Author’s response to reviews

Title: Prognostic impact of tumor location in colon cancer: the Monitoring of Cancer Incidence in Japan (MCIJ) project.

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Version: 1 Date: 29 Mar 2019

Author’s response to reviews:

Dr. Alexandros Houssein
Editor-in-Chief
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29 March 2019

Dear Dr. Alexandros,

Please find attached a revised version of our manuscript entitled “Prognostic impact of tumor location in colon cancer: the Monitoring of Cancer Incidence in Japan (MCIJ) project.”, which we would like to resubmit for publication as an Original Article in BMC Cancer.

The comments from the reviewers were highly insightful and enabled us to greatly improve the quality of our manuscript. In the following pages we summarize our responses to the comments in a point-by-point manner.

Revisions in the text are shown using yellow highlighting for additions, and strikethrough (example) for deletions. We hope that the revisions in the manuscript will be sufficient to make our manuscript suitable for publication in the BMC Cancer.
We shall look forward to hearing from you at your earliest convenience.

Yours sincerely,

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Responses to the comments of editor:

1. Please explain why net-survival was used rather than cancer-specific survival.

Response: We appreciate the editor’s comment. First, net survival is most frequently quantified using the following two methods: relative survival and cause-specific survival. This study used net relative survival method rather than cause specific survival (cancer-specific survival). Cancer-specific survival is a survival measure representing survival of cancer of death in the absence of other causes of death. Estimates are calculated by specifying the cause of death information entered in death certificates. Individuals who die of causes other than those specified, cancer, are considered to be censored. Accurate coding of the cause of death in all death cases is essential for cancer-specific survival estimates. However, in population-based cancer registries, cause of death is obtained from death certificates, which are sometimes inaccurately reported. For example, cancer at the site of recurrence or metastasis may be reported as the cause of death instead of cancer at the primary site. Therefore, analysis of cancer registry data usually relies on relative survival methods that do not require cause of death information. Net relative survival was used rather than cancer-specific survival in this study. Thank you again for the comment.

We have added the sentences below in the Method section (pages 9, lines 15 – pages 10, lines 2).

“Two methods are available to calculate net survival: cause-specific survival and relative survival. The population-based cancer registries usually use relative survival to give estimates net survival”
Responses to the comments of Reviewer #1 (Remarks to the Author):

This is a population-based study to assess the prognostic impact of the tumor site for colorectal cancer in Japanese patients. Overall this is a well conducted study. A few comments are below:

Major comments

1. Some major limitations of this study include - that stage is lacking for 14% of patients, the authors were unable to control for the use of adjuvant chemotherapy in stage III disease and the authors have already mentioned significant issues with the quality of the registry data. These limitations should be clearly identified.

Response: We appreciate the reviewer’s comment. As you pointed out, there are several limitations to this study. We did not have information on adjuvant chemotherapy in the patients with stage III colon cancer, and were accordingly unable to adjust for the use of adjuvant chemotherapy in stage III colon cancer in this study. In addition, stage was lacking for 14% of patients. However, because the proportion of stage unknown patients did not differ among anatomical subsites (Table 1), we believe that the effects of stage unknown cases might be small. We have added these limitations to the Discussion section. Thank you again for this valuable comment.

We have revised the sentences below in the Discussion section (page 21, lines 2-14).

Before revision: “Second, information on BRAF mutation, MSI, CpG island methylation and chemotherapeutic treatment of patients can not be ascertained from the MCIJ data.”

After revision: “Second, information on BRAF mutation, MSI, CpG island methylation and chemotherapeutic treatment of patients can not be ascertained from the MCIJ data. Since the middle of the 2000’s, oxaliplatin with a fluoropyrimidine has been standard adjuvant chemotherapy for stage III colon cancer patients, and is suggested to improve overall survival. Information on adjuvant chemotherapy in the patients with stage III colon cancer also can not be ascertained from the MCIJ data, and we were unable to adjust for the use of adjuvant chemotherapy in stage III colon cancer in this study. In addition, only extent of disease, and not specific stage groupings, was available in the Japanese population-based cancer registries. Furthermore, 14% of the patients were diagnosed with stage unknown. However, because the proportion of stage unknown patients did not differ among the anatomical subsites, we believe that the effects of this stage unknown status are likely small.”
2. I am unsure why the authors chose to classify extent of disease as local, regionalized and distant rather than specific stage groupings (unless this was not available/reliable from the registry data). A comment regarding this would be helpful in the manuscript.

