

Suppression of the postoperative neutrophil leucocytosis following neoadjuvant chemoradiotherapy for rectal cancer and implications for surgical morbidity

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Abstract

Objective The extent to which neoadjuvant chemoradiotherapy for rectal cancer influences postoperative morbidity is controversial. This study investigated whether this treatment suppresses the normal perioperative inflammatory response and explored the clinical implications.

Method Prospective databases were queried to identify 37 consecutive study patients undergoing definitive surgery following 5-FU/capecitabine-based chemoradiotherapy and 35 consecutive untreated control patients operated upon for rectal or rectosigmoid cancer. Preoperative (< 10 days) and postoperative (< 24 h) neutrophil counts, along with morbidity data, were confirmed retrospectively. Univariate and multivariate analyses assessed the apparent effect of chemoradiotherapy on change in neutrophil count. The latter's association with postoperative morbidity was then examined.

Results Sufficient data were available for 34 study and 27 control patients. Repeated-measures ANCOVA

revealed significant differences between their perioperative neutrophil counts ($P = 0.02$). Of the other characteristics which differed between the groups, only age and tumour location were prognostically significant regarding perioperative change in neutrophil count. Accounting for relevant covariates, chemoradiotherapy was significantly associated with a suppressed perioperative neutrophil leucocytosis. Local postoperative complications affected 25 of 61 patients, who had lower perioperative neutrophil increases than their counterparts ($P = 0.016$).

Conclusion Chemoradiotherapy appears to suppress the perioperative inflammatory response, thereby increasing susceptibility to local postoperative complications.

Keywords Rectal cancer, neoadjuvant chemoradiotherapy, surgery, postoperative complications, immunosuppression, leucocyte

Introduction

Meticulous surgical dissection along embryological planes represents the mainstay of treatment for resectable rectal cancer, but significant recurrence rates with surgery alone and advances in imaging techniques have contributed to the rationale for preoperative therapy. Neoadjuvant radiotherapy has been demonstrated to improve local control and overall survival and the addition of chemotherapy reduces local recurrence further [1].

Short-course radiotherapy, delivered over 1 week and followed by surgery a few days later, increases postoperative morbidity [2–5]. The extent to which this also applies to chemoradiotherapy, typically administered over 5 weeks and followed by surgery several weeks later, is more controversial. It is theoretically plausible that the combined myelosuppressive effects of chemotherapy and pelvic radiotherapy attenuate the normal inflammatory response to surgical trauma, thereby increasing susceptibility to complications. Objective evidence of immunosuppression at the time of surgery following chemoradiotherapy for rectal cancer has been reported previously, but any correlation with clinical morbidity was not investigated [6]. However, among patients treated with short-course radiotherapy, a suppressed

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postoperative neutrophil leucocytosis appears to predict postoperative morbidity [7].

The purpose of this study was to investigate whether the normal postoperative neutrophil leucocytosis following chemoradiotherapy and delayed surgery is: (i) suppressed; (ii) associated with local postoperative complications; and (iii) related to the time interval to surgery.

Method

Extensive data on all rectal cancer patients treated with neoadjuvant chemoradiotherapy and definitive surgery at Barnet Hospital have been prospectively collected since 1994. The 37 most recently and consecutively treated patients were selected from this database as the study group. A control group of 34 consecutive patients undergoing elective surgery for cancer of the rectum or rectosigmoid without neoadjuvant therapy was identified from a second prospectively compiled database of all colorectal cancer patients diagnosed since 2006. The use of all data for the purposes of this study was approved by the local research ethics committee.

