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Responses to the reviewers' comments

Name of journal: World Journal of Gastroenterology

Manuscript No: 42847

Title: Nomograms for Predicting the Pathological Response to Neoadjuvant Treatments in Patients with Rectal Cancer

Authors: Dong-Lin Ren, Juan Li, Hui-Chuan Yu, Shao-Yong Peng, Wei-Da Lin, Xiao-Lin Wang, Roshan Ara Ghoorun, Yan-Xin Luo

Dear Reviewers,

Thank you for reviewing of our manuscript (ID: 42847). We appreciate your concerns and the suggestions you provided, and have revised our manuscript accordingly. At this time, we have resubmitted the revised MS through the Author Center, and we hope to have an opportunity to publish this paper in World Journal of Gastroenterology.

Please find the revised MS for your approval. In addition, a revised MS with corrected sections marked in red is attached as part of the supplemental material for easier editing and review purposes.

Below, please find our point-by-point responses to the comments.

Sincerely yours,

Reviewer 1

1. Pages are not numbered : difficult to point the comments

Reply:

Thank you for your thorough review and we apologize for the inconvenience you

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encountered when you reviewing the manuscript because the pages were not numbered. We have numbered the pages in the revised manuscript.

2. Introduction : NT has increased … sphincter preservation, …DFS… : this statement is not fully valid. No NT (even Sauer) has been able to improve sphincter preservation and in most the phase III DFS is not improved. This sentence must be modified.

Reply:

Thank you for your thorough review and we apologize for the inaccurate description. We have changed the expression in the revised manuscript.

Revision:

Page8, paragraph1

NT was reported to decrease the risk of local recurrence and have reduced toxicity[2, 3].

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3 Sauer R, Liersch T, Merkel S, Fietkau R, Hohenberger W, Hess C, Becker H, Raab HR, Villanueva MT, Witzigmann H, Wittekind C, Beissbarth T, Rodel C. Preoperative versus postoperative chemoradiotherapy for locally advanced rectal cancer: results of the German CAO/ARO/AIO-94 randomized phase III trial after a median follow-up of 11 years. *J Clin Oncol* 2012; 30(16): 1926-1933 [PMID: 22529255 DOI: 10.1200/JCO.2011.40.1836]

3. Patients … assessed by MRI or TR ultra sound: it is necessary to know exactly how

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many patients underwent MRI for staging ? MRI is the key image for staging especially for MRF; can you confirm that all patients underwent MRI and TR ultrasound.

Reply:

Thank you for your thorough review and we apologize for not providing sufficient information. All patients underwent MRI for staging and only about 44 (11%) patients underwent transrectal ultrasound (TRU), which has also been shown to be a good assessment of rectal cancer boundaries.

Revision:

Page 9, paragraph 2

All patients were assessed via abdominal-pelvic computed tomography (CT), and pelvic magnetic resonance imaging (MRI), and 44 (11%) patients received transrectal ultrasound testing.

4. Tumor length TL : this parameter appears of prognostic value; it is necessary to know how it was defined and how it was measured : endoscopy, DRE, MRI, EUS et c…??

Reply:

Thank you for your thorough review. Tumor length was measured using MRI image measurement to measure the maximum diameter of tumor.

Revision:

Page 9, paragraph 3

All tumor-related parameters such as cT, cN, MRF status, DTAV, and TCE were assessed by MRI. Tumor length was also measured by using MRI, to measure the maximum diameter of tumor. CT, transrectal ultrasound and endoscopy provided additional verification. Tumor differentiation was identified by enteroscopic pathology.

5. Therapy How many patients of this study were included in the FOWARC trial ?

Reply:

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Thank you for your interest in FOWARC trial and current study. 273 (67%) patients in our study were included in the FOWARC trial.

Revision:

Page 10, paragraph 2

Consequently, 273 patients (67.7%) in our study were included in the FOWARC trial.

6. de Gramont –RT : what was the dose of RT delivered in this protocol. Was this RT dose the same in mFOLFOX6 +RT ?

