Original article

The impact of blood loss, obstruction and perforation on survival in patients undergoing curative resection for colon cancer

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Background: Previous studies have drawn attention to the high postoperative mortality and poor survival of patients who present as an emergency with colon cancer. However, these patients are a heterogeneous group. The aim of the present study was to establish, having adjusted for case mix, the size of the differences in postoperative mortality and 5-year survival between patients presenting as an emergency with evidence of blood loss, obstruction and perforation.

Methods: The study included 2068 patients who presented with colon cancer between 1991 and 1994 in Scotland. Five-year survival rates and the adjusted hazard ratios were calculated.

Results: Thirty-day postoperative mortality following potentially curative resection was consistently higher in patients who presented with evidence of blood loss, obstruction or perforation (all $P < 0{\cdot}005$) than in elective patients. Following potentially curative surgery, cancer-specific survival at 5 years was 74·6 per cent compared with 60·9, 51·6 and 46·5 per cent in those who presented with blood loss, obstruction and perforation respectively (all $P < 0{\cdot}001$). The corresponding adjusted hazard ratios (95 per cent confidence interval) for cancer-specific survival, relative to elective patients, were 1·62 (1·22 to 2·15), 2·22 (1·78 to 2·75) and 2·93 (1·82 to 4·70) for patients presenting with evidence of blood loss, obstruction or perforation (all $P < 0{\cdot}001$).

Conclusion: Compared with patients who undergo elective surgery for colon cancer, those who present as an emergency with evidence of blood loss, obstruction or perforation have higher postoperative mortality rates and poorer cancer-specific survival.

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Introduction

Colon cancer remains the third commonest cause of cancer death in Western Europe and North America. For example, each year in the UK, there are approximately 22 000 new cases[1] and almost 10 500 deaths attributable to the disease[2]. Overall survival is poor. Many patients have locally advanced or metastatic disease at the time of presentation; even of those who undergo potentially curative resection, only half survive 5 years.

Approximately one-third of patients with colon cancer present as an emergency. Previous studies have highlighted the high postoperative mortality rate and poor survival in these patients[3–9]. However, many of these studies were small retrospective studies based on a single institution, some reported only immediate postoperative mortality, and few reported long-term overall and cancer-specific survival. Most studies did not adjust for case mix.

Furthermore, patients with colon cancer who present as an emergency are a heterogeneous group, some presenting with overt or occult blood loss, some with obstruction and others with perforation. The outcome is likely to be very different among these three groups, yet few studies have focused on this aspect or provided any insight into the underlying reasons for any differences in survival in these patients.

The aim of the present study was to establish, having adjusted for case mix, the size of the differences in

postoperative mortality, and overall and cancer-specific survival between patients with colon cancer who presented as an emergency with evidence of blood loss, those with obstruction and those with perforation.

Patients and methods

The study included 2068 patients who underwent resection for colon cancer between 1 January 1991 and 31 December 1994 in 11 hospitals in the central belt of Scotland. Information was abstracted from the case notes by two specially trained data managers. Data for the first 2 years were collected retrospectively, and for the second 2 years, prospectively. Details included age, sex, socioeconomic status, mode of presentation, site of tumour, extent of tumour spread, Dukes' stage[10], nature of surgery, 30-day postoperative mortality and adjuvant therapy. Socioeconomic status was defined using the Carstairs index[11], an area-based measure derived from the 1991 census data based on the postcode of residence at diagnosis.

Patients who were admitted as an emergency were allocated to one of three groups. Those with perforation with or without evidence of obstruction or blood loss were allocated to a perforation group. Those with obstruction with or without evidence of blood loss were allocated to an obstruction group. Those with evidence of blood loss without obstruction or perforation were allocated to a blood loss group.

Patients with bleeding severe enough to be the main reason for emergency admission were deemed to have overt bleeding. Those who presented with symptoms secondary to the presence of anaemia were deemed to have occult bleeding. Patients who were admitted for elective surgery for colon cancer acted as a comparative group.