For all patients, local staging was based on a combination of clinical assessment and pelvic magnetic resonance imaging (MRI), while distant metastases were excluded by computed tomography (CT) of abdomen and thorax. Treatment was recommended to patients in light of discussion by a multidisciplinary team, comprising surgeons, oncologists, radiologists and pathologists. Eligibility criteria for neoadjuvant chemoradiotherapy included histologically confirmed rectal adenocarcinoma involving or threatening the anticipated resection margin, World Health Organisation (WHO) performance status 0–2 and acceptable haematological and renal function, i.e. neutrophils $> 1.5 \times 10^9/l$, platelets $\geq 100 \times 10^9/l$ and serum creatinine < 1.25 times the institution's upper limit of normal range.

Megavoltage external beam radiotherapy was delivered using a three- or four-field box technique in the prone position using CT-based three-dimensional planning. To derive a planning target volume, margins were added to the gross tumour volume as follows: 3 cm laterally, superiorly and inferiorly; 2 cm anteriorly. The posterior border was always located on the most posterior aspect of the bony sacrum. All study patients received a total of 45 Gy, delivered in 25 daily fractions of 1.8 Gy over 33 days.

Concurrent chemotherapy was in the form of 5-fluorouracil (5-FU) or its oral equivalent capecitabine. The former was usually administered as a 60-min infusion at a dose of 350 mg/m^2 , along with 20 mg/m^2 folinic acid, on each of the first five and last 5 days of

radiotherapy. Alternatively, a prolonged venous infusion of 5-FU was administered at a daily dose of 200 mg/m^2 for the entire duration of radiotherapy and for 3 weeks beyond. Capecitabine was prescribed at a twice daily dose of 850 mg/m^2 during each day of radiotherapy.

Local protocol recommended that surgery be scheduled for 6–12 weeks following completion of radiotherapy. In practice, patients were usually assessed at 6 weeks by the operating surgeon, who decided whether to allow additional time for tumour shrinkage. Surgery was performed by, or under the direct supervision of, one of four consultant surgeons with colorectal expertise, who routinely carried out total mesorectal excision.

Surgical specimens were examined grossly and microscopically using TNM criteria, according to the Royal College of Pathologists' minimum dataset for colorectal cancer [8]. All lymph nodes retrieved were examined histologically and any extramural deposits larger than 3 mm in diameter were considered to be nodal. Patients were usually reviewed by the surgical team within 6 weeks of their operation. For the purposes of this study, complete wound healing was defined as intact skin with no evidence of erythema, tenderness, fluctuance, discharge or a sinus. Anastomotic leakage was diagnosed on the basis of intra-operative findings, or clinically directed imaging alone if laparotomy was not performed.

Neutrophil counts were obtained retrospectively from the hospital's laboratory computer system. Preoperative counts were defined as having been collected within 10 days prior to surgery, while postoperative neutrophil counts were all collected on the first postoperative day. The incidences of local postoperative complications, namely delayed perineal wound healing, anastomotic leakage and re-laparotomy for any other reason, were confirmed by retrospective review of discharge letters and outpatient correspondence. Patients were excluded from subsequent analysis if neutrophil counts were not available from these specific times or if sufficient details of their postoperative recovery could not be obtained.

Data were analysed using statistical software (SPSS version 15, SPSS, USA). Shapiro–Wilks tests assessed the degree of normality for all baseline and outcome variables. Depending on these, chi-square tests (for categorical variables) and Mann–Whitney *U*-test, ANOVA or unpaired *t*-tests (for continuous data) were used to assess differences between the chemoradiated and untreated patients. Effect sizes were measured using Cohen's *d* or Cramer's ϕ , depending on the variable type and the comparison test used [9]. Correlation and equivalency tests were used to study the prognostic value of baseline variables in predicting changes in neutrophil count and complications. Repeated-measures ANCOVA models were developed incorporating relevant covariates

to study the association between chemoradiotherapy and change in neutrophil count. Similarly, ANCOVA models were developed to study the association between change in neutrophil count and postoperative complications. The association between change in neutrophil count and interval length was assessed using unpaired *t*-tests.

