Long-term follow-up of patients undergoing resection of TNM Stage I colorectal cancer: An analysis of tumour and host determinants of outcome

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Abstract

Background

Screening for colorectal cancer improves cancer specific survival (CSS) through the detection of early stage disease, however its impact on overall survival (OS) is unclear. The present study examined tumour and host determinants of outcome in TNM Stage I disease.

Methods

All patients with pathologically confirmed TNM Stage I disease across 4 hospitals in the North of Glasgow between 2000 and 2008 were included. The preoperative modified Glasgow Prognostic Score (mGPS) was used as a marker of the host systemic inflammatory response (SIR).

Results

There were 191 patients identified, 105 (55%) were males, 91 (48%) were over the age of 75 years and 7 (4%) patients underwent an emergency operation. In those with a pre-operative CRP result (n=150), 35 (24%) patients had evidence of an elevated mGPS. Median follow-up of survivors was 116 months (minimum 72 months) during which 88 (46%) patients died; 7 (8%) had postoperative deaths, 15 (17%) had cancer-related deaths and 66 (75%) had non cancer-related deaths. 5-year CSS was 95% and OS was 76%. On univariate analysis, advancing age ($p<0.001$), emergency presentation ($p=0.008$) and an elevated mGPS ($p=0.012$) were associated with reduced OS. On multivariate analysis, only age (HR = 3.611, 95% CI: 2.049–6.365, $p<0.001$) and the presence of an elevated mGPS (HR = 2.173, 95% CI: 1.204–3.921, $p=0.010$) retained significance.

Conclusions

In patients undergoing resection for TNM Stage I colorectal cancer, an elevated mGPS was an objective independent marker of poorer OS. These patients may benefit from a targeted intervention.

Introduction

Population screening for colorectal cancer using the faecal occult blood test (FOBt) has been shown to improve cancer specific mortality through the detection of early stage disease [1-3]. Through this detection of early stage tumours, such screening programmes have the potential to change the entire landscape of the management and outcome of colorectal cancer. For example, studies in the pre-screening era noted that less than 20% of all patients presented with TNM Stage I disease [4,5]. However, it has been shown that TNM Stage I tumours can account for approximately 50% of colorectal cancers detected through FOBt screening programmes [6-8]. Hence, an overall stage-shift towards early stage disease is anticipated over the next decade [9].

Cancer outcome following a diagnosis of TNM Stage I colorectal cancer is very good, and an average 5-year cancer specific survival of over 90% is widely reported [10]. As such, adjuvant chemotherapy is not recommended in these patients [11,12]. Nevertheless, some will develop metastatic disease and ultimately succumb to their illness and others will die of alternate causes, such as cardiovascular disease. This would be increasingly relevant to those detected through screening, as while screening improves cancer specific mortality, no effect on overall survival has been shown on mature follow up [13].

Many risk factors associated with a diagnosis of colorectal cancer are similar to those for cardiovascular disease [14], which is the leading cause of death in individuals over the age of 50 [15]. It is now increasingly recognised that independent of TNM Stage, there are host factors that may be of importance in predicting outcome. In particular, the presence of an elevated systemic inflammatory response [16,17] as evidenced by an alteration in circulating acute phase proteins, such as C-

reactive protein (CRP) and albumin (modified Glasgow Progostic Score (mGPS)), is associated not only with poorer outcome in colorectal cancer, but more recently it has been linked to all-cause mortality in a large incidentally sampled cohort [18]. There is a paucity of evidence examining tumour and, in particular, host factors in determining outcome specifically in patients with TNM Stage I colorectal cancer. This is something that is of increasing importance in the post-screening era.

The aim of the present study was to examine tumour and host determinants of outcome in patients undergoing resection for TNM Stage I colorectal cancer with mature follow-up.

Materials and Methods

From January 2000 to December 2008 (inclusive), all patients undergoing a resection, with pathologically confirmed TNM Stage I disease, across four hospitals in the north of Glasgow were identified. Data was collected in both a prospective (Glasgow Royal Infirmary) and retrospective (Stobhill Hospital, Western Infirmary, Gartnavel General Hospital) manner. Any patient with a synchronous cancer, inflammatory bowel disease or who had received neo-adjuvant therapy was excluded. Those with their disease managed entirely endoscopically, without formal colonic or rectal resection, were also excluded from the study.

Tumours were staged according to the conventional tumour node metastasis (TNM) classification (5th Edition)[19]. Further details on high-risk tumour features, such as the presence of venous invasion [20], poor differentiation [21] or those in whom less than 12 lymph nodes were examined [21] were extracted from pathology reports. Those with inadequate information on the number of nodes examined in pathology reports were excluded from the analysis.

