Roxburgh, C.S.D. and Wallace, A.M. and Guthrie, G. and Horgan, P.G. and McMillan, D.C. (2009) *Comparison of the prognostic value of tumour and patient related factors in patients undergoing potentially curative surgery for colon cancer.* Colorectal Disease . ISSN 1462-8910

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Deposited on: 1 December 2009

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Original Article

Comparison of the prognostic value of tumour and patient related factors in patients undergoing potentially curative surgery for colon cancer

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Keywords: Colon cancer, pathology, clinical biochemistry, Dukes stage, Glasgow Prognostic Score, survival

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Abstract

Aim: To comprehensively compare the prognostic value of tumour and patient-related factors in patients undergoing curative surgery for colon cancer.

Methods: From a database of 287 patients who underwent elective resection between 1997-2005, tumour factors including stage and host factors including systemic inflammatory response (modified Glasgow Prognostic Score (mGPS)) were identified.

Results: Median follow-up was 65 months. Over this time period 125 patients died, 80 from cancer. On multivariate analysis of all significant patient and tumour related factors, Dukes stage ($P<0.01$), vascular invasion ($P<0.01$), and the mGPS ($P<0.01$) were independently associated with cancer-survival. Of the patient-related factors, age ($P<0.01$), haemoglobin ($P<0.01$), white-cell ($P<0.01$), neutrophil ($P<0.01$) and platelet ($P<0.01$) counts and alkaline phosphatase ($P<0.01$) were most significantly associated with the mGPS.

Conclusion: In addition to tumour-related factors such as Dukes stage and vascular invasion, the pre-operative mGPS should be included to guide prognosis in patients undergoing curative resection for colon cancer.

Introduction:

Colorectal cancer remains the second most common cause of cancer death in Western Europe and North America. Each year, in the UK, the disease accounts for over 16,000 deaths with 35,000 new cases [1]. Colon cancer accounts for majority of disease with approximately 22,000 new cases and over 10, 000 deaths per year [1]. Overall survival remains poor with only 60% of those patients undergoing resection with curative intent surviving 5 years [2].

Following curative resection for colon cancer, pathological analysis for tumour related factors guides prognosis and provision of adjuvant therapy. A variety of high risk features including tumour stage, nodal status, the ratio of metastatic to examined lymph nodes and presence or absence of venous invasion are considered to be important in planning adjuvant therapy and follow-up [3-7].

However, it is also now recognised that cancer outcomes are not solely determined by tumour-related factors but also by patient-related factors [8 9]. Indeed, the presence of a pre-operative systemic inflammatory response, as evidenced by a simple objective score (modified Glasgow Prognostic Score (mGPS) based on circulating levels of two acute phase proteins, C-reactive protein and albumin, is independently associated with poor cancer outcomes in patients undergoing surgery for colon and rectal cancer [10 11 12].

The acute phase protein response is only one aspect of the systemic inflammatory response [13]. Previous work has also identified a significant relationship between cellular components of the pre-operative systemic inflammatory response including white cell, neutrophil, lymphocyte, monocyte and platelet counts and cancer survival in patients colorectal cancer [11 14-19]. Also, the combination of these cellular components such as the neutrophil-lymphocyte ratio and the platelet-lymphocyte ratio have been proposed to have prognostic value [20-22].

The systemic inflammatory response, as evidenced by the mGPS, also appears to be associated with a number of routine biochemical parameters, in particular alkaline phosphatase and γ-glutamyl transferase [23]. Therefore, it of interest that alkaline phosphatase, aspartate transaminase and γ-glutamyl transferase have been reported to have prognostic value in patients undergoing surgery for colon and rectal cancer [24-29].

To date, there has been no comprehensive comparison of the prognostic value of tumour and patient-related factors, including the systemic inflammatory response. The aim of the present study was to examine the relationship between tumour and patient related factors, including the mGPS, and cancer specific survival in patients under going potentially curative surgery for colon cancer.

Materials and methods

Patients with histologically proven colon cancer who, on the basis of laparotomy findings and pre-operative abdominal computed tomography, were considered to have undergone potentially curative resection between January 1997 and July 2005 in a single surgical unit, were included in the study. Patients were identified from a prospectively maintained colorectal cancer database. Exclusion criteria were: (i) emergency surgery (ii) death within 30 days of surgery (iii) clinical evidence of infection or other inflammatory conditions such as inflammatory bowel disease or rheumatoid arthritis. Tumours were staged using the conventional Dukes classification [30].

