City of Hope™

1500 East Duarte Road
Duarte, CA 91010-3000
Phone 626-471-7100
Fax 626-301-8865
www.cityofhope.org

November 14, 2013

Dear Editor:

Please find enclosed the edited manuscript in Word format (file name: 4770-edited.doc).

Title: Timing of Chemotherapy and Survival in Patients with Resectable Gastric Adenocarcinoma

Authors: Amanda K Arrington, Rebecca A Nelson, Supriya S Patel, Carrie Luu, Michelle Ko, Julio Garcia-Aguilar, Joseph Kim

Name of Journal: *World Journal of Gastrointestinal Surgery*

ESPS Manuscript NO: 4770

The manuscript has been improved according to the suggestions of the editor and the reviewers:

1. **The format has been updated**

2. **In the process of revising the manuscript, we discovered an error in coding that included patients with Stage I gastric cancer in our analysis. The coding has been corrected and all analyses, figures, and tables have been revised and updated. Please note that this has not changed our overall hypothesis or conclusions.**

3. **Revisions have been made according to the suggestions of Reviewer 00069855:**
   'There is a main concern on the survival time of patients without chemotherapy. I check the Figure 1 and Table 1-3 in the manuscript, and could not found this important information. In my opinion, according to the tittle and statements in the manuscript, it will be better for authors to provide survival time for both patients with and without chemical treatment, and then compare these data in either Figure 1 or Table 3.'
   We have included median Overall Survival (OS) and 1, 3, and 5 year OS in Figure 1. The log-rank p-value indicates in Figure 1, there is no statistical difference between comparison groups.

4. **Revisions have been made according to the suggestions of Reviewer 02439559:**
   Whether the patients with preoperative chemotherapy also receive postoperative chemotherapy? In general, it is better to preoperative chemotherapy combined with postoperative chemotherapy.
   We have indicated in the revised Methods: Since the CSP database codes only for the date of first chemotherapy treatment and not any subsequent chemotherapy, we cannot distinguish between neoadjuvant and perioperative chemotherapy. By

virtue of this inherent limitation, the current study was designed to compare neoadjuvant chemotherapy to adjuvant chemotherapy.

When does preoperative chemotherapy began, how many times, chemotherapy dose?
We have indicated in the methods section that only the receipt of therapy and the date of the first chemotherapy received are available from the CSP database. Therefore, exact timing of chemotherapy, number of chemotherapy treatments, and type of chemotherapy medications used is not available.

Preoperative chemotherapy group were too little, it was not balanced compared with postoperative chemotherapy group, Too few patients will affect the reliability of the results.
Although the neoadjuvant cohort is smaller than the adjuvant cohort, our data does not appear to be underpowered We performed a post-hoc survival simulation which showed that based on median survival times of 29 and 27 months in stage II neo-adjuvant vs adjuvant chemotherapy patients, respectively, it would take 14,722 total patients to find a significant difference between groups. This sample size assumes 80% power and a 2-sided log-rank alpha of 0.05. Even with 14,722 patients, however, our Kaplan-Meier plot shows that survival advantage of one group is not consistently longer than the other, with 1-year survival superior in the neoadjuvant group but 3-year and 5-year survival superior in the adjuvant group.

5. **<u>Revisions have been made according to the suggestions of Reviewer 02453874:</u>**
The most important question when reporting a null result, as in this manuscript, is what is the power of the study to identify a true difference. Please provide a power calculation for comparing neo-adjuvant and adjuvant regimens.
Please see Response #4 above.

As you have mentioned you are not comparing preoperative chemotherapy with postoperative. The correct comparison is "at least preoperative chemo" with "postoperative chemo". Please revise your wording throughout and in the abstract so that your manuscript accurately reflects this comparison.
We have revised our manuscript accordingly. In addition, a clarification of the chemotherapy groups was added to the Methods section.

Please clearly specify your outcome and time scale in the methods section, as right now it is not stated clearly in the manuscript. For example: time to relapse/all cause death/ death attributable to malignancy since diagnosis/chemo/surgery.
We have revised the methods section to include: Survival was defined as survival throughout the study period (1988-2006). Mortality was defined through the database used as all-cause mortality since date of diagnosis of gastric cancer. .

