Original article

The relationship between emergency presentation, the systemic inflammatory response and cancer specific survival in patients undergoing potentially curative surgery for colon cancer.

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Abstract

Emergency presentation is recognized to be associated with poorer cancer specific survival following curative resection for colorectal cancer. The present study examined the hypothesis that an enhanced systemic inflammatory response, prior to surgery, might explain the impact of emergency presentation on survival. In all, 188 patients undergoing potentially curative resection for colorectal cancer were studied. Of these, 55 (29%) presented as emergencies. The systemic inflammatory response was assessed using the Glasgow Prognostic Score (mGPS) which is the combination of an elevated C-reactive protein (>10mg/l) and hypoalbuminaemia (<35g/l). In the emergency group, tumour stage was greater ($p<0.01$), more patients received adjuvant therapy ($p<0.01$) more patients had an elevated mGPS ($p<0.01$) and more patients died of their disease ($p<0.05$). The minimum follow-up was 12 months; the median follow-up of the survivors was 48 months. Emergency presentation was associated with poorer 3 year cancer specific survival in those patients aged 65-74 years ($p<0.01$), males and females ($p<0.05$), in the deprived ($p<0.01$), in TNM stage II ($p<0.01$), in no adjuvant therapy ($p<0.01$) disease and in the mGPS 0 and 1 ($p<0.05$) groups. On multivariate survival analysis of those patients undergoing potentially curative surgery for TNM stage II colon cancer, emergency presentation ($p<0.05$) and the mGPS ($p<0.05$) were independently associated with cancer specific survival. Therefore, these results suggest that emergency presentation and the presence of systemic inflammatory response prior to surgery are linked and account for poorer cancer specific survival in patients undergoing potentially curative surgery for colon cancer. Both emergency presentation and an elevated mGPS should be taken into account when assessing likely outcome of these patients.

Introduction

Colorectal cancer remains the second commonest cause of cancer death in Western Europe and North America. Each year in the UK, there are approximately 35,000 new cases and 16,000 deaths attributable to the disease [1].

It has long been recognized that emergency presentation is associated with high postoperative mortality rate [2-4]. Furthermore, not only is emergency presentation associated with higher post-operative mortality but, compared to those who undergo elective curative resection, there is also a reduction in overall and cancer specific survival [3,4]. In particular, emergency presentation is a feature of colon cancer[4] and predicts poorer cancer specific survival independent of other clinicopathological factors including tumour stage[5].

The reasons for the increase in cancer specific mortality in those colon cancer patients who present as an emergency are not clear. However, the presence of a systemic inflammatory response prior to surgery, as evidenced by an elevated C-reactive protein concentration or hypoalbuminaemia, predicts overall and cancer specific survival, independent of stage, in patients undergoing potentially curative resection for both colon and rectal cancer [6-8].

We have recently combined C-reactive protein and albumin to form a new score, the Glasgow Prognostic score (GPS, recently modified to mGPS), which has prognostic value, independent of stage, in patients with advanced or primary operable cancer [9,10]. Since it is likely that emergency presentation would be associated with a pre-operative systemic inflammatory response, it may be that the mGPS might explain the impact of emergency presentation on cancer specific survival [5]. To our knowledge no previous study has examined the relationship between emergency presentation, the systemic inflammatory response and cancer specific survival in patients undergoing potentially curative resection for colon cancer.

Therefore, the aim of the present study was to examine the relationship between emergency presentation, the pre- operative mGPS and cancer specific survival in patients undergoing curative resection for colon cancer.

Patients and Methods

Patients

Patients with histologically proven colon cancer who, on the basis of laparotomy findings and preoperative abdominal computed tomography, were considered to have undergone a potentially curative resection between November 1999 and August 2006 in a single surgical unit at Glasgow Royal Infirmary and in whom C-reactive protein and albumin were measured prior to surgery were prospectively included in the study.

For the purpose of this analysis, outcome in patients who presented as an emergency with evidence of blood loss, obstruction or perforation was compared with those patients admitted for elective surgery [5].

The extent of deprivation was defined using the Carstairs deprivation index [11]. This is an area-based measure derived from the 1991 census, using the postcode of residence at diagnosis, which divides the score into a seven-point index. For illustrative purposes, the results are presented by amalgamating the seven categories into three groups: affluent (categories 1 and 2), intermediate (categories 3–5) and deprived (categories 6 and 7). The Carstairs deprivation index has been extensively utilised in cancer patients and is particularly appropriate for use in the central belt of Scotland [12].

