Original Article

Title: The relationship between systemic inflammation and stoma formation following anterior resection for rectal cancer: a cross-sectional study

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Abstract

Introduction

There is evidence that temporary defunctioning stoma formation in patients undergoing anterior resection reduces the risk of anastomotic leakage. The aim of the present study was to investigate the relationship between stoma formation, the postoperative systemic inflammatory response and complications following anterior resection for rectal cancer.

Methods

Data was recorded prospectively for patients who underwent anterior resection for histologically proven rectal cancer, from 2008 to 2015 at a single centre, n=167. Patients had routine preoperative and postoperative blood sampling including serum C-reactive protein (CRP). Postoperative complications including anastomotic leakage were recorded.

Results

Of the 167 patients, the majority were male (61%) and over 65 years old (56%) with node negative disease (60%). 36 patients (22%) underwent preoperative neoadjuvant treatment. 100 patients (60%) had a stoma formed at the time of surgery. Stoma formation was significantly associated with male sex (69% vs. 50%, p=0.017), neoadjuvant chemoradiotherapy (30% vs 9%, p=0.001) and open surgery (71% vs. 55%, p=0.040). Of those 100 patients who had a stoma formed, 80 had it reversed. Permanent stoma was significantly associated with increasing age (p=0.011), exceeding the established CRP threshold of 150mg/L on postoperative day 4 (67% vs 37%, p=0.039), higher incidence of

postoperative complications (76% vs 47%, p=0.035), anastomotic leakage (24% vs 2%, p=0.003) and higher Clavien Dindo score (p=0.036).

Conclusions

There was no significant association between stoma formation during anterior resection and the postoperative systemic inflammatory response. However, in these patients both the postoperative systemic inflammatory response and complications were associated with permanent stoma.

Highlights

- Postoperative inflammatory response associated with morbidity following colorectal surgery
- No association with temporary stoma formation following anterior resection for rectal cancer.
- Both inflammatory response and complications were associated with permanent stoma.

1. Introduction

Rectal cancer is one of the most prevalent cancers diagnosed in the Western world [1]. Anterior resection with total mesorectal excision (TME) is the preferred surgical technique, to preserve the anal sphincter and avoid a permanent colostomy where abdominoperineal resection is not required [2]. However, anterior resection is associated with increased risk of anastomotic leakage, a major complication of this type of rectal surgery, when compared to resection of colorectal cancer in other locations [3]. Furthermore, anastomotic leakage has been indicated to be associated with increased risk of local recurrence and decreased short and long term survival of patients who have undergone potentially curative resection [4-5].

Recent evidence suggests that the postoperative systemic inflammatory response, measure by C-reactive protein (CRP), is important in both short and long term outcomes of colorectal patients and that it may be a causal factor in development of postoperative complications [6-10]. A recent comprehensive review has suggested that CRP concentrations exceeding 150mg/L on postoperative days 3 to 5 should alert clinicians to the possible development of postoperative complications, including anastomotic leakage, precluding early discharge [11].

Several studies have suggested that construction of a defunctioning stoma in patients who are undergoing anterior resection reduces the incidence of postoperative complications, including anastomotic leakage, and reoperation [12-14]. Although it has traditionally been thought that this reduction in anastomotic leak rate is due to diversion of the faecal stream, it may be that the formation of a stoma attenuates the magnitude of the postoperative systemic inflammatory response and that it is through this mechanism by which they reduce the rate of postoperative complications.

Therefore, the aim of the present study was to investigate the relationship between defunctioning stoma formation, and reversal, the magnitude of the postoperative systemic inflammatory response, and complications in rectal cancer patients who have undergone anterior resection.

2. Patients and methods

2.1 Patients

Patients with histologically proven rectal cancer, who underwent anterior resection, between February 2008 and April 2015 at a single centre were included in the study. Patients who underwent emergency surgery, palliative procedures, or who had existing inflammatory conditions were excluded. Neoadjuvant treatment was offered to patients with histologically proven, locally advanced (T3-T4, borderline operable or inoperable) rectal tumours following discussion at a multi-disciplinary colorectal oncology meeting.

