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Observational Study

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

ANSWERING REVIEWERS

Many thanks to the reviewers for their comments. Please find our responses below.

Reviewer 1: Previously, it has been repeatedly reported that the activated systemic immunogenic response, high and low lymph node accounts are significantly related to patient survival. Thus the only possible new information from this study could come from the assessment of the relationship between lymph node account and systemic inflammatory response. The authors need to show that the reduced lymph node account is significantly associated with the activated systemic inflammatory response with a proper statistical assessment.

Thank you for your comments. In our study, serum albumin and the neutrophil-lymphocyte ratio was chosen as surrogate markers of systemic inflammatory response. In keeping with previous studies, an NLR of ≥ 4 and albumin <35 were used as cut-off levels indicating an activated SIR. Using student's t-test and chi squared test where applicable, our results show that patients with NLR of ≥ 4 had lower mean lymph node yields than patients with NLR <4 (17.6 \pm 7.1 vs. 19.2 \pm 7.9 and this was statistically significant with a p value of 0.036.

Hypoalbuminaemia did not impact on lymph node count, and furthermore patients with low albumin *and* an elevated NLR were not more likely to have a significantly reduced lymph node count than patients with elevated NLR alone. This was not an unexpected finding as previous studies have not found hypoalbuminaemia alone to be a significant prognostic indicator.

Although a difference of two nodes between the groups may raise questions as to the relevance of these findings, studies such as that conducted by Cserni et al on the SEER database (reference no. 18) demonstrated an improvement in prognosis with each additional node resected.

Reviewer 2: 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. Despite of limited number and quality of the data used in this study, the analytical results presented likely support the conclusion made by authors. The information given may be helpful to promote the further advance in the treatment of colon cancer. This reviewer has no essential criticism to the contents.

Reviewer 3: The manuscript by Kennelly and co-authors describes a database study of a rather small cohort of colon cancer patients, evaluating whether the number of lymph nodes negatively correlates with the systemic response represented by the Neutrophil-lymphocyte ratio. Although the hypothesis is interesting, the number of patients and the methods used are adequate to establish a statistically/clinically significant conclusion. Minor remarks: The patients should have been selected/corrected for specific TNM stages. CRP data should be included. The legends are too concise. Figure 1 is redundant. Table 4 is confusing.

Many thanks for your comments. While CRP data would indeed be an ideal addition, it was not possible in this retrospective study unfortunately as CRP is not a routine pre-operative blood test performed in our centre. In conducting further prospective research on this

fascinating subject, I would include CRP data and correct data for specific TNM stages as suggested. Figure 1 was omitted at the request of reviewer 3. Positive to negative lymph node ratios are a strong prognostic indicator in colonic carcinoma with poorer prognosis associated with a higher ratio. A lymph node ratio (LNR) of 0.25 i.e. 1 in 4 nodes positive has shown particular prognostic significance and is therefore often used as a cut-off for LNR. In the group in whom SIR was *not* identified pre-operatively, 18% of patients with node-positive disease had a lymph-node ratio of >0.25 . In contrast, 34% of patients with node-positive disease in the SIR group had a lymph-node ratio of >0.25 . This was statistically significant at 0.044. In other words, patients in whom SIR was indentified were more likely to have a LNR >0.25 . The wording of the table has been changed in order to hopefully clarify this.

Name: Rory Kennelly

Signature:_____Date:_____