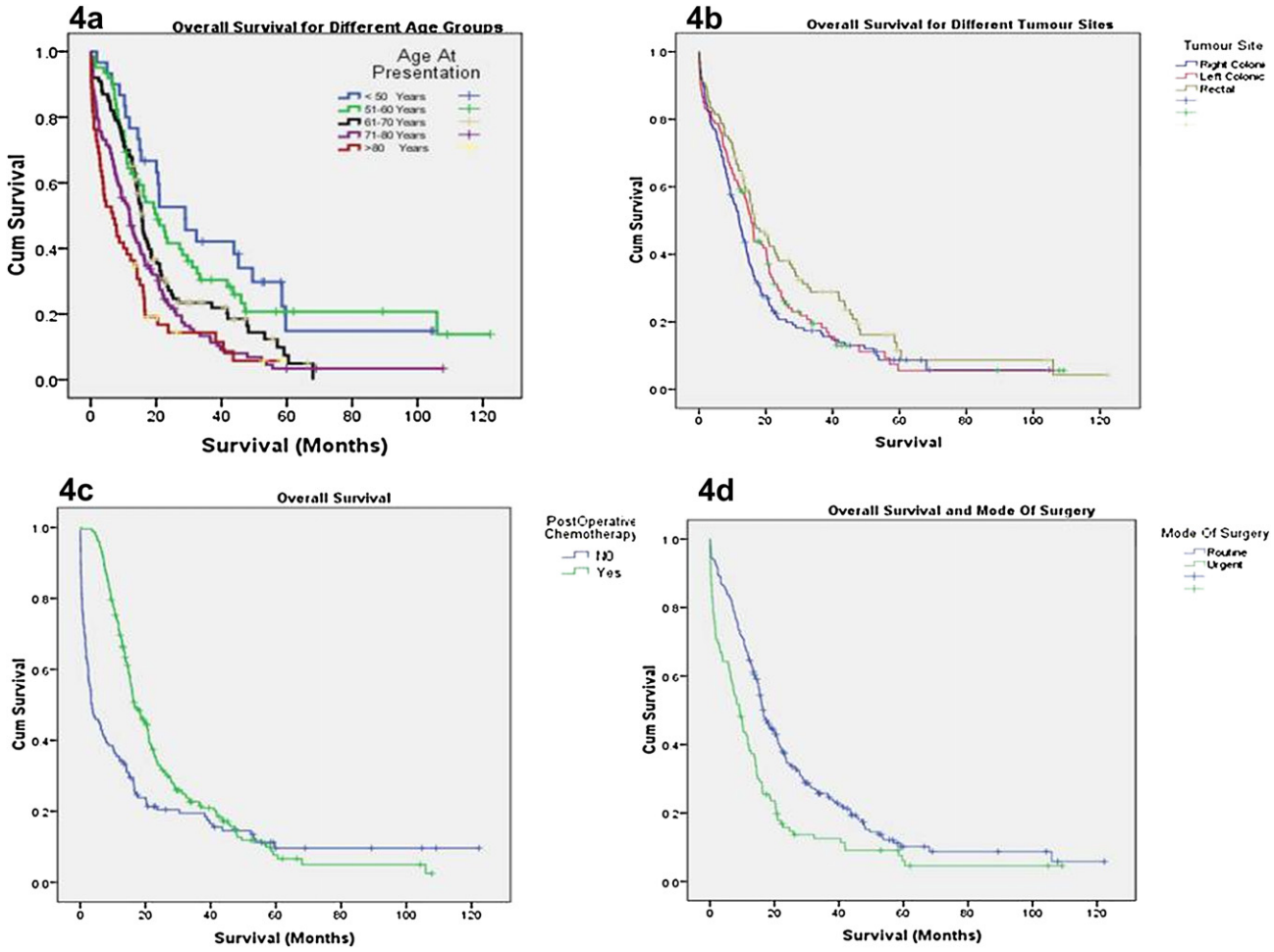

Fig. 4. Kaplan–Meier Survival curves for different variables in Resection group. The curves were compared with long-rank test. 4-a) Survival comparison for different age groups shows higher survival for patients less than 50 years old and significantly reduced survival for patients >80 years of age ($p < 0.001$). 4-b) Resection of rectal tumours was associated with higher survival (median; 16.6 Vs 13 months, $p < 0.05$) when compared with colonic tumours. Authors conclude that such survivals might have been contributed by pre-operative radiotherapy for rectal tumours. 4-c) 63% of the patients received post-operative systemic chemotherapy and benefited from prolonged survival. 4-d) Resection of primary tumour for symptomatic patients on urgent basis was associated with shorter survival when compared with routine elective resections (median; 9.16 Vs 16.6 months, $p < 0.001$).