All patients received prophylactic antibiotics and venous thromboprophylaxis prior to the induction of anaesthesia as per hospital policy. All patients had a primary anastomosis formed and the decision to form a proximal defunctioning stoma, with temporary intent, was at the discretion of the operating surgeon. Patients had routine preoperative blood sampling including a full blood count (FBC), serum CRP and albumin concentration.

On each postoperative day patients were clinically assessed and had blood samples, including serum CRP, obtained routinely until discharged. Further postoperative investigation and intervention was at the discretion of the patient's surgical team who were not blinded to blood results. This study was approved by the West of Scotland Research Ethics Committee.

2.2 Methods

Data was collected prospectively in a database, anonymised, and subsequently analysed retrospectively. Recorded information included patient demographics, clinicopathological, operative data, postoperative data, and date of stoma reversal if applicable.

Serum concentrations of CRP (mg/L) were measured using an autoanalyzer (Architect; Abbot Diagnostics, Maidenhead, UK) with a lower detectable limit of 0.2 mg/L as was serum albumin (normal range 35-50g/L). The preoperative modified Glasgow Prognostic Score (mGPS) was calculated in patients for whom serum CRP and albumin concentrations were available [15]. Exceeding the established postoperative CRP threshold of 150mg/L on postoperative days 3or 4 was recorded [11].

Postoperative complications were recorded up to and including the first follow up clinic, usually 6 weeks after discharge from hospital. Infective complications were categorised as described elsewhere and summarised here briefly [8]. Wound (superficial surgical site) infection was defined as the presence of pus either spontaneously discharging from the wound or requiring drainage. Deep surgical site infection was defined as surgical or image-guided drainage of intra-abdominal pus. Anastomotic leak was defined as radiologically verified fistula to bowel anastomosis or diagnosed at laparotomy. Pneumonia was defined by fever above 38.5^{o}C and consolidatory chest X-ray findings requiring antibiotic treatment. Septicaemia was defined by the presence of sepsis combined with positive blood culture. Urinary tract infection was only included if complicated by septicaemia and confirmed with positive urine culture. Complications were also classified by severity using the Clavien Dindo grade [16].

2.3 Statistical Analysis

Categorical data were compared using the Chi square test. Continuous data were non-normal so were displayed as medians and ranges, and were compared using the Mann-Whitney U test. Significant differences were found in the rate of defunctioning stoma formation dependent on whether a laparoscopic or open surgical approach was used and so a post hoc subgroup analysis was performed in those patients who underwent open surgery. Binary logistic regression of factors associated with permanent stoma was performed using a backward conditional model with removal of terms with $p>0.05$ at each step. Statistical analyses were performed using IBM SPSS version 22 for Windows (Chicago, IL, USA). Two tailed p values <0.05 were considered statistically significant. Missing data were excluded from analysis.

3. Results

3.1 Patients

After exclusion of those patients who underwent emergency or palliative surgery, or with existing inflammatory disease, 869 resections for colorectal cancer were performed during the study period, with 251 patients undergoing surgery for rectal cancer, of which 167 patients underwent anterior resection and were included in the study. The majority were male (102, 61%), over 65 years old (93, 56%) and underwent open surgery (109, 65%). 36 patients (22%) underwent neoadjuvant chemoradiotherapy. 7 patients (4%) had metastatic disease at the time of surgery, all located in the liver, of which 4 underwent synchronous resection, and 3 underwent staged liver resection following anterior resection. 79 patients (47%) developed a postoperative complication of which 73 were infective. There were 12 reported anastomotic leaks (7%). There were 3 deaths (2%) within the immediate postoperative period. Of the 79 patients who developed a postoperative complication, 61 were Clavien Dindo grade 1-2 and 18 were Clavien Dindo grade 3-5. 100 (60%) patients who underwent anterior resection had a defunctioning stoma formed.

3.2 Variables associated with stoma formation

Defunctioning stoma formation (Table 1) was significantly associated with male sex (69% vs. 50%, p=0.017), neoadjuvant chemoradiotherapy (30% vs 9%, p=0.001) and open surgery (71% vs. 55%, p=0.040). There was no significant association between stoma formation and other patient factors including age, BMI, smoking status, ASA grade or TNM staging. No significant association was found between stoma formation and preoperative mGPS. There was no significant association between stoma formation and CRP on postoperative days 3 or

4. There was no significant difference in the incidence or severity of postoperative complication, or in the rate of anastomotic leak between either group.