The mGPS was used as an estimate of the SIR as has been described previously~~, using pre-operative blood results taken most immediately and not more than 1 month prior to surgery~~ [22]. Bloods were taken as routine care at preoperative assessment using standard aseptic technique and processed according to standard laboratory protocols. The mGPS was constructed as follows; ~~Briefly,~~ patients with a CRP $\leq$ 10 mg/L were allocated a score of 0, a CRP >10 mg/L and albumin $\geq$ 35g/L a score of 1 and a CRP >10mg/L and albumin <35g/L a score of 2. Due to limited events during follow-up, for survival analysis the mGPS was further dichotomised into being elevated (mGPS = 1 or 2) or not elevated (mGPS = 0).

Survival was determined from both individual electronic patient records and by matching patients to the Registrar General (Scotland). Date of censor was 12th December 2014. Overall survival (OS) was the primary outcome measure and was calculated from date of surgery until date of death. Cancer specific survival (CSS) was calculated from date of surgery until date of death from recurrent or metastatic colorectal cancer. A post-operative death was defined as a death within 30 days of operation.

The study was discussed and approved by the local research and ethics committee.

Statistical analyses

The relationship between clinicopathological features and survival was examined using Kaplain-Meier log-rank survival analysis and univariate Cox proportional hazards regression to calculate hazard ratios (HR) and 95% confidence intervals (95% CI). Statistically significant variables on univariate analysis were then taken forward into a multivariate model using a backwards conditional method. Associations between variables were examined using the Chi-squared test. Fisher's exact test was used for assessing associations where the expected individual cell counts were less than 5. A value of $p<0.05$ was considered statistically significant. Statistical analysis was performed using SPSS software (SPSS Inc., Chicago, IL, USA)

Results

A total of 191 patients were identified and included in the study. There were 105 (55%) males, 91 (48%) were over the age of 75 years and 7 (4%) patients underwent an operation as an emergency. Of the emergency operations, 5 (71%) patients underwent a right hemicolectomy due to an obstructing caecal tumour, 1 (14%) patient underwent a sigmoid colectomy for concurrent diverticulitis and 1 (14%) patient underwent a panproctocolectomy following an iatrogenic caecal perforation during colonoscopic diagnosis of an early rectal tumour. In those with a pre-operative CRP result (n=150), 35 (24%) patients had evidence of an elevated mGPS (Table 1).

The median follow-up of survivors was 116 months with a minimum follow-up of 72 months. During follow-up 88 (46%) patients died of which 7 (8%) were postoperative deaths, 15 (17%) were colorectal cancer-related deaths and 66 (75%) were non-colorectal cancer-related deaths. The causes of non-colorectal cancer-related deaths were; 20 (30%) patients non-colorectal cancer, 15 (23%) patients cardiovascular disease, 8 (12%) patients respiratory disease, 8 (12%) patients cerebrovascular disease and 15 (23%) patients miscellaneous causes. ~~This~~ The 1, 2 and 5 year ~~resulted in a 5 year~~ CSS ~~of 95%~~ and ~~a 5 year~~ OS ~~of 76%~~ was 98%, 95% and 95%, and 90%, 83% and 76% respectively. Excluding postoperative deaths, on univariate analysis, advancing age ($p<0.001$), emergency presentation ($p=0.008$) and an elevated mGPS ($p=0.012$) were associated with reduced OS. On multivariate analysis, only age (HR = 3.611, 95% CI:2.049 - 6.365, $p<0.001$) and the presence of an elevated mGPS (HR = 2.173, 95% CI:1.204 – 3.921, $p=0.010$) retained significance (Table 2, Figure 1).

There was an association between an elevated mGPS and emergency presentation (p=0.040). In view of this, survival in elective procedures was examined independently (Table 3). Excluding postoperative deaths, on univariate analysis, advancing age (p<0.001) and an elevated mGPS (p=0.034) were associated with reduced OS. On multivariate analysis, both age (HR = 3.503. 95% CI:1.980 – 6.196, p<0.001) and the presence of an elevated mGPS (HR = 2.104, 95% CI:1.155 – 3.835, p= 0.015) retained significance (Table 3). There were no further associations between the presence of an elevated mGPS and additional clinicopathological variables (Table 4). The unadjusted difference in mean OS between those with an elevated mGPS and those without was 31 months (Table 4).

