

REVISION WORKSHEET

We wish to thank reviewers for their helpful comments which were fully considered to improve the quality of the manuscript. English language has been revised by American Journal Experts as required and the certificate of English revision is provided with this submission.

Highlighted contents have been added and audio core tip as well.

REPLY TO REVIEWER 3669108 COMMENTS

I read a good article with a well designed study, a significant group of patients and an excellent statistics. I believe you can extract more conclusions from such a good study, but even now you wrote a very useful article.

We wish to thank the reviewer for nice comments to our manuscript.

REPLY TO REVIEWER 3478870 COMMENTS

The Dworak system is now widely applied on rectal cancer who had received preoperative radiochemotherapy with 5-FU/50Gy . However, the Dworak system described in late 90s based on a very small sample size. The most impressive sample size of 215 patients in this retrospective analyze was expected to improve the scientific nature of tumor regressive grade. The authors applied a simplified two-tiered system in order to more consistent with prognostic significance. The authors analyzed lots of clinical pathological variations factors which could correlated to the DFS, CSS and DFS/CSS.

1.The authors recommended careful histological examination is mandatory in order to exclude residual mucinous carcinoma. Consider the paper tried to clarify the relationship between clinical

pathological variations and the prognostic significance. In discussion part of the manuscript, this point is better to be highlighted.

1. Thank you for the comment. This aspect has now been more deeply discussed, as suggested.

2. The author also mentioned merely twice that T and/or N unchanging/upstaging was significantly more frequent in female patients. This is attractive for readers needed to be discussed in some extent, or the authors should delete the related contents.

2. Thank you for the comment. A short paragraph commenting on this finding has been included in the discussion section.

3. The tables are too complicate, especially table 1. I suggest the authors should be extensively simplified all tables. For instance, the contents of table2 have some overlap with the figure 3, and, the table 2 and the table 3 both have two “Dworak Regression grade”.

3. According to the suggestion, Tables 1 and 2 have been simplified by erasing data on univariate and multivariate analyses. Table 2 has been erased and information on recurrence has been put in Table 1. Statistical analyses had been performed twice: once considering acellular mucin pools separately from Dworak grade 4, and once considering them together with Dworak grade 4 tumors. We have now erased the former from the table.

4. Did all patients received the 5-fluorouracil? And according to the protocol in Modena center, the dose and schedule of the drug infusion?

4. Yes, all patients received 5-FU. Dose and schedule have been specified in the materials and methods section.

5. Although it is clearly an issue in any non-randomized study, cTNM and yTNM staging had been performed by using the different types of examination. What is the difference of them? CT and MRI and B-us?

5. yTNM staging was performed through the histopatological examination of the surgical specimen for T and N stage. On the other hand, CT and MRI scans were used for M stage. When resection of the metastatic tumor was possible, we also performed its histological analysis.

REPLY TO REVIEWER 2861643 COMMENTS

Dworak TRG grade is widely used in evaluating the effects of neoadjuvant therapy on rectal carcinoma. However, the inter-observer discordance does exist. The most interesting finding of this manuscript is the authors applied a simplified two-tiered system, which has prognostic significance and may also reduce the inter-observer discordance. The authors also put “careful histological examination is mandatory in order to exclude residual mucinous carcinoma” in their conclusion, however, this has been well known and their study did not add new evidence in this aspect. The tables are too complicate, especially table 2 and table3. I suggest the authors should better simplify them. In addition, table2 and table 3 both have two “Dworak Regression grade”, what is the difference?

According to the suggestion, Tables 1 and 2 have been simplified by erasing data on univariate and multivariate analyses. Table 2 has been erased and information on recurrence has been put in Table 1. Statistical analyses had been performed twice: once considering acellular mucin pools separately from Dworak grade 4, and once considering them together with Dworak grade 4 tumors. We have now erased the former from the table.