3.3 Variables associated with stoma formation in patients who underwent an open operation

Within the patients who underwent open surgery, there was significant association (Table 2) between stoma formation and neoadjuvant chemoradiotherapy (34% vs 14%, p=0.029). There was no significant association between stoma formation and other patient factors including age, BMI, smoking status, ASA grade, TNM staging or operation type. There was no significant difference in CRP between the patient groups with and without stoma on postoperative days 3 or 4 (Figure 1). There was no significant association between stoma formation and the incidence or severity of postoperative complications.

3.4 Variables associated with permanent stoma in patients undergoing open surgery

Of the 71 patients who had open surgery and a defunctioning stoma formed, 53 (75%) had their stoma reversed. The median time from anterior resection to stoma reversal was 8 months (range 1-23). Permanent stoma was significantly associated with increasing age (p=0.011), higher CRP on postoperative days 3 (212mg/L vs 144mg/L, p=0.048) and 4 (179mg/L vs 128mg/L, p=0.044), the proportion of patients exceeding the established CRP threshold of 150mg/L on postoperative day 4 (67% vs 37%, p=0.039), a higher incidence of postoperative complications (76% vs 47%, p=0.035), anastomotic leakage (24% vs 2%, p=0.003) and higher Clavien Dindo grade (p=0.036). However, there was no significant association between permanent stoma and patient factors including age, BMI, smoking status, ASA grade, TNM staging and neoadjuvant chemoradiotherapy. At binary logistic regression

of those factors found to be significantly associated with permanent stoma, increasing age (OR 3.46, 95% CI 1.46-8.12, p=0.005), and Clavien Dindo grade (OR 3.00, 95% CI 1.14-7.84, p=0.025) remained significantly independently associated.

4. Discussion

The results of the present study suggest that temporary defunctioning stoma formation is not associated with the magnitude of the postoperative systemic inflammatory response or complications in patients who have undergone anterior resection for rectal cancer. However they do suggest that increasing age, inflammation and a complicated postoperative course increases the likelihood of having a permanent stoma.

In keeping with some earlier published reports, the present study reports that males and patients who have undergone neoadjuvant chemoradiotherapy are more likely to have a defunctioning stoma at anterior resection [17, 18]. In addition, the present study is also in agreement with a single study which demonstrated that stoma formation is not associated with body mass index [19]. The present study also reports that stoma formation is not associated with ASA grade, TNM staging and age group which is in keeping with other published work [17].

To the author's knowledge, there has been no prior study examining the association between stoma formation and preoperative systemic inflammatory status. There is limited evidence which examines the association between stoma formation the postoperative systemic inflammatory response; a single study which investigated CRP on the first and third postoperative day which reported a significant difference in CRP on postoperative day 3 [20]. In contrast, the present study reported no association between CRP levels on postoperative days 3 or 4 between patient groups with and without stoma. The anastomotic leak rate in the present study was around half that (8%) of Ma and colleagues study (16%) which may in part explain this difference.

The present study demonstrates no association between stoma formation and postoperative complications when all included patients were considered. However, the

present study reports a trend towards reduced incidence of anastomotic leakage in patients with stoma, although it did not reach statistical significance due to cohort size. As surgical approach is a significant confounder with regard to the postoperative systemic inflammatory response, and was associated with the incidence of stoma formation in the present study, subgroup analysis was performed.

It was of interest that there was no significant association between stoma formation and patient factors such as BMI, ASA, or smoking status. There was however a significant association between stoma formation and neoadjuvant treatment although recent evidence suggests no reduction in postoperative complication, unplanned reoperation or mortality in patients who have a stoma formed following neoadjuvant treatment [21]. It may be that perceived differences in rectal dissection in patients who have had neoadjuvant treatment prompts some surgeons to create more temporary defunctioning stomas in this patients group.