Tumours were classified according to site; lesions of the caecum, ascending colon and hepatic flexure were classified as right-sided lesions, whereas lesions of the transverse colon, splenic flexure and descending colon were classified as left-sided lesions. The extent of tumour spread was assessed by conventional Dukes' classification based on histological examination of the resected specimen.

Patients were deemed to have had a curative resection if the surgeon considered that there was no macroscopic residual tumour once resection had been completed. Patients with distant metastases who underwent resection or in whom inadequate local clearance was achieved were deemed to have had a palliative resection.

Information on date and cause of death was checked with that received by the cancer registration system through the Registrar General (Scotland). Deaths up to the end of 1999 were included in the analysis.

Statistical analysis

Comparison of the association between prognostic factors, treatment and mode of presentation was made using the χ^2 test or χ^2 test for trend where appropriate. The percentages of patients surviving 2 and 5 years were calculated using the Kaplan–Meier technique. To compare survival in patients who presented with evidence of blood loss, obstruction or perforation with those who underwent elective surgery, while taking into account the patients' characteristics at presentation, Cox's proportional hazards model was used. The procedure was carried out separately for patients undergoing curative and palliative resection.

Results

Of the 2068 patients included in the study, 37·7 per cent were aged 75 years or over, 52·8 per cent were women, 18·1 per cent were socioeconomically deprived, 38·8 per cent presented as an emergency and 21·2 per cent had evidence of metastatic spread at the time of surgery (*Table 1*). Some 1412 (68·3 per cent) patients had an apparently curative resection and 656 had a palliative resection. Postoperative mortality (30-day) was 4·2 per cent after curative resection and 11·7 per cent after palliative resection (*Table 2*); 2·6 per cent of patients received adjuvant 5-fluorouracil-based chemotherapy.

There were 1352 deaths, of which 976 were cancer-related. A further 376 patients died of intercurrent disease, mainly cardiovascular. Overall survival at 5 years was 40·3 per cent; 53·6 per cent of those undergoing apparently curative resection survived 5 years and 23·8 per cent of those who had palliative resection survived 2 years. Cancer-specific survival after apparently curative resection was 67·4 per cent at 5 years; cancer-specific survival following palliative resection was 27·1 per cent at 2 years.

Emergency presentation

Of the 2068 patients included in the study, 1266 (61·2 per cent) presented electively, 263 (12·7 per cent) presented with evidence of overt or occult blood loss, 471 (22·8 per cent) with obstruction, and 68 (3·3 per cent) with perforation.

The baseline characteristics of the patients are shown in *Table 1*. Compared with the elective patients, proportionately more elderly patients ($P = 0·016$), more women ($P = 0·003$) and more patients with right-sided tumours ($P = 0·011$) presented as an emergency with evidence of blood loss. The proportion of patients who underwent potentially curative resection was similar in patients who presented electively and those who presented with blood

Table 1 Baseline characteristics of patients who underwent resection for colon cancer by mode of presentation

		Elective ($n = 1266$)	Blood loss ($n = 263$)	P*	Obstruction ($n = 471$)	P†	Perforation ($n = 68$)	P‡
Age group (years)	< 65	364 (28·8)	79 (30·0)		133 (28·2)		19 (27·9)	
	65–74	462 (36·5)	73 (27·8)		140 (29·7)		19 (27·9)	
	≥ 75	440 (34·8)	111 (42·2)	0·016#	198 (42·0)	0·009#	30 (44·1)	0·281#
Sex	Male	614 (48·5)	101 (38·4)		229 (48·6)		32 (47·1)	
	Female	652 (51·5)	162 (61·6)	0·003§	242 (51·4)	1·000§	36 (52·9)	0·901§
Deprivation	Affluent	255 (20·1)	45 (17·1)		92 (19·6)		6 (8·8)	
	Intermediate	783 (61·8)	156 (59·3)		303 (64·3)		49 (72·1)	
	Deprived	226 (17·9)	62 (23·6)	0·081#	74 (15·7)	0·519#	13 (19·1)	0·069#
Site	Right	577 (45·6)	140 (53·2)		163 (34·6)		17 (25·0)	
	Left	240 (19·0)	55 (20·9)		175 (37·2)		23 (38·8)	
	Sigmoid	449 (35·5)	68 (25·9)	0·011§	133 (28·2)	< 0·001§	28 (41·2)	< 0·001§
Dukes' stage	A	77 (6·1)	8 (3·0)		8 (1·7)		3 (4·4)	
	B	592 (46·8)	127 (48·3)		197 (41·8)		32 (47·1)	
	C	347 (27·4)	76 (28·9)		143 (30·4)		20 (29·4)	
	'D'	250 (19·7)	52 (19·8)	0·272#	123 (26·1)	< 0·001#	13 (19·1)	0·938#
Procedure	Curative	896 (70·8)	176 (66·9)		301 (63·9)		39 (57·4)	
	Palliative	370 (29·2)	87 (33·1)	0·236§	170 (36·1)	0·007§	29 (42·6)	0·021§