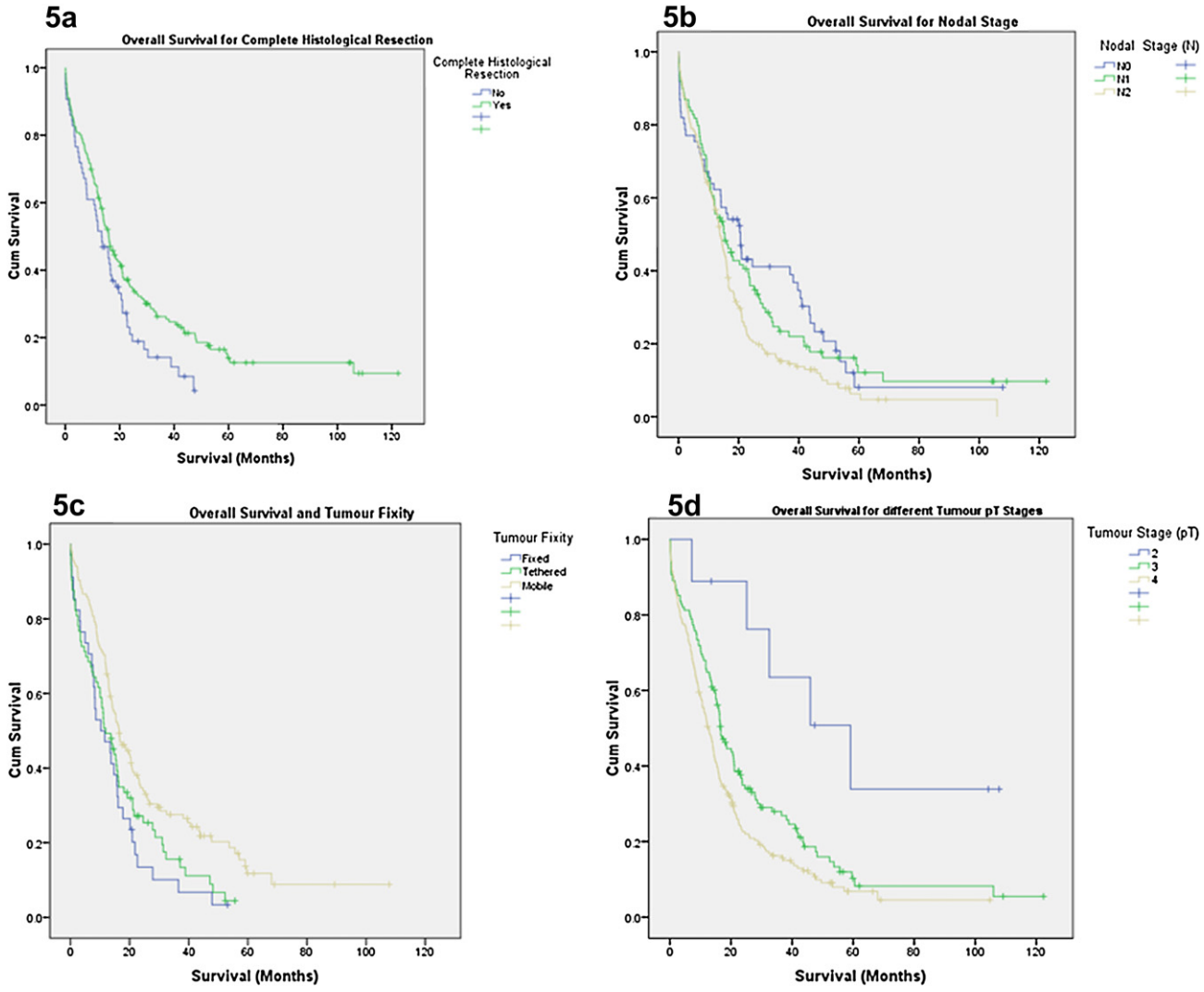

Fig. 5. Kaplan–Meir survival analysis for different histo-pathological features of resected primary colorectal tumours. 5-a) Survival curves are compared for patients who had complete and incomplete histological excision of primary tumour. There is no significant differences in the distribution of curves in first 18 months, After 18 months the curves diverge significantly suggesting long term survivals benefits associated with complete excision of primary tumours. 5-b) Operative findings of tumour fixity or tethering to surrounding structures were associated with comparatively shorter ($p = 0.01$) survivals (median; 10.26 & 11.9 months) when compared with survivals of mobile tumours (median; 16.6 months). 5-c & 5-d) Histological staging from resected tumour (pT) and nodal involvement (pN) are used for comparison of overall survivals. Lower tumour burden (pT2) and lesser extent of lymph nodes involvement (pN0 & pN1) are associated with prolonged survivals.

(Non-Resection Group). However, argument can be made that the these survival differences might have been contributed by the significant differences in two groups in terms of the distribution of primary tumours, burden of metastatic disease, ASA score, gender and chemotherapy. Nevertheless, these finds are in line with the previously reported comparative studies of surgical resection and non-resectional treatments for stage IV colorectal cancers.[10–17] Although these studies have reported possible survival benefits with surgery, due to a lack of prospective clinical trials in this area, no firm conclusions can be drawn with respect to whether resectional surgery should be offered to this group of patients. Conducting such a trial poses practical difficulties which have been highlighted during discussions regarding a potential UK study of Initial Surgery in Advanced Asymptomatic Colorectal cancer (ISAAC). Some clinicians also believe that the surgical resection of the primary tumour may delay or even preclude systemic therapy and many patients may die from progressive systemic disease before they develop any primary tumour specific complications.[18,19] Nonetheless, the debulking surgery for other advanced metastatic tumours such as ovarian[20] and renal[21,22] cancers have shown significant survival benefits.