Reply:

Thank you for your thorough review. The radiation dose for radiotherapy was 46.0-50.4 Gy, delivered as 1.8-2.0 Gy/d during NT. The dose of RT are same in de Gramont –RT and mFOLFOX6 +RT groups.

Revision:

Page 10, paragraph 2

The radiation dose for the radiotherapy was 46.0-50.4 Gy, delivered as 1.8-2.0 Gy/d and the dose was the same in the capecitabine/deGramont-RT and mFOLFOX6-RT groups.

7. approximately 6-12 weeks later: this interval is very important as it has a strong influence on the yp TN staging. Six or 12 weeks makes a wide difference. It must be analyzed in more details. May be all the patients in mFolfox 6+RT are operated at 12 weeks and all the others at 6 weeks. This is a crucial point. This interval must be taken into account in multivariate analysis.

Reply:

Thank you for your critical comments. The interval between radiation and surgery is very important, we apologize for not including this in the analysis. This interval has now been accounted for in the analysis. The interval between radiation and surgery was

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6-12 weeks in mFolfox6+RT and de Gramont–RT groups. There is no significance difference between two groups. The interval between chemotherapy and TME radical surgery was about 2-4 weeks in mFolfox 6 group.

Reversion:

Page 10, paragraph 2

Method: Patients in the capecitabine/deGramont-RT and mFOLFOX6-RT groups underwent standard TME radical surgery after NT. The interval between radiation and surgery was 6-12 weeks in mFOLFOX6+RT and de Gramont –RT groups. The interval between chemotherapy and TME radical surgery was about 2-4 weeks in mFOLFOX6 group.

Page 12, paragraph 2

Result:

The interval between radiation and surgery was 52(47-59) days in mFOLFOX6+RT group and 54(49-58.25) days in de Gramont-RT group. There is no significance difference between two groups. The interval between chemotherapy and surgery was 22（18-25.75)days in mFOLFOX6 group, which is much shorter than the other two groups.

8. It is also necessary to know what means radical surgery: especially how many patients underwent APR or sphincter-saving surgery .

Reply:

Thank you for your thorough review. All patients received total mesorectal excision (TME) surgery (28 underwent APR and 375 underwent sphincter-saving surgery).

Revision:

Page 10, paragraph 2

Results

All patients received total mesorectal excision (TME) surgery (28 underwent APR

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and 375 underwent sphincter- saving surgery).

9. Results … were calculated to counting data … This wording is not clear. This statement should be written in a method chapter and not in results.

Reply:

Thank you for your thorough review. We have add this statement to the method section. This sentence means that parameters such as age, BMI , CEA, HB, NLR, DTAV and TL were used as dichotomized variables by cut-off values in previous studies.

Revision:

Page 11, paragraph 3

Method:

Parameters such as age (≤60y, >60y), BMI (<25kg/cm^2, ≥25kg/cm^2), CEA(>5ng/mL, ≤5ng/mL), HB (≤125g/L, >125g/L), NLR (>3, ≤3), DTAV(<5cm, ≥5cm) and TL (>3cm, ≤3cm) were dichotomized according to previous studies[24,29-30]. PLT, ApoA1, ApoB and the interval were used as continuous variables, however, all these variables were not normally distributed, so a nonparametric test was used.

REFERENCE

24 Kalady MF, de Campos-Lobato LF, Stocchi L, Geisler DP, Dietz D, Lavery IC, Fazio VW. Predictive factors of pathologic complete response after neoadjuvant chemoradiation for rectal cancer. *Ann Surg* 2009; 250(4): 582-589 [PMID: 19710605 DOI: 10.1097/SLA.0b013e3181b91e63]

29 **Restivo A**, Zorcolo L, Cocco IM, Manunza R, Margiani C, Marongiu L, Casula G. Elevated CEA levels and low distance of the tumor from the anal verge are predictors of incomplete response to chemoradiation in patients with rectal cancer. *Ann Surg Oncol* 2013; 20(3): 864-871 [PMID: 23010737 DOI: 10.1245/s10434-012-2669-8]