Results

Sufficient data on perioperative neutrophil counts and morbidity were available for 34 of 37 study patients and 27 of 34 control patients. Among the study patients, 19 had received oral capecitabine and 15 had received intravenous 5-FU, of which the prolonged regimen throughout the entire duration of radiotherapy and for 3 weeks beyond was administered to only two patients.

One study patient was treated for recurrent rectal cancer; all other patients had primary disease. One patient in each group underwent simultaneous cystoprostatectomy and urinary diversion, while two study and one control patients underwent hysterectomy and bilateral salpingo-oophorectomy. Other baseline, operative and pathological characteristics for each of the groups are shown in Table 1. Both preoperative and postoperative neutrophil counts were approximately normally distributed.

Figure 1 portrays the perioperative change in neutrophil count for each group. Correlation and equivalency tests determined that age, tumour distance from anal verge and chemoradiotherapy were the only prognostically significant variables for this outcome. Although the two groups' preoperative neutrophil counts were similar, repeated-measures ANCOVA revealed significant differences between study and control patients ($P = 0.02$), with a marked effect size ($\eta^2 = 0.14$) and observed power (0.85). When relevant covariates were incorporated in this 'between-subjects' comparison, neither age nor tumour distance from anal verge had significant effects

Table 1 Baseline, operative and pathological characteristics.

	Study (<i>n</i> = 34)	Control (<i>n</i> = 27)	<i>P</i> -value	Effect size*
Male	19	20	0.14	0.19
Age (years)	62.3 ± 2.1	73.6 ± 2.1	0.004	0.84
Distance from anal verge (cm)	4.3 ± 0.2	11.0 ± 0.9	< 0.001	1.62
AR:APR:Hartmann's	6:26:2	20:4:3	< 0.001	0.86
Laparoscopic	0	8	< 0.001	0.43
(y)T3-4	18	20	0.09	0.70
Preop neutrophil count (×10 ⁹ /l)	4.26 ± 0.41	4.42 ± 0.50	0.64	0.15

Continuous data presented as mean ± SE.

*Calculated as Cohen's *d* and Cramer's ϕ , for continuous and categorical variables, respectively.

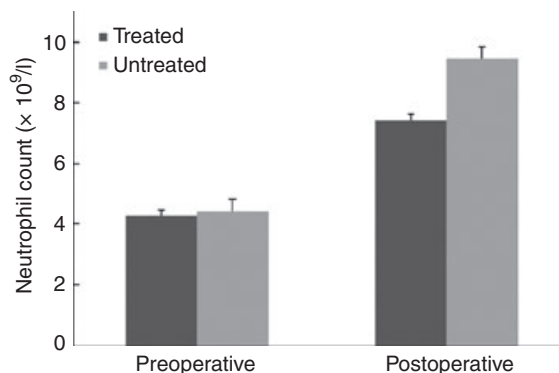


Figure 1 Perioperative neutrophil counts.

(Table 2). Figure 2 portrays the perioperative increases in neutrophil count in terms of estimated marginal means, i.e. means after the covariates have been accounted for.

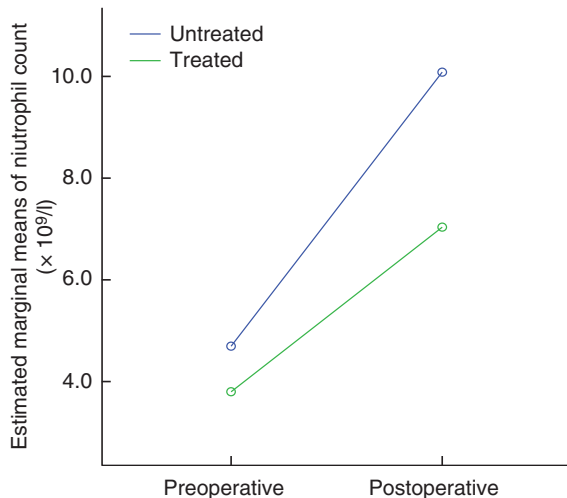
'Within-subjects' comparison tests confirmed a significant postoperative increase in neutrophil count, irrespective of group (Table 3). The interaction of measurement points with the variables included in the model did not reveal any significant differences for age or distance, whereas chemoradiotherapy did appear to be a major determinant of this increase (Figure 3).

