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The Relationship between Tumour Pathology, CT-Body Composition, Systemic Inflammation and Patterns of Colonic Cancer Recurrence

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1. Abstract

1.1. Background: Recurrence of colorectal cancer has been attributed to aggressive tumour subtypes, advanced disease stage and emergency presentation. While host factors such as body composition and systemic inflammation are associated with recurrence free survival in patients undergoing surgical resection, whether they can delineate patterns of colorectal cancer recurrence is unknown.

1.2. Methods: Consecutive patients who underwent resection for colon cancer (TNM I-III) at our institution, between April 2008 and April 2018, were identified from a prospectively maintained database. Tumour and patient characteristics including CT-body composition and systemic inflammation were recorded. The incidence and pattern of recurrence (locoregional or systemic) were recorded during minimum follow-up of 3-years post-operatively. Categorical variables were analysed using $\chi 2$ test for Mantel Haenszel (linear-by-linear) association. Survival analysis was carried out using univariate and multivariate Cox regression.

1.3. Results: 536 patients met the study inclusion criteria. 14% (n=73) of patients were diagnosed with cancer recurrence within 3-years following surgery, with median time to diagnosis of recurrence 18 months (11-30). 4% (n=21) of patients developed locoregional recurrence and 10% (n=52) systemic recurrence. On univariate analysis, locoregional recurrence was associated with tumour stage ($p<0.001$) and mGPS ($p<0.05$). On multivariate analysis, mGPS ($p<0.05$) remained significantly associated with recurrence free survival.

1.4. Conclusion: In patients undergoing potentially curative treatment of colon cancer, pre-operative systemic inflammation identifies those at increased risk of locoregional recurrence and poor recurrence free survival. These patients may benefit from enhanced pre-operative staging and more rigorous follow-up than routinely offered.

2. Introduction

Despite advances in the staging and treatment of colon cancer (CC), disease recurrence following radical resection with curative intent remains a major source of mortality [1]. Contemporary data suggests up to 20% of patients develop CC recurrence following treatment [1-3], with recognised sites of recurrence including the peritoneum and liver [4]. However, recurrent CC often presents late, with advanced disease, when treatment options are limited and consequently survival remains poor [1, 5]. Therefore, there is continued interest in factors that may stratify those at risk of recurrence following treatment to guide surveillance regimens.

Following surgical resection of primary CC with curative intent, patients undergo a combination of clinical, endoscopic and CT surveillance to identify local and distant recurrence [6]. Longitudinal studies of patients undergoing treatment of CC with curative intent have shown that up to 80% of recurrences are diagnosed within two-years of primary resection [7], rising to approximately 90% within 5 years [8]. However, despite robust surveillance programs [6, 9], recent large cohort studies from the Netherlands found that most patients with CC recurrence were asymptomatic [10, 11], and nearly half of those with recurrent CC were diagnosed outwith scheduled follow-up [11]. Therefore, factors which delineate

patterns of recurrence would not only be informative for resource allocation for surveillance, but also have the potential to improve survival outcomes in patients with CC [12].

Patients with recurrent CC are typically thought to die of distant metastatic disease [13]. Pre-operative host factors such as a systemic inflammatory response and CT-derived body composition have previously been associated with recurrence free survival following surgery for CC [14, 15]. Furthermore, patients who are systemically inflamed or have poor muscle status respond poorly to anti-cancer therapy [16, 17] and exhibit altered biology, promoting disease recurrence [18, 19]. However, it is unclear if sarcopenic body composition influences recurrence per se or is simply a reflection of patients who are not robust enough to deal with CC upon recurrence, leading to expedited demise.

At present, whether these pre-operative host measures can identify those at risk of locoregional or systemic recurrence is unknown. Therefore, the aim of the present study was to examine the relationship between tumour pathology, CT-body composition, systemic inflammation and patterns of recurrence in patients undergoing surgery for CC.