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30 **Berkel AE**, Woutersen DP, van der Palen J, Klaase JM. Prognostic factors for postoperative morbidity and tumour response after neoadjuvant chemoradiation followed by resection for rectal cancer. *J Gastrointest Surg* 2014; 18(9): 1648-1657 [PMID: 24939597 DOI: 10.1007/s11605-014-2559-4]

10. Table 1 It is an excellent table : pCR rate using mFOLFOX 6 + RT is 40.71%. in DENG Y Fowarc JCO 2016, the pCR rate was27.5%. Any explanation for this unusually high rate of 40% ???.

Reply:

Thank you for your critical address to make our study more convincible and reliable. That's absolutely an important issue. We went back to go through the original dataset generating from a consecutive collecting cohort of colorectal cancer patients, and we have to acknowledge that a potential selection bias may contribute to this high pCR rate. The data missing were more frequently in patients not reaching pCR than those with pCR, possibly resulting from more attentions pCR-patients got in clinical practice, follow up, or research work. We had to exclude the patients with missing data prior to the primary analysis. To eliminate this effect, we traced back the medical record and follow-up dataset of these patients, supplemented missing data, included these patients, and re-analyzed the new dataset with the same workflow in the first version of manuscript. The updated pCR rate using mFOLFOX 6 + RT is 35.7%. Of note, this pCR rate is in first quantile compared with the rates reported in previous publications, including FORWARC trial. It is expected since this is a single-center statistic result, while FORWARC trial is muli-center research. Importantly, it has been reported in more and more studies that the regimen combinded mFOLFOX 6 with RT is getting higher pCR

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rate, as high as 38% in a clinical trial on Lancet Oncology (Lancet Oncol. 2015 Aug;16(8):957-66). Therefore, we believe the updated dataset and results are reliable, convincible and representative for all the patients receiving treatment in our institute.

Revision:

Page 16, paragraph 1

In our model, the mFOLFOX6-RT group had a higher probability of pCR compared with the capecitabine /de Gramont-RT group. We acknowledge that a potential selection bias may contribute to this high pCR rate. The data missing were more frequently in patients not reaching pCR than those with pCR, possibly resulting from more attentions pCR-patients got in clinical practice, follow up, or research work. The pCR rate is 35.7% for mFOLFOX6-RT, which is higher than FOWARC[26, 27], It is expected since this is a single-center statistic result, while FORWARC trial is muli-center research. Though the benefits of oxaliplatin have not been demonstrated and it is not part of standard NT regimens, oxaliplatin is a standard component of chemotherapy for treating colon cancer.[35] Importantly, it has been reported in more and more studies [36,37] that the regimen combinded mFOLFOX 6 with RT is getting higher pCR rate, as high as 38% in a clinical trial on Lancet Oncology[38]. However, the role of oxaliplatin adding to fluorouracil-based neoadjuvant chemoradiotherapy is unclear for LARC patients, more studies are needed in the future.

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26 **Deng Y**, Chi P, Lan P, Wang L, Chen W, Cui L, Chen D, Cao J, Wei H, Peng X, Huang Z, Cai G, Zhao R, Xu L, Zhou H, Wei Y, Zhang H, Zheng J, Huang Y, Zhou Z, Cai Y, Kang L, Huang M, Peng J, Ren D, Wang

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J. Modified FOLFOX6 With or Without Radiation Versus Fluorouracil and Leucovorin With Radiation in Neoadjuvant Treatment of Locally Advanced Rectal Cancer: Initial Results of the Chinese FOWARC Multicenter, Open-Label, Randomized Three-Arm Phase III Trial. *J Clin Oncol* 2016; 34(27): 3300-3307

27 **Zhang J**, Cai Y, Hu H, Lan P, Wang L, Huang M, Kang L, Wu X, Wang H, Ling J, Xiao J, Wang J, Deng Y. Nomogram basing pre-treatment parameters predicting early response for locally advanced rectal cancer with neoadjuvant chemotherapy alone: a subgroup efficacy analysis of FOWARC study. *Oncotarget* 2016; 7(4): 5053-5062 [PMID: 26646794 PMCID: PMC4826265 DOI: 10.18632/oncotarget.6469]

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11. Rate of pCR : 13.19 and 12.24 are more in line with standard results. In Fowarc (DENg JCO 2016) with Folfox chemo alone pcR was 6.6% in the present paper it is 13.19 % (more than double!) any explanation??

