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Emergency Presenting Colon Cancer Is an Independent Predictor of Adverse Disease-Free Survival

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Twenty percent of colon cancers present as an emergency. However, the association between emergency presentation and disease-free survival (DFS) remains uncertain. Consecutive patients who underwent elective (CC) and emergent (eCC) resection for colon cancer were included in the analysis. Survival outcomes were compared between the 2 groups in univariate/multivariate analyses. A total of 439 patients underwent colonic resection for colon cancer during the interval 2000–2010; 97 (22.1%) presented as an emergency. eCC tumors were more often located at the splenic flexure ($P = 0.017$) and descending colon ($P = 0.004$). The eCC group displayed features of more advanced disease with a higher proportion of T4 ($P = 0.009$), N2 tumors ($P < 0.01$) and lymphovascular invasion ($P < 0.01$). eCC was associated with adverse locoregional recurrence ($P = 0.02$) and adverse DFS ($P < 0.01$) on univariate analysis. eCC remained an independent predictor of adverse locoregional recurrence (HR 1.86, 95% CI 1.50–3.30, $P = 0.03$) and DFS (HR 1.30, 95% CI 0.88–1.92, $P = 0.05$) on multivariate analysis. eCC was not associated with adverse overall survival and systemic recurrence. eCC is an independent predictor of adverse locoregional recurrence and DFS.

Key words: Emergency presentation – Colon cancer – Disease free survival – Locoregional recurrence

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Colorectal cancer (CRC) is a significant cause of mortality, with over 40,000 new cases diagnosed annually in the UK contributing to over 16,000 deaths (Bowel Cancer UK).[1,2] Up to 20% of colon cancers (CC) present as an emergency (eCC) necessitating emergent surgery.[3,4] Although eCC has been shown to be associated with poorer overall survival (OS), much discrepancy exists in the literature regarding its association with disease-free survival (DFS).[5–7]

Studies reporting the oncologic outcomes of CRC presenting as an emergency consist of heterogeneous populations of patients with colon and rectal cancers.[3,5] Colon and rectal cancers are 2 distinct entities with different molecular, clinical, pathologic, and biologic characteristics and treatment modalities.[8,4,9–11] Since the incorporation of combined multimodal treatment and total mesorectal excision the disparity in OS and DFS between colon and rectal cancer has increased.[12–17] Rectal cancer patients may alter the impression of outcomes in emergency presenting colon cancer. Consequently, previous studies assessing outcomes in eCC may be flawed. Furthermore, the negative impact of eCC has previously been attributed to immediate postoperative complications with an inpatient hospital mortality of approximately 15%. Inclusion of such cases in studies assessing long-term outcomes may have overestimated the negative impact of eCC.[18]

The aim of the current study was to determine the association between eCC and disease-free/overall survival.

Materials and Methods

This is a retrospective comparative observational study of all consecutive patients undergoing colon cancer resection with curative intent between January 2000 and December 2010 at a single institution. Data was collected from HIPE (Hospital Inpatient Inquiry System), histology/endoscopy reports and direct contact with primary care physicians.

Data regarding patient demographics (age, gender), tumor characteristics (stage/AJCC, lymphovascular invasion, grade, size, anatomic location), details of surgery and adjuvant therapy were collected and compared between CC and eCC. The number of lymph nodes retrieved and margin status were noted and used as metrics of adequacy of oncological resection. Long-term oncologic outcomes including locoregional recurrence (LR), systemic recurrence (SR), OS and DFS were recorded.

The aim of this study was to evaluate the association, if any, between eCC and OS/DFS. Inclusion criteria were as follows: histologic diagnosis of colonic adenocarcinoma and adequate follow-up. Exclusion criteria included rectal adenocarcinoma, patients who died within 30 days of surgery and patients with inadequate follow-up. Patients with metastasis at diagnosis (stage IV disease) were excluded from the survival (univariate and multivariate) analysis. Patients were categorized as (1) emergency presenting colon cancer (eCC; e.g., obstruction, perforation, abscess) and (2) elective colon cancer (CC). Primary endpoints included overall and disease-free survival (locoregional and systemic recurrence). Difference in distribution of clinical, demographic and pathological data was evaluated using a chi-square test for categoric variables and student's t test for continuous variables. Survival/recurrence rates were plotted and compared in Kaplan-Meier estimates (eCC *versus* CC). Differences in distribution of survival/recurrence rates were assessed using a log-rank test. Factors significant on univariate analysis were incorporated into a forward conditional cox proportional hazards multivariate model to determine the independent association between eCC and OS/DFS. $P < 0.05$ was considered statistically significant. All calculations were performed in SPSS (version 15, Chicago, Illinois).