3. Patients and Methods

3.1. Patients

Consecutive patients who underwent elective, potentially curative resection for CC, within NHS Greater Glasgow and Clyde (NHSGGC), between April 2008 and October 2018, were identified from a prospectively maintained database. Those patients with a pre-operative CT scan, recorded height and weight, pre-operative assessment of the systemic inflammatory response, and TNM stage I-III colonic tumours were assessed for inclusion.

3.2. Clinicopathological characteristics

Routine demographic details collected included age, sex and BMI. Age categories were grouped into <64, 65-74 and > 74 years. BMI was categorized as <20, 20-24.9, 25-29.9 and ≥30 kg/m2.Patient comorbidity was classified using the American Society of Anaesthesiologists (ASA) grading system [20]. Tumour site was identified from pre-operative CT imaging, endoscopic and pathology reports. Tumour site was broadly categorised as right sided (from terminal ileum to hepatic flexure) and other (transverse colon to rectosigmoid junction). All tumours were staged using the fifth edition of the AJCC TNM-staging system [21]. Tumour pathological characteristics recorded included differentiation and venous invasion, identified from pathology reports.

3.3. Patient Follow-up

Patients were followed up according to local surveillance guidelines. Upon discharge following resection, patients were typically reviewed in an outpatient clinic at six weeks, six months and then annually, for a minimum of three years. Surveillance for recurrence included a complete colonoscopy, or CT-colonoscopy, performed within one year of surgery in addition to yearly thoracoabdominal CT scanning.

Disease recurrence and vital status were obtained from the included patients' electronic case records. The date of and site of recurrence was confirmed using CT or PET-CT imaging reports. The date of last recorded follow-up or last review of electronic case records was 1st October 2021, which acted as the censor date. Recurrence was categorised as loco-regional or systemic. Loco-regional recurrence was defined as peri-anastomotic, involvement of local lymph nodes (mesenteric, paracolic and retroperitoneal) and peritoneal disease. All other sites of metastatic recurrence, such as liver or lung, were categorised as systemic [22, 23]. Metachronous colorectal cancers were not defined as cancer recurrence and excluded.

Ethical approval was granted by the West of Scotland Research Ethics Committee, Glasgow.

3.4. Body composition analysis

CT images were obtained at the level of the third lumbar vertebra as previously described [24] . Patients with CT imaging taken 3 months or more prior to their surgery were excluded from the study. Furthermore, scans with significant movement artefact or missing region of interest were not considered for inclusion. Each image was analysed using a free-ware program (NIH Image J version 1.47, http://rsbweb.nih.gov/ij/), previously shown to provide reliable measurements [25].

Region of interest (ROI) measurements were made of visceral fat (VFA), subcutaneous fat (SFA), and skeletal muscle areas (SMA) (cm^2) using standard Hounsfield Unit (HU) ranges (adipose tissue -190 to -30, and skeletal muscle -29 to +150), as previously described. These were then normalised for height in meters squared (m^2) to create the subcutaneous fat (SFI, cm^2/m^2), and skeletal muscle indices (SMI, cm^2/m^2). Skeletal muscle radiodensity (SMD, HU) was measured from the same ROI used to calculate SMI, as its mean HU.

Subcutaneous obesity was defined as ≥ 50.0 cm^2/m^2 in males and ≥42.0 cm^2/m^2 in females [26]. Visceral obesity was defined as VFA >160cm^2 for male patients and >80cm^2 for female patients [27]. Sarcopenia was defined as described by Martin and colleagues and an SMI<43cm^2/m^2 if BMI <25kg/m^2 and SMI<53cm^2/m^2 if BMI >25kg/m^2 in male patients and SMI <41cm^2/m^2 in female patients [28]. Myosteatosis was defined by Martin and colleagues as an SMD <41HU in patients with BMI <25kg/m^2 and <33HU in patients with BMI >25kg/m^2 [28].

3.5. Systemic Inflammation

Pre-operative haematological and biochemical results were identified from medical records and prospectively recorded. Blood samples were either obtained at pre-operative assessment, within 30 days of surgery, for elective patients or on admission for patients undergoing emergency surgery. An autoanalyzer was used to measure serum CRP (mg/L) and albumin (g/L) concentrations

(Architect; Abbot Diagnostics, Maidenhead, UK).

