Dear Editor,

We would like to answer Reviwers's question about our article Manuscript NO: 35768

(Neoadjuvant hyperfractionated accelerated radiotherapy plus concomitant chemotherapy in locally advanced rectal cancer: a phase II study)

We have enlighted the answers with yellow marker in the main text.

Reviwer (03094792) 1;

Question 1:

In Table 1, you should include the estadio And specify the T and N parameters together. For example, knowing the percentage of T2N0 and T3N0 gives great information about the characteristics of the analyzed series.

Answer 1:

The table has been changed accorting to recommendation.

Question 2: "Positive margins have been found in two patients (6.6%)." You should include the number of cases in which the mesorectal fascia was involved in MR staging. And contrast this information with the state of the surgical margins. "In our study, radial surgical margin positivity was 7%" It would be a great contribution to the discussion if you included the relation of the appreciated local recurrences and the state of the resection margins. "Therefore, a biological effective dose (BED) formula was used for dose calculations instead of the given dose, according to a time-corrected linear quadratic model [30-31]." It would be interesting to specify in the text the BED of the scheme you used and compare it with the BED of the standard schemes. "The ongoing Stockholm III study is expected to shed some light on the effects of the timing of surgery [35]" This study is already published and you can refer to its results. "Surgical margin seems to be the most important factor for local recurrence [36]. " For this reason you should provide the status of the mesorectal fascia in the staging MR.

Reviwer (03094792) Answer 2.

The relation between local recurrences and surgical margins has been added to discussion part. Newly added Table 5 has all the answers for BED schemes. Stockholm study has been updated from 2010 to 2015.Limitian of stocholm III study is in that study, 21.5 and 23.9% of the patients had upper rectal lesions rather than infraperitoneal location. On the other hand, only infraperitoneal and unresectable patients were included in our study. Stockholm III trial had equal rates of CRM

positivity in both arms, although overall survival data were lacking (Pettersson et al. 2015). Answer has been enlighted with yellow marker in the text

Reviewer (02411100)3:

Question 1:

This is a very small group of patients with limited follow up – this is a major limitation that should be discussed in the discussion section.

Answer 1: This is a phase II study and studying safety and toxicity. Follow-up is five year. When we look the all rectal cancer studies, five year is very good follow-up especially in phase II studies.

Question 2: Suggest to change a part of the title from "concomitant chemotherapy" to concomitant 5fu infusion"

Answer 2: We are pleased to change concomitant chemotherapy" to concomitant 5- FU infusion"

Question 3. In the introduction, you state that " In randomized studies, local-regional recurrence despite mesorectal resection has been reported to occur in 15 to 30% of the patients undergoing surgery alone [3-8]." This statement is based on old data. Currently the rate of local recurrence without neoadjuvant radiotherapy for stage 2-3 rectal cancer averages 10%. (the Dutch trial and others)

Answer 3: Reviwer 02411100's comment is true but Dutch study was done between 1996 and 1999, including 30% extraperitoneal disease(12-15 cm) and mostly 59% stage I and II could not be compare to our group

Question 4. There is a growing evidence that T3 rectal cancer with large circumferential margins (CRM) can be spared the preoperative treatment. Preoperative CRM is evaluated with MRI. It would be interesting to know how many patients in your group had T3N0 with a preoperative MRI evaluation of CRM > 2 mm and what was their long-term outcome.

Answer 4: Table 1 shows the clinical stage of our patients.Preoperative clinical stage results is N2 positive 50%;43% N1 positive totaly 93%. Because of lymph positiveness we did not consider first line surgery.These group has been defined locally advanced . There were only 2 patients staged as T3N0 and preoperative MRI evaluation and long - term results has been added to results part.

Question 5. In your very small series and limited follow up, one patient, (3.3%) had local recurrence. This rate is comparable to known data from larger studies with larger follow up time that evaluated preoperative radiotherapy without concomitant chemotherapy (5% local recurrence in the Dutch study). Thus, you cannot state, as you stated in your conclusions, that your protocol achieves better local control.

Answer 5:

Median follow up is 60 months and it this follow up time is enough for all rectum studies. .

Question 6. You have shown to achieve a 52% of complete or near-complete pathological response (which is a nice percentage). However, you did not report whether this was translated into a better disease-free and overall survival. Please report on the disease-free and over all survival of patients with complete or near-complete pathological response compared to patients with less favorable pathological response. If the 52% was not translated into better long-term outcome coupled with the fact that you did not show a better local control than standard preoperative radiotherapy (comment no. 5), It wouldn't be accurate to state that your results are "encouraging".

Answer 6:

This study is phase II and we did not think to write PCR. In our study Randomised Istanbul R01 we have shown that pathological complete response did not effect survival. This phase II small study is hard to interpretation of traslated to overall survival. Petrelli JGO 2017 2017;8(1):39-48 showed **pCR is not surrogate marker. We included DFS and OS for 2 groups and find similar results with randomised İstanbul R01 study.**

Question 7. In the 3rd line of the discussion, I believe that the word "adjuvant" was a grammatical mistake and should be changed to "neoadjuvant"

Answer 7

We have changed the word adjuvant to neoadjuvant.

Reviwer 3 (00739752)

Questions 1: In the abstract, in the conclusions word of the end of the first sentence (and) must be remove.

Answer 1: The Word ‘’and’’ has been removed.