Pathological details were obtained from reports issued following tumour resection. The lymph node ratio was calculated by dividing the number of metastatic lymph nodes identified by the total number of lymph nodes sampled. In the present study, cut offs of 0.25 and 0.5 were used to stratify patients as high or low risk within the Stage III or node positive patients as previously described [31 32]. Routine laboratory measurements for haemoglobin, white cell, neutrophil, lymphocyte, platelet counts, bilirubin, aspartate transaminase, alanine transaminase, γ-glutamyl transferase, alkaline phosphatase, adjusted calcium, globulins, albumin and C-reactive protein concentration prior to surgery were recorded.

The calcium concentrations were adjusted for albumin using the formula: adjusted calcium = measured calcium + ((43-measured albumin) x 0.07. Coefficient of variation for these methods, over the range of measurement, was less than 10% as established by routine quality control procedures.

The GPS was constructed as previously described [33]. Briefly, patients with both an elevated C-reactive protein (>10mg/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, however, this has been modified based on evidence that

hypoalbuminaemia, in patients with colorectal cancer 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 [10].

The provision of adjuvant chemotherapy following surgery was at the discretion of the medical or clinical oncologists present at multi-disciplinary assessment. All clinical and pathological data, including co-morbidities, were available to the oncologist in making these decisions and the treatment offered was based on the treatment guidelines for colon cancer at that time.

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

Statistics

Grouping of the variables was carried out using standard thresholds for laboratory parameters [11 34-37]. The relationships between the mGPS and other variables were analysed using the Mantel–Haenszel (X^2) test for trend as appropriate. Deaths up to August 2008 were included in the analysis. Univariate survival analysis was performed using the Kaplan–Meier method with the log-rank test. Multivariate survival analysis, including all significant covariates 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 greater than 0.05. Because of the number of statistical comparisons, a *P* value of $\leq$0.01 was considered to be significant. Analysis was performed using SPSS software (SPSS Inc., Chicago, IL, USA).

Results

Two hundred and eighty seven patients undergoing elective potentially curative resection for colon cancer were studied. All pathological data and criteria for the mGPS were available in all 287 patients. Biochemistry including full liver function testing was available for 224 patients. Pre-operative haematology results were available for 167 patients.

The tumour characteristics and relationships with overall and cancer specific survival are shown in Table 1. The majority of patients had Dukes A/B disease (59%), moderate to well differentiated tumours (86%), had no evidence of vascular invasion (65%), no evidence of peritoneal involvement (71%), clear surgical margins (90%), no evidence of tumour perforation (96%), no evidence of perineural invasion (93%), a lymph node ratio of 0 (59%) and 12 or more lymph nodes sampled (63%). Median number of lymph nodes sampled was 14 (range 2-52). Sixty patients (21%) received adjuvant chemotherapy (Table 1).

The patient related characteristics and relationships with overall and cancer specific survival are shown in Table 2. The majority of patients were 65 years or older (70%), male (54%). The majority of patients had pre-operative total white cell counts (59%), neutrophil counts (82%), lymphocyte counts (92%) and platelet counts (73%) in the normal range. Therefore, the majority of patients had a neutrophil/ lymphocyte ratio (77%) and platelet/ lymphocyte ratio (76%) within the normal range (Table 2). The majority of patients had a pre-operative bilirubin (96%), aspartate transaminase (99%), alanine transaminase (99%), γ-glutamyl transferase (79%) and alkaline phosphatase (55%) within the normal range. The majority of patients had globulin (94%), adjusted calcium (97%) and mGPS (57%) within the normal range (Table 2).

The median follow-up for survivors was 65 months (minimum 36 months). Over this period one hundred and twenty-five patients died, eighty-one from their cancer. On univariate survival analysis of tumour-related factors, Dukes stage ($P<0.001$), extramural vascular invasion ($P<0.001$), peritoneal involvement ($P<0.01$), margin involvement ($P<0.001$)

and increasing lymph node ratio (P<0.001) were significantly related to cancer specific survival (Table 1).

On univariate survival analysis of patient-related characteristics, age (P<0.001), white cell count (P<0.01) and the mGPS (P<0.001) were significantly related to cancer specific survival (Table 2).

On multivariate analysis of significant tumour and patient related factors, Dukes stage (HR 3.01, 95% CI 1.50-6.06, P=0.002), extramural vascular invasion (HR 3.16, 95% CI 1.53-6.58, P=0.002), and the mGPS (HR 1.96, 95% CI 1.19-3.21, P=0.008) were independently related to cancer specific survival (Table 3).