Systemic inflammatory status was retrospectively assessed by calculating the neutrophil/lymphocyte ratio (NLR) and modified Glasgow Prognostic Score (mGPS) for each patient, using pre-operative blood results. The NLR was calculated by division of the neutrophil count by the lymphocyte count, obtained from the patient's full blood count (FBC). NLR values were grouped as <3, 3–5 and >5, as previously described [25]. The mGPS was calculated as previously described, CRP ≤ 10 mg/L = 0, CRP > 10 mg/L & albumin ≥ 35 g/L = 1, CRP > 10 mg/L and albumin < 35 g/L = 2 [29].

3.6. Statistical Analysis

Demographic data, clinicopathological variables, CT-body composition measurements, NLR, mGPS and 3-year survival were presented as categorical variables. Categorical variables were analysed using $\chi 2$ test for linear-by-linear association.

Recurrence free survival (RFS) was defined as time from surgery to diagnosis of recurrence or death of any cause. Univariate and multivariate survival analysis was performed using Cox proportional hazards regression to calculate hazard ratios (HR) and 95% confidence intervals (95% CI). Clinicopathological factors that had a p value <0.1 were taken into a multivariate model using a backward conditional model to identify independently significant factors.

Missing data were excluded from analysis on a variable-by-variable basis. Two-tailed p values <0.05 were considered statistically significant. Statistical analysis was performed using SPSS software version 25.0. (SPSS Inc., Chicago, IL, USA).

4. Results

4.1. Patient Cohort

Patients who underwent treatment for colorectal cancer within the study timeframe were eligible for inclusion (n=632). Patients were excluded because of emergency presentation (n =51); no or insufficient post-operative follow-up (n=4); unsuitable or missing CT scans (n=22); missing clinicopathological data or pre-operative blood results (n=16); and metastatic disease at presentation (n=3).

The clinicopathological characteristics of the included patients are shown in Table 1. 53% (n=286) of patients were male and 71% (n=379) were aged 65 years or older. 40 % (n=212) of patients were ASA grade ≥3. 64% (n=345) of patients had right sided colonic tumours, with 36% (n=191) having a tumour at another site. 22% (n=119) of patients had TNM stage I disease, 42% (n=228) stage II, and 36% (n=191) had stage III. 75% (n=402) of patients had T3 or 4 disease and 36% (n=191) had lymph node involvement. 90% (n=486) of patients had moderately-well differentiated disease and 59% (n=316) had venous invasion. The median BMI of the cohort was 26.9 kg/m^2 and 32% (n=174) of patients had a BMI≥ 30 kg/m^2. 74% (n=398) of patients were viscerally obese and 81% (n=435) were subcutaneously obese. Sarcopenia and myosteatosis were present in 53% (n=283) and 70% (n=375), respectively. 16% (n=84) of patients had an NLR>5 and 32% (n=173) had an mGPS≥1.

83% (n=449) were alive 3-years post operatively. 14% (n=73) of patients were diagnosed with cancer recurrence within 3 years of surgery. 4% (n=21) of patients developed locoregional recurrence and 10% (n=52) systemic recurrence. Of those with systemic recurrence, 37% (n=19) had isolated liver metastasis, with the remaining 63% (n=33) having metastasis to other viscera or at multiple sites. The median time to diagnosis of recurrence was 18 months (11-30). When stratified by pattern of recurrence (locoregional or systemic), the median time to diagnosis of recurrence for patients with locoregional recurrence was 11 months (8-21.5) and 20.5 months (12-31) in those with systemic recurrence.

The relationship between clinicopathological characteristics, tumour pathology, CT-body composition, systemic inflammation and disease recurrence in patients who underwent potentially curative resections for colon cancer is shown in Table 1. On univariate analysis, cancer recurrence was significantly associated TNM stage (p<0.001), tumour stage (p<0.001), nodal involvement (p<0.001), and venous invasion (p<0.05). There was no association between CT body composition measurements or common measures of systemic inflammation and recurrence.