The tumours were staged using the conventional TNM classification [13]. Patients who had neo-adjuvant therapy or who died within 30 days of surgery were excluded from the study.

The study was approved by the Research Ethics Committee, Royal Infirmary, Glasgow.

Methods

Routine laboratory measurements of C-reactive protein and albumin at the time of diagnosis were carried out. The limit of detection of the C-reactive protein assay was <6mg/l. The coefficients of variation of these methods, over the range of measurements, was less than 5% as established by routine quality control.

The GPS was constructed as previously described [14]. Briefly, patients with both an elevated C-reactive protein (>10 mg/l) and hypoalbuminaemia (<35g/l) were allocated a score of 2. Patients in whom only one of these biochemical abnormalities was present were allocated a score of 1. Patients in whom neither of these abnormalities was present were allocated a score of 0.

Recently, this has been modified based on evidence that hypoalbuminaemia, in patients without an elevated C-reactive protein concentration, had no significant association with cancer specific survival. Therefore, patients with an elevated C-reactive protein were assigned a modified GPS score (mGPS) of 1 or 2 depending on the absence or presence of hypoalbuminaemia [9].

Statistics

Comparisons between groups of patients were carried out using contingency table analysis (X^2) as appropriate. Deaths to the end of August 2007 were included in the analysis. The percentages of patients surviving 3years were calculated using the Kaplan-Meier technique. Survival analysis of the group variables was performed using the Cox proportional hazard model. Multivariate survival analysis was performed using a stepwise backward procedure to derive a final model of the variables that had a significant independent relationship with survival. To remove a variable from the model, the corresponding p-value

had to be >0.10. Analysis was performed using SPSS software (SPSS Inc., Chicago, IL, USA).

Results

The baseline characteristics of the 188 patients who underwent potentially curative resection for colon cancer are shown in Table 1. The majority of patients were male, aged 65 years or more, were deprived and had TNM stage I or II disease.

One hundred and nine (58%) patients had an elevated C-reactive protein concentration (>10 mg/l) and 34 (18%) patients had hypoalbuminaemia prior to surgery. Of the 34 patients with hypoalbuminaemia, 30 (88%) had an elevated C-reactive protein concentration. Fifty four (29%) patients received adjuvant 5FU- based chemotherapy.

Fifty five patients (29%) presented as emergencies. Of those patients who presented as an emergency 10 patients presented with blood loss, 31 patients with obstruction and 14 patients presented with perforation. In the emergency group, tumour stage was greater ($p<0.001$), more patients received adjuvant therapy ($p<0.01$), more patients had an elevated mGPS ($p<0.01$) and more patients died of their disease ($p<0.05$). An elevated mGPS did not vary with the proportion of patients presenting with blood loss, obstruction or perforation.

The minimum follow-up was 12 months; the median follow-up of the survivors was 48 months. Cancer specific survival was 85% and 62% at 3 years in the elective and emergency groups respectively (Table 2). Emergency presentation was associated with poorer 3 year cancer specific survival in those patients aged 65-74 years ($p<0.01$), males and females ($p<0.05$), in the deprived ($p<0.01$), in TNM stage II ($p<0.01$), in no adjuvant therapy ($p<0.01$) disease and in the mGPS 0 and 1 ($p<0.05$) groups (Table 2).

Non-cancer survival was 90% and 92% at 3 years in the elective and emergency groups respectively (Table 3). Emergency presentation was not significantly associated with poorer 3 year non-cancer specific survival in any of the factors examined.

Survival analysis of those patients undergoing potentially curative surgery for TNM stage II colon cancer is shown in Table 4. On univariate analysis, emergency presentation

($p<0.01$), age ($p<0.10$), sex ($p<0.10$) and the mGPS ($p<0.05$) were associated with cancer specific survival. On multivariate analysis including emergency presentation, age, sex, deprivation, adjuvant chemotherapy and the mGPS and as covariates, emergency presentation ($p<0.05$) and the mGPS ($p<0.05$) were independently associated with cancer specific survival (Table 4).