Values in parentheses are percentages. *Comparison between elective and blood loss groups; †comparison between elective and obstruction groups; ‡comparison between elective and perforation groups. §χ^2 test; #χ^2 test for trend.

Table 2 Postoperative mortality (30-day) in patients who underwent resection for colon cancer by mode of presentation

	Age (years)	Elective	Blood loss	P*	Obstruction	P†	Perforation	P‡
Curative resection	< 75	9 (1·5)	4 (4·1)		8 (4·6)		1 (5·3)	
	≥ 75	10 (3·2)	9 (11·5)		14 (11·0)		5 (25·0)	
	All ages	19 (2·1)	13 (7·4)	< 0·001	22 (7·3)	< 0·001	6 (15·4)	< 0·001
Palliative resection	< 75	10 (4·1)	8 (14·8)		11 (11·1)		4 (21·1)	
	≥ 75	16 (12·8)	8 (24·2)		16 (22·5)		4 (40·0)	
	All ages	26 (7·0)	16 (18·4)	0·003	27 (15·9)	0·003	8 (27·6)	0·001

Values in parentheses are percentages. *Comparison between elective and blood loss groups; †comparison between elective and obstruction groups; ‡comparison between elective and perforation groups; χ^2 test.

loss. The median time from admission to surgery in those who presented with blood loss was 8 days.

Compared with elective patients, those who presented with obstruction were older ($P = 0·009$) and more had left-sided tumours ($P < 0·001$). Fewer patients who presented with obstruction had Dukes' A/B tumours (43·5 per cent *versus* 52·9 per cent) and more had evidence of liver metastases (26·1 per cent *versus* 19·7 per cent; $P < 0·001$). Fewer underwent potentially curative resection (63·9 per cent *versus* 70·8 per cent; $P = 0·007$). The median time to surgery was 2 days.

Compared with elective patients, a higher proportion of those who presented with perforation had left-sided or sigmoid tumours ($P < 0·001$); fewer underwent potentially curative resection (57·4 per cent *versus* 70·8 per cent; $P = 0·021$). The median time to surgery was less than 24 h.

Postoperative mortality (30-day)

In all groups, postoperative mortality increased with age (*Table 2*; $P < 0·001$). Compared with elective patients, postoperative mortality following potentially curative resection was consistently higher in patients presenting as an emergency with evidence of blood loss, obstruction or perforation (all $P < 0·001$). For example, postoperative mortality was 2·1 per cent following an elective curative resection compared with 7·4 per cent, 7·3 per cent and 15·4 per cent in those who presented with blood loss, obstruction and perforation respectively.