The relationship between clinicopathological characteristics, CT-body composition, systemic inflammation and pattern of cancer recurrence is shown in Table 2. On univariate analysis, locoregional recurrence was associated with tumour stage (p<0.001), and mGPS (p<0.05). Although diagnosed earlier, those with local recurrence were more likely to survive 3 years, while those with systemic recurrence died earlier. There were no strong host factors that determined systemic recurrence.

The relationship between host factors and RFS in patients undergoing potentially curative resections for CC is shown in Table 3. On univariate analysis, age (p<0.05), NLR (p<0.05) and mGPS (p<0.001) were significantly associated with RFS. On multivariate analysis, mGPS (p<0.05) remained significantly associated with RFS.

Table 1: The relationship between clinicopathological variables, tumour pathology, CT-BC measurements, systemic inflammatory status and the incidence of recurrence, in patients undergoing potentially curative resections for colonic tumours (n=536).

	No recurrence (n=463)/ %	Recurrence (n=73) / %	p value [1]
Age (years)			
<65	129 (27.9)	28 (38.4)	0.084
65-74	169 (36.5)	24 (32.9)	
>74	165 (35.6)	21 (28.8)	
Sex			
Male	241 (52.1)	45 (61.6)	0.127
Female	222 (47.9)	28 (38.4)	
ASA Grade			
1	68 (14.7)	15 (20.5)	0.124
2	207 (44.7)	34 (46.6)	
≥3	188 (40.6)	24 (32.9)	
Tumour Site			
Right	296 (63.9)	49 (67.1)	0.597
Other	167 (36.1)	24 (32.9)	
TNM Stage			
I	114 (24.5)	5 (6.8)	<0.001
II	209 (44.9)	19 (26.0)	
III	142 (30.5)	49 (67.1)	
Tumour Stage			
1/2	128 (27.5)	8 (11.0)	<0.001
3	237 (51.0)	30 (41.1)	
4	100 (21.5)	35 (47.9)	
Nodal Stage			
0	322 (69.2)	25 (34.2)	<0.001
1	110 (23.7)	29 (39.7)	
2	33 (7.1)	19 (26.0)	
Differentiation			
Moderately well	415 (85.9)	62 (84.9)	0.28
Poor	50 (10.8)	11 (15.1)	
Venous Invasion			
No	200 (43.0)	22 (30.1)	0.038
Yes	265 (57.0)	51 (69.9)	
BMI (kg/m^2)			
<20	26 (5.6)	7 (9.6)	0.551
20-24.9	137 (29.5)	19 (26.0)	
25-29.9	150 (32.3)	25 (34.2)	
≥30	152 (32.7)	22 (30.1)	
Subcutaneous obesity			
No	82 (17.7)	19 (26.0)	0.091
Yes	381 (82.3)	54 (74.0)	
Visceral Obesity			
No	114 (24.6)	24 (32.9)	0.134
Yes	349 (75.4)	49 (67.1)	
Sarcopenia			
No	214 (46.2)	29 (53.4)	0.252
Yes	249 (53.8)	34 (46.6)	
Myosteatosis			
No	134 (28.9)	27 (37.0)	0.163
Yes	329 (71.1)	46 (63.0)	
NLR			
<3	239 (51.6)	37 (50.7)	0.714
03-May	153 (33.0)	23 (31.5)	
>5	71 (15.3)	13 (17.8)	
mGPS			
0	302 (68.8)	47 (67.1)	0.843
1	50 (11.4)	9 (12.9)	
2	87 (19.8)	14 (20)	

[1]P value from $\chi 2$ analysis

NLR- Neutrophil: lymphocyte ratio

mGPS- modified Glasgow Prognostic score

Table 2: The relationship between clinicopathological variables, tumour pathology, CT-BC measurements, systemic inflammatory status and cancer recurrence, in patients undergoing potentially curative resections for colonic tumours, stratified by pattern of recurrence (n=536).

