Author's response to reviews

Title: The Prognostic Values of EGFR Expression and KRAS Mutation in Patients with Synchronous or Metachronous Metastatic Colorectal Cancer

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Response sheet

Dear Reviewers:
Thank you again for your valuable comments on our manuscript. We have made changes and corrections to our article accordingly and below are our point-by-point replies:

Reviewer Marianna Di Martini
Q: I think that it would be useful for the reader to have more details about the difference between synchronous and metachronous cancer.
A: We much appreciated for your suggestions. We have made a table (supplementary table 1) to show the differences between synchronous and metachronous cancer.

Reviewer Ingrid Ljuslinder
Major comments: This is a retrospective study showing that EGFR status has a prognostic value and that KRAS status did not. Unfortunately, none of these observations are novel even though there are few studies that have investigated it by grouping the metastases into syn/metachrone. The level of EGFR mutation is rather high even if there are other studies that have reported high levels of EGFR positive tumours.
Reply 1: It has been reported that there are many differences in colorectal cancers between various ethnic groups by epidemiological, clinical, and molecular biological studies. It is different between Chinese patients and patients from Western countries. Moreover, there are differences between Chinese and Japanese. (J Natl Cancer Inst 1990; 82:915–926; Int J Epidemiol 1991; 20:76-81.; World J Gastroenterol.2003: 9:721–725.; Eur J Cancer Prev 1995;4:195–199). There are no relevant studies to discuss the prognostic value of EGFR expression and KRAS mutation status in Taiwanese simultaneous. I think it is crucial to evaluate this issue in Taiwanese. Additionally, there are remaining controversies about this issue; hence, the current study is helpful to clarify the controversies definitely.
A: Although the high positive rate (83.8%) of EGFR expression by IHC is reported in our study, it is still in the range reported in the literatures (Reference #7). This variation might also result from the differences in the IHC methodology. Additionally, a high positive rate (84.66%) of EGFR expression by IHC was also noted in another study from Taiwan (Chin J Physiol 2012;55:352-360). An ethnic factor may be another cause.

Minor comments: I think the methods used in the study should be mentioned in the abstract. I also think a short explanation of the terms mets/synchrone should be
explained in the introduction. Even though it is a nice study with a well written
discussion the study presents few new data.
Reply 2
1. The EGFR expressions were determinate by IHC (immunohistochemistry)
analysis and categorized 1+ (weak intensity), 2+ (moderate intensity), and 3+
(strong intensity). Genomic DNA was isolated from primary CRC tissues and
direct sequencing of KRAS was performed.” is mentioned in the abstract (page 4,
lines 9-12).
2. The terms of metachronous metastasis and synchronous metastasis are explained
in the background. (page 7, lines 17-19; page 8, Line 1).

We sincerely appreciate your effort in reviewing our manuscript again and kind
assistance for the improvement of the manuscript quality. They are very helpful in
presenting our study in a form suitable to be published in BMC Cancer.

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