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Reply:

Thank you for your critical address to make our study more convincible and reliable. The reasons are same with question 10. We acknowledge that a potential selection bias may contribute to this high pCR rate. The data missing were more frequently in patients not reaching pCR than those with pCR, possibly resulting from more attentions pCR-patients got in clinical practice, follow up, or research work. We had to exclude the patients with missing data prior to the primary analysis. To eliminate this effect, we traced back the medical record and follow-up dataset of these patients, supplemented missing data, included these patients, and re-analyzed the new dataset with the same workflow in the first version of manuscript. The updated pCR rate using mFOLFOX6 is 8.64%. Also, this is a single-center statistic result, while FORWARC trial is muli-center research. Therefore, we believe the updated dataset and results are reliable, convincible and representative for all the patients receiving treatment in our institute.

12. Discussion Excision or a "watch and see". This is incorrect it should be "watch and wait".To see and to watch is the same ! This must be modified in all the paper.

Reply: Thank you for your thorough review. This phrase was modified to "watch and wait" throughout the manuscript.

Revision:

Page 15, paragraph 2

Conversely, to accurately determine an excellent pathological response after NT, surgeons may choose to perform local excision or a **"watch and wait"** strategy.

pCR after NT is repotred to have an excellent long-term prognosis irrespective of

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the treatment strategy, so noninvasive treatment strategies, such as the **"watch and wait"** strategy.

Patients with well differented tumor have a higher pCR probability indicating that a mild NT regimen, local resection or **"watch and wait"** strategy can be considered after NT.

Page16, paragraph 3

For patients with a high probability of pCR after NT, local resection or a **"watch and wait"** strategy can be used to avoid complications.

Page19, paragraph 3

which patients need radical surgery, which patients can undergo local excision and which patients can be managed with a **"watch and wait"** strategy after achieving a good response, we need more studies in the future.

13. Type of NT regimen … predictors of pCR: as we ignore the interval for the 3 different NT regimen no conclusion is possible.

Reply:

Thank you for your thorough review. The interval between radiation and surgery is very important, we apologize for not including this in the analysis. This interval has now been accounted for in the analysis. The interval between radiation and surgery was 52（47-59) days in mFOLFOX6+RT group and 54（49-58.25) days in de Gramont-RT group. There is no significance difference between two groups. The interval between chemotherapy and surgery was 22（18-25.75)days in mFOLFOX6 group, which is much shorter than the other two groups.

Revision:

Page 14, paragraph 2

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Updated results

The nomogram for predicting pCR probability showed that NT regimen and tumor differentiation influenced the probability of pCR, followed by TL and MRF status(Figure 1). When developing the nomogram to predict the probability of good downstaging, tumor differentiation and MRF status were the most important, followed by cT(Figure 2). Because only one significant factor was found for the capecitabine/deGramont-RT regimen, but we could not develop a nomogram. MRF status and TL were the significant factors for the mFOLFOX6-RT group(Figure 3). For the mFOLFOX6 group, tumor differentiation and TL were the significant factors in the nomogram for predicting pCR probability (Figure 3).

14. FOLFOX6-RT higher rate of pCR : This consistent with Fowarc but not with the other phase III trials (STAR, ACCORD 12, RTOG, CAO/ARO, PETACC 6) in most trials adding oxaliplatin does not increase pCR rate. Oxaliplatin is not a potent radiosensitizer (Folkvord S Radioth Oncol 2008;86:428-34). In Rodel (CAO/ARO) no difference in R0 rate and sphincter preservation; pCR was increased with oxaliplatin but the 5FU regimen was different in the two arms. Common consensus belief is : oxaliplatin is not in rectal cancer a good radiosensitizer.

