Author's response to reviews

Title: Characteristics, survival, and related factors of newly diagnosed colorectal cancer patients refusing cancer treatments under a universal health insurance program

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Author's response to reviews: see over
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Dear Editor:

Thank you very much for the decision letter of Mar. 17, 2014, and the reviewers’ comments for our above referred manuscript. We have revised the manuscript following your instructions and responded to the reviewers’ comments point by point. Both a blue-marked copy and a clean copy of the revised manuscript are attached. We have provided our responses to the reviewers’ comments on the next pages.

We appreciate very much again for your review of the revised manuscript and consideration for publication in the outstanding journal.

Yours sincerely,

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Reviewers’ Reports and Authors’ Response

Reviewer: Rhay-Hung Weng

This paper examines characteristics, survival, and related factors of newly diagnosed colorectal cancer patients refusing cancer treatments program in Taiwan. This is a very interesting and important study for the readers of BMC Cancer. The research methods are described clearly and reasonably. The overall results are good. Overall, the paper does make a sufficient contribution to global health environments and the study results could provide useful information for health care professionals. There are some comments to make the paper clearer below.

1. Please explain which database each variable does come from in the section of Data Collection.

1. We appreciate this comment. The relevant variables have been added to the description of the databases in the Methods section (pp. 8–9 of the revised manuscript) as follows: “The patient data analyzed in this study were retrieved from four complete databases as follows. (i) The 2004–2008 Taiwan Cancer Registry Database (TCRD) of Taiwan’s Health Promotion Administration, Ministry of Health and Welfare provided data on sex, age at diagnosis, cancer stage, and treatment vs. no treatment. (ii) The National Health Insurance Research Database (NHIRD) of Taiwan’s National Health Insurance Administration provided data on sex, age at diagnosis, urbanization level of residence location, insured monthly salary, low-income household status, other catastrophic illnesses or injuries, comorbidity for calculating Charlson Comorbidity Index (CCI), level of diagnosing or treatment hospital, and ownership type of diagnosing or treatment hospital. (iii) Taiwan’s cause-of-death database profile: survival or not at the end of 2010 provided data on post-diagnosis survival in deceased patients. (iv) The Aboriginal Committee’s aboriginal status records of Taiwan’s Ministry of the Interior provided data on aboriginal status.”

2. Please provide more information on the practical implications for health care professional in the section of Conclusion.

1. We appreciate this suggestion. The requested information has been added to the Conclusion section (p. 22 of the revised manuscript) as follows: “Our results show a lower 5-year survival and a 2.66-fold increased risk of death for colorectal patients who refused treatment than for those who underwent treatment within 4 months. Therefore, we urge newly diagnosed cancer patients to actively seek treatment in order to enhance their chances of survival.”
3. **This study only explored limited factors in the analysis model. The authors should provide some statement about this research limitation.**

   1. We appreciate this suggestion. The requested information has been added to the Discussion section (p. 21 of the revised manuscript) as follows: “Due to the use of secondary databases, which did not collect information on such variables as patient health behaviors, health belief and health awareness, we were not able to further ascertain patients’ reasons for refusing treatment with respect to these other variables.”

4. **Stylistic Comments: BMC Cancer style requirements on the reference list were not consistently followed, e.g. “Alan Radley & Sheila Payne” should be “Alan R & Sheila”.

   1. We thank the Reviewer for pointing this out. We have corrected the style of reference 24 (p. 27 of the revised manuscript) in the References list accordingly.

**Reviewer**: Ya-Hsin Li

**Major Compulsory Revisions**

**Abstract section**

1. **I would suggest that the author should mention about the colorectal cancer in the background section. The objective is not very clear from this background.**

   1. We appreciate this suggestion. The requested information has been added to the background portion of the Abstract (p. 3 of the revised manuscript) as follows: “Colorectal cancer is the third most commonly diagnosed cancer worldwide. Few studies have addressed the causes and risks of treatment refusal in a universal health insurance setting.”

2. **In the methods section, analysis methods should be addressed here.**

   1. We appreciate this comment. The requested information has been added to the methods portion of the Abstract (p. 3 of the revised manuscript) as follows: “Factors associated with treatment refusal were identified through logistic regression using the generalized estimating equation method, and survival analysis was performed using the Cox proportional hazards model.”