Survival

Overall and cancer-specific survival is shown in *Table 3*. Overall survival at 5 years was 47·9 per cent following

Table 3 Overall and cancer-specific survival of patients who underwent resection for colon cancer by mode of presentation

	Elective (%)	Blood loss (%)	*P*‡	Obstruction (%)	*P*§	Perforation (%)	*P*#
Overall survival							
All patients*	47·9	30·4	< 0·001	27·6	< 0·001	25·0	< 0·001
Curative resection*	61·5	43·8	< 0·001	38·5	< 0·001	33·3	< 0·001
Palliative resection†	30·8	12·6	< 0·001	13·5	< 0·001	27·6	0·296
Cancer-specific survival							
All patients*	58·0	42·8	< 0·001	37·8	< 0·001	34·9	< 0·001
Curative resection*	74·6	60·9	< 0·001	51·6	< 0·001	46·5	< 0·001
Palliative resection†	33·7	14·0	< 0·001	17·6	< 0·001	29·3	0·403

*Kaplan–Meier estimates of 5-year survival; †Kaplan–Meier estimates of 2-year survival. ‡Comparison between elective and blood loss groups; §comparison between elective and obstruction groups; #comparison between elective and perforation groups.

Table 4 Overall and cancer-specific survival hazard ratios for patients who underwent emergency curative resection for colon cancer by mode of presentation

	Elective	Blood loss	*P**	Obstruction	*P*†	Perforation	*P*‡
Overall survival							
Adjusted for age, sex and socioeconomic status	1	1·59 (1·29, 1·97)	< 0·001	1·96 (1·65, 2·31)	< 0·001	2·14 (1·45, 3·17)	< 0·001
Adjusted for age, sex, socioeconomic status, site and Dukes' stage	1	1·64 (1·32, 2·03)	< 0·001	1·89 (1·59, 2·25)	< 0·001	2·23 (1·51, 3·31)	< 0·001
Cancer specific survival							
Adjusted for age, sex and socioeconomic status	1	1·59 (1·20, 2·11)	< 0·001	2·27 (1·84, 2·81)	< 0·001	2·78 (1·74, 4·45)	< 0·001
Adjusted for age, sex, socioeconomic status, site and Dukes' stage	1	1·62 (1·22, 2·15)	< 0·001	2·22 (1·78, 2·75)	< 0·001	2·93 (1·82, 4·70)	< 0·001

Values in parentheses are 95 per cent confidence intervals. *Comparison between elective and blood loss groups; †comparison between elective and obstruction groups; ‡comparison between elective and perforation groups; Cox's proportional hazard model.

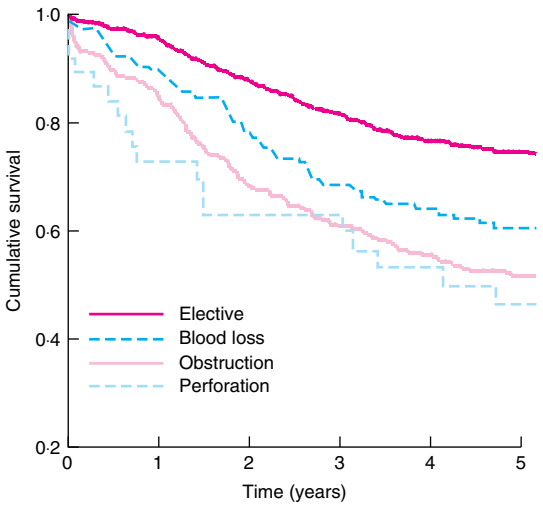
elective surgery compared with 30·4, 27·6 and 25·0 per cent in those who presented with blood loss, obstruction and perforation respectively (all $P < 0·001$). Following potentially curative resection, overall survival at 5 years was 61·5 per cent following elective surgery compared with 43·8, 38·5 and 33·3 per cent in those who presented with blood loss, obstruction and perforation respectively (all $P < 0·001$).

Cancer-specific survival at 5 years was 58·0 per cent after elective surgery compared with 42·8, 37·8 and 34·9 per cent in those who presented with blood loss, obstruction and perforation respectively (all $P < 0·001$). After potentially curative surgery, cancer-specific survival at 5 years was 74·6 per cent compared with 60·9, 51·6 and 46·5 per cent in those who presented with blood loss, obstruction and perforation respectively (all $P < 0·001$; *Fig. 1*).

Excluding postoperative (30-day) mortality, overall survival following potentially curative resection was 62·8 per cent in patients who presented electively compared with 47·2, 41·6 and 39·4 per cent (all $P < 0·002$) in those who presented with evidence of blood loss, obstruction or perforation. The corresponding cancer-specific survival rates were 75·3 per cent, 61·9 per cent, 54·6 per cent and 51·9 per cent respectively (all $P < 0·002$).