Reply:

Thank you for your thorough review. Though the benefits of oxaliplatin have not been demonstrated and it is not part of standard NT regimens, oxaliplatin is a standard component of chemotherapy for treating colon cancer. Importantly, it has been reported in more and more studies that the regimen combinded mFOLFOX 6 with RT is getting higher pCR rate, as high as 38% in a clinical trial on Lancet Oncology. The role of

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oxaliplatin adding to fluorouracil-based neoadjuvant chemoradiotherapy is unclear for LARC patients, more studies are needed in the future.

Revision:

Page16, paragraph 1

In our model, the mFOLFOX6-RT group had a higher probability of pCR compared with the capecitabine /de Gramont-RT group. We acknowledge that a potential selection bias may contribute to this high pCR rate. The data missing were more frequently in patients not reaching pCR than those with pCR, possibly resulting from more attentions pCR-patients got in clinical practice, follow up, or research work. The pCR rate is 35.7% for mFOLFOX6-RT , which is higher than FOWARC[26, 27], It is expected since this is a single-center statistic result, while FORWARC trial is muli-center research. Though the benefits of oxaliplatin have not been demonstrated and it is not part of standard NT regimens, oxaliplatin is a standard component of chemotherapy for treating colon cancer.[35] Importantly, it has been reported in more and more studies [36,37] that the regimen combinded mFOLFOX 6 with RT is getting higher pCR rate, as high as 38% in a clinical trial on Lancet Oncology[38]. However, the role of oxaliplatin adding to fluorouracil-based neoadjuvant chemoradiotherapy is unclear for LARC patients, more studies are needed in the future.

15. Tumor Length (TL) and CEA > 5 ng/ml are interesting findings. Main question is how to accurately measure tumor length!

Reply:

Thank you for your thorough review. Tumor length was measured using MRI image measurement to measure the maximum diameter of tumor.

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Revision:

Page 9, paragraph 2

All tumor-related parameters such as cT, cN, MRF status, DTAV, and TCE were assessed by MRI. Tumor length was measured using MRI image measurement to measure the maximum diameter of tumor. CT, transrectal ultrasound and endoscopy provided additional verification. Tumor differentiation was identified by enteroscopic pathology.

16. General comments on nomogram : The C index 70% is quite good but the 3 groups according to treatment have small number of patients and the power is not so strong. One single group of 300 patients would strengthen the index.

Reply:

Thank you for your thorough review. Yes, the number of patients per group was small, and we hope to have a larger number of patents to enhance the prediction accuracy in future studies.

17. Usually there is a test cohort and a second cohort for validation. Having such a validation external cohort would also probably strengthen the reliability of the nomogram.

Reply:

Thank you for your advice. In future studies, we plan to add a second external cohort for validation to strengthen the nomogram's reliability.

Reviewer 2

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1. The authors provide a study on an interesting topic, the response of rectal cancer to neoadjuvant chemoradiotherapy, using 3 regimens.

Reply:

We deeply appreciate your review and comments on our work, and thank you for your interest in our research.

2. The abstract is far too long, with too many redundant and repetitive words. It makes it hard to read for the usual reader because of the circumlocution.

Reply:

Thank you for your thorough review. We apologize for the long abstract and have shortened this section.

Revision:

Page 5-6

Abstract:

BACKGROUND

In recent decades, neoadjuvant therapy (NT) has been the standardized treatment for locally advanced rectal cancer (LARC). Approximately 8-35% of patients with LARC who received NT were reported to have achieved complete pathological response (pCR). If the pathological response can be accurately predicted, these patients may not need surgery. In addition, no response after NT implies that the tumor is destructive, resistant to both chemotherapy and radiotherapy, and prone to having a high metastatic potential.

