Feb 18, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 7018-review.doc).

Title: Neoadjuvant treatment for esophageal squamous cell carcinoma

Author: Yoshifumi Baba, Masayuki Watanabe, Naoya Yoshida, and Hideo Baba

Name of Journal: *World Journal of Gastrointestinal Oncology*

ESPS Manuscript NO: 7018

We appreciate the reviewers' suggestions and comments. As a consequence of these valuable suggestions, we believe that our manuscript has been much improved.
To aid in the re-review of this manuscript, we have included a point by point response to each comment. Reviewers' comments are italicized and in square brackets. In addition, within the revised manuscript, changes to the text in response to the reviewers' comments are underlined.

Reviewer #00204529
[The authors need to update references, in particular the comments about EGFr targeted agents, with all recent reports of these agents indicating failure to improve outcome.]

According to the reviewer's comment, we have updated references as follows:
"A phase II study with cetuximab and radiation therapy for patients with surgically resectable esophageal carcinomas (Hoosier Oncology Group G05-92) has shown that cetuximab and radiation therapy results in a pathologic complete response rate (67% for squamous cell carcinoma) that seems at least comparable with that of chemotherapy and radiation therapy [46]." (Page 11)

[The authors should qualify the statement that the "rapid" increase in adenocarcinoma is actually starting to level off in the West. The authors should clarify that squamous cancer incidence is not increasing.]

We agree with the reviewer that the following sentence was confusing. Thus, we have omitted this sentence.
"More than 450,000 new cases are diagnosed each year, and the incidence is rapidly increasing."

[The authors should point out that patients reported in purely surgical series are selected for surgery and do not reflect all patients diagnosed with squamous cancer, therefore survival in surgery only series is likely higher than for all comers diagnosed with locally advanced disease.]

According to the reviewer's comment, we have revised the manuscript as follows:
"We of course acknowledge that these results may be influenced by the patient selection bias for surgical procedure." (Page 4)

[*Page 5 confusing phrasing: patients who are node positive should be called node positive, not 'metastatic." Degrade tumor stage should be downgrade or downstage. The comment about selection of drug resistant clones being "inconclusive" makes no sense.]*

According to the reviewer's comment, we have revised the manuscript as follows:
"In addition, even if tumors were completely resected, the prognosis was poorer in patients with LN metastasis than in patients without LN metastasis; the 1-year, 3-year, and 5-year survival rates of patients with LN metastasis were 77%, 45%, and 35%, respectively [9]." (Page 4-5)

"First, preoperative therapies can potentially downstage and degrade tumor size, and thus increase the possibility of complete resection." (Page 5)

We have omitted the following sentence.
"A third limitation is that selection of drug-resistant clones may be inconclusive."

[OEO2 was a positive trial only because rates of R0 resection were improved with preoperative chemotherapy. There was no impact on distant recurrence of disease, which is surprising for an adjuvant chemotherapy trial.]

In response to the reviewer's comment, we have revised the manuscript as follows:
"However, the pattern of first disease progression was similar between the two treatment groups, in particular there was no clear trend toward fewer patients with distant metastases as first site of relapse in the preoperative CT + surgery group." (Page 7)

[The JCOG study is flawed because the design was hampered by observations from subset analyses of prior studies. Nearly half of the post op chemo arm patients on this trial did not receive chemotherapy. The primary endpoint of this trial (disease free survival) was not met, and the benefit of preoperative chemotherapy was limited to clinical N0 patients, in contrast to their prior post op study where a benefit was limited to N+ patients. These inconsistencies and weaknesses of JCOG 9907 need to be reviewed.]

In response to the reviewer's comment, we have revised the manuscript as follows:
"However, we need to acknowledge that the trial design of JCOG 9907 had some limitations [35]. In the postoperative treatment group, patients with LN metastasis negative cancer did not receive chemotherapy because JCOG 9204 did not find a benefit for adjuvant chemotherapy in a subset analysis of LN metastasis-negative patients. Thus, this imbalance in treatment arms does not allow us to conclude that preoperative therapy is superior to postoperative therapy because not all patients in the postoperative chemotherapy arm received treatment. In addition, the primary end point of disease free survival was not met, yet overall survival was in favor of the preoperative group." (Page 8)

[Page 9: The authors underplay the greater impact of preoperative chemoradiotherapy reported on the CROSS trial for squamous cancers, with a path CR rate of nearly 50% and a HR for survival improvement indicating a near doubling of survival for squamous cancer patients.]

"Importantly, the benefit of neoadjuvant CRT was confirmed in an SCC subgroup (HR, 0.45; 95% CI, 0.24-0.84; P = 0.007)." (Page 9)

Reviewer #02567684

[*1. There were a handful of publication on this topic in 2013 but the review cite only two. There were, for instance, japanese (Jpn J Clin Oncol. 2013 Jul;43(7):752-5. doi: 10.1093/jjco/hyt061) and italian trials (Cancer. 2013 Mar 1;119(5):939-45. doi: 10.1002/cncr.27822) about docetaxel.]*

In response to the reviewer's comment, we have cited these studies in the revised version:
"This background has initiated the JCOG1109 (NExT study) trial, a three-arm Phase III trial started in November of 2012. The aim of this study is to confirm whether docetaxel, CDDP + 5-FU is superior to CDDP + 5-FU, and whether CDDP + 5-FU is superior to CRT over CDDP + 5-FU, as preoperative therapies for ESCC [42]." (Page10)

"Importantly, the phase 2 study for neoadjuvant CRT (docetaxel, CDDP, 5-FU and concurrent radiotherapy) showed promising results; pathological complete remission (pCR) was found in 47%, and the 3- and 5-year survival rates were, respectively, 83% and 77% for pCR cases [43]." (Page 10)

[2. Missed some comments on CRT drawbacks.

We have made some comments on the limitations of CRT in page 5.
"Currently, however, the relationship between preoperative therapy and postoperative morbidity and mortality remains controversial. Hirao et al. have reported that preoperative CT of JCOG9907 does not increase the risk of complications or hospital mortality after surgery for advanced thoracic ESCC [13]. The meta-analysis conducted by Kranzfelder et al. revealed no evidence of increased mortality resulting from neoadjuvant CT and CRT [14]. By contrast, randomized trials conducted by two independent groups did report increased postoperative mortality rates following neoadjuvant CRT [15, 16]."

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

Sincerely yours,

Hideo Baba, MD, PhD, FACS,
Department of Gastroenterological Surgery,
Graduate School of Medical Science, Kumamoto University,
1-1-1 Honjo, Kumamoto 860-8556, Japan.
Tel: +81-96-373-5211; Fax: +81-96-371-4378;
E-mail: hdobaba@kumamoto-u.ac.jp