Author’s response to reviews

Title: Standard (8 weeks) vs long (12 weeks) Timing to Minimally-Invasive Surgery after NeoAdjuvant Chemoradiotherapy for Rectal cancer: a multicenter randomized controlled parallel group trial (TiMiSNAR). Protocol paper.

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Reviewer 1:

1) MRI treatment response is a major endpoint. How will the investigators ensure reliability of the assessments? There is no description of central review.

All MRI exams are collected and sent to the Promoting Center for final revision by a well-trained Pelvic MRI expert radiologist. Every participating center must fill in a structured MRI form according to the facsimile provided by the ESGAR (European Society of Gastrointestinal and Abdominal Radiology).

I’ve added this sentence in the MRI section.


2) Why is IMRT required? The need for IMRT for rectal cancer has not been demonstrated. Please explain this decision.

Several studies have compared IMRT of rectal cancer to 3D Conformal Radiotherapy. Although results from comparative randomized clinical trial are not available yet, IMRT is usually
associated with less dose to organ at risk, such as urinary bladder, small bowel and anal sphincters (in selected cases). This is translated into better clinical outcomes, in terms of gastrointestinal toxicity, genitourinary toxicity and skin side effects. On the other hand, this technique allows to deliver dose escalated RT, using a concomitant simultaneous integrated boost (SIB) to the gross tumor volume to a total dose of 55 Gy. Literature data suggesting that this IMRT escalated dose is well tolerated and resulting in a high rate of pCR.

Considering these data, after the multicentric evaluation by different Ethical Commettee, we decide to enroll in our trial only patients treated with this technique, suggesting the dose escalated RT, to optimize the safety and the efficacy of treatment.

I specify these consideration in the materials and methods section and added references.


3) Please explain rationale for encouraging ICG. Again, no proven benefit. Seems it does not contribute to the research question.

Several studies have shown that ICG test could reduce anastomotic leakage and thus postoperative complications, that are important in light of the secondary endpoints. A recent systematic review and meta-analysis by Blanco-Colino et al. has shown that “ICG fluorescence imaging seems to reduce AL rates following colorectal surgery for cancer…Large well-designed RCTs are needed to provide evidence for its routine use in colorectal surgery.” Our trial could be one of the requested RCT that could demonstrate the efficacy of ICG in rectal cancer surgery.
I’ve added this specification in the surgery section and replaced the term “encouraged” with “suggested”.


4) Please describe the futility rules in more detail—perhaps a table may be helpful here.

In the sample size section test for futility rules has already been specified. “The conservative Haybittle-Peto [23] boundary will be used as a stopping guidance in order to perform the final analysis at the significance level of 4.9%, two sides.”

5) The authors indicate block randomization but provide limited detail about the blocks nor how they will balance between TaTME and traditional robotic/laparoscopic, apr vs LAR, etc—particularly in light of the secondary endpoints.

The primary endpoint of the study is the pCR. Stratification of surgical technique is not useful or mandatory in this trial. After consulting of the Ethical Committee, it has been suggested not to insert a stratification. Block randomization assures that both the two groups are well-balanced for the timing of surgery.

Reviewer 2

1. This article describes the results of an ongoing trial.

No. It’s a draft of an ongoing trial.

2. First you could discuss how important and relevant this ongoing trial is? In my view it is not particularly important to explore the rates of pCR.

In the last years several studies confirmed the correlation between the pathologic response after neoadjuvant RT-CT and overall survival and progression free-survival. Recently, published results of randomized Stockholm III trial confirmed that a complete tumor response is associated with superior OS [Erlandsson J et al. Radiotherapy Oncology, 2019]. Meta-analysis by Kong JC et al [ Colorectal Disease, 2018] showed that “the degree of TRG was of prognostic value in predicting long-terms outcomes” and confirmed that “the current challenge is the development of a high- validity tests to predict pCR”.

More recently, another systematic review and meta-analysis of 21 studies by Wan T et al [Ann Surg Oncol, 2019] analized the prognostic value of pCR after neoadjuvant therapy for digestive cancer. The authors confirmed that pCR is correlated with favorable survival outcomes compared with a non pCR for digestive cancer patients after neoadjuvant treatment, including rectal cancer patients.
On the other hand, in the last years an increasing number of studies analyzed the role of MRI to predict the pCR. Recently, Cui Y et al [Eur Radiol, 2019] confirmed that a radiomics analysis of MRI images could predict pCR in patients with rectal cancer, but further prospective trials are needed to confirm this suggestions.

Our trial will investigate the role of surgical timing to improve the pCR rate and will evaluate the effective predictive role of MRI.

3. As actually said in the manuscript, all cell killing occurs at the time of radiation and thus, any delay cannot improve the results beyond pCR.