This study shows substantially prolonged survivals for younger patients undergoing the resection of their primary tumour. The decreased survivals associated with the increasing age have been reported previously for stage IV colorectal cancers.[9,12] The survival analysis in this study has also elicited the increasing age as an independent predictor of survival outcome for both Resection and Non-Resection Groups. It is to be noted that 88% ($n = 49$) of the patients over the age of 80 years did not receive chemotherapy in the Resection group on the basis that the oncologist felt that chemotherapy would not be well tolerated, although the fact that these patients had undergone a resection may have influenced this decision. In this era in which the efficacy of chemotherapy has so dramatically improved,[23] the treatment strategies for stage IV colorectal cancers in elderly patients may need re-evaluation.[24] This study may help promote a dialogue at multidisciplinary meetings between the surgical team and medical oncologist to establish a rationale for selection of treatment strategies and their

timings for elderly patients. The study results also emphasize the importance of the completeness of excision of the primary tumour in stage IV colorectal cancer. Intra-operative findings about the mobility of primary tumour in addition to the tumour stage and completeness of resection should be considered at multidisciplinary meetings for selection of further treatment strategies.

In this study patients with solitary lung and liver metastasis did not undergo resection of those metastases. This could be due to patient choice or poor fitness for the second operation. There is now a trend towards resection of metastasis in lung and liver, and it is possible to perform resectional surgery for synchronous multiple metastasis in liver and/or lungs.[25] This aggressive approach may be justifiable in younger patients, who from this study tend to do better, in attempt to gain useful prolonged survival. Such an approach should be combined with systemic chemotherapy for which evidence exists concerning the reduction in the number and the volume of the metastasis in patients receiving systemic chemotherapy in whom some initially unsuitable metastasis were made suitable for resection.[26,27]

Previous studies have reported decreased survivals for patients having peritoneal involvement with stage IV colorectal cancers.[9,28] In the Resection group, forty nine patients had peritoneal metastasis/involvement (Table 4). When compared with those with no peritoneal involvement authors found no significant differences in survivals. This parameter was not a significant variable on the univariate and multivariate analysis, the important variables being age, burden of primary tumour and extent of liver involvement.

This study has shown a 30-day post-operative mortality of 7.6% for patients who underwent resection of the primary tumour. These finds are in line with the 30 days post-operative mortality (0–9%) reported in previous studies.[11,14,16,17] Significantly higher rates of peri-operative morbidities (37%) are noted for this set of patients albeit reports exist where such high morbidity from 20% to 50% has been reported.[9,10,14,29] Some studies[11,13,16] have reported lower rates of peri-operative morbidities (9%–18.7%) however the number of patients in such studies were significantly small when compared to this study.

In this data set, 30% of the patients had the distant metastasis detected at the time of surgery. Given the poor outcomes in patients in whom resection is not possible, pre-operative cross-sectional imaging is mandatory in this group of patients. This will allow a more accurate assessment of whether resection of the primary tumour can be achieved in patients presenting with metastatic disease.

This study reports confirms significantly lower mortality for elective resection of the primary tumour compared to urgent surgery, a finding which also applies to patients without metastatic disease. This is confirmed in other studies of patients with stage IV disease. (3%–6%), compared with the (20%–40%) operative mortality for emergency resections.[19,29,33] These findings raise the question of whether a stent should be offered as a bridge to surgery in advanced disease as well as in patients with non-metastatic disease.[30,31,32]

Although this study has shown significant survival after resectional surgery, we have no data on the quality of life of these patients. So, far no studies have been published where quality of life is compared for operative and non-operative treatments for primary tumour of stage IV colorectal cancers. In addition to the survival advantage, the resection of the primary tumour in stage IV disease helps in the prevention of symptoms arising from tumour burden and carcinamatosis[9,10] which can be considered a reasonable justification for surgical intervention. Reduction in other complications such as intractable bleeding, obstruction and perforation has also been noted.[11,18,38,39] This may in part be explained by the lower levels of cytokines and growth factors, leading to an improved immune response and effective delivery of cytotoxic drugs to the residual tumour seen in patients undergoing surgical debulking of the primary tumour.[34–37] Prospective measurement of parameters such as quality of life, number of hospital days, and interval from surgery to initiation of chemotherapy would provide additional insights into the rationale for surgery.

To conclude, the resection of primary tumour in stage IV colorectal cancers is associated with prolonged overall survival in selected patients. Careful selection of patients and electively planned resections are associated with favourable outcomes. Prospective studies evaluating the quality of life and symptoms control need to be conducted to develop better insights into the rationale of resection of primary tumours.

Conflict of interest statement
None to declare.

Ethical approval
Not required.

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