

Peer Review File

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Reviewers' Comments in Bold Letters

Authors' replies in blue letters

Reviewer A

In this manuscript ATM-21-3170-RV10-7831, the authors developed a novel classification of colon cancer, TLNR, which is composed of only two factors including LNR and pT stage, and showed that TLNR is statistically superior to AJCC TMN classification in the ability to predict the prognosis of colon cancer patients.

Reply: Thank you very much for your kind interest in our manuscript.

Comment 1: Adjuvant therapy must influence the prognosis of stage II -III colon cancer patients. The authors should show the information about the chemotherapy administered for the patients enrolled in this study.

Reply 1: Thank you for pointing out this important issue. We fully agree and have added the information about adjuvant chemotherapy regimens administered for patients in the main text (see Pages 10-11, lines 201-208), and we added the baseline information of adjuvant chemotherapy in the validation cohort, and there was no significant difference in the baseline of chemotherapy between patients with retrieved <12 retrieved lymph nodes and those ≥ 12 retrieved lymph nodes (Supplementary Table 2). Besides, we newly performed univariate and multivariable analyses, and confirmed that adjuvant chemotherapy was an independent prognostic factor in patients with <12 retrieved lymph nodes, and also in patients with ≥ 12 lymph nodes in the validation cohort (Supplementary Table 3).

Change in the text: (see Pages 10-11, lines 201-208; Supplementary Tables 2-3)

Comment 2: (a) I wonder why T1LNR3 is catabolized in stage IIA but T1LNR4 in stage I in TLNM. The authors should mention this issue. (b) TLNR might be a powerful tool for predicting the prognosis of colon cancer patients with inadequate lymph nodes retrieved. Do authors have any speculations about the reason why TLNR is adaptable for that kind of patient? (c) And it also means that the benefit of lymphadenectomy on survival is unclear?

Reply 2: Thank you for pointing out this important issue. (a) Although 62,294 patients of colon cancer were applied to develop this TLNR classification, only 65 patients were in T1LNR3. We think this deviation was possibly caused by a relatively small number

of patients in this subgroup. Therefore, future studies are still required to validate the novel TLNR classification. We have added this as a limitation in the discussion section (see Page 17, lines 335-338). (b) We are sorry that we did not clearly describe our conclusions, we originally meant that this novel TLNR classification might be a powerful tool not only for patients with adequate lymph nodes (≥ 12), but also for patients with inadequate lymph nodes (< 12). Accordingly, we have modified the conclusions (see Page 4, lines 73-77; Page 17, lines 341-346). Regarding the reason why TLNR is adaptable for patients with inadequate lymph nodes (< 12), we have discussed in the discussion section (see Pages 15-16, lines 296-325). (c) We think that the benefit of lymphadenectomy on survival (e.g., 5-year overall survival) is clear for that patients with adequate number of retrieved lymph nodes (≥ 12) were associated with better survivals compared with those with inadequate number of lymph nodes (< 12), though reasons are still unclear (Supplementary Table 3). Based on results of Supplementary Table 3, we found that patients with adequate number of retrieved lymph nodes (≥ 12) showed better 5-year OS than those with inadequate number of lymph nodes (< 12) in most stratifications of populations.

Change in the text: (see Page 4, lines 73-77; Pages 17, lines 341-346; Supplementary Table 3)

Comment 3: Are there any differences in background between the colon cancer patients with retrieved < 12 lymph nodes and the patients with retrieved > 12 ?

Reply 1: Based on this comment, we have added the baseline characteristics of the training and validation cohorts in relation to the number of retrieved lymph nodes are presented in Supplementary Table 2. In the training cohort, there were significant baseline differences between patients with < 12 and ≥ 12 retrieved lymph nodes in terms of age, sex, race, tumor size, histological grade, AJCC 8th pT stage, and AJCC 8th pN stage, whereas the validation cohort showed significant baseline differences among these two groups in age, tumor size, histological grade, AJCC 8th pT stage, and AJCC 8th pN stage (Supplementary Table 2).

Change in the text: (see Page 10, lines 194-200; Supplementary Table 2)

Reviewer B

The authors have conducted an interesting study with a proper validation of their findings in an external cohort. I have the following comments

Reply: Thank you very much for your positive comments.

Comment 1: The authors should consult a native English speaker to improve grammaticality and spelling.

Reply 1: Based upon this comment, we sent our manuscript to the International Science Editing (<http://www.internationalscienceediting.com>) for the help in polishing our paper. We have added our acknowledge to International Science Editing in the Acknowledgments section

Change in the text: (see Page 18, lines 360-361)

Comment 2: The TLNR ratio may be superior overall, but when looking at the KM curves this seems to be true only for patients with stage IIB, IIC or IIIA. The curves for subgroups of the other stages are all almost overlapping and thus do not represent groups with a significantly different outcome. This should be incorporated in the manuscript, and the conclusions should be downgraded accordingly.

Reply 2: Thank you very much for pointing out this important issue. We have added this as a limitation in the discussion section, and modified and downgraded the conclusions.

Change in the text: (see Page 4, lines 73-77; Page 17, lines 333-346)