	Locoregional (n=21)/ %	Systemic (n=52) / %	p value [1]
Age (years)			
<65	10 (47.6)	18 (34.6)	0.497
65-74	5 (23.8)	19 (36.5)	
>74	6 (28.6)	15 (28.8)	
Sex			
Male	8 (38.1)	20 (38.5)	0.977
Female	13 (61.9)	32 (61.5)	
ASA			
1	3 (14.3)	12 (23.1)	0.224
2	9 (42.9)	25 (48.1)	
≥3	9 (42.9)	15 (28.8)	
Tumour Site			
Right	15 (71.4)	34 (65.4)	0.619
Other	6 (28.6)	18 (34.6)	
TNM Stage			
I	0 (0)	5 (9.6)	0.162
II	5 (23.8)	14 (26.9)	
III	16 (76.2)	33 (63.5)	
Tumour Stage			
01-Feb	0 (0)	8 (15.4)	0.008
3	5 (23.8)	24 (42.6)	
4	16 (76.2)	20 (38.5)	
Nodal Stage			
0	6 (28.6)	19 (36.5)	0.672
1	10 (47.6)	19 (36.5)	
2	5 (23.8)	12 (26.9)	
Differentiation			0.132
Moderately well	9 (42.9)	13 (25.0)	
Poor	12 (57.1)	39 (75.0)	
Venous Invasion			0.132
No	9 (42.9)	13 (25.0)	
Yes	12 (57.1)	39 (75.0)	
BMI (kg/m^2)			
<20	4 (19.0)	3 (5.8)	0.119
20-24.9	5 (23.8)	14 (26.9)	
25-29.9	8 (38.1)	17 (32.7)	
≥30	4 (19.0)	18 (34.6)	
Subcutaneous obesity			
No	5 (23.8)	14 (26.9)	0.784
Yes	16 (76.2)	38 (73.1)	
Visceral Obesity			
No	9 (42.9)	15(28.8)	0.249
Yes	12 (57.1)	37 (71.2)	
Sarcopenia			
No	11 (52.4)	28 (53.8)	0.91
Yes	10 (47.6)	24 (46.2)	
Myosteatosis			
No	8 (38.1)	13 (25.0)	0.901
Yes	13 (61.9)	39 (75.0)	
NLR			0.52
<3	9 (42.9)	28 (53.8)	
03-May	8 (38.1)	15 (28.8)	
>5	4 (19.0)	9 (17.3)	
mGPS			
0	10 (47.6)	40 (76.9)	0.007
1	3 (14.3)	6 (11.5)	
2	8 (38.1)	6 (11.5)	
Time to recurrence (months)	11	20.5	0.055
3-year Survival			
Yes	13 (61.9)	16 (30.8)	0.014
No	8 (38.1)	36 (69.2)	

[1] P value from $\chi 2$ analysis

NLR- Neutrophil: lymphocyte ratio

mGPS- modified Glasgow Prognostic score

Table 3: The relationship between host factors and RFS, in patients undergoing potentially curative resections for colonic tumours (n=536).

Variables	Univariable HR (95% CI)	p value	Multivariable HR (95% CI)	p value
Age	1.26 (1.01-1.58)	0.042	-	0.076
Sex	1.30 (0.92-1.85)	0.144		
ASA	1.12 (0.87-1.42)	0.381		
Visceral Obesity	1.34 (0.92-1.96)	0.129		
Sarcopenia	1.34 (0.94-1.90)	0.099	-	0.324
Myosteatosis	1.10 (0.75-1.60)	0.629		
NLR	1.06 (1.01-1.12)	0.024	-	0.054
mGPS	1.41 (1.15-1.72)	<0.001	1.27 (1.03-1.57)	0.027

NLR- Neutrophil: lymphocyte ratio

mGPS- modified Glasgow Prognostic Score

5. Discussion

In the present study, 14% of patients who underwent elective treatment with curative intent for non-metastatic colorectal cancer developed recurrence within 3 years of surgery, consistent with findings from large multicentre cohort studies of patients undergoing potentially curative treatment for CC [22, 23, 30]. Our findings confirm that TNM staging remains the most powerful predictor of disease recurrence in our cohort. However, despite the majority of host factors being found to have limited prognostic value in stratifying those at risk of overall CC recurrence, pre-operative systemic inflammation was associated with both the incidence of locoregional recurrence and recurrence free survival. As such, the results are informative in identifying inflamed patients that may benefit from enhanced pre-operative staging, such as PET-CT imaging, in addition to more rigorous surveillance than routinely offered post colonic resection.