Results

Patient and tumor characteristics

A total of 439 patients underwent surgery with a diagnosis of colonic adenocarcinoma during the study period; 65 patients were diagnosed with distant metastasis (stage IV) at presentation (40 in the CC group and 25 in the eCC group). Stage IV cases were included in the analysis of clinical and demographic data and excluded from the survival analysis. A total of 439 patients underwent curative-intent surgery during the study interval. Of these cases, 97 (22.1%) presented as an emergency. The mode of presentation within the emergency group included intestinal obstruction (n = 67, 69.1%), perforation (n = 20, 20.6%) and local abscess (n = 10, 10.3%). Patient and tumour characteristics are summarized in Table 1. There were more left-sided tumors in the eCC group (splenic flexure, $P = 0.017$; descending colon, $P = 0.004$). Overall, eCC displayed features of more advanced disease with a significantly higher proportion of T4 ($P = 0.009$), N2 tumors ($P < 0.01$) with lymphovascular invasion (P

Table 1 Patient and tumor characteristics (all patients, stages I, II, III, and IV

	Overall Number (%)	CC Number (%)	eCC Number (%)	*P* value
Total	439 (100)	342 (77.9)	97 (22.1)	-
Male	248 (56.5)	193 (77.8)	55 (22.2)	0.540
Age (years)*	68 (60–76)	69 (61–76)	64.45 (58–73)	0.41
Location:				
Caecum	103 (23.5)	83 (24.3)	20 (20.6)	0.493
Ascending	33 (7.5)	27 (7.9)	6 (6.2)	0.668
Hepatic flexure	16 (3.6)	13 (3.8)	3 (3.1)	0.513
Transverse	30 (6.8)	20 (5.8)	10 (10.3)	0.168
Splenic flexure	20 (4.6)	11 (3.2)	9 (9.3)	0.017
Descending	29 (6.6)	16 (4.7)	13 (13.4)	0.004
Sigmoid	161 (36.7)	129 (37.7)	32 (33.0)	0.336
Rectosigmoid	43 (9.8)	40 (11.7)	3 (3.1)	0.006
Appendix	4 (0.9)	3 (0.9)	1 (1.0)	0.633
Differentiation:				
Well	84 (19.1)	75 (21.9)	9 (9.3)	0.003
Moderate	301 (68.6)	229 (67.0)	72 (74.2)	0.141
Poor	54 (12.3)	38 (11.1)	16 (16.5)	0.164
T stage:				
T1	16 (3.6)	16 (4.7)	0 (0.0)	0.017
T2	54 (12.3)	49 (14.3)	5 (5.2)	0.008
T3	302 (68.8)	234 (68.4)	68 (70.1)	0.495
T4	67 (15.3)	44 (12.9)	23 (23.7)	0.009
N stage:				
N0	261 (59.4)	213 (62.3)	48 (49.5)	0.016
N1	125 (28.5)	100 (29.2)	25 (25.8)	0.527
N2	53 (12.1)	29 (8.5)	24 (24.7)	<0.01
Over 12 nodes retrieved	131 (29.8)	95 (27.8)	36 (37.1)	0.080
Stage I	66 (15)	59 (17.3)	7 (7.2)	0.04
Stage II	179 (40.8)	145 (42.4)	34 (35.1)	0.28
Stage III	129 (29.4)	98 (28.7)	31 (32)	0.14
Stage IV	65 (14.8)	40 (11.7)	25 (25.8)	<0.01
R1 resection	11 (2.5)	9 (2.6)	2 (2.1)	0.959
Lymphovascular invasion	99 (22.6)	59 (17.3)	40 (41.2)	<0.01

* median (interquartile range)

CC, elective colon cancer resection; eCC, emergent colon cancer resection; R1, microscopic margins involvement.

< 0.01). There were fewer stage I tumors ($P = 0.04$) and more stage IV tumors in the eCC group.