Therefore, developing accurate models to predict pathological response (PR) has great clinical significance and can help to achieve individualized treatment in LARC patients.

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AIM:

To establish nomograms for predicting PR to different NT regimens based on pretreatment parameters for patients with LARC.

METHODS:

Rectal cancer patients were identified from the database of The Sixth Affiliated Hospital, Sun Yat-sen University, from Jan. 2012 to Dec. 2016. Logistic regression and nomograms were developed to predict the probability of pCR and good downstaging to ypT0-2N0M0 (ypTNM 0-I), respectively, based on pretreatment parameters for all LARC patients. Nomograms were also developed for three NT regimens (capecitabine/deGramont-RT, mFOLFOX6, and mFOLFOX6-RT) to predict pCR probability.

RESULTS:

Four hundred three patients were included in this study; 72 (17.9%) had pCR at the final pathology report, and 177 (43.9%) achieved good downstaging to ypT0-2N0M0 (ypTNM 0-I). The nomogram for predicting pCR probability showed that NT regimens, tumor differentiation, mesorectal fascia (MRF) status and tumor length significantly influenced pCR probability. When predicting the probability of good downstaging, tumor differentiation mesorectal fascia (MRF) status and clinical T stage were the significant factors. Nomograms were developed based on NT regimens. For the capecitabine/de Gramont-RT group, the multivariate analysis showed that the neutrophil-lymphocyte ratio (NLR) was the only significant factor, thus we could not develop a nomogram for this regimen. For the mFOLFOX6-RT group, the analysis showed that the significant factors were tumor length and mesorectal fascia (MRF) status; and for the mFOLFOX6

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group, the significant factors were tumor length and tumor differentiation.

CONLUSION:

We established accurate nomograms for predicting the PR to preoperative NT regimens based on pretreatment parameters for LARC patients.

3. First time RT is mentioned in abstract there is no full-word version.

Reply:

Thank you for your thorough review that we have we have now defined RT at its first mention.

Revision:

Page 8, paragraph 1

In recent decades, **neoadjuvant therapy (NT)** has been the standardized treatment for locally advanced rectal cancer (LARC).

4. Colorectal surgeons want to know the clinical relevance of these nomograms, not just predictive %.

Reply:

Thank you very much for your advice; we have placed more emphasis on how colorectal surgeons can use the nomogram in their clinical work.

Revision:

Page 18, paragraph 4

These models can be used to assist with individualized therapy, as follows. For LARC patients expected to have a poor pathological response, NT and NT-related harm can be avoided. For patients expected to have a good pathological responses to

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chemotherapy alone, radiotherapy can be avoided. For patients who are not expected to have good pathological response from a standard NT regimen, an enhanced mFOFOLX6-RT regimen can be considered. For patients with a high probability of pCR after NT, local resection or a "watch and wait" strategy can be used to avoid complications.

5. How do the researchers intend to use this data in the future? I appreciate that in the last paragraph of the discussion they say more studies are needed, BUT, can they state a hypothesis please for a future study based on their present data.

Reply:

Thank you very much for your advice. In the future, we plan to include more patients to enhance the prediction accuracy. We also plan to add a second external cohort for validation to strengthen the nomogram's reliability.

6. Much of the writing that is in the first person e.g. 'we developed' and 'we collected' are better as 'were…' and 'was' and placed after the action or noun. E.g. logistic regression was performed.

Reply:

Thank you very much for your advice. These expressions have been revised throughout.

Revision:

Page 6, paragraph 1

Nomograms were developed based on NT regimens.

Page 23, paragraph 6

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Nomograms were developed based on the significant factors in the multivariate logistic regression analysis.

7. Introduction: good Results, page 9, para 3, Table 8 shows, NOT 'showed'

Reply: Thank you very much for your careful review. These expressions have been revised on page 9, paragraph 3, and Table 8.

Revision:

Page 13, paragraph 3

Table 8 shows TL and MRF status were significant factors predicting pCR probability in the univariate analysis of the mFOLFOX6-RT regimen.