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ORIGINAL ARTICLE

Observational Study

Activated systemic inflammatory response at diagnosis reduces lymph node count in colonic carcinoma

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Abstract

AIM: To investigate a link between lymph node yield and systemic inflammatory response in colon cancer.

METHODS: A prospectively maintained database was interrogated. All patients undergoing curative colonic resection were included. Neutrophil lymphocyte ratio (NLR) and albumin were used as markers of SIR. In keeping with previously studies, NLR $\geqslant$ 4, albumin < 35 was used as cut off points for SIR. Statistical analysis was performed using 2 sample *t*-test and χ^2 tests where appropriate.

RESULTS: Three hundred and two patients were included for analysis. One hundred and ninety-five patients had NLR < 4 and 107 had NLR $\geqslant$ 4. There was no difference in age or sex between groups. Patients with NLR of $\geqslant$ 4 had lower mean lymph node yields than patients with NLR < 4 [17.6 ± 7.1 *vs* 19.2 ± 7.9 (P = 0.036)]. More patients with an elevated NLR had node positive disease and an increased lymph node ratio ($\geqslant$ 0.25, P = 0.044).

CONCLUSION: Prognosis in colon cancer is intimately linked to the patient's immune response. Assuming standardised surgical technique and sub specialty pathology, lymph node count is reduced when systemic inflammatory response is activated.

Key words: Systemic inflammatory response; Lymph node yield; Lymph node count; Colon cancer; Colonic cancer; Neutrophil-lymphocyte ratio; Neutrophil to lymphocyte ratio; Lymph node ratio

Core tip: A fascinating field of research is the relationship between systemic inflammatory response and loco-regional inflammatory response in colorectal cancer. This manuscript examines this relationship in a large cohort of patients from a tertiary referral centre. We measured systemic response by assessing serum markers at diagnosis and we measured local response by looking at pathological lymph node counts in the post operative surgical specimen. This is the first report to show that patients with evidence of an activated systemic inflammatory response at diagnosis have a reduced nodal harvest at time of surgery. This finding sheds light on the complex interaction between cancer and the patient. This host-tumour response forms the basis for the most advanced cancer research today.

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INTRODUCTION

Prognosis in colon cancer is largely predicted by clinico-pathological criteria, namely the TNM system which divides patients into groups based on tumour invasion, local nodal involvement and distant metastatic spread. Since its inception over 50 years ago[1], TNM has been used to predict patient prognosis following surgery. While easy to apply and reproducible, recent research has highlighted deficiencies in the TNM system. Higher absolute lymph node counts improve patient prognosis regardless of stage[2] and an increased lymph node ratio in node positive disease reduces prognosis[3], two variables not measured by TNM.

Tumour-host immunological response is an important factor in prognosis at both a local and systemic level[4,5], another feature not measured by TNM. Local response has been assessed by looking at lymphocytic infiltration of colonic tumour and an improved survival is seen in patients who have mounted a local lymphocytic response[6]. Readily available markers of systemic inflammatory response (SIR) have prognostic value in patients undergoing surgery for colon cancer[7]. A combination of C-reactive protein and albumin (the modified Glasgow prognostic score) and the neutrophil-lymphocyte ratio (NLR) have been proposed as surrogate markers of patient systemic immune response to cancer. A high modified Glasgow Prognostic Score (mGPS) and/or an elevated NLR ($\geqslant$ 4) infer a poorer prognosis. A combination of an activated local response and the lack of an activated SIR imparts an improved prognosis[7], strengthening the link between cancer survival and immune response at both a local and systemic level.

To date, the information gleaned from lymph node harvest has revolved around absolute number and the presence or absence of cancer spread. Improved prognosis from higher lymph node counts has been explained as essentially a sampling error in patients with sub optimal surgical resection[8]. This explanation cannot account for the wide variance in yields experienced even in centres where radical excisions are performed as a matter of routine[9].

Lymph nodes are the first line of defence in the loco-regional immune response to cancer. It is possible that an increased local response to cancer results in lymph node hypertrophy resulting in an increased lymph node yield. Failure of a local response may result in less lymph node activation and allow for systemic "escape" resulting in activation of the systemic immune response. If this is the case, assuming standardised surgical and pathology techniques, a lower lymph node yield could be expected in patients with signs of an activated SIR in the preoperative period.

The aim of this study was to investigate a link between lymph node yields and systemic inflammatory response in patients undergoing surgery for colonic carcinoma.