Association between eCC and disease-free survival

On univariate analysis, eCC ($P < 0.01$), T4 tumors ($P < 0.01$), lymphovascular invasion ($P < 0.01$), N1 ($P = 0.04$), and N2 nodal status ($P < 0.01$) were associated with adverse DFS (Table 2). On multivariate analysis, eCC persisted as an independent predictor of adverse DFS (HR 1.30, 95% CI 0.88–1.92, $P = 0.05$; Table 2). The role of eCC in DFS was further assessed in a Kaplan-Meier estimate and log-rank test (Fig. 1A). There was a significant difference in distribution of curves representing eCC and CC ($P = 0.01$). Modes of presentation within eCC (obstruction, perforation and abscess) were also plotted and compared in a Kaplan-Meier estimate. Curves representing each mode differed significantly from the CC group ($P = 0.04$; Fig. 1B).

Association between eCC and locoregional recurrence

On univariate analysis, eCC ($P = 0.02$), T4 tumors ($P < 0.01$), N2 nodal status ($P = 0.05$), and the presence of lymphovascular invasion ($P < 0.01$) were associated with adverse LR (Appendix Table 1). On multivariate analysis, eCC (HR 1.86, 95% CI 1.50–3.30, $P = 0.03$) remained an independent predictor of LR (Appendix Table 1).

Association between eCC and systemic recurrence

eCC was associated with systemic recurrence on univariate analysis ($P = 0.024$) but this association

Table 2 Univariate (log rank) and multivariate analysis (forward conditional Cox proportional hazards model) of variables associated with disease-free survival (DFS; stage IV patients excluded).

	Univariate	Multivariate		
	P Value	HR	95% CI	*P* value
Male	0.50	-	-	-
Age >65 years	0.61	-	-	-
Differentiation:				
Well	0.65	-	-	-
Moderate	0.38	-	-	-
Poor	0.75	-	-	-
T stage:				
T1	0.14	-	-	-
T2	0.20	-	-	-
T3	0.15	-	-	-
T4	<0.01	1.66	1.10 – 2.51	0.02
N stage:				
N0	<0.01	0.59	0.35 – 1.00	0.05
N1	0.04	0.59	0.56 – 1.65	0.89
N2	<0.01	2.10	1.50 – 2.36	<0.01
Lymphovascular invasion	<0.01	1.50	0.99 – 2.27	0.05
Emergency presentation	<0.01	1.30	0.88 – 1.92	0.05
Obstructed presentation	0.07	-	-	-

HR, hazard ratio; CI, confidence interval.

did not persist on multivariate analysis (HR 1.34, 95% CI 0.87–2.07, $P = 0.18$).

Association between eCC and overall survival

On univariate analysis, eCC was not associated with adverse OS ($P = 0.14$). N0 nodal status was associated with improved OS ($P < 0.01$) while lymphovascular invasion ($P < 0.01$), N1 ($P = 0.02$) and N2 nodal status ($P < 0.01$) were associated with adverse OS (Appendix Table 2). The role of eCC in OS was further evaluated in a Kaplan-Meier estimate and log-rank analysis. Distribution of curves representing eCC and CC did not differ significantly ($P = 0.14$) (Appendix Fig. 1A). Modes of presentation within eCC (obstruction, perforation, and abscess) were also compared with respect to OS. Curves representing each mode differed from the CC group but this did not reach statistical significance ($P = 0.17$; Appendix Fig. 1B).

Association between eCC and disease-free-survival in stage II

The incidence of stage II disease was similar between CC (42.4%) and eCC (35.1%), $P = 0.28$ (Table 1). In this cohort (stage II only), eCC was associated with adverse DFS on univariate ($P = 0.01$) and multivariate analysis (HR 1.4, 95% CI 1.31–3.44, $P = 0.03$). A Kaplan-Meier estimate was generated comparing DFS between eCC and CC. There was a significant difference in distribution of curves representing eCC and CC ($P = 0.01$; Fig. 2A). Modes of presentation within eCC (obstruction, perforation, and abscess) were compared with respect to DFS in stage II alone. There was a significant association between the mode of emergency presentation and DFS ($P = 0.04$; Fig. 2B).

