Peer Review File

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Reviewer A

This is an interesting study aiming to examine the impact of the combination of the ratio between metastatic and harvested lymph nodes (RML) and negative lymph node (NLN) count on overall survival (OS) in patients with advanced gastric cancer (GC). The authors present data on 1182 patients treated with curative intent!

They conclude that The RML was an independent prognostic predictor of overall survival in advanced gastric cancer patient and the NLN count may serve as a supplementary strategy for the present tumor-node-metastasis (TNM) classification to further improve the prognostic prediction efficiency.

Specific comments: the manuscript could be reduced in 20%, specially the discussion section;

How many patients were treated by minimally invasive approach? Is there a difference in survival? Is there any difference between subtotal and total gastrectomy?

Reply 1: (1) After careful consideration, we had reduced our manuscript by about 383 words in the main text, most in the discussion section.

(2) We thank the reviewer for the astute comment. Minimally invasive surgery was widely applied to clinical practice in recent decade. Since our study was a retrospective study, the patients in our cohort were treated between January 1994 and December 2015. Over the long time, surgical procedures have all developed and may have caused bias in the long span. Based on this consideration, we did not include this variable into our model. But, a large multicenter study (Chinese Laparoscopic Gastrointestinal Surgery Group 01, CLASS01) in which our center participated confirmed that minimally invasive surgery to be non-inferior in overall survival to traditional open surgery for patients with advanced gastric cancer.

(3) In our cohort, there was about 52% patients underwent subtotal gastrectomy and 48% underwent total gastrectomy. No significant difference in overall survival was found between the two groups.

Changes in the text: Page 19, Line 283-284. Page 19-20, Line 293-308. Page 21, Line 320-323. Page 21, Line 325-328. Page 22-23, Line 360-367. Page 24, Line 385-386. Page 24, Line 402-404. Page 28-29, Line 473-496.

Reviewer B

The authors examined the impact of the combination of the ratio between metastatic and harvested lymph nodes (RML) and negative lymph node (NLN) count on overall survival in patients with advanced gastric cancer. This article contains many scientific problems and is not worthy of publication.

RML has been investigated by many researchers and the results of these studies were similar. The topic of this article is quite old and there is no new finding.

The advantage of the N-number in TNM classification is that the stage can be

determined by only the number of metastatic lymph nodes, even if the surgical treatment is not uniform. However, if RML and NLN are used as prognostic factors, they cannot be evaluated without uniformity in surgical treatment. In this respect, RML and NLN are not superior to the N-number of TNM, and this type of study is meaningless unless an advantage over the N-number of TNM is found. For example, the molecular profile would be superior to the N-number of TNM in that it could provide a tailor-made adjuvant therapy. Does RML have such an advantage?
The number of dissected lymph nodes in gastric cancer is highly dependent on the surgical procedure and degree of nodal dissection. It also depends significantly on the skills of the person in charge of harvesting the node. In addition, it is highly dependent on how the dissected lymph nodes are handled in the pathology section. OS of gastric cancer patients after curative resection is also greatly influenced by the method of adjuvant chemotherapy and the patient's comorbidities. Therefore, such an examination is meaningless unless the skill of the operator, the resection method, the degree of nodal dissection, and the adjuvant chemotherapy are aligned.
This article does not discuss important factors. It does not mention who was in charge of harvesting the nodes and how adjuvant chemotherapy was administrated.

Reply 2: We thank the reviewer for the incisive and thorough comment. As the reviewer mentioned, accurate pathologic staging is highly dependent on standard surgical procedure, experienced surgeons, and pathologists and so on. However, pathologic lymph node stage determined only by the number of metastatic lymph nodes is not that accurate. Lymph node micrometastasis and its anatomical site had great impact on overall survival in patients with advanced gastric cancer. These two factors were not considered in current N-number of TNM strategy. We here present that RML and NLN may serve as a **supplementary** strategy for current TNM classification in experienced centers.
In our center, a professional team lead by attending surgeons harvests the nodes once the tumor is removed; they are fully trained by experienced surgeons.
Adjuvant chemotherapy was widely applied to clinical practice only in recent years. Since our study was a retrospective study, the patients in our cohort were treated between January 1994 and December 2015. Over the long time, chemotherapy regimens have developed and may have caused bias in the long span. Based on this consideration, we did not include this variable into our model.
Changes in the text: No changes.