Author's response to reviews

Title: Tumor Budding as a Risk Factor of Lymph Node Metastasis in Submucosal Invasive T1 Colorectal Carcinoma: a retrospective study

Authors:

Bong-Hyeon Kye (ggbong@catholic.ac.kr)
Ji-Han Jung (apjjh225@catholic.ac.kr)
Hyung-Jin Kim (hj@catholic.ac.kr)
Se-Goo Kang (neokans@catholic.ac.kr)
Hyeon-Min Cho (hmcho@catholic.ac.kr)
Jun-Gi Kim (jgkim@catholic.ac.kr)

Version: 2 Date: 5 June 2012

Author's response to reviews: see over
Reviewer's report

Title: Tumor Budding as a Risk Factor of Lymph Node Metastasis in Submucosal Invasive T1 Colorectal Carcinoma: a retrospective study

Version: 1 Date: 18 February 2012

Reviewer: Frank Pfeffer

Reviewer's report:

The present study deals with the question if tumour budding is a risk factor of lymph node metastasis in T1 colorectal cancer.

To clarify this question, the authors perform a retrospective analysis of 55 patients who underwent curative radical resection. Data for tumour budding an other risk factors are available in 44 patients.

As the main result, the authors found lymph node metastasis in eight patients (14.5%). Analyzing their data by univariate (p=0.047) and multivariate analysis (p=0.042) the authors conclude that tumour budding was an independent factor for predicting lymph node metastasis.

This is a well-written manuscript and the question of risk factors for lymph node metastasis in T1 colorectal cancer is of ongoing interest and clinical importance. However, I have some concerns not allowing me to recommend this paper for publication in BMC Surgery.

1. The question posed by the authors is well defined.
   ➔ Thank you for your thorough review.

2. The method is not appropriate. This is a retrospective study with 55 patients. In eleven patients (20%) data regarding risk factors are missing. The number of 6 patients with lymph node metastasis is too small to perform appropriate statistical analysis.
   ➔ Thank you for your careful review. We agree with you. However, because lymph node metastasis rate in case with tumor budding was significantly higher than in without tumor budding, although there was a limitation caused by small number of case, we thought that tumor budding in T1 colorectal cancer may be regarded as an important risk factor.

3. The data are not sound. 15 patients with tumour budding had no lymph node metastasis. What does it mean?
   ➔ In this study, a positive predictive value of tumor budding for lymph node metastasis was 0.25. But, a negative predictive value was 0.958. We think that a high negative predictive value may be more important than positive predictive value for clinician in order to decide whether an additional radical resection after local excision or
Colonoscopic excision for submucosal invasive T1 colorectal cancer would be required or not.

Data for tumour size, circumference ratio, depth of invasion, Kudo`s classification are confusing. Is this effect of small sample size?

➔ Yes, we agree with you. In this study, risk factors for lymph node metastasis in T1 colorectal cancer which were reported previous studies were not statistically significant. However, we submitted our manuscript because the tumor budding in this study was significant risk factor and we thought that pathologic examination for tumor budding should be performed routinely after local excision or colonoscopic excision for submucosal invasive T1 colorectal cancer.

4. Percentages in table 1 are unclear and confusing. Percentages should be reported as percentage of the total group. Another opportunity to present the data could be logistic regression and odds ratio.

➔ Thank you. We corrected Table 1 as you commented.

5. The discussion and conclusion are well balanced. Some aspects are not highlighted. 75% of patients with tumour budding had no metastasis. It would have been interesting to discuss sensitivity, specificity, negative and positive predictive value of tumour budding. Although not appropriate due to small sample size, tumour budding seems to have a high sensitivity (83%), acceptable specificity (61%) and a high negative predictive value (0.96). If these results could be confirmed in a larger study, tumour budding seems to be a promising risk factor.

➔ We revised our manuscript as you mentioned above in results and discussion section.

But the discussion is not supported by the present data. In addition, the authors findings to other risk factors (tumour size, Kudo’s classification and depth of invasion) are discordant with previous reported data. The authors should discuss these discrepancies in findings.

➔ We think that the important reason was a small number of cases in this study. We revised our manuscript as you mentioned in methods discussion section.

6. The limitations are not clearly stated. The authors mention only missing data in 2 patients with lymph node metastasis.

➔ We revised our manuscript some limitations.

8. The title and abstract do not accurately convey what has been found. The title reveals tumour budding as risk factor, whereas the abstract is focusing on all risk factors although there is no statistical significance.

➔ We revised our manuscript as you mentioned in abstract section.

In summary: The minimal sample size of six patients with lymph node metastasis and available data to risk factors is too small to allow appropriate statistical analysis. The data could be presented as a series of individual cases.
Once again, we appreciate your meticulous review and expect to hear positive answer. Thank you.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests
Reviewer's report

Title: Tumor Budding as a Risk Factor of Lymph Node Metastasis in Submucosal Invasive T1 Colorectal Carcinoma: a retrospective study

Version: 1

Date: 18 February 2012

Reviewer: Ulrich Friedrich Wellner

Reviewer’s report:

The authors present a well-designed retrospective study aiming at identification of risk factors for lymph node metastasis in T1 colorectal cancer. The methodology, results and conclusions are acceptable. Tumor budding is a well-characterized risk factor in colorectal cancer as has been shown by many previous studies. The authors focus on the subgroup of T1 stage cancer.

I have one minor remark which is: given that in univariate analysis only tumor budding qualifies as a statistically significant risk factor, I feel there is no need for multivariate analysis with inclusion of other non-significant factors.

➤ Thank you for your thorough review. We performed multivariate analysis for searching that compared with other risk factors which have been already well known but were not statistically significant in this study, tumor budding was very meaningful risk factor

☐ Once again, we appreciate your meticulous review and expect to hear positive answer. Thank you.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

I declare that I have no competing interests