On univariate analysis of the above factors and non-cancer survival, emergency presentation ($p= 0.8574$), age ($p= 0.2296$), sex ($p= 0.1946$), deprivation ($p= 0.1648$), adjuvant chemotherapy ($p= 0.2828$) and the mGPS ($p= 0.3372$) did not show a significant association.

Discussion

In the present study, in patients undergoing potentially curative surgery for colon cancer, emergency presentation was associated with poorer cancer specific survival, independent of TNM stage. The percentage of patients with colon cancer presenting as an emergency (29%) in the present study over the period of 1999-2006 is in line with that (39%) previously reported in a large audit of colorectal cancer in the central belt of Scotland between 1991-1994 [4]. Also, these results are consistent with our previous study of approximately 2,000 patients which showed that, even after excluding deaths within 30 days of surgery, emergency presentation was independently associated with poorer cancer specific survival [5].

We have also shown that emergency presentation is associated with the presence of a systemic inflammatory response prior to surgery, as evidenced by the mGPS. However, on multivariate survival analysis in patients TNM stage II disease, both emergency presentation and an elevated mGPS were significant independent predictors of cancer specific survival. Therefore, it would appear that not all of the deleterious impact of emergency presentation on cancer specific survival can be accounted for by the presence of a systemic inflammatory response prior to surgery [5].

It has been recognised for some time that pre-operative hypoalbuminaemia is associated with poor outcome following surgery [15,16]. Similarly, hypoalbuminaemia has been associated with poor long term outcome following surgery for colorectal cancer [17-19]. In the past, this hypoalbuminaemia has been thought to be the result of nutritional depletion secondary to the tumour. However, it has been postulated that the reduction in albumin concentration is secondary to the presence of a systemic inflammatory response, as evidenced by elevated circulating concentrations of C-reactive protein [20]. In the present study of the 34 patients with hypoalbuminaemia, 30 (88%) had an elevated C-reactive protein concentration. This is consistent with results reported in other gastrointestinal tumours [21-23] and is consistent

with concept that the systemic inflammatory response is a major determinant of albumin concentrations in patients with cancer. It may be that the presence of a chronic systemic inflammatory response, with its increased demand for specific amino acids for acute phase protein synthesis, promotes the degradation of available body protein including albumin [24,25,21]. There is also a consistent link between the presence of a systemic inflammatory response and comorbid disease [26]. Therefore, albumin may not only reflect underlying nutritional status but also comorbid disease.

The basis of the independent relationship between an elevated mGPS prior to surgery and poor long term survival in patients with primary operable colon cancer is not clear. A plausible explanation is that an elevated mGPS may reflect compromised cell mediated immunity since an elevated C-reactive protein and hypoalbuminaemia are associated with lymphocytopenia[27] and an impaired T-lymphocytic response in the tumour [28]. Furthermore, the presence of an elevated C-reactive protein concentration and hypoalbuminaemia have also been shown to be associated with upregulation of components of innate immune system, including complement and macrophage function [29,30]. Therefore, these results would suggest that immune function is compromised prior to surgery, resulting in disease progression and poorer long term survival.

It is of interest to speculate on the temporal relationship between these events. Does the tumour stage lead to emergency presentation and to a systemic inflammatory response and therefore primarily determines poorer cancer specific survival? Alternatively, does the systemic inflammatory response lead to emergency presentation and poor survival? In the present study, emergency presentation was associated with both increased T stage and an increased mGPS. However, there was no difference in nodal involvement between the elective and emergency groups. It may therefore be that the latter explanation is more likely;

namely that a systemic inflammatory response leads to emergency presentation, impaired host immune response and poor cancer specific survival.

In summary, the results of the present study suggest that emergency presentation and the presence of systemic inflammatory response prior to surgery are associated and the systemic inflammatory response may account, in part, for the deleterious effect of emergency presentation on cancer specific survival in patients undergoing potentially curative surgery for colon cancer. Both emergency presentation and an elevated mGPS should be taken into account when assessing likely outcome of these patients.

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Table 1. Clinicopathological characteristics in patients undergoing potentially curative surgery for colon cancer according to mode of presentation (n= 188).

