Author's response to reviews

Title: Clinical implications of thymidylate synthetase, dihydropyrimidine dehydrogenase and orotate phosphoribosyl transferase activity levels in colorectal carcinoma following radical resection and administration of adjuvant 5-FU chemotherapy

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Author's response to reviews:

Dr Annabel Phillips
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Clinical implications of thymidylate synthetase, dihydropyrimidine dehydrogenase and orotate phosphoribosyl transferase activity levels in colorectal carcinoma following radical resection and administration of adjuvant 5-FU chemotherapy

Masashi Ishikawa, Toshihiro Ichimori, Akihiro Sakata, Takayuki Miyauchi and Yutaka Kashiwagi

Dear Dr Annabel Phillips,

Thank you for your E-mail. The comments of a reviewer have been helpful in allowing us to revise our manuscript. We checked some mistakes and have attempted to address the questions raised by reviewers according to the following. We are enclosing the new manuscript entitled "Clinical implications of thymidylate synthetase, dihydropyrimidine dehydrogenase and orotate phosphoribosyl transferase activity levels in colorectal carcinoma following radical resection and administration of adjuvant 5-FU chemotherapy" for consideration as a publication in "BMC CANCER."

Thank you for your consideration of the revised version.

We appreciate your review of this work.
Sincerely,

Masashi Ishikawa MD Ph.D.
Department of Surgery
Tokushima RedCross Hospital

Reviewer:

Major
1) Discussion were shortened extensively and rewritten carefully, by deleting general statement of enzymes. The number of words in Discussion were shortened from 917 words to 848 words. Some statement was removed.
(P11,12,) In order to discuss the different methods, the following sentences were added. P11,L20-P12L7 (The disparate conclusions reached regarding role of TS, DPD and OPRT in colorectal tumors may be explained by the different methodologies. The optimal method of assessing TS, DPD and OPRT expression is unclear, but current methods include immunohistochemistry (IHC), reverse transcriptase polymerase chain reaction (RT-PCR) and enzyme activity assay. The most common technique used for survival analysis is IHC, which determines qualitatively protein quantity based on intensity of immunostaining but is difficult to standardize and cannot provide a measure of enzyme activity. RT-PCR allows for measuring marker expression in a highly sensitive manner but needs technical skill and fresh sample, and also cannot determine levels of enzyme protein nor activity. We chose to assay enzyme activity because this method not only provides an estimate of the absolute intracellular content, but also allows the measurement of the level of enzyme functionality, although a potential drawback is decreased enzyme activity due to protein instability.)
Furthermore, regarding the meaning of OPRT activity, the following sentences were added. P12,L15-P12L23 (Similar to our findings, Ichikawa14) and Fujii8) have also reported a correlation between low OPRT expression and worse prognoses or decreased responses to chemotherapy. The increased expression of these enzymes may promote proliferation of cancerous cells via increased pyrimidine nucleotide biosynthesis. In particular, biosynthesis of nucleic acid via increased salvage synthesis is thought to be closely connected to tumor growth. Using combined OPRT and TS quantitation, we are able to identify a subgroup of Dukes\textsuperscript{C} B or C patients with a high recurrence rate and a low disease-specific survival although this study was not performed in patients with surgery alone.)

Minor
Missing labels on figures, the wrong use of a term and mistype were revised as a reviewer pointed out. I copyedited the manuscript to improve the style of written English.
The sentences or words which were repetition were deleted.