The relationships between an increasing mGPS and patient related factors are shown in Table 4. An increased mGPS was associated with increased age (P<0.001), lower haemoglobin (P<0.001), increased white cell (P≤0.001), neutrophil (P≤0.001) and platelet (P≤0.001) counts and increased neutrophil/lymphocyte ratio ≥5:1 (P<0.001) and increased alkaline phosphatase (P≤0.001).

Discussion

In the present study, in addition to Dukes stage, the most important tumour-related factors associated with cancer specific survival was extramural vascular invasion. These results are consistent with current guidelines, which identify patients undergoing potentially curative resection for colon cancer at high risk of recurrence [3-7].

In the present study, the mGPS was the most important patient-related factor associated with cancer specific survival. These results are consistent with previous studies confirming the role of the mGPS in primary operable colon and rectal cancer [10 12]. Ishizuka and colleagues [12] have called for the 'worldwide adoption of the GPS for postoperative prognostication of patients with colon and rectal cancer".

Recently, in addition to the Glasgow Prognostic Score, a variety of inflammation-based scores have been developed to predict cancer specific survival in patients with primary operable gastrointestinal cancer, including the neutrophil/ lymphocyte ratio and the platelet lymphocyte ratio [20-22]. In the present study, neither the neutrophil/ lymphocyte ratio nor the platelet/ lymphocyte ratio were significantly associated with cancer specific survival. Therefore, these new scores based on the cellular components of the systemic inflammatory response cannot be recommended for routine use in predicting survival in patients undergoing potentially curative resection for colon cancer.

In the present study, in addition to the cellular components of the systemic inflammatory response, alkaline phosphatase was directly associated with the mGPS. These results are consistent with those previously reported in patients with advanced lung and gastrointestinal cancer [23]. Given that circulating concentrations of enzymes primarily reflect that synthesised by the liver in response to systemic inflammation, this increased functional requirement may be important for regulating other enzyme activity in the liver. For example, it has recently been reported that cytochrome P450 3A4 activity is reduced as part of the systemic inflammatory response in patients with advanced cancer [38]. This mechanism may

account for the observation that a raised mGPS is associated with a poor tolerance to chemotherapy in patients with colorectal cancer [39 40]. Irrespective of the mechanisms involved the results of this study indicate that, along with its prognostic value, the mGPS is associated with a cluster of cellular and biochemical changes in patients undergoing potentially curative resection for colon cancer.

In the present study neither CEA or CA-19-9, proposed tumour markers were measured prior to surgery. There is some evidence that the combination of pre-operative serum CEA and CA-19-9 have independent prognostic value in patients undergoing resection for colorectal cancer [41]. However, Ishizuka and coworkers [12] recently reported that, compared with tumour markers such as CEA, CA 19-9 and CA 72-4, the mGPS had superior prognostic value. Further work is required to determine whether a combination of tumour markers offers prognostic value in addition to pathological staging and the mGPS.

The results of the present study add further evidence to the importance of the systemic inflammatory response and the prognostic value of the mGPS in patients with colon cancer [10-12 42]. Therefore, the mGPS has the potential to aid detection of early tumour recurrence following surgery. In contrast, the role of the mGPS in predicting response to neoadjuvant or adjuvant chemotherapy is less clear. There are some recent reports from other centres that suggest that the mGPS might be useful in predicting response to chemotherapy [12 40 43]. This is of particular interest given a recent report from the UK National Confidential Enquiry into Patient Outcome and Death (NCEPOD) which concluded that chemotherapy had probably hastened or caused death, in over a quarter of patients who died within 30 days of receiving treatment [44]. They suggest therefore, that greater caution be used in prescribing chemotherapy in very sick patients [44]. However, they do not suggest how this problem might be avoided or how the very sick patients are to be identified. Therefore, the mGPS has also the potential to guide the selection of chemotherapy for colorectal cancer patients. However, the impact of using the mGPS as a therapeutic target has as yet not been explored.

In summary, both tumour-related and patient-related factors are important predictors of survival in patients undergoing potentially curative resection of colon cancer. In addition to tumour stage, and vascular invasion, the systemic inflammatory response, as evidenced by the mGPS, should be included in the routine clinical assessment, planning of treatment and the stratification of randomized trials of patients with colon cancer.

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Conflict of interest and funding statement

The authors have no conflicts of interest or sources of funding to declare.