		Elective	Emergency	p-value
		n= 133 (%)	n= 55 (%)	
Age group	<65 years	34 (26)	20 (36)	
	65-74 years	48 (36)	17 (31)	
	≥75 years	51 (38)	18 (33)	0.204
Sex	Male	68 (51)	33 (60)	
	Female	65 (49)	22 (40)	0.268
Deprivation	Affluent (1, 2)	3 (2)	0 (0)	
	Intermediate (3, 4, 5)	54 (41)	18 (33)	
	Deprived (6, 7)	76 (57)	37 (67)	0.142
Tumour	T1	3 (2)	0 (0)	
	T2	14 (10)	1 (2)	
	T3	78 (59)	24 (44)	
	T4	38 (29)	30 (55)	<0.001
Nodal involvement	N0	83 (62)	26 (47)	
	N1	36 (27)	21 (38)	
	N2	14 (11)	8 (15)	0.086
TNM stage	I	15 (11)	0 (0)	
	II	68 (57)	27 (49)	
	III	50 (38)	28 (51)	0.013
Adjuvant therapy	No	103 (77)	31 (56)	
	Yes	30 (23)	24 (44)	0.004
mGPS	0	63 (47)	16 (29)	
	1	54 (41)	26 (47)	
	2	16 (12)	13 (24)	0.009
Died	cancer	26 (61)	21 (88)	
	non-cancer	17 (39)	3 (12)	0.021

Table 2. Cancer specific survival at 3 years in patients undergoing curative resection for colon cancer by mode of presentation (n= 188).

		Elective	Emergency	p-value
		n= 133	n= 55	
		% (SE)	% (SE)	
Age group	<65 years	94 (4)	81 (10)	0.1045
	65-74 years	87 (5)	50 (14)	0.0026
	≥75 years	76 (6)	51 (14)	0.1019
Sex	Male	82 (5)	57 (10)	0.0242
	Female	87 (4)	70 (10)	0.0214
Deprivation	Affluent (1, 2)	67 (27)		
	Intermediate (3, 4, 5)	80 (6)	57 (12)	0.0753
	Deprived (6, 7)	89 (4)	65 (9)	0.0019
TNM stage	I	100 (0)		
	II	92 (4)	64 (11)	0.0010
	III	71 (7)	60 (10)	0.4337
Adjuvant therapy	No	85 (4)	60 (10)	0.0017
	Yes	83 (7)	65 (11)	0.2006
mGPS	0	90 (4)	71 (13)	0.0009
	1	86 (5)	56 (11)	0.0224
	2	59 (13)	66 (17)	0.3946

Table 3. Non-cancer survival at 3 years in patients undergoing curative resection for colon cancer by mode of presentation (n= 188).

		Elective	Emergency	p-value
		n= 133	n= 55	
		% (SE)	% (SE)	
Age group	<65 years	100 (0)	100 (0)	0.4795
	65-74 years	90 (5)	81 (12)	0.4820
	≥75 years	83 (6)	92 (7)	0.2944
Sex	Male	93 (3)	96 (4)	0.3046
	Female	88 (4)	85 (10)	0.8795
Deprivation	Affluent (1, 2)	100 (0)		
	Intermediate (3, 4, 5)	91 (4)	84 (10)	0.9585
	Deprived (6, 7)	90 (4)	96 (3)	0.2199
TNM stage	I	93 (6)		
	II	91 (4)	86 (8)	0.8572
	III	89 (5)	100 (0)	0.1192
Adjuvant therapy	No	88 (4)	86 (8)	0.7119
	Yes	100 (0)	100 (0)	
mGPS	0	91 (4)	89 (10)	0.9669
	1	94 (4)	95 (5)	0.4626
	2	72 (14)	89 (10)	0.1928

Table 4. Clinicopathological characteristics and cancer specific survival in patients undergoing potentially curative surgery for TNM stage II colon cancer

	Survival analysis			
	Univariate Hazard ratio (95% CI)	p-value	Multivariate Hazard ratio (95% CI)	p-value
Presentation (elective/ emergency)	4.57 (1.69-12.34)	0.0027	3.19 (1.14-8.93)	0.0270
Age group (<65/ 65-74/ ≥75)	1.74 (0.91-3.33)	0.0930		0.3202
Sex (male/ female)	0.36 (0.12-1.13)	0.0795		0.1027
Deprivation (affluent/ intermediate/ deprived)	1.48 (0.52-4.19)	0.4626		0.9784
Adjuvant therapy (no/ yes)	0.33 (0.04-2.49)	0.2812		0.1985
mGPS (0/ 1/ 2)	2.49 (1.23-5.06)	0.0116	2.22 (1.04-4.74)	0.0391