The hazard ratios for overall and cancer-specific survival following potentially curative resection, adjusted for age, sex, socioeconomic status, site and Dukes' stage, are shown in *Table 4*. The adjusted hazard ratios for overall survival, for patients presenting with evidence of blood loss, obstruction or perforation, relative to elective patients, were 1·64, 1·89 and 2·23 respectively (all $P < 0·001$). The corresponding hazard ratios for cancer-specific survival were 1·62, 2·22 and 2·93 respectively (all $P < 0·001$).

The adjusted hazard ratios (95 per cent confidence interval) for intercurrent death, for patients who presented with evidence of blood loss, obstruction or perforation, relative to elective patients, were 1·61 (1·19 to 2·27; $P = 0·002$), 1·46 (1·10 to 1·95; $P = 0·010$) and 1·33 (0·65 to 2·72; $P = 0·435$) respectively.



No. at risk

Elective	896	816	731	655	590	551
Blood loss	176	139	118	99	87	76
Obstruction	301	239	183	153	133	116
Perforation	39	23	20	19	16	13

Fig. 1 Cancer-specific survival in patients undergoing curative resection for colon cancer

Discussion

The results of the present study show that, compared with patients who underwent elective surgery for colon cancer, postoperative mortality was higher and overall and cancer-specific survival was lower in those patients who presented as an emergency with evidence of blood loss, obstruction or perforation. Compared with patients who underwent elective surgery, the risk of dying of colon cancer was more than 50 per cent higher in patients who presented as an emergency with evidence of blood loss, more than twofold in those who presented with obstruction, and almost threefold in those who presented with perforation.

Clearly, it is not surprising that postoperative mortality was higher in the emergency groups. Many of these patients were elderly; many were therefore likely to have suffered from significant cardiovascular or respiratory dysfunction before their acute admission[12]. Indeed, the combination of pre-existing co-morbidity and the specific pathophysiological disturbances associated with blood loss, fluid and electrolyte imbalance, and sepsis has long been recognized to be associated with a high mortality rate, especially in the elderly. However, even after excluding deaths within 30 days of surgery, both overall and cancer-specific survival was lower in those patients who presented with blood loss, obstruction or perforation.

In the present study, there was a relatively modest increase in cancer-specific mortality in patients who presented with evidence of blood loss. In contrast, there was a more substantial increase in cancer-specific mortality in those patients who presented with obstruction or perforation. The reasons for this increase in cancer mortality are not clear. However, previous studies have shown that a proportion of elective patients undergoing apparently curative resection for colorectal cancer harbour occult hepatic metastases at the time of surgery, and it is the presence or absence of these occult metastases that determines the likelihood of dying of disseminated disease[13].

The mechanism whereby these residual cells might progress is also not clear. One plausible explanation is that preoperative blood loss, obstruction, perforation and postoperative anastomotic leak have their effect on cancer survival through the elaboration of a systemic inflammatory response. It is known that, as part of the systemic inflammatory response, there is a release of proinflammatory cytokines and growth factors which promote tumour growth[14] and compromise immune function[15]. This would be consistent with the observation that the presence of a systemic inflammatory response, as evidenced by elevated concentrations of C-reactive protein prior to and following surgery for colorectal cancer, is associated with poorer survival[16–19].

Moreover, given the relationship between an elevated C-reactive protein concentration and an increased risk of death from cardiovascular disease[20–22], the presence of a systemic inflammatory response might also explain the relationship between blood loss, obstruction and the increased risk of death from intercurrent disease. Taken together these results might suggest that the duration and magnitude of the systemic inflammatory response is an important factor in determining long-term outcome in patients who present with blood loss, obstruction or perforation.

The results of the present study show that, compared with patients who undergo elective surgery for colon cancer, those who present as an emergency with evidence of blood loss, obstruction or perforation have more advanced disease, a lower curative resection rate, a higher postoperative mortality rate, and poorer overall and cancer-specific survival.

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