

August 03, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name Manuscript11488-edited revised.doc).

**Title:** Survival in gastric cancer in relation to postoperative adjuvant therapy and determinants

**Author:** Sevgi Ozden, Zerrin Ozgen, Hazan Ozyurt, Cengiz Gemici, GokhanYaprak, Huseyin Tepetam, Alpaslan Mayadagli

**Name of Journal:** *World Journal of Gastroenterology*

**ESPS Manuscript NO:** 11488

The manuscript has been improved according to the editor's suggestions (e.g., adding information about authors, author contributions, and telephone and fax numbers, references) as well as to suggestions of reviewers:

**Reviewer 1**

Comment 1. Major concern: It is not necessary to show the data of Table 5 in the context and Table 5 should be deleted.

Response 1. Table 5 is revised in accordance with the comments of other referees on the basis of appropriate style of reporting a survival analysis

**Reviewer 2:** My comments are as below:

Comment 1. 201 cases during 13 years; 15 cases each year; shows a center with very low refer of cases with cancer. The results are not so generalizable to other referral centers.

Response 1. We agree with the referee that our findings are not so generalizable to other referral centers because of small sample size. Although, number of cases increased to 35-45 per year at our center with improvement in technology, the present study was based on only available data regarding retrospective cases and consistent with other published studies<sup>1</sup> with similar design in terms of small sample size. Nevertheless our findings may help to increase patient referral per year.

<sup>1</sup>Quero L, Bouchbika Z, Kouto H, Baruch-Hennequin V, Gornet JM, Munoz N, Cojean-Zelek I, Houdart R, Panis Y, Valleur P, Aparicio T, Maylin C, Hennequin C. Postoperative chemotherapy followed by conformal concomitant chemoradiotherapy in high-risk gastric cancer *Int J Radiat Oncol Biol Phys*. 2012 Jun 1;83(2):574-80. doi: 10.1016/j.ijrobp.2011.07.031. Epub 2011 Nov 16.

Comment 2. Since distribution of some of their data like time is not normal, median  $\pm$  IQR is preferred to mean $\pm$ SD in these situations.

Response 2. Necessary revisions are made.

Comment 3. It is important to know which variables have included in cox regression analysis and why? What was the approach of the authors for including these variables as independent variables in this analysis? Significance cannot be a good pre-requisite for such inclusion. Hosmer-Lemeshow method (entering variables with  $P < 0.2$ ) sounds more plausible.

Response 3. Cox regression analysis is updated with inclusion of independent variables using Hosmer-Lemeshow method (entering variables with  $P < 0.2$ ). Accordingly, results and discussion

sections as well as Table 5 are revised in line with new analysis. (Please see Pages 4,9,11,12,16 for the redline/highlighted text)

Comment 4. What is the logic of dividing follow ups to these two periods?

Response 4. Follow up was divided into two consecutive periods (from 1998 to 2008 and from 2008 to 2010) based on introduction of 3-D conformal technique in radiotherapy in 2008 at our clinic which otherwise would likely to result in misinterpretation of survival outcome given the discrepancy between patients in terms of type of the devices.(Please see Page 7 for the redline/highlighted text)

Comment 5. Reporting all variables and all indices (columns) as the software output shows (Table 5) is not necessary at all. Only beginners may report in this form. I suggest that authors consult with an expert statistician or epidemiologist for the style of reporting a survival analysis. Moreover, more advanced techniques are also available like parametric survival analysis and so on that can increase the level of this manuscript .Statisticians can help authors more efficiently

Response 5. Table 5 is revised accordingly. Since use of parametric models is based on meeting certain prerequisites in the database such as being in accordance with exponential, Weibull and Gompertz distributions, cox regression analysis is selected as a less presumptive method enabling more convenient variable control<sup>1,2</sup>

<sup>1</sup>[https://www.utexas.edu/cola/centers/prc/\\_files/cs/Fall2012\\_Brown\\_Introduction%20to%20Survival%20Analysis%20v3.pdf](https://www.utexas.edu/cola/centers/prc/_files/cs/Fall2012_Brown_Introduction%20to%20Survival%20Analysis%20v3.pdf)

<sup>2</sup>Kadir Sümbüloğlu, Beyza Akdağ, *Advanced Biostatistical Methods*, Hatipoglu Press, 2009, page 245.