As such, the present study is informative, clarifying that while many of the host factors included have previously been associated with recurrence free survival in patients with colorectal cancer [31, 32], they have limited prognostic value in delineating the incidence or pattern of recurrence. Furthermore, the results of the present study highlight that patients with high levels of pre-operative inflammation, as measured by mGPS or NLR, are at greater risk of locoregional recurrence, suggesting a relationship with priming of the local site for recurrence. These observations are in keeping with the work of Coussens and co-workers, who highlighted that inflammation is a critical component of tumour progression and that inflammatory cells have powerful effects on tumour development [33]. As such, modulation of systemic inflammation may confer better outcomes in patients with CC [34]. Indeed, in a study of 2308 patients undergoing colorectal cancer surgery, Schack and co-workers found that perioperative use of non-steroidal anti-inflammatory drugs was associated with a reduced risk of cancer recurrence [35].

CT-body composition has garnered interest in recent years for its ability to predict likely outcome in colorectal cancer [36, 37]. Indeed, recent cohort studies by Hopkins and co-workers [31]; Nakanishi and co-workers [38] and Miyamoto and co-workers [39] found that pre-operative sarcopenia, defined by a low CT-derived skeletal muscle mass, was associated with recurrence free survival in patients undergoing surgery for colorectal cancer. This contrasts the observations of the present study which found neither sarcopenia nor myosteatosis were associated with the incidence of cancer recurrence, pattern of recurrence, or recurrence free survival in patients undergoing elective surgical resection for non-metastatic colonic tumours. The studies are difficult to compare with heterogeneity in the methodology, namely the absence of standardized thresholds for low skeletal muscle mass and differences in recurrence rates observed when combining colonic and rectal cancers. However, the disparity in observations may be related to differences in the host-tumour interactions and subsequent systemic inflammatory response experienced on a background sarcopenia, recently shown to be endemic in cancer[40]. This is highlighted in recent work by our group who found that tumour metabolic activity on PET-CT was associated with the systemic inflammatory response and poorer survival, but not sarcopenia, in patients with recurrent colorectal and advanced lung cancer [41, 42]. Furthermore, that sarcopenia was associated with ongoing systemic inflammatory response [41]. Therefore, further research is required to delineate the relationship between tumour pathology, systemic inflammation, sarcopenia and clinical outcomes in patients with cancer.

There are several limitations to the present study. Firstly, this is a single centre study, and therefore subject to bias. Secondly, all patients were followed-up for 3 years post-operatively, which is standard for CC in the UK and captures the vast majority of recurrences post-surgery. Extended follow-up may help identify factors associated with late recurrence. However, the observations of the present study are comparable with those of other large multicentre cohort studies [22, 23]. Nevertheless, external validation of these findings would be illuminating. Our hospital serves one of the most deprived regions of Western Europe and comparison in a fitter group of patients would help ratify the importance of our findings. Lastly, around 9% (n=51) of the non-metastatic colonic resections performed during the study timeframe were emergency presentations and therefore excluded. Given the association between emergency presentation and recurrence of colorectal cancer [43], further study is required to delineate the relationship between tumour pathology, CT-body composition, systemic inflammation and clinical outcomes in emergency presentations.

In conclusion, our work infers that in patients undergoing potentially curative treatment of colonic cancer, tumour factors remain the most important determinant of disease recurrence. Pre-operative systemic inflammation may help identify those at increased risk of locoregional recurrence. As such these patients may benefit from enhanced pre-operative staging and more rigorous follow-up than routinely offered. Further research is required to delineate the relationship between tumour biology, systemic and local inflammation and clinical outcomes in patients with CC.

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