Four patients died prior to discharge, including three within 30 post-operative days; all four had experienced anastomotic leakage. In total, seven of 26 anterior resections were complicated by clinically apparent anastomotic leakage. Two other patients with small bowel obstruction, one with intra-abdominal haemorrhage and one with a small intestinal fistula required re-laparotomy prior to discharge. Complete perineal healing was not achieved by 6 weeks following 16 of 30 abdominoperineal resections.

In total, 25 of 61 (41.0%) patients experienced at least one of these local postoperative complications. Their preoperative neutrophil counts were similar to those of

Table 2 Tests of 'between-subjects' effects (*computed using alpha = 0.05).

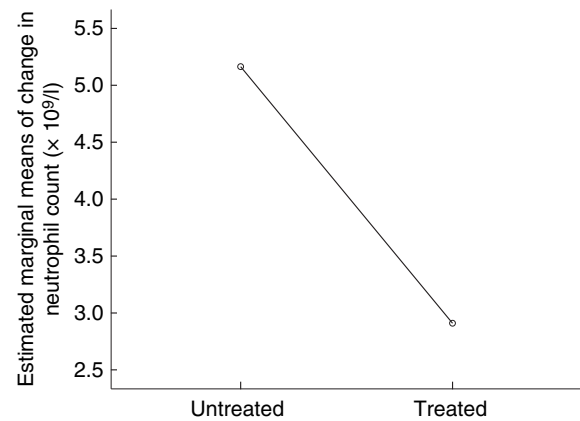
Source	df	F	P-value	η^2	Observed power*
Intercept	1	35.608	0.000	0.39	1.00
Distance	1	0.825	0.367	0.02	0.15
Age	1	0.037	0.848	0.001	0.05
Chemoradiotherapy	1	6.255	0.015	0.10	0.69

**Figure 2** Estimated marginal means of perioperative neutrophil counts.**Table 3** Tests of 'within-subjects' effects (*computed using alpha = 0.05).

Source	df	F	P-value	η^2	Observed power*
Neutrophil increase	1	11.641	0.001	0.17	0.92
Distance	1	0.172	0.680	0.003	0.07
Age	1	2.009	0.162	0.04	0.29
Chemoradiotherapy	1	6.236	0.015	0.10	0.69

their 36 counterparts, with means of $4.5 \times 10^9/l$ and $4.2 \times 10^9/l$ respectively ($P = 0.348$). Mean perioperative increases in neutrophil count were $3.0 \times 10^9/l$ and $4.7 \times 10^9/l$ respectively ($P = 0.016$). With ANCOVA, the association between change in neutrophil count and complications failed to reach statistical significance ($P = 0.09$), although the effect size was moderate ($\eta^2 = 0.05$),

For the 34 study patients, the median interval from completion of radiotherapy to surgery was 74.5 (range 50–118) days. This value was used to divide these

**Figure 3** Estimated marginal means of change in neutrophil count.

patients into two equally sized groups. Mean preoperative neutrophil count was $4.3 \times 10^9/l$ for the short interval group and $4.2 \times 10^9/l$ for the long interval group ($P = 0.747$). Mean perioperative increases in neutrophil count were $3.1 \times 10^9/l$ and $3.2 \times 10^9/l$ respectively ($P = 0.905$).