Data was further stratified to assess any temporal trends that may have developed over the timeframe. Comparing patients operated on between 2001 and 2004 to those operated on between 2005 and 2008, there were no differences in age (p=0.548), sex (p=0.292), mode of presentation (p=0.345), site of tumour (p=0.149), t-stage (p=0.969), tumour differentiation (p=0.656) or the presence of an elevated mGPS (p=0.520). Patients operated on between 2001 and 2004 were more likely to have less than 12 lymph nodes examined (61% vs 44%, p=0.020) and there was a trend towards a lower venous invasion rate (17% vs 28%, p=0.073). Date of operation was not associated with OS (Tables 2 & 3).

Discussion

The results of the present study show that with mature follow-up, although cancer specific survival was 95%, overall survival was 76% in patients undergoing resection for TNM Stage I colorectal cancer. Furthermore, in these patients, the presence of an elevated SIR, as measured by the mGPS, was associated with poorer outcome. Taken together, this supports the argument that the SIR can be used as a means of identifying patients with a poorer outcome even within very early stage colorectal cancer.

The results of the present study confirm previous work that has shown that long-term oncological outcome in TNM Stage I disease is excellent [10]. However, a significant amount of patients will die of other causes and there is a paucity of evidence focussing on OS, which is ultimately of most relevance in patient outcome. In particular, to our knowledge, there have been no studies examining the relationship between the SIR and OS in TNM Stage I disease. Given that the SIR has been shown to be associated with adverse outcomes in both cardiovascular disease as well as cancer, it may represent a nexus from which overall survival may be predicted and improved in this patient cohort. For example, several large prospective cohort studies have identified inflammatory mediators including as C-RP and albumin, as being predictive of both all cause, cancer-specific mortality and cardiovascular mortality in the over 50s [23,24].

It is of interest to compare this to previous work in our geographical area that has identified that age and emergency presentation are associated with survival in Stage II disease [25]. In the present study when adjusted for the SIR, as evidenced by mGPS, emergency presentation failed to retain prognostic significance. This is in contrast to a previous study, predominantly in Stage II disease, that had shown that

while emergency presentation and the SIR were linked, they both represented independent predictors of CSS [26]. This disparity is likely due to the focus on OS in the present study and the low number of cancer-related deaths. Furthermore, it may be speculated that within very early stage disease, emergency presentation, and its relationship with OS, represents a surrogate for a pro-inflammatory state that the mGPS more accurately recapitulates.

In addition to the long-term sequelae, there are short-term consequences of an elevated preoperative SIR that are important to consider. In the present study the overall postoperative mortality of 3.7% was in line with a large scale audit within the UK [27]. However, colorectal~~Colorectal~~ resections can be associated with significant morbidity including both infective and non-infective postoperative complications. The preoperative SIR has been previously shown to be predictive of the development of a postoperative infection [28~~7~~] and is associated with an elevated postoperative SIR, as measured by CRP [29~~8~~]. Such a rise in the postoperative CRP is associated with higher rates of both surgical-site and remote infective complications [30~~29~~]. In particular, in a recent meta-analysis the use of Day 3 CRP as a predictor of an anastomotic leak in the postoperative course at a threshold of 172 mg/l was found to have a negative predictive value of 97% [31~~0~~].

It is important to ~~identify~~ consider why individuals may have an elevated preoperative SIR in order to potentially identify ~~a~~ targets for intervention. The SIR has been linked to a number of patient-related factors including smoking [32~~1~~], diabetes [33~~0~~] ~~and~~ obesity [34~~3~~] and cardiovascular disease [23]. In the context of colorectal cancer specifically, the SIR has been found to be associated with preoperative impaired patient physiology, including an elevated physiological and operative severity score for the enumeration of mortality and morbidity (POSSUM)

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[35].~~,~~ A full assessment of comorbidity was not carried out in the present study. However, the SIR has previously been shown to determine outcome independent of comorbidity [35]. Therefore, although there is a relationship between the SIR and comorbid disease their impact on survival on survival is likely to be complex and reflects the interaction between the tumour and the host. It is proposed that the SIR represents an objective global assessment of the patient and as such may be a therapeutic target for potential intervention [36].