It is reported in the manuscript that effects of radiation therapy still occur after several weeks from the treatment: “These results may be explained on the relationship between radiation therapy and tumor regression: DNA damage occurs during irradiation, but cellular lysis occurs within the next weeks [10]. A recent pilot study on comparison of resonance imaging and histopathological responses at two times, has suggested that volume reduction and down-staging occur between week 9 and week 14 after neoadjuvant treatment, with a 23% pCR rate at longer time [11].”

4. The second aspect to discuss is if this manuscript is properly written. In my view it is not. Many references are improper and the language is not stringent.

A language editing has been performed. No references are improper, but a more stringent reading of the manuscript could help in confirming what I wrote.

5. In the Background, the first reference which I haven't read describes results that are not present in any Western world environment today. Locally recurrence rates about 50% and survival rates of 30% are not seen any longer.

In the background, as stated before, it is described a historical pathway of the rectal cancer treatment. So this observation is futile.

6. The second sentence describes the German pre- versus postoperative trial where chemoradiotherapy was given not only chemotherapy. What about improved local recurrence rates to 7% from what? It is not proper to mix the Stockholm III trial that tested immediate surgery versus delayed surgery against the other trials that compared different time intervals, all allowing downstaging or downsizing.

The rationale of our trial is specified in the introduction and in the previous answers. In the background section we illustrated the historical role of radiotherapy associated with chemotherapy in the treatment of rectal cancer, in adjuvant and neoadjuvant setting. We further cited principal trial on long course RT-CT and short- course RT, to show the importance of surgical timing in the treatment of rectal cancer. The purpose of manuscript introduction is not to compare results of these different studies, or to suggest superiority of one study to another one, but to highlight the need of further prospective studies to investigate the impact of delayed surgery on pCR and to evaluate the prognostic value of MRI.
7. When giving reference to GRECCAR-6, it is stated that no impact on technical performance was seen. If I read the paper properly that was just what was reported. Further down absence of randomization but Stockholm III was a randomized trial.

Stockholm III trial is on short course RT. This is a RCT on LONG-COURSE RT. Stockholm III trial however is of a relevant importance, so I’ve cited it into the text.

I report the conclusion of the abstract of GRECCAR-6: “Conclusion: Waiting 11 weeks after RCT did not increase the rate of pCR after surgical resection.”

This is the sentence extracted from the backgound section of the manuscript: “Conversely, several reports have shown no impact of the interval after chemoradiation on pCR and technical performance”. The first part of the sentence refers to the GRECCAR-6 while the second part refers to the STARRCAT trial.

The main concern of the GRECCAR is that about 20% of the patient were treated by open surgery, so it could be of no significtive importance their conclusion on surgical technique.

8. It is discussed that delayed surgery may delay the start of adjuvant chemotherapy, but nothing is said in the manuscript about whether adjuvant chemotherapy should be provided or not. What actually is NOS scale? The very last sentence in the Background is not possible to understand.

Patients will be candidate for adjuvant chemotherapy according to the national and international guidelines and after multidisciplinary evaluation. NOS Scale is the Newcastle-Ottawa Scale, In statistics, the Newcastle–Ottawa scale is a tool used for assessing the quality of non-randomized studies included in a systematic review and/or meta-analyses. But it refers to a sentence referring a meta-analysis, not to the current manuscript. NOS Abbreviation has been specified in the list of abbreviation.

The very last sentence in the Background is not possible to understand: a deep reading of the sentence and of the whole manuscript might have avoided some personal opinions from this reviewer.

9. Stratification is unclear. Or is it meant that substaging should be performed?

There is no stratification. For what???

10. Another sentence further down at page 8 is also difficult to understand. It starts with "Due to the nature of intervention…".

So...blind randomization is not possible as patients will underwent surgery, so patients need to be informed about the surgical approach, and allocation cannot be discussed but accepted. What is so difficult to understand?
11. When is capecitabine given, every day during the treatment or every irradiated day?

Every day, as usually.

12. The Discussion is not much of a discussion. The whole first paragraph is a repetition of an earlier paragraph.

This is a trial draft not a manuscript with result. Discussion is a preface to further preliminary results that will be published afterwards.

13. In the Discussion it is brought-up but that one of the goals is to determine whether MRI can be used to evaluate response, but nothing is said about that earlier.

There is a complete description of the importance of MRI in rectal cancer evaluation before and after neoadjuvant treatment and a paragraph dedicated to.

14. This study will not change the current pathway of the treatment for patients with mostly intermediate and some locally advanced rectal cancers.

This is a personal opinion. We didn’t suppose that this manuscript would change the pathway of the treatment for rectal cancer but can assess some key-points, thus being a potential milestone in the treatment for rectal cancer.