Discussion

This study characterizes the effect of emergency presentation on long-term oncologic outcomes in patients undergoing resection with curative intent for colon cancer. Discrepancy exists within the literature regarding the role of eCC in DFS. A number of issues have hampered the development of a consensus regarding this topic including (1) the combination of colon and rectal cancers, (2) failure to incorporate significant findings into a multivariate analysis, (3) inclusion of stage IV cases/postoperative mortality and (4) the relative rarity of this presentation.[19–22] With the exclusion of rectal cancer and in-hospital mortality, this study specifically evaluates the impact of emergency surgery on the long-term oncologic outcomes of colon cancer.

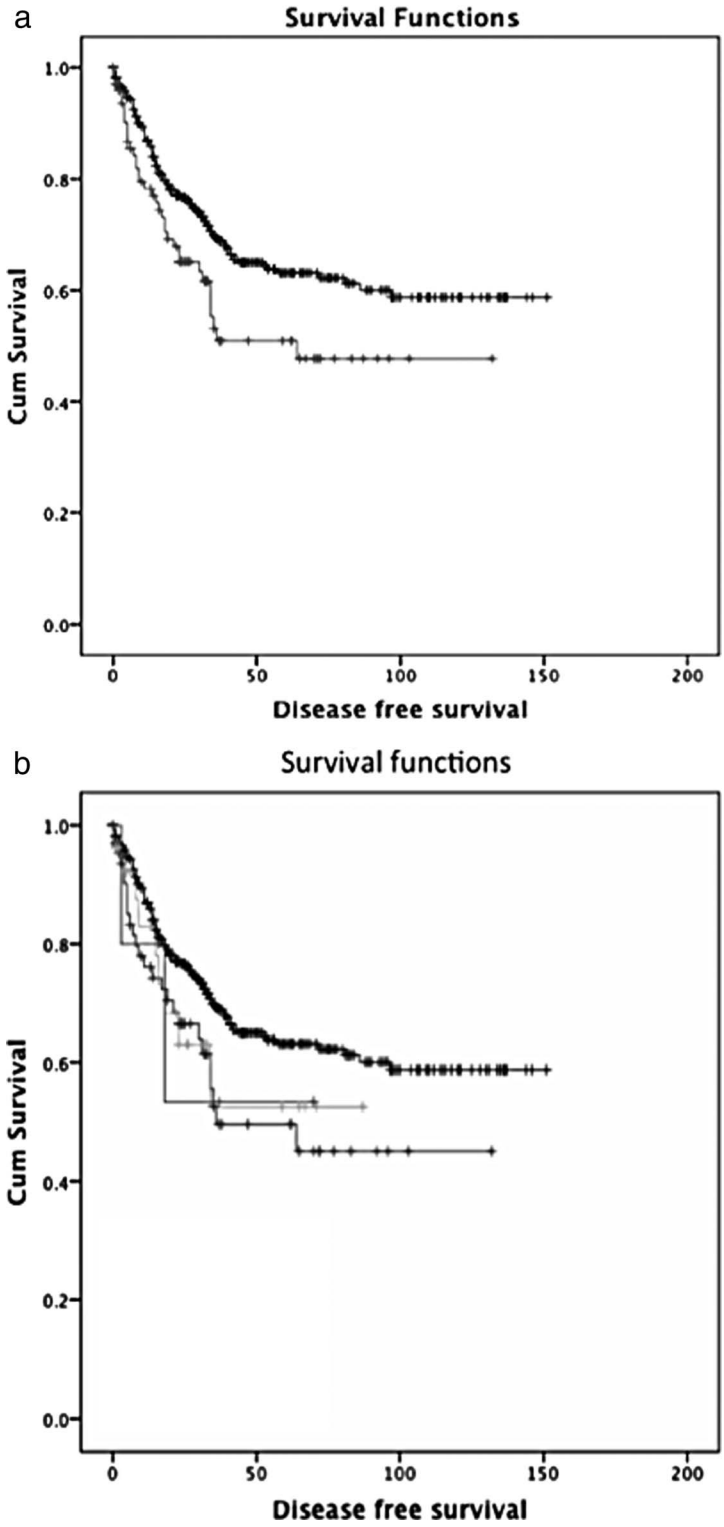

Fig. 1 (A) Kaplan-Meier estimate of disease-free survival (DFS). Two curves are displayed in the graph representing emergency presenting colon cancer (eCC) and elective presentation colon cancer (CC). Difference in distribution of both curves was confirmed through log-rank analysis ($P = 0.01$). The upper line represents CC. (B) Kaplan-Meier estimate of disease-free survival (DFS). This graph compares DFS in elective presentation colon cancer (CC) and emergency presenting colon cancer (eCC). eCC was further categorized by mode of presentation—obstruction, perforation, and abscess formation. Difference in distribution of curves was confirmed through log rank analysis ($P = 0.04$). The upper most line represents CC.