Are your Log-rank test adjusted (for example using standardization) ? If not and considering the baseline differences among groups you should exert caution in interpreting the results of the Log-rank tests. Also, please report the results of the Log-rank test among stages II and III combined.
The log rank tests are adjusted in that they're stratified by stage but otherwise they are not adjusted using standardization. In the multivariate analysis (MVA) model, the HRs and p-values are adjusted for age and AJCC stage. Because AJCC stage is in the model, we cannot include the components, such as T stage or N stage, which

make up AJCC stage. Alternatively, we can use T stage and N stage in the MVA instead of AJCC stage. When we ran this, the results did not change. We have added a figure with stage II and III combined, with a log-rank p-value of 0.7819.

Please report the HRs and the P-values for all the comparisons mentioned in the results section. Also, please revise your table 3, as for example right now the HR/Pvalue for age in the multivariate analysis is not reported.
We have added p-values to the revised Table 3.

Please test the proportional hazards assumption for your Cox models and report it.
We performed a check of the Cox proportional hazards assumptions by calculating the scaled Schoenfeld residuals for our models. In each of these calculations, OS in stage II and III, stage II alone, and stage III alone, the p-values were non-significant at 0.849, 0.662 and 0.85, respectively, indicating that the proportional hazards assumptions were met. We have added this sentence to the methods section "*Proportional hazard assumptions for the Cox models were tested by calculating scaled Schoenfeld residuals with results indicating model fit."*

In the discussion you have mentioned that your results support the findings of the MAGIC trial. But you have not reported a comparison between the no chemo group and the perioperative chemo group (combined).
We have revised the Discussion to capture this comparison.

The largest part of your discussion is a detailed evaluation of the findings of the other studies, especially MAGIC and CLASSIC trials. Please discuss your own results and their implications more.
We have revised the Discussion accordingly.

You have mentioned selection bias as a potential limitation of your study. Please explain more and clarify the exact mechanism and direction of selection bias that you think may have happened here.
We have expanded on selection bias in the Discussion section.

I would suggest that instead of using an automatic stepwise approach for your multivariate analysis you perform a manual one to include some of the important variables such as tumor size and N-stage/Node-status a priori in your model. Although they may not be important for prediction, but your analysis here is evaluating the role of chemo timing and not predicting survival, and your treatment groups were significantly different according to these factors, so it is better that you include them in your models as adjustment variables.
We respect the comments of the reviewer. We have changed our analysis to a multivariate model but felt, due to the multicollinearity of the size, T stage and node status variables with the AJCC stage variable that we should not include all of these variables. Instead we included only age, AJCC stage and chemotherapy timing. We have also added this sentence to the Methods: "*Because tumor size, T stage and node status are multicollinear with AJCC stage, the multivariate model included AJCC stage alone to represent the staging variables."*

As mentioned earlier, your comparison groups are not well defined which results to a dilution of the effect and bias towards the null. Additionally, you are not able to adjust for specific regimens used or completion of chemotherapy. All of these make your null results less reliable/conclusive, especially in the absence of a power calculation.

We did not state that our groups were not "well-defined". We have run a power calculation and included our justification in the discussion (see Response 4). In addition, although it would be informative to adjust for specific chemotherapy regimens and completion of chemotherapy, we were unable to perform these analyses as the registry dataset does not contain this information.

6. **References were corrected and expanded to include at least 26 references.**

Thank you again for publishing our manuscript in the *World Journal of Gastrointestinal Surgery.*

Sincerely yours,

Amanda K Arrington, MD
Associate Professor
University of South Carolina
Amanda.arrington@uscmed.sc.edu

Joseph Kim, M.D., F.A.C.S | Associate Professor
Section Chief, UGI and Mixed Tumors
Director, Surgical Oncology Training Program
Email: jokim@coh.org

City of Hope
Division of Surgical Oncology
1500 East Duarte Road, Duarte, CA 91010
Tel: 626-471-7100