MATERIALS AND METHODS

Patients who had undergone elective surgery for colon cancer between January 2007 and July 2013 were identified from a prospectively maintained database. Due to the known effect of radiotherapy on lymph node counts[10], rectal cancer patients were excluded. All surgeries were performed by the same subspecialty trained consultant surgeons and all samples analyzed by the same pathology department. Laparoscopic and open procedures were included.

Using a hospital-wide electronic patient record computer system, the results of pre-operative bloods drawn either on the day prior to or morning of surgery were recorded.

Neutrophil-lymphocyte ratio was derived from a standard white cell differential and in keeping with previous studies, an NLR of $\geqslant$ 4 and albumin < 35 were used as cut off levels indicating an activated SIR.

Statistical analysis was performed using Minitab v16 (Minitab Ltd. Coventry, United Kingdom). Continuous and categorical variables were analysed with 2 sample student's *t*-test and χ^2 tests where appropriate. Statistical analysis was performed by author RPK who has training in statistical methodology.

RESULTS

Three hundred and sixteen patients were identified for inclusion in the study. Fourteen patients were excluded due to incomplete data and analysis of CRP was ultimately abandoned as it was not routinely measured pre-operatively. The majority of the patients were male (168 *vs* 124) and the median age was 71. One hundred and seventy-eight patients had a laparoscopic

Table 1 Demographic data of study cohort

n = 302	
Age median (range)	71 (30-99)
Sex (M/F)	168/134
Stage	
Ⅰ	42
Ⅱ	137
Ⅲ	114
Ⅳ	9
Lymph node count Median (range)	17 (3-47)

M: Male; F: Female.

Table 2 Analysis of impact of operative technique and patient factors on lymph node counts

n = 302	*n*	Lymph node yield	*P* value
Surgical approach			
Lap/lap assisted	178	18.7 ± 7.3	0.828
Open/lap converted to open	124	18.5 ± 8.3	
Age			
< 70 yr	152	18 ± 7.1	0.171
⩾ 70 yr	150	19.3 ± 8.2	
Sex			
M	168	18.7 ± 8.2	0.894
F	134	18.6 ± 7.1	

M: Male; F: Female.

or lap-assisted operation. One hundred and twenty-four patients had a either a planned open operation or a lap to open conversion. Most patients were either stage Ⅱ (45%) or stage Ⅲ (37%) (Table 1). Lymph node count did not vary significantly based on operative approach, age or gender (Table 2).

Of the 302 patients included for analysis. One hundred and ninety-five patients had NLR < 4 and 107 had NLR ⩾ 4. Patients with an NLR ⩾ 4, (*i.e.*, activated systemic inflammatory response) had a reduced total nodal count (17.6) compared to patients with an NLR of < 4 (19.2). Hypoalbuminaemia did not impact on lymph node count. Patients with low albumin and an elevated NLR were not more likely to have a reduced lymph node count than patients with elevated NLR alone (Table 3). NLR ⩾ 4 correlated with an elevated lymph node ratio. A higher proportion of patients with NLR ⩾ 4 had lymph node positive disease (Table 4).

DISCUSSION

The host-tumour response is at the forefront of cancer research and exploration of the relationship between the patient and their cancer has yielded success in areas previously resistant to traditional chemotherapy[11]. Higher lymph node counts correspond with improved prognosis in colon cancer[8]. The relationship is preserved within cancer stages[2]. An activated systemic inflammatory response, in the preoperative period,

Table 3 Analysis of impact of pre-operative markers of systemic inflammatory response on lymph node counts

n = 302	*n*	Lymph node count	*P* value
NLR ⩾ 4	107	17.6 ± 7.1	0.036
NLR < 4	195	19.2 ± 7.9	
Albumin < 35	66	18.8 ± 7.9	0.951
Albumin ⩾ 35	226	18.7 ± 7.7	
NLR ⩾ 4 and albumin < 35	39	17.9 ± 8.0	0.381
NLR < 4	195	19.2 ± 7.9	

NLR: Neutrophil lymphocyte ratio.

Table 4 Analysis of association between neutrophil/lymphocyte ratio and previously described predictors of poor prognosis

n = 302	NLR < 4	NLR ⩾ 4	*P* value
n	195	107	
Lymph node positivity	72/195 (36.9%)	50/107 (46.7%)	0.085
Lymph node ratio > 0.25	13/72 (18%)	17/50 (34%)	0.044

NLR: Neutrophil lymphocyte ratio.

correlates with poor prognosis in colon cancer[12]. While the reason for this finding is not clearly defined it is possible that an activated SIR represents a loss of local control and is an early marker of systemic awareness of a heretofore localised cancer process. The data presented here propose a unifying explanation for these separately defined phenomena.