Discussion and conclusions

At present, it is difficult to determine from the literature the extent to which neoadjuvant chemoradiotherapy for rectal cancer influences postoperative morbidity. Most of the large randomized trials of short-course radiotherapy have demonstrated a detrimental effect of this regimen, particularly with respect to perineal wound healing [2–5]. In turn, three randomized trials of preoperative chemoradiotherapy *vs* short-course radiotherapy have reported that the rates of postoperative complications were not significantly different between the two regimens [10–12]. Combined modality treatment has also been implicated as a cause of surgical morbidity by some retrospective analyses [13–15]. By contrast, the only completed randomized trial of preoperative *vs* postoperative chemoradiotherapy reported no significant difference in postoperative morbidity between the two groups [16]. However, it is possible that a true detrimental effect of chemoradiotherapy *per se* was obscured by the fact that this treatment caused down-staging and altered the operative strategy in some patients.

This study provides evidence that neoadjuvant chemoradiotherapy for rectal cancer suppresses the normal inflammatory response to surgical trauma, as measured by the postoperative neutrophil leucocytosis, even at a median of 11 weeks following treatment completion. This is broadly consistent with Wichmann *et al.*'s prospective study, in which various inflammatory and

immunological markers were suppressed perioperatively among 15 rectal cancer patients treated with chemoradiotherapy in comparison with 15 matched controls [6]. Their discrepant finding that preoperative granulocyte count also differed significantly between the two groups may be due to the fact that their patients proceeded to surgery within a shorter interval of 4–6 weeks. Differences in the perioperative changes in granulocyte count between the two groups were not reported in their study and the implications for clinical morbidity were not investigated.

This study also found evidence of a suppressed postoperative neutrophil leucocytosis among those patients subsequently developing local postoperative complications in comparison with their counterparts who had uncomplicated recoveries. This resembles Hartley *et al.*'s experience with short-course preoperative radiotherapy [7]. Although this secondary association lost statistical significance on multivariate analysis, this may simply reflect the small sample size, particularly as there was a moderate effect size. A larger series of patients would be required to explore satisfactorily the clinical significance of any myelosuppressive effect of chemoradiotherapy.

The findings of any small study such as this should be interpreted with caution, as it is possible that they could have arisen by chance. Much of the principal data were collected retrospectively and, although consecutive patients were recruited to minimize selection bias, some were subsequently excluded due to incomplete data. Perhaps its main limitation is that the study and control patients were not optimally matched: for example, the former were younger and had lower rectal tumours and two factors which would have contributed to their selection for neoadjuvant therapy. However, the statistical analysis suggests that the apparent effect of chemoradiotherapy is unlikely to be attributable to any of the other observed differences between the groups.

Although pathological tumour stage was similar between the groups, the study patients might have had considerably larger tumours prior to treatment, which one might speculate could have contributed to immunosuppression. It could also be argued that each of the patient groups was rather heterogeneous: for example, all the study patients did not receive exactly the same chemotherapeutic regimen. A few patients underwent synchronous resection of adjacent organs, but they were at least evenly distributed between the groups. The single measurements of wound healing and postoperative neutrophil count are rather crude outcome data, albeit consistently collected. Finally, the relatively high rate of anastomotic leakage may simply reflect the small sample size and has broad confidence intervals.

It might have been expected that the chemoradiotherapy-induced suppression of the postoperative neutrophil leucocytosis would have become less pronounced with longer intervals to surgery, as the bone marrow recovered. This could have provided one explanation for the positive association between shorter intervals and postoperative morbidity reported recently by the authors [17]. Although no such influence of interval length was apparent in this study, a definitive exploration of this hypothesis would require a larger series of patients.

In summary, neoadjuvant chemoradiotherapy is increasingly employed in the management of rectal cancer but its implications for surgical morbidity remain controversial. Consistent with the limited available evidence, this study suggests that the normal perioperative inflammatory response is suppressed by this treatment, increasing susceptibility to local postoperative complications. Further research is needed to ensure that patients with rectal cancer derive the optimal long-term oncological benefit of chemoradiotherapy at minimal cost to their prospects of an uncomplicated postoperative recovery.

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