

**Dear Editor;**

- Title page post codes were added.
- In abstract, aim was revised.
- Core tip and audio core tip were added.
- Article highlights was added.
- References were revised as suitable to publish
- Figure file names were revised.

➤ **In accordance with the reviewer 1 recommendations;**

- **Questions/concerns:** Some informations are not clear in the results section of the abstract; which p-value is there for right CC and for left CC respectively, both for DFS and OS? It is not clearly understandable.
  - In abstract, results was corrected
- **Questions/concerns:** The article contains 15 references only, this number is low for such a kind actual subject. PubMed contains more than hundred references when you enter “right versus left colon cancer”. I recommend especially adding two more highly relevant references that you can find below
  - Recommended references were added to discussion.
- **Questions/concerns:** Figure-1 and Figure-2 show comparative DFS and OS in patients with stage II and III CC, according to adjuvant chemotherapy (CT) intake, but the number of patients not receiving adjuvant CT according to the stages separately is missing even in the manuscript. This number and its reason is highly important for especially stage III patients. It seems that only 241 patients received oxaliplatin-based CT for total patient population.
  - Case numbers were added to figures
- **Questions/concerns:** The number of stage III patients is 375, so, what is the percentage of patients with stage III receiving oxa-based CT? What is the effect of this subgroup to DFS and OS?
  - In stage 3 group, new figures were performed according to chemotherapy regimens for patients received adjuvant therapy.
- **Questions/concerns:** The number and completeness of adjuvant CT cycles effect also survival analysis in stage III, and these details are not in the manuscript.
  - Completion rates of adjuvant therapy were added to results and table-1

➤ **In accordance with the reviewer 2 recommendations;**

- **Questions/concerns:** The authors should indicate the Figure regarding K-M curves of RCC vs. LCC in each stage, not stratified by adjuvant chemotherapy. In Stage II colon cancer, adjuvant therapy is not a standard of care; therefore, there would be no clinical impact in analysis of stage II RCC vs. LCC by adjuvant chemotherapy.
  - Because the aim of our study was prognostic significance of tumor location in patients received or not received adjuvant therapy, this request could not be performed.
- **Questions/concerns:** Please explain method of the multivariate analysis in the ‘Statistical Analysis’ section. Also, in the Table 3, some data may be missing (for instance, PT stage, pN, Surgical margin).
  - pT and pN were not added to multivariate analysis because of correlation between pt-pn and tnm stage.
  - Since the p values of the parameters were not given for  $p > 0.050$  in forward stepwise model analysis, surgical margin p value was not added to multivariate analysis.
- **Questions/concerns:** The authors reported, “Rate of mucinous adenocarcinoma histology, rate of LN number of  $\geq 12$ , mean number of LNs dissected were significantly higher in RCC group.” These results may be different between Stage II and III. Therefore, it would be of interest to analyze them according to the Stage
  - Histologic subtypes and lymph node status were discussed request of reviewer
- **Questions/concerns:** There was no statistically significant difference in median survival time after recurrence between RCC and LCC cases (log rank  $p = 0.092$ ). Previously, Kerr DJ et al have reported important findings using data of prospective adjuvant trials (Lancet Oncol 2016;17:1480-1482). They suggested that recurrences arising from right-sided primary tumors might have an inherently more aggressive phenotype or perhaps that they are more resistant to our current therapeutic options for advanced colorectal cancer than metastases arising from left-sided tumors. Please discuss this important point.
  - Recommended references were added to discussion

➤ **In accordance with the reviewer 3 recommendations;**

- **Questions/concerns:** However, the variable in the survival figures should include the adjuvant therapy group or without adjuvant therapy group. The tables and figures should be more professional for publish.

- Figures and tables were revised.

➤ **In accordance with the reviewer 4 recommendations;**

- **Questions/concerns:** About abstract: In the “AIM” section, last sentence should define a purpose, not what you had done
  - The aim section was corrected in abstract.
- **Questions/concerns:** In addition, the number of patients, timeline also should be mentioned in “results” section. In the results part; descriptive data about gender, age should be mentioned in the first sentences. You can change “log rank p” to only “p”.
  - The conclusion section of abstract was corrected in the direction of request of reviewer.
  - In the results section, “log rank p” was changed as p.
- **Questions/concerns:** In addition, median length of survival should be added.
  - Because of median OS could not reached, median OS value could not calculated, but life tables were added to result section.
- **Questions/concerns:** The sentence “However, post-recurrence OS appeared to be worse in RCC patients.” Should be revised, because it is not statistically significant. It should be discussed in “discussion” section in the manuscript.
  - Because of the number of case with post recurrence was not enough to reach statistically significance but in patients with RCC, clinically significance was discussed in discussion section.
- **Questions/concerns:** The analysis concluded some prognostic factors, those should be added in the results and conclusion sections.
  - The factors, affecting to OS and DFS, were given in results and discussion sections.
- **Questions/concerns:** About Introduction: In this section, there are too many preclinical data about colon cancer. It should be revised and made more clear. In addition there is no data about the new findings that has gained popularity in the last 3-4 years. The 2nd reference is written in 1990. Do we really need it? The last paragraph should include what your hypothesis was. You should mention about the background

studies that conveyed you to work on that subject. In addition, you should mention why we need such a study.

- We explained that why needed to this trial in introduction section.
  - The last sentence in introduction was revised.
  - Because of the general informations about of colon cancer were received from ‘*Ann Intern Med* 1990, **113**:779-788’, this reference was not excluded.
- **Questions/concerns:** About Methods and results: The inclusion criteria should be more clear. For example, did you include patients less than 18? The “sex” should be changed to “gender”, because it was mentioned as “gender in tables.”
    - Inclusion criteria were corrected.
    - “sex” was corrected as “gender” in directed of reviewer request in manuscript.
- **Questions/concerns:** In table 3; surgical margin was not included in cox regression. However, it has a p value of 0.008. In st. analysis section, p values of  $p < 0.250$  was determined as a cut off value for multivariate analysis, but their results in analysis are not present in tables.
    - Since the p values of the parameters were not given for  $p > 0.050$  in forward stepwise model analysis, surgical margin p value was not added to multivariate analysis.
- **Questions/concerns:** The mode of recurremces (Locoregional or systemic) are not present in results sections. The mode of recurrence can be an important determinant of OS2 difference in RCC and LCC. It should be included in the analysis and discussed.
    - Recurrence locations and rate of metastasectomy were added to table-1 and results section.
- **Questions/concerns:** In addition, according to recent studies, instead of grouping adjuvant regimen into ox vs 5-fu based, it would be much better to group them by including capecitabine vs 5-Fu based
    - This recommendation was added to results section as “ In stage 3 group, new figures were performed according to chemotherapy regimens for patients received adjuvant therapy” in directed of reviewer 1 request. Therefore, additional analysis was not performed.

- **Questions/concerns:** While presenting results, it would be better to first write the univariate- multivariate of DFS, the univariate- multivariate of OS can be presented.
  - In result section, DFS and OS were given as univariate- multivariate of DFS, the univariate- multivariate of OS, respectively.
- **Questions/concerns:** Discussion section: In this part, first paragraph should summarize your purpose and what you had found. For example “In our study, we aimed to.....(1 sentence). We concluded that.....(short 1-2 sentences). In some parts “emergency surgery” was used as “presentation of ileus”. It can cause confusion.
  - Discussion section was revised .
- **Questions/concerns:** The discussion should focus on the adjuvant studies, the studies containing metastatic cases should be excluded
  - We also focused on post recurrence OS in this trial therefore the references about of metastatic disease were not excluded.

Best regards...

Dr. Abdullah Sakin