Previous work has shown that neutrophil lymphocyte ratios can predict survival in many cancer types[13]. Different ratios have been tested to find a reliable measure of activated systemic inflammatory response[14,15]. The ratio that carries the greatest level of evidence is NLR ⩾ 4[16,17]. In our patient cohort, a preoperative elevated NLR correlated with a reduced lymph node yield (19 *vs* 17).

The clinical significance of a two-node difference may be questioned. While the finding is statistically significant it is worth asking whether there is any useful information to be gained. Cserni *et al*[18] examined a large cohort of colon patients in the SEER database looking at the impact of nodal yield on survival. An improvement in prognosis was observed with increasing lymph node harvest. This finding was maintained in node negative and node positive patients. Indeed it was shown that with each additional node resected there is an associated increase in survival. Given this information, the findings in the current study may well provide important prognostic information.

Many studies have examined lymph node number and oncological outcome[19]. Lymph node counts below 12 correlate with poor outcome, a finding largely explained by variances in surgical quality[20]. However, even in good surgical specimens, low yields are sometimes encountered and many centres have questioned the validity of a binary marker of surgical quality in colon cancer[21,22]. Regardless of this on-running controversy,

Table 5 Description of modified glasgow prognostic score

mGPS	Score
Crp ⩽ 10, albumin ⩾ 35	0
Crp ⩽ 10, albumin < 35	0
Crp > 10	1
Crp > 10 and albumin < 35	2

mGPS: Modified glasgow prognostic score.

the lymph node count in both categories in the present study was well above 12 therefore surgical quality is not in question.

Other factors can impact on lymph node yield. Age, gender and laparoscopic surgery can affect lymph node count however these factors were not found to influence yields in the present study. Lymph node counts are highly dependent on quality of pathological examination and this may represent the single greatest factor that influences inter-institutional variability in nodal yields[23]. A single sub-specialty pathology department analysed all specimens in the present study limiting the impact of the pathologist on lymph node harvest.

NLR ⩾ 4 was compared to established measures of patient prognosis. Positive to negative lymph node ratios are a strong prognostic indicator in colonic carcinoma[3]. Prognosis falls as ratios increase and a cut off of 0.25 (1 in 4 nodes positive) has particular prognostic significance[24]. In the current patient cohort, a significant link is apparent between NLR and LNR of 0.25 and above. Lymph node ratios are dependent on absolute lymph node count and it is possible that previous findings regarding lymph node ratios are in fact a surrogate for the relationship between local and systemic inflammatory responses to cancer.

How systemic inflammatory response and cancer interact is a matter of debate. One theory suggests suppression of anti-tumour immunity by recruiting regulatory T cells and activating chemokines[25] resulting in tumour growth and spread. It has been proposed that SIR acts as a marker of pre-existing comorbid disease and high risk pathological tumour characteristics (*i.e.,* lymphovascular invasion, peritoneal involvement.) Interestingly, studies designed to explore this question have not shown a link[7].

A significant relationship was not shown for albumin and lymph node yield in our study. This was not an unexpected finding given previous work by the Glasgow group. The original Glasgow Prognostic Score assigned a score of 1 for hypoalbuminaemia. Further work showed no prognostic significance for hypoalbuminaemia alone[26] (Table 5). The modified score only attributes a score for a low albumin if there is a concomitant elevated C reactive protein. As CRP was not measured in the present study, albumin levels did not provide any added benefit.

Our study has limitations. Due to the nature of the institutional database, patient information is not available regarding co-morbid conditions. However, all included patients represent elective surgical candidates, deemed fit for surgery with no acute illness precluding an operation. The exclusion of emergency procedures lends some security regarding confounding causes of elevated markers of systemic inflammatory response. We were unable to complete our analysis of CRP due to levels not being available on the majority of our patients. While a pre-operative CRP is desirable, it does not form part of the standard pre-operative work up for our patients and is unlikely to be a routine test performed in most institutions. All patients undergo a full blood count prior to surgery therefore neutrophil lymphocyte ratio should be a readily available measure in all hospitals.