**Introduction section**

1. **Is that possible the paper can add more information about how serious of colorectal cancer in Taiwan. And how serious of it when comparing with other countries.**
1. We appreciate this comment. The following additional information has been inserted in the Introduction section (p. 5 of the revised manuscript): “with an age-adjusted annual incidence per 100,000 of 51.7 in men and 39.1 in women in 2006–2010, down from 57.2 and 42.5, respectively, in 2003–2007 [3]. In Taiwan, colorectal cancer is on the rise, and the age-adjusted annual incidence per 100,000 increased from 37.99 in men and 29.29 in women in 2003 to 54.39 in men and 36.84 in women in 2010 [4], rivaling the rates observed in the United States.”

2. Is there any information about the proportion of cancer patients refuse to treatment in Taiwan and other countries?

   We appreciate this comment. The following additional information has been inserted in the Introduction section (pp. 5–6 of the revised manuscript): “Most, but not all, patients diagnosed with colorectal cancer receive treatment. In the United States, proportion of colon cancer patients who received no treatment in 2012 was 1% for stages I and II, <1% for stage III, and 12% for stage IV; among rectal cancer patients, the proportions were 2% for stages I and II and 4% for stages III and IV [6]. Huchcroft and Snodgrass found that 7.5 out of 1000 cancer patients refused treatment [7]. A small study in older cancer patients observed a rate of 15.2% for partial or complete treatment refusal [8]. Various studies have found that 15.2% of patients refused recommended chemotherapy [9]; 8% of cancer patients did not undergo conventional cancer treatment [10]; 32% failed to complete cancer treatment [11]; and among breast cancer patients, 6% of those less than 65 years old and 22.2% of those 65 years or older did not receive standard treatment [12]. As most of the above studies were small-scale analyses, we were interested in conducting a nationwide study to examine treatment refusal among colorectal cancer patients in Taiwan. A limited number of studies have examined the risks and possible causes of under treatment of cancer.”

3. Most literature focused on patients refused to chemo, however, this study focused on overall treatment. Therefore, I will suggest that the author should provide more literature on it.

   We appreciate this comment. We have added the relevant literature in the Introduction section (pp. 5–6 of the revised manuscript).

Research methods section

1. Why the paper chooses 4 months as a time point when defining the refusing group?

   We appreciate this question. The explanation for it has been added to the Methods section (p. 8 of the revised manuscript) as follows: “This 4-month period was chosen because it is also the time frame of cancer treatment used by Taiwan’s National Cancer Registry. As reported by Tsai in 2013, the cumulative treatment rate for colorectal cancer was 87.71% at 1 month of diagnosis, 94.01% at 4 months, 94.35
at 5 months, and 95.48% at 12 months [20], indicating very little increase in the cumulative treatment rate from the fifth month, thus supporting our assumption of treatment refusal for newly diagnosed cancer patients who remained untreated after 4 months.”

2. Does patients’ comorbidity level will affect their willingness of treatment?

We appreciate this question. We included Charlson comorbidity index (CCI) as part of our analysis but omitted to include it in our tables. In response to the Reviewer’s inquiry, our CCI data have been added to Tables 2 and 4 are described in the Results section of the revised manuscript (pp. 13–15 of the revised manuscript).

3. I will suggest excluding patients with stage 0 from the study since probably surgery or chemotherapy is not needed in this stage.

We appreciate this suggestion, but respectfully differ with the Reviewer on the inclusion of stage 0 patients in our analysis. When designing our study, we consulted with oncologists who indicated that stage 0 patients constitute an important patient group in colorectal cancer. Moreover, the American Cancer Society posts the following information on its website regarding stage 0 colorectal cancer: "Since these cancers have not grown beyond the inner lining of the colon, surgery to take out the cancer is all that is needed. This may be done in most cases by polypectomy (removing the polyp) or local excision through a colonoscope. Colon resection (colectomy) may occasionally be needed if a tumor is too big to be removed by local excision.”(accessed 26 March 2014; available at http://www.cancer.org/cancer/colonandrectumcancer/detailedguide/colorectal-cancer-treating-by-stage-colon). Taking both sources of information into consideration, we believe that since surgery and other forms of treatment are recommended for stage 0 colorectal cancer patients, this group of patients should be included in our analysis.