~~however, it has been shown that it can determine outcome independent of comorbidity [34]. Therefore, to equate the SIR to a mere surrogate of comorbid disease would be to oversimplify a more complex interaction between tumour and host. Assessment of comorbidity was not available in the population included in the present study and therefore this was not included as a covariate. It is proposed, however, that the SIR represents a global assessment of the patient and may be a therapeutic target for potential intervention [35].~~

~~———~~A diagnosis of cancer has been identified as a 'teachable moment' whereby individuals are more receptive to changes in risk-related lifestyle and behaviour [3~~7~~6]. Indeed, the recently published BeWEL study has identified that a weight loss programme can be successfully instigated in patients who have adenomata identified at colonoscopy following a positive FOBt screening test [3~~8~~7]. The authors reported that interventions including exercise not only reduced weight, but improved blood pressure and glucose metabolism markers after 1 year. The SIR was not reported on within the BeWEL study, however weight control and exercise programmes have previously been shown to reduce the SIR [3~~9~~8]. The present study identifies a subgroup of patients that have a poorer outcome and hence may be suitable for targeting with such a programme. Further studies could include the

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instigation of such a rehabilitation programme, in a manner not dissimilar to cardiac rehabilitation, which is now a standard of care for patients who have undergone a cardiac event.

In addition to lifestyle measures such as diet and exercise, there is potential to manipulate the SIR through pharmacological methods. There is evidence that both statin~~s~~ [40~~39~~,41~~0~~] and aspirin [42~~1~~] use can reduce circulating CRP levels and this can have a positive effect on outcomes from cardiovascular disease [34~~3~~]. Furthermore, these medications have also been shown to have a potential role in the prevention of colorectal cancer development [43~~2~~,44~~3~~] and progression [45~~4~~]. The argument for a 'polypill', combining blood pressure and cholesterol lowering medication as well as antiplatelet treatments, has previously been made to reduce deaths from cardiovascular disease [46~~5~~] however its benefits remain uncertain when used in a relatively unselected patient population [47~~6~~]. Prospective studies are required to assess whether these medication~~s~~ should be routinely recommended in early stage colorectal cancer due to these combined effects of cardiovascular protection and chemoprevention.

Strengths & Limitations

The strengths of the present study include the relatively large numbers with long-term follow-up. In addition, the present study has included detailed high-risk tumour factors such as the presence of venous invasion. The main limitation of the study is that ~~-~~this is a historic cohort captured over a prolonged timeframe. As such, temporal changes in staging and management may have taken place. Indeed, the proportion of patients with less than 12 nodes examined was lower in those operated

on in earlier years. Such a problem is inherent when examining early stage disease that was uncommon prior to the introduction of screening. However, this has been adjusted for within survival analysis and it is reassuring that date of operation was not associated with OS in this cohort. In addition, applicability of the findings to a screen-detected cohort may be questionable. Patients with screen-detected tumours differ in terms of patient demographics and comorbidities, and as such may have different determinants of outcome [48~~7~~]. Due to the relatively recent introduction of population screening in the UK and a lack of mature follow-up of screen-detected TNM Stage I disease this remains to be determined. Nevertheless, it should be noted that, despite the introduction of national screening programmes, a large proportion of patients continue to present through alternative routes [49]~~Due to the relatively recent introduction of population screening in the UK, mature follow-up of screen-detected TNM Stage I disease is not yet possible.~~.

Within the pathological reporting of specimens there were a large number of patients who had suboptimal lymph node examination and hence may be perceived as being understaged. The present study has shown this to be associated with historic changes in processing of specimens. In addition, it may also be due to the relatively high proportion of rectal tumours in this cohort. However, if this were to have introduced bias of understaging then it would be expected that outcomes would be poorer in this group, which was not the case. Finally, a perceived limitation may be the lack of cancer specific survival analysis within the present study. However, due to the small proportion of cancer deaths in this cohort, such analysis is problematic. Also, the relevance of CSS to the individual patient is limited and, particularly in the screened population, recommendations for reporting effects on OS have been made [5048~~48~~].

In summary, patients undergoing resection for TNM Stage I colorectal cancer have an excellent oncological outcome, however only around three quarters of our cohort were alive at 5 years. The presence of an elevated preoperative SIR, as measured by the mGPS, is an objective independent marker that identifies patients with poorer overall survival and potentially identifies a subgroup that may benefit from ~~targeted~~ pharmacological or lifestyle interventions aimed at reducing systemic inflammation.

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Table 1: Baseline characteristics of patients undergoing resection for TNM Stage I colorectal cancer

	All patients n(%)
	191
Age	
<75	100 (52)
≥75	91 (48)
Sex	
Female	86 (45)
Male	105 (55)
Mode of presentation	
Emergency	7 (4)
Elective	184 (96)
Tumour Site	
Colon	122 (64)
Rectum	69 (36)
T-stage	
1	54 (28)
2	137 (72)
Venous invasion[a]	
Present	37 (22)
Absent	130 (78)
Differentiation	
Poor	3 (2)
Moderate/well	188 (98)
Less than 12 lymph nodes	
Yes	102 (53)
No	89 (47)
mGPS[b]	
0	115 (77)
1	22 (15)
2	13 (9)
Date of operation	
2001 - 2004	103 (54)
2005 - 2008	88 (46)
Outcome at date of censor	
Alive	103 (54)
Postoperative death	7 (4)
Cancer-related death	15 (8)
Non cancer-related death	66 (35)