The current study showed that eCC was an independent predictor of locoregional recurrence and adverse DFS, but not systemic recurrence and OS. These findings suggest that patients who developed early locoregional recurrence may be amenable to repeated curative surgical resection and this cohort of patients may subsequently survive beyond 5 years, therefore not influencing

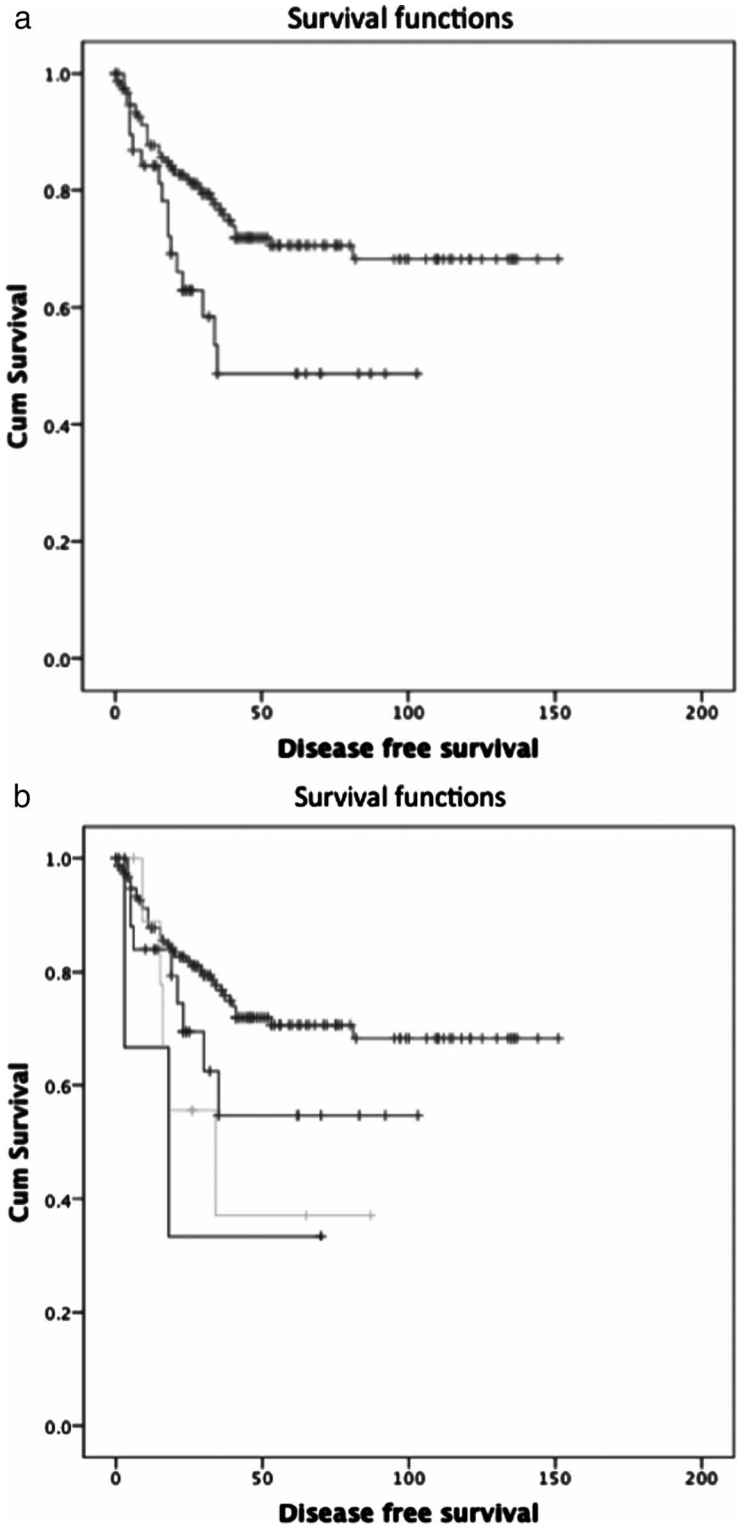

Fig. 2 (A) Kaplan-Meier estimate of disease-free-survival (DFS) in stage II disease. Two curves are displayed in the graph representing emergency presenting colon cancer (eCC) and elective presentation colon cancer (CC). Difference in distribution of both curves was confirmed through log-rank analysis ($P = 0.01$). The upper line represents CC. (B) Kaplan-Meier estimate of disease-free-survival (DFS) in stage II disease. The graph compares elective presentation colon cancer (CC) and emergency presenting colon cancer (eCC). eCC is further categorized according to mode of presentation – obstruction, perforation and abscess formation. Difference in distribution of curves was confirmed through log rank analysis ($p = 0.04$). The upper most line represents CC.

OS. Similar findings have been reported by others.[23] Furthermore, the negative impact of eCC on locoregional recurrence and DFS remained in patients with stage II disease in the subgroup analysis. These findings have important implications on the use of adjuvant chemotherapy and surveillance strategy.

Up to 20% of stage II (node negative) CRC patients develop disease recurrence on follow-up, reflecting limitations of the current staging system.[24] However, there is still a lack of strong evidence for adjuvant chemotherapy in this cohort of patients despite multiple large international trials. Several poor prognostic factors including lymphovascular invasion, T4 tumors, poor differentiation, and emergency presentation are currently used as adjuncts to the TNM staging to guide adjuvant chemotherapy.[25–27] The findings of this study further validated the prognostic value of emergency presentation and its indication for adjuvant therapy in patients with stage II disease.[28]

Moreover, this study showed a significant association between eCC and locoregional recurrence. This implies a more stringent surveillance strategy including computed tomography and endoscopy to detect early recurrence. Early locoregional recurrences may be amenable to further curative resections, thus conferring overall survival benefit as shown in this study.

There are several limitations to this study. It is a retrospective study that incorporates patients over a 10-year period. Varying surgeons, pathologists, and radiologists were involved during this time. Surgical techniques and treatment modalities have evolved during the study period. Despite these limitations, this study reaffirms that eCC is associated with adverse pathologic features, and is an independent predictor of locoregional recurrence and DFS. Patients with eCC may be considered for adjuvant chemotherapy following curative surgery and should undergo more stringent surveillance strategy.