The paper needs only minor revisions as mentioned above.

### Reviewer 3

The authors performed retrospective single center analysis of survival data (1998-2010) in patients with gastric carcinoma after curative resection. Their findings emphasize the likelihood of postoperative adjuvant chemoradiotherapy (CRT) to have a survival benefit in patients with resectable gastric carcinoma. The authors concluded that prognosis of gastric cancer cases after curative resection with postoperative adjuvant chemoradiotherapy was better than that of cases without postoperative adjuvant. But these results were already proved by several large scale prospective randomized clinical studies. So, I don't think that this study has novel results.

Response. Indeed, adjuvant treatment strategies in patients in resectable gastric cancer still remains debated<sup>1,2</sup> and our findings provide data not only on the survival benefit of postoperative adjuvant but also the on the impact of interval between surgery and radiotherapy initiation on survival times and valuable in this regard given the data scarcity.

<sup>1</sup>Brooks GA, Enzinger PC, Fuchs CS. *Adjuvant therapy for gastric cancer: revisiting the past to clarify the future. J Clin Oncol* 2012; 30: 2297-2299.

<sup>2</sup>Michel P, Breysacher G, Mornex F, Seitz JF, Pere-Verge D, Martel-Lafay I, Faroux R, Chapet S, Sobhani I, Pezet D, Aparicio T, Nguyen S, Dousset B, Jouve JL, Maillard E. *Feasibility of preoperative and postoperative chemoradiotherapy in gastric adenocarcinoma. Two phase II studies done in parallel. Fédération Francophone de Cancérologie Digestive* 0308. *Eur J Cancer* 2014; 50: 1076-1083.

Comment 1. The authors should separate D2 lymph node dissection case from D0,D1. Because the prognosis of long duration after curative resection gastric cancer cases with D2 dissection was better than that with D0,D1 dissection.

Response 1. Since data on type of lymph node dissection are available only in 2 cases, it seems not possible and appropriate to provide detailed data on D0/1 vs. D2 dissection. Accordingly this statement is removed (Please See Pages 7 and 14 for the redline/highlighted text).

Comment 2. If the patients of this study were curative resection cases, the authors should exclude the surgical margin positive cases.

Response 2. Our study population is not composed of entirely curative resection cases, so this statement is revised accordingly (Please See Pages 3-7 for the redline/highlighted text).

Comment 3. The authors studied about Stage IB ~ IIIC cases. The authors should analysis the relationship between prognosis and postoperative adjuvant on each stage.

Response 3. While possible, due to small sample size of the overall study population, this seems not reasonable in terms of statistical analysis. In fact, available data on the number of positive lymph nodes seem to provide necessary explanation.

Comment 4. How about prognosis of scirrhous carcinoma? The authors should exclude the scirrhous carcinoma. Because schirrhous carcinoma has high frequent peritoneal and poor prognosis metastasis even if curative resection and postoperative adjuvant were done.

Response 4. None of our cases was diagnosed with scirrhous carcinoma.

Comment 5. There were many regimens of postoperative chemotherapy, the author should limit to single regimen.

Response 5. Our study is a retrospective study based on available data, while the difference in survival with respect to postoperative chemotherapy is one of the study findings. Although the number of cases with TCF is very low and hence could be omitted, these are cases in the "chemotherapy per se" protocol.

Comment 6. The authors should illustrate the schema of regimen of postoperative chemoradiotherapy.

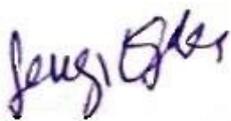
Response 6. The schema of postoperative chemotherapy is added (Please See Fig 1).

Comment 7. There were no contents about complication of adjuvant chemotherapy and radiation.

Response 7. We agree with the referee but data on complications of adjuvant chemotherapy were available only for a limited number of cases and therefore not appropriate for performing a reliable safety analysis.

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

Sincerely yours,



Sevgi Ozden, MD, PhD.

Dr. Lutfi Kirdar Kartal Training and Research Hospital,

Radiation Oncology

Cevizli -Kartal-Istanbul, Turkey

Phone: + 90 216 4413900

E-mail: [sevgiozden@gmail.com](mailto:sevgiozden@gmail.com)