4. The author should define the urbanization level in methods section.

We appreciate this suggestion. The requested information has been added in the Study Population and Data Collection subsection of Methods (p. 9 of the revised manuscript) as follows: “Urbanization levels of residence locations were assigned according to Liu et al.’s classification system, which includes seven levels (from the most to the least urbanized): level 1, highly urbanized cities; level 2, moderately urbanized cities; level 3, developing cities; level 4, average towns; level 5, aging towns; level 6, agricultural towns; and level 7, remote villages [21].”

Results section

1. In table 3, there is no hospital characteristics information, which is not parallel to the research methods (p7).
1. We appreciate this comment, but believe that the requested information is not an important component of Table 3. Table 3 analyzes the survival of treated and untreated (treatment-refusing) patients. Because patients who refused treatment did not seek treatment at hospitals after being diagnosed, hospital characteristics were not important variables for this patient group. Therefore, we simultaneously controlled for hospital level and hospital ownership type when we performed the analysis presented in Table 3. To reflect this fact, we have added the following information to the Table 3 footnote: "controlled for level of diagnosing hospital and ownership type of diagnosing hospital."

2. **The survival analysis, there should be a begin and track end time.**

   1. We thank the Reviewer for pointing this out. The following has been added to the Statistical Analysis subsection of Methods (p. 10 of the revised manuscript): “The starting point of the survival analysis was a confirmed cancer diagnosis, and the endpoint was patient death or the last follow-up on survival status at the end of 2010, whichever was sooner.”

3. **In Table 2, the reference group was misleading.**

   1. We thank the Reviewer for pointing this out. In Table 2, we mistakenly designated the reference group for insured monthly salary as “insured dependent group”; this has been corrected in the revised Table 2 as “≤17,280”.

Discussion section

1. **The study revealed no significant difference in gender between 2 groups, and the paper mentioned about lifestyle and cultural background difference with literature review. What are the background difference between Eastern and Western?**

   1. We appreciate this comment. We have made changes in the Discussion section (p. 16 of the revised manuscript) as follows: “The discrepancies between our finding and those of Kleffens et al. and Chadha et al. could have arisen from differences in the health insurance systems in the patients’ countries. Due to the national health insurance program that provides universal coverage in Taiwan, health care is highly accessible to all Taiwanese, thus minimizing the effect of economic factors on patients’ willingness to seek medical treatment.” That we did not observe a difference in treatment refusal rates between genders among Taiwanese patients is consistent with the idea that gender-associated economic factors play a role in the gender disparity in cancer treatment rates in Western countries.

2. **I will suggest that the factors which are not related to the results should not be discussed in this section (ex, p15). I will suggest either remove it or move into the introduction section.**
We appreciate this suggestion. We have removed the following information from the Discussion section as requested:” Huchcroft and Snodgrass also found that besides terminal-stage patients’ refusal of treatment, some of the treatment-refusing cancer patients refused to undergo advanced medical examination for cancer staging, and hence had unstaged disease [17]. In our study, a portion of the cancer patients also had undefined cancer stage; it is possible that these cases represent omissions by cancer registration personnel, but they may also include patients who chose not to undergo further examination for cancer staging.”

3. There is no discussion about the hospital characteristics here.

We appreciate this comment. We have added discussion on hospital characteristics in the Discussion section (p. 18 of the revised manuscript) as follows: “In the present study, our GEE-based regression modeling also uncovered the level of the diagnosing hospital to be a factor in treatment refusal, as colorectal cancer patients diagnosed at regional and district hospitals were significantly less likely to undergo treatment. Therefore, we suggest that physicians at lower-level hospitals refer their patients to medical centers for second opinions and encourage the patients to actively seek treatment.”

Because hospital characteristics were not important variables for survival analysis among treatment-refusing patients, we simultaneously controlled for hospital level and hospital ownership type in the Cox proportional hazards model when performing the analysis presented in Tables 3 and 4. To reflect this fact, we have added the following to the footnotes of Tables 3 and 4: "controlled for level of diagnosing hospital and ownership type of diagnosing hospital.”

Conclusion section

I thought Conclusion section is not covered well here. The first paragraph is not a real conclusion. And the authors can add more useful information in conclusion section.

We appreciate this suggestion. Accordingly, the following information has been added to the Conclusion section (p. 22 of the revised manuscript): “Our results show a lower 5-year survival and a 2.66-fold increased risk of death for colorectal patients who refused treatment than for those who underwent treatment within 4 months. Therefore, we urge newly diagnosed cancer patients to actively seek treatment in order to enhance their chances of survival.” We have also adjusted the content of conclusion section.