The present study is in line with a few published studies, reporting that permanent stoma is associated with older patients (age<65) [22] and higher incidence of postoperative complications, including anastomotic leakage [22-26]. The present study also reports that permanent stoma is associated with higher CRP on postoperative days 3 and 4, and a higher proportion of patients who breached the CRP threshold on postoperative days 4. Given the greater anastomotic leak rate and higher Clavien Dindo grade this may simply reflect that patients experiencing significant complications are less likely to have subsequent stoma reversal, which would be in keeping with the result of the binary logistic regression analysis. However, to the author's knowledge, there have not been any previous studies that have examined the relationship between postoperative systemic inflammatory response and permanent stoma. Furthermore, the question of whether the magnitude of the postoperative systemic inflammatory response is causal, or merely an epiphenomenon of postoperative complications remains unanswered.

It is therefore possible that the rate of postoperative complications, and thus the likelihood of having a permanent stoma after anterior resection, could be reduced by attenuation of the magnitude of the postoperative systemic inflammatory response. This hypothesis may be tested by prospective trials of factors understood to attenuate the magnitude of the postoperative systemic inflammatory response, including the administration of preoperative corticosteroids [26], non-steroidal anti-inflammatory drugs and statins [27], and by carrying out laparoscopic surgery [28].

The main limitation of the present study is the relatively small number of patients undergoing anterior resection as a proportion of all patients operated on for colorectal cancer during the period. However, this group was chosen, rather than the inclusion of resections at other locations, due the relatively high rate of stoma formation and to allow direct comparison. Furthermore, the retrospective nature of the study means that not all patients had CRP measured in the pre and postoperative periods studied.

5. Conclusions

In conclusion, the present study reports a lack of association between stoma formation and postoperative systemic inflammatory response in patients who have undergone anterior resection for rectal cancer. However, both the systemic inflammatory response and postoperative complications were associated with permanent stoma.

Authors Contributions

Study conception and design: SM, PH, DM. Acquisition of data: BK, SM. Analysis and interpretation of data: BK, SM, DM. Drafting of manuscript: BK, SM, PH, DM. Critical revision of manuscript: SM, PH, DM

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Ethical approval

This study was approved by the West of Scotland Research Ethics Committee.

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Conflicts of interest

None

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Tables and footnotes

Table 1: Relationship between temporary defunctioning stoma formation and clinicopathological variables in patients undergoing elective anterior resection of rectal cancer (n=167)

Characteristic	All	Stoma		P
		No	Yes	
Sex (male/female)	102/65	33/34	69/31	0.017
Age (<65/65-74/>74)	74/69/24	27/31/9	47/38/15	0.566
BMI (median/range)/ kg/m^2	27 (17-50)	27 (19-42)	26 (17-50)	0.842
ASA Grade (1/2/3/4)	44/71/40/2	13/29/19/0	31/42/21/2	0.235
Smoking (no/ex/current)	77/66/23	32/27/8	45/39/15	0.839
Preoperative mGPS (0/1/2)	135/14/9	51/8/4	84/6/5	0.356
Neoadjuvant chemoradiotherapy (yes/no)	36/131	6/61	30/70	0.001
Operative (laparoscopic/open)	58/107	29/36	29/71	0.040
TNM stage (0/1/2/3/4)	4/40/56/58/7	0/19/26/18/2	4/21/30/40/5	0.141
POD 3 CRP (median,range.mg/L)	147 (2-386)	143(21-354)	149(2-386)	0.464
POD 4 CRP (median,range.mg/L)	128 (2-425)	133(20-425)	124(2-408)	0.495
POD 3 CRP >150mg/L (yes/no)	70/80	25/34	45/46	0.396
POD 4 CRP >150mg/L (yes/no)	55/84	19/31	36/53	0.777
Any postoperative complication (yes/no)	79/82	29/35	50/47	0.439
Anastomotic leakage (yes/no)	12/149	7/57	5/92	0.172
Clavien Dindo Classification (0/1-2/3-5)	82/61/18	35/21/8	47/40/10	0.784
Adjuvant therapy (yes/no)	41/126	16/51	25/75	0.704