[a] Data complete 167 (87%) patients
[b] mGPS = modified Glasgow Prognostic Score. Data complete 150 (79%) patients

Table 2: Factors associated with overall survival following resection for TNM Stage I colorectal cancer (excluding post operative deaths)

	Univariate survival analysis HR (95% C.I.)	p-value	Multivariate survival analysis HR (95% C.I.)	p-value
Age *(<75 / ≥75)*	**3.722 (2.310 – 5.996)**	**<0.001**	**3.611 (2.049 – 6.365)**	**<0.001**
Sex *(Female / Male)*	0.895 (0.579 – 1.385)	0.620	-	
Mode of presentation *(Elective / Emergency)*	**3.443 (1.387 – 8.543)**	**0.008**	1.036 (0.240 – 4.469)	0.962
Tumour Site *(Colon / Rectum)*	0.915 (0.580 – 1.442)		-	
T-stage *(1 / 2)*	1.104 (0.676 – 1.804)	0.692	-	
Venous invasion *(No / Yes)*	1.304 (0.762 – 2.229)	0.333	-	
Differentiation *(moderate-well / poor)*	1.661 (0.407 – 6.778)	0.479	-	
Less than 12 lymph nodes *(No / Yes)*	1.122 (0.721 – 1.745)	0.610	-	
mGPS *(0 / 1+2)*	**2.076 (1.172 – 3.677)**	**0.012**	**2.173 (1.204 – 3.921)**	**0.010**
Date of operation *(2001-2004 / 2005 – 2008)*	1.233 (0.769 – 1.976)	0.385	-	

Table 3: Factors associated with overall survival following resection for TNM Stage I colorectal cancer (excluding emergency presentation and post operative deaths)

	Univariate survival analysis	p-value	Multivariate survival analysis	p-value
	HR (95% C.I.)		**HR (95% C.I.)**	
Age *(<75 / ≥75)*	**3.634 (2.228 – 5.926)**	**<0.001**	**3.503 (1.980 – 6.196)**	**<0.001**
Sex *(Female / Male)*	0.832 (0.530 – 1.305)	0.423	-	
Tumour Site *(Colon / Rectum)*	0.939 (0.589 – 1.498)	0.791	-	
T-stage *(1 / 2)*	1.042 (0.634 – 1.713)	0.871	-	
Venous invasion *(No / Yes)*	1.343 (0.772 – 2.336)	0.297	-	
Differentiation *(moderate-well / poor)*	1.745 (0.427 – 7.130)	0.438	-	
Less than 12 lymph nodes *(No / Yes)*	1.041 (0.661 – 1.641)	0.861	-	
mGPS *(0 / 1+2)*	**1.908 (1.050 – 3.467)**	**0.034**	**2.104 (1.155 – 3.835)**	**0.015**
Date of operation *(2001-2004 / 2005 – 2008)*	1.229 (0.753 – 2.004)	0.410	-	

Table 4: Relationship between clinicopathological factors, overall survival (OS) and the modified Glasgow Prognostic Score (mGPS) in patients undergoing resection for TNM Stage I colorectal cancer

	mGPS		
	0	**1/2**	**p-value**
	n(%)	**n(%)**	
	115	35	
Age			
<75	65 (56)	17 (49)	
≥75	50 (44)	18 (51)	0.410
Sex			
Female	49 (43)	16 (46)	
Male	66 (57)	19 (54)	0.746
Mode of presentation			
Emergency	1 (1)	3 (9)	
Elective	114 (99)	32 (91)	0.040
Tumour Site			
Colon	69 (60)	25 (71)	
Rectum	46 (40)	10 (29)	0.223
T-stage			
1	37 (32)	6 (17)	
2	78 (68)	29 (83)	0.086
Venous invasion[a]			
Present	28 (27)	6 (19)	
Absent	75 (73)	25 (81)	0.382
Differentiation			
Poor	3 (3)	0	
Moderate/well	112 (97)	35 (100)	0.448
Less than 12 lymph nodes			
Yes	60 (52)	19 (54)	
No	55 (48)	16 (46)	0.827
Date of operation			
2001 – 2004	52 (45)	18 (51)	
2005 – 2008	63 (55)	17 (49)	0.520
Mean OS			
(months (95% CI))	122 (112 – 131)	91 (71 – 110)	0.010

[a] data complete for 134 (89%) patients