Acknowledgments

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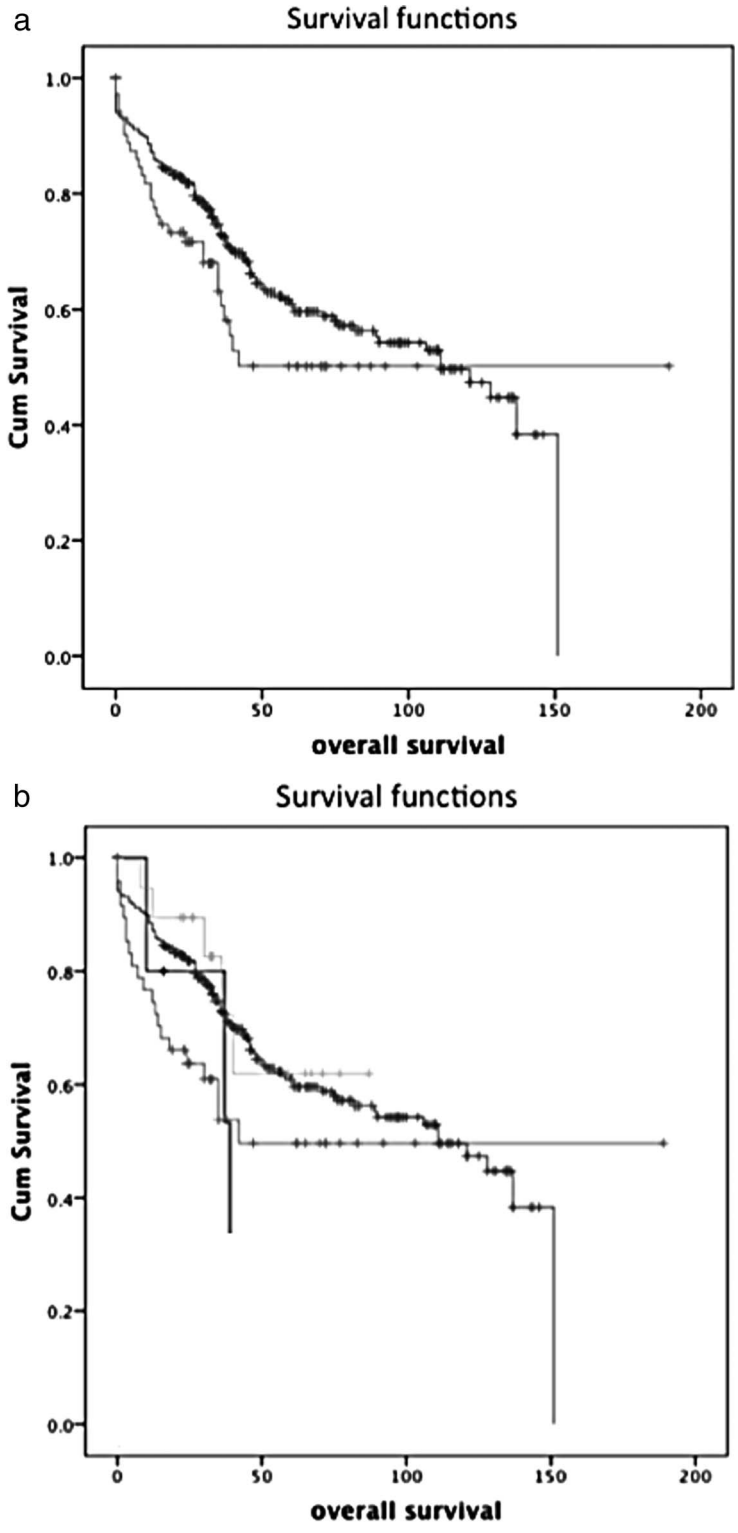
Appendix Table 1 Univariate (chi square test) and multivariate analysis (forward conditional Cox proportional hazards model) of factors affecting locoregional recurrence (LR) (Stage IV patients excluded).

Variable	Univariate	Binary logistic regression	HR	*P* value	95% CI
Male	0.89	-	-	-	-
Age >65 years	0.56	-	-	-	-
Differentiation:					
Well	0.20	-	-	-	-
Moderate	0.08	-	-	-	-
Poor	0.64	-	-	-	-
T stage:					
T1	0.24	-	-	-	-
T2	0.22	-	-	-	-
T3	0.26	-	-	-	-
T4	<0.01	0.009	2.4	<0.01	0.23−0.80
N stage:					
N0	0.18	-	-	-	-
N1	0.43	-	-	-	
N2	0.05	0.03	1.45	<0.01	0.64−3.29
Lymphovascular invasion	<0.01	0.05	1.89	0.04	0.30−0.96
Emergency presentation	0.02	0.04	1.86	0.03	1.50−3.30
Obstructed presentation	0.008	0.04	1.90	0.04	0.28−0.98

HR, hazard ratio; CI, confidence interval.

Appendix Table 2 Univariate (log rank) of factors affecting overall survival (OS; stage IV patients excluded)

	Univariate *P* value
Male	0.99
Age >65 years	0.48
Differentiation:	
Well	0.27
Moderate	0.81
Poor	0.23
T stage:	
T1	0.70
T2	0.39
T3	0.82
T4	0.90
N stage:	
N0	<0.01
N1	0.02
N2	<0.01
Lymphovascular invasion	<0.01
Emergency presentation	0.14
Obstructed presentation	0.12



Appendix Fig. 1 (A) Kaplan-Meier estimate of overall survival (OS). Two curves are displayed in the graph representing emergency presenting colon cancer (eCC) and elective presentation colon cancer (CC). Difference in distribution of both curves was assessed through log rank analysis ($P = 0.14$). The uppermost line represents CC. (B) Kaplan-Meier estimate of overall survival (OS). This graph compares OS in elective presentation colon cancer (CC) and emergency presenting colon cancer (eCC). eCC was further categorized by mode of presentation—obstruction, perforation, and abscess formation. Difference in distribution of curves was assessed through log-rank analysis ($P = 0.17$). The uppermost line represents CC.