The primary focus of our study is on the peri-operative period but there is much scope for further research in this field. We have not reported long term outcomes and survival data in our patient cohort as the median follow-up time period in the study group was not of sufficient length. These patients will be followed prospectively and outcome will be reported in future planned analyses.

This study, albeit preliminary, may yield important prognostic value for our patients. Pre-operative identification of SIR could potentially alter treatment decisions, *i.e.,* serve as an indication for adjuvant chemotherapy, determine frequency of clinical and radiological surveillance as well as confer additional prognostic information.

Although the mechanism remains poorly understood, it is evident that there is an intrinsic link between the host immune response and patient outcome in colon cancer. The results of this study indicate that lymph node count is reduced where systemic inflammatory response is activated in colon cancer. We propose that neutrophil-lymphocyte ratio can therefore be used to predict nodal yield and provide additional valuable information regarding prognosis.

COMMENTS

Background

A host systemic inflammatory response to a tumour has been shown to negatively affect prognosis in patients undergoing surgery for colonic carcinoma. Surrogate markers of systemic inflammatory response researched to date have included routine laboratory investigations such as serum albumin, C-reactive protein and the neutrophil-lymphocyte ratio which together comprise the modified glasgow prognostic score. A more pronounced systemic inflammatory response as shown by a high glasgow prognostic score infers a poor prognosis in colon cancer. Lymph node count in colon cancer has long been established as a surgical quality indicator. Research has shown that a higher lymph node yield confers improved prognosis, a phenomenon which appears to be independent of nodal disease burden. This has previously been attributed to selection bias with lower nodal yield thought to be associated with the quality of the operating surgeon and examining histopathologist. However, this does not explain the large variation in nodal yields that sub-specialist centres encounter, where departments of highly specialised surgeons and histopathologists are routinely involved in multi-disciplinary cancer care.

Research frontiers

The host-tumour immune response is a fascinating field of cancer research

that promises success in offering new treatment modalities in areas previously resistant to more conventional therapies. Current research supports that neutrophil lymphocyte ratios and similar markers of systemic inflammatory response can predict survival in many cancer types, likewise with local inflammatory response as characterised by tumour-infiltrating lymphocytes. These phenomena are at present not incorporated into any staging or classification system for colon cancer, despite the overwhelming evidence that they provide invaluable prognostic information. Considering this wealth of information, current research is exploring the exciting realm of immunotherapy, for which many clinical trials are underway.

Innovations and breakthroughs

The relationship of prognosis in colon cancer with systemic inflammatory response has been researched to date, as has that with lymph node yield. To the authors' knowledge however, this is the first study to examine a link between these two phenomena. The study supports that poor prognosis in colon cancer is due in part to failed or impeded local immune response to a tumour and subsequent systemic loss of control. The findings may also explain why lymph node counts are often highly variable, even in sub-speciality tertiary referral centres where variance in surgical and histopathological quality is unlikely to be a major confounding factor. This research suggests that the current focus on an absolute number of nodes as an indicator of quality is perhaps flawed, and a change in perspective with regards to lower-than-expected nodal yields should be employed.

Applications

The results of this study may offer important prognostic value for the patients. In identifying SIR pre-operatively, the authors can identify patients in whom lower nodal yield and a poorer prognosis is anticipated. This may potentially alter post-operative course of treatment, *i.e.,* serve as an indication for adjuvant chemotherapy, determine frequency of clinical and radiological surveillance, as well as pave the way for the development of novel pre-operative immunotherapeutic interventions.

Terminology

Systemic inflammatory response (SIR): Reaction to an infectious or non-infectious stimulant by activation of whole body inflammatory cascade following failure of local immunological homeostasis; lymph node yield: Number of lymph nodes identified in pathological specimen following oncological resection; neutrophil-lymphocyte ratio (NLR): Ratio of circulating neutrophils to lymphocytes. A circulating neutrophilia relative to a lymphopaenia is a surrogate marker of systemic inflammatory response. In keeping with previous studies, we chose a NLR of $\geqslant$ 4:1 as the cut-off for SIR; lymph node ratio: Ratio of positive to negative nodes in a specimen.

Peer-review

The manuscript describes findings of statistical-analysis to assess a link between lymph node yields and systemic inflammatory response in patients undergoing for colon carcinoma. Authors suggest an intrinsic link between the host immune-response and patient outcome in colon cancer, and propose that neutrophil-lymphocyte ration can be used to predict nodal yield and provide additional valuable information regarding prognosis. This article is concisely written, and contains interesting findings.

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