Table 1: The relationship between tumour related factors and overall survival and cancer specific survival in patients undergoing potentially curative resection for colon cancer

			Overall survival		**Cancer Specific Survival**	
		Patients n=287 (%)	5 year survival rate % (SE)	P value (log rank)	5 year survival rate %(SE)	P value (log rank)
Dukes Stage	A	19 (7)	88 (4)		85 (8)	
	B	149 (52)	68 (5)		85 (4)	
	C	119 (41)	48 (5)	<0.001	65 (5)	<0.001
Differentiation	Mod-well	248 (86)	64 (3)		78 (3)	
	Poor	39 (13)	43 (8)	0.017	70 (9)	0.171
Extramural vascular invasion						
	Absent	188 (65)	69 (4)		84 (3)	
	Present	19 (35)	45 (5)	<0.001	62 (6)	<0.001
Peritoneal involvement						
	Absent	205 (71)	65 (4)		83 (3)	
	Present	82 (29)	52 (6)	0.021	62 (7)	0.006
Margin involvement						
	Absent	259 (90)	64(3)		79 (3)	
	Present	28 (10)	32 (9)	<0.001	33 (16)	<0.001
Tumour perforation						
	Absent	276 (96)	62 (3)		78 (3)	
	Present	11 (4)	27 (13)	0.002	20 (24)	0.018
Perineural invasion						
	Absent	268 (93)	62 (3)		81 (3)	
	Present	19 (7)	39 (12)	0.113	46 (11)	0.042
Lymph nodes sampled						
	≥12	180 (63)	63 (4)		80 (4)	
	<12	107 (37)	57 (5)	0.288	70 (6)	0.848
Lymph Node Ratio	0	166 (59)	70 (4)		86 (3)	
	0.01-0.24	78 (27)	51 (6)		60 (6)	
	0.25-0.49	32 (11)	59 (9)		61 (9)	
	≥0.5	11 (4)	9 (9)	<0.001	21 (13)	<0.001
Adjuvant chemotherapy						
	Yes	60 (21)	58 (3)		80 (3)	
	No	227 (79)	71 (6)	0.059	69 (7)	0.972

Table 2: The relationship between patient related factors and overall survival and cancer specific survival in patients undergoing potentially curative resection for colon cancer.

		Overall Survival		**Cancer Specific Survival**	
	Patients n=287 %	5 year survival rate % (SE)	P value (log rank)	5 year survival rate % (SE)	P value (log rank)
Age <65 years	85 (30)	82 (4)		86 (4)	
65-74years	87 (30)	66 (5)		75 (5)	
>75years	115 (40)	42 (5)	<0.001	62 (5)	<0.001
Sex Female	133 (46)	58 (4)		74 (4)	
Male	154 (54)	63 (4)	0.474	73 (4)	0.866
Haemoglobin					
≥13g/d (men) ≥11.5g/dl (women)	66 (40)	66 (6)		79 (5)	
<13g/dl (men) <11.5g/dl (women)	101 (60)	61 (5)	0.555	78 (4)	0.671
White cell count <8.5x10^9	98 (59)	67 (4)		82 (4)	
8.5-11x10^9	45 (27)	69 (7)		82 (6)	
>11x10^9	24 (14)	32 (9)	0.001	56 (10)	0.004
Neutrophil count <7.5x10^9	137 (82)	66 (4)		81 (4)	
≥7.5x10^9	30 (18)	47 (10)	0.055	66 (9)	0.051
Lymphocyte count >3.0x10^9	10 (6)	38 (14)		55 (17)	
1.0-3.0x10^9	143 (86)	66 (5)		81 (4)	
<1.0x10^9	14 (8)	69 (8)	0.035	70 (12)	0.160
Platelet count <400 x10^9	122 (73)	65 (5)		81 (4)	
≥400 x10^9	45 (27)	57 (8)	0.084	70 (7)	0.020
Neutrophil/ lymphocyte ratio					
<5:1	129 (77)	67 (5)		82 (4)	
≥5:1	38 (23)	48 (8)	0.047	66 (8)	0.056
Platelet/ lymphocyte ratio					
≤150:1	40 (24)	62 (8)		74 (8)	
>150:1	127 (76)	63 (5)	0.611	80 (4)	0.719
Bilirubin ≤22 μmol/L	215 (96)	61 (4)		74 (3)	
>22 μmol/L	9 (4)	40 (18)	0.379	74 (16)	0.910
Aspartate transaminase ≤50 U/L	223 (99)	60 (4)		74 (3)	
>50 U/L	1 (1)	100 (0)	0.502	100 (0)	0.591
Alanine transaminase ≤50 U/L	223 (99)	60 (4)		74 (3)	
>50 U/L	1 (1)	100 (0)	0.497	100 (0)	0.591
Alkaline phosphatase ≤ 200 U/L	123 (55)	55 (5)		80 (4)	
> 200 U/L	101 (45)	45 (5)	0.037	67 (5)	0.060
γ-glutamyl transferase					
<55U/L (men), <35U/L (females)	175 (79)	63 (4)		76 (3)	
≥55U/L (men), ≥35U/L (females)	50 (21)	53 (7)	0.054	70 (7)	0.324
Globulin ≥22g/L	207 (94)	60 (4)		75 (3)	
<22g/L	14 (6)	62 (14)	0.999	73 (14)	0.756
Calcium Adjusted					
>2.5mmol/L	190 (97)	61 (4)		74 (3)	
≤2.5mmol/L	6 (3)	50 (20)	0.418	82 (16)	0.874
mGlasgow Prognostic Score					
Low Risk (0)	143 (57)	74 (4)		83 (3)	
Intermediate (1)	102 (33)	56 (5)		70 (5)	
High Risk (2)	42 (10)	28 (7)	<0.001	46 (9)	<0.001