Response: We appreciate this valuable comment. As the reviewer pointed out, we chose to classify by extent of disease. This is because only extent of disease, and not specific stage groupings, was available in the Japanese population-based cancer registries. Extent of disease, the Japanese staging system, was based on SEER (the Surveillance, Epidemiology, and End Results) summary criteria. We have added information about this in the Methods section. Thank you again for the comment.

We have revised the sentences below in the Methods section (page 9, lines 3-5).

Before revision: With regard to the extent of disease, patients were classified into the three stages of localized, regional and distant disease groups.

After revision: With regard to the extent of disease, patients were classified into the three stages of localized, regional and distant disease groups. Extent of disease was available in the Japanese population-based cancer registries. The Japanese staging system, extent of disease, was based on the Surveillance, Epidemiology, and End Results (SEER) staging criteria.

We have added the sentences below in the Discussion section as a limitation (page 21, lines 9-11).

“In addition, only extent of disease, and not specific stage groupings, was available on the Japanese population-based cancer registries.”

3. What is the follow-up time in this analysis?

Response: We appreciate this important comment. We included the patients diagnosed in 2006-2008 and followed them through Dec 31, 2013. The Japanese population-based cancer registries had follow-up system as follows: The Japanese population-based cancer registries collected all death certificates, and matched the death certificates with the registered cancer patients’ records every year. They recorded the date of death for those that matched our cancer patients. Patients were also followed-up using an official register of residents at 5 years after their diagnosis. This date becomes the last “survival date” as alive or deceased on our records. Japanese population-based cancer registries start to follow patients at the date of diagnosis and do not register the date of operation or starting treatment. Thank you again for this comment.

We have added the sentences below in the Methods section (Page 8, lines 3-6)
“We included those patients diagnosed in 2006-2008 and followed through Dec 31, 2013. Japanese population-based cancer registries start to follow patients at the date of diagnosis and do not register the date of operation or starting treatment.”

4. In addition to references 15 and 16, the analysis of the SEER database by Schrag et al presented at ASCO 2016 should be added as a reference.

The relationship between primary tumor sidedness and prognosis in colorectal cancer. Schrag et al.

DOI: 10.1200/JCO.2016.34.15_suppl.3505 Journal of Clinical Oncology 34, no. 15_suppl (May 2016) 3505-3505.

Response: We appreciate the reviewer’s information and suggestion. We have added the reference you suggested as a reference in addition to reference 15 and 16 (Page 6, line 10 and page 18, line 4). Thank you again for the comment.

Responses to the comments of Reviewer #2:

The authors provide limitations of their study including the lack of MSI or other biologic data. All told this is an important effort which should stimulate more detailed work in this area.

1. REQUESTED REVISIONS:

In addition, rather than assessment by whether the tumor was locoregional, etc. the TNM system should be used because of its prognostic importance as a factor of outcome. Most of the impact of sidedness is relative for metastatic disease patients and for the non-metastatic patients and the question of sidedness needs more precise information to include BRAF, MSI and TNM multifactorial analyses.

Response: We appreciate this valuable comment. As you pointed out, the extent of disease was used for analysis of prognostic impact. This is because only extent of disease, and not TNM system groupings, was available in the Japanese population-based cancer registries. Extent of disease, the Japanese staging system, was based on SEER (the Surveillance, Epidemiology, and End Results) summary criteria. We have added this information in the Methods section. We totally agree with the comment that the question of sidedness needs information such as BRAF, MSI and TNM for analysis. We have mentioned this in the Discussion as a limitation (page 21, lines 2-14). Thank you again for the comment.
We have added the sentences below in the Discussion section as limitation (page 21, lines 9-11).

“In addition, only extent of disease, and not specific stage groupings, was available on the Japanese population-based cancer registries.”