ASA American Society of Anaesthesiology score, *BMI* Body Mass Index, *CRP* C-reactive protein, *mGPS* modified Glasgow Prognostic Score

Table 2: Relationship between temporary defunctioning stoma formation and clinicopathological variables in patients undergoing elective, open anterior resection of rectal cancer (n=107)

Characteristic	**All**	**Stoma**		**P**
		No	**Yes**	
Sex (male/female)	63/44	18/18	45/26	0.184
Age (<65/65-74/>74)	47/44/16	15/17/4	32/27/12	0.580
BMI (median/range)/ kg/m^2	26 (17-50)	27(20-42)	26 (17-50)	0.842
ASA Grade (1/2/3/4)	29/46/26/1	6/18/10/0	23/28/16/1	0.309
Smoking (no/ex/current)	49/42/15	19/13/4	30/29/11	0.597
Preoperative mGPS (0/1/2)	89/7/8	26/4/4	63/3/4	0.175
Neoadjuvant chemoradiotherapy (yes/no)	29/78	5/31	24/47	0.029
TNM stage (0/1/2/3/4)	3/23/31/43/6	0/7/13/13/2	3/16/18/30/4	0.589
POD 3 CRP (median,range.mg/L)	152 (37-386)	148(37-354)	153(40-386)	0.829
POD 4 CRP (median,range.mg/L)	134 (2-408)	136(20-369)	133(2-408)	0.752
POD 3 CRP >150mg/L (yes/no)	51/47	16/18	35/29	0.472
POD 4 CRP >150mg/L (yes/no)	39/57	10/20	29/37	0.327
Any postoperative complication (yes/no)	57/49	19/17	38/32	0.883
Anastomotic leakage (yes/no)	8/98	3/33	5/65	0.826
Clavien Dindo Classification (0/1-2/3-5)	49/45/12	17/15/4	32/30/8	0.785
Adjuvant therapy (yes/no)	27/80	10/26	17/54	0.813

ASA American Society of Anaesthesiology score, *BMI* Body Mass Index, *CRP* C-reactive protein, *mGPS* modified Glasgow Prognostic Score

Table 3: Relationship between permanent stoma and clinicopathological variables in patients with stoma formation during elective, open anterior resection of rectal cancer (n=71)

Characteristic	**All**	**Permanent Stoma**		**P**
		No	**Yes**	
Sex (male/female)	45/26	34/19	11/7	0.817
Age (<65/65-74/>74)	32/27/12	29/18/6	3/9/6	0.011
BMI (median/range)/ kg/m^2	26(17-50)	27(17-50)	25(19-38)	0.579
ASA Grade (1/2/3/4)	23/28/16/1	18/20/12/1	5/8/4/0	0.884
Smoking (no/ex/current)	30/29/11	23/19/10	7/10/1	0.241
Preoperative mGPS (0/1/2)	63/3/4	46/3/3	17/0/1	0.579
Neoadjuvant chemoradiotherapy (yes/no)	24/47	19/34	5/13	0.532
TNM stage (0/1/2/3/4)	3/16/17/30/4	2/13/13/22/3	1/3/4/8/1	0.974
POD 3 CRP (median,range.mg/L)	152(37-386)	144(40-386)	212(55-333)	0.048
POD 4 CRP (median,range.mg/L)	134(2-408)	128(2-388)	179(33-408)	0.039
POD 3 CRP >150mg/L (yes/no)	35/29	24/25	11/4	0.097
POD 4 CRP >150mg/L (yes/no)	29/37	19/32	10/5	0.044
Any postoperative complication (yes/no)	38/32	25/28	13/4	0.035
Anastomotic leakage (yes/no)	5/65	1/52	4/13	0.003
Clavien Dindo Classification (0/1-2/3-5)	32/30/8	28/22/3	4/8/5	0.036
Adjuvant therapy (yes/no)	17/54	14/39	3/15	0.510

ASA American Society of Anaesthesiology score, *BMI* Body Mass Index, *CRP* C-reactive protein, *mGPS* modified Glasgow Prognostic Score

Figures and legends

Figure 1: Impact of stoma formation on postoperative systemic inflammation following elective, open anterior resection of rectal cancer