

Dear, Lian-Sheng Ma,

President and Company Editor-in-Chief
Baishideng Publishing Group Inc

I am sending herewith an invited manuscript (ID02738953, or new manuscript number 24863) entitled “High circulating tumor cell concentrations in a specific subtype of gastric cancer with diffuse bone metastasis at diagnosis. Specific type of gastric circulating tumor cell”, which I have completed our revision.

First of all, we thank the reviewers’ critical reading and comments to our manuscript. We also thank warm opinions from them. According to their comments, we added some sentences and rewrote them as described bellow.

#1. We have added case 4 patient and reanalyzed the correlation between the initial CTC count and survival time. In case 4, we applied the present survival time. As a result, the corresponding sentences are changed as below. Page 12, line 4

Although case 4 is still alive (over 263 days), the correlation between CTC count and survival time showed a trend towards significance but did not reach significance (Fig. 2, $Y = 234.6 - 0.03X$, $r = -0.83$, $P = 0.085$).

According to this change, we also rewrote the figure 2 and its legend as below.

Survival time likely correlates with the initial CTC count ($r = -0.82$, $P = 0.085$).

We also changed abstract as bellow. Page 4, line2

The correlation between CTC count and survival time showed a trend, but did not reach significance ($Y = 234.6 - 0.03X$, $r = -0.83$, $P = 0.085$).

#2. The reviewer asked why case 4 patient has a better prognosis. To this comment, we added the sentences bellow. Page 12, line 7

Concerning case 4, the CTC was additionally examined 2 times during this period. Those are suppressed, and they were 33 and 60 cells/7.5 mL, respectively. That indicates the first line chemotherapy S1 plus cis-platinum is still effective for case 4.

#3. The reviewer asked us to show the incidence of this subtype. We again searched the reports describing this subtype through PubMed. There are not a few reports found out, but most of them are case reports. Furthermore, many of them are written in Japanese. China, South Korea and Japan are the big 3 of gastric cancer patient. These facts indicate that this subtype really exists, but it is

not fully defined medically or biologically. Among a few cohort studies, we found out the description corresponding to the incidence of this subtype, and added the sentences as bellow. Page 6, line 9
Rhee reported 21 patients with DIC at diagnosis among 1216 advanced gastric cancer patients, in whom 18 patients had bone metastases simultaneously ($18/1216 = 1.5\%$) [3]. Although they are rare, they have outstanding features besides diffuse bone metastases and DIC.

We also added percentage of the corresponding situation reported in Toyoshima's paper as 11.9 % as bellow. Page 6, line 17

For examples, Etoh reported 15 cases over the course of 20 years [1] and Toyoshima described 5 of the 42 reported cases (11.9 %) [4].

Further, we added the sentences in discussion part as bellow. Page 12, line 17

The incidence of cGC is roughly estimated to range from 1.5 % to 11.9 % of gastric cancer in the literature [3, 4]. However, if CTC count is characteristics of this subtype, we can estimate the incidence more precisely.

We have revised our manuscript according to the reviewers' comments. All changed are indicated in red. If our revision met your publication criteria, it is our great pleasure.

Yours sincerely

Hiroyuki Shibata

Department of Clinical Oncology, Akita University

Hondo 1-1-1, Akita, Japan, 010-8543

Tel: 81-018-884-6262

Fax: 81-018-884-6455

E-mail: hiroyuki@med.akita-u.ac.jp