Table 3: Tumour and patient related factors and relationship with cancer specific survival in colon cancer. Multivariate analysis of significant variables (P<0.01).

		Overall Survival		**Cancer Specific Survival**	
Tumour Related Factors	(n=287)	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
Dukes Stage (A/ B/ C)	19/ 149/ 119	1.51 (0.93-2.48)	0.099	3.01 (1.50-6.06)	0.002
Extramural Vascular Invasion (absent/ present)	188/ 19	2.01 (1.14-3.55)	0.016	3.16 (1.53-6.58)	0.002
Peritoneal Involvement (absent/ present)	205/ 82		0.424		0.262
Margin Involvement (absent/ present)	259/ 28	2.25 (0.93-5.45)	0.072		0.410
Lymph node ratio (0/ 0.01-0.24/ 0.25-0.49/ $\geq$0.5)	166/ 78/ 32/ 11		0.869		0.832
Patient Related Factors					
Age (<65/ 65-75/ >75years)	85/ 87/ 115	1.91 (1.34-2.72)	<0.001		0.110
White Cell Count (<8.5/ 8.5-11 >11x10^9)	98/ 45/ 24		0.607		0.878
mGlasgow Prognostic Score (0/ 1/ 2)	143/ 102/ 42	1.73 (1.18-2.55)	0.005	1.96 (1.19-3.21)	0.008

Table 4: The relationship between an inflammation based prognostic score (mGlasgow Prognostic Score) and other patient- related factors in colon cancer patients.

	mGPS 0 n=143	**mGPS 1 n=102**	**mGPS 2 n=42**	**P value**
Age Group				
<65/ 65-74/ >75years	51/ 49/ 43	27/ 48/ 27	7/ 10/ 25	<0.001
Sex				
Male/ Female	65/ 78	47/ 55	21/ 21	0.646
Haemoglobin				
≥13g/d (men), ≥11.5g/dl (women)/				
<13g/dl (men) <11.5g/dl (women)	46/ 36	16/ 49	4/ 16	<0.001
White cell count				
$<8.5x10^9$/ $8.5\text{-}11x10^9$/ $>11x10^9$	60/ 17/ 5	29/ 21/ 15	9/ 7/ 4	0.001
Neutrophil count				
$<7.5x10^9$/ $\geq 7.5x10^9$	76/ 6	47/ 18	14/ 6	0.001
Lymphocyte count				
$<1x10^9$/$1\text{-}3x10^9$/$>3x10^9$	6/ 73/ 3	4/ 54/ 7	0/ 16/ 4	0.012
Platelet count				
<400 $x10^9$/ ≥400 $x10^9$	71/ 11	39/ 26	12/ 8	0.001
Neutrophil-lymphocyte ratio				
<5:1/ ≥5:1	76/ 6	44/ 21	9/ 11	<0.001
Platelet-lymphocyte ratio				
≤150:1/ >150:1	23/ 59	12/ 53	5/ 15	0.408
Bilirubin				
≤22 μmol/L/ >22 μmol/L	100/ 5	84/ 3	31/ 1	0.610
Aspartase transaminase				
≤50 U/L/ >50 U/L	105/ 0	86/ 1	32/ 0	0.647
Alanine transaminase				
≤50 U/L/ >50 U/L	105/ 0	86/ 1	32/ 0	0.647
Alkaline phosphatase				
≤ 200 U/L/ > 200 U/L	69/ 36	43/ 44	11/ 21	0.001
γ-Glutamyl transferase				
<55U/L (men), <35U/L in females/				
≥55U/L (men), ≥35U/L in females	86/ 20	68/ 19	21/11	0.094
Globulin				
≥22/ <22g/L	96/ 7	82/ 4	29/ 3	0.847
Calcium Adjusted				
>2.5/ ≤2.5mmol/L	84/ 4	77/ 0	29/ 2	0.884