Peer Review File

Article information: http://dx.doi.org/10.21037/atm-20-1278

Reviewer A

This was an interesting paper that examined the effect of post-operative chemotherapy in patients who had already had pre-operative chemoradiotherapy for advanced rectal cancer. The study suggested that post-operative chemotherapy did not improve outcome.
The paper is generally well written, although it was confusing in parts, particularly in the abstract. For this reason it would benefit from proof reading by a natural English speaker.
My main concerns are:

1. This is a retrospective analysis, and the study has small numbers.

Reply: We thank the reviewer for the positive comments and valuable advice. We agreed that this is a retrospective analysis and the number of patients is relatively small. This limitation "Firstly, this is a single-center, retrospective study with a small number of patients." is added to the discussion part of the manuscript (line 283-284, page 15).

2. The patients were not randomly allocated to post-operative chemotherapy. Indeed it looks as though those patients who fared badly post-operatively (anastomotic leak, unwell, decided against chemotherapy) were the patients who comprised the non-chemotherapy group. For these reasons the data should be treated with caution, as the data are likely to be heavily skewed. The authors should include these limitations in their discussion.

Reply: Thank you very much for your suggestion. We agree the reviewers that the patients with non-chemotherapy have a higher chance of faring badly postoperative. This may cause the risk of bias when we compare the outcome between the non-chemotherapy and chemotherapy groups. This is already explained in the results part: "The incidence of anastomotic leakage in the non-chemo group was significantly higher than that in the chemo group (19.4% vs. 6.7%, P = 0.042) (Table 1)" (line 200-201, page 11), "The age of patients in the chemo group was significantly lower than that in the non-chemo group (55.6 ± 10.6 vs. 61.2 ± 10.4 years, P = 0.012)" (line 198-200, page 11). For these reasons, we add the following contents into the discussion part: "Secondly, some baseline characteristics, including age and anastomotic leakage, were different in the non-chemo and chemo groups. Thus, multivariate analysis was utilized to avoid the possible bias" (line 285-288, page 15).

3. This study, at best, provides interesting data that could be used to test the hypothesis in a randomised fashion.

Reply: We thank the reviewer for the suggestions of randomised clinical trials. As our research is one retrospective study which may bring some limitation, multi-center prospective randomized clinical trials should be encouraged to validate our findings, provide higher evidence level and support its implementation into general clinical practice. The following content was added to the discussion part "As ypT0-2N0 patients represent a large proportion of patients with rectal cancer after neoadjuvant chemoradiotherapy, randomized clinical trials should be performed in the future."

4. Lastly, the majority of the discussion is a reprise of previous studies. The authors should try and abbreviate this, to concentrate more on the results of their own study e.g the limitations as discussed above.

Reply: Thank you very much for your advice. We agreed with the reviewer that the discussion can be shorter and focus on the results of our own results. The corresponding contents are adjusted in the discussion part (page 13-15).

Reviewer B

In this retrospective analysis, the authors evaluated the role of adjuvant chemotherapy in ypT0-2N0 patients after neoadjuvant chemoradiation. This is an important topic clinically in patients with rectal cancer with no specific guidelines. The study identified 121 patients, 91 of which received postoperative adjuvant chemotherapy (minimum 3 cycles), the other 30 patient received less than 3 cycles. Median follow-up time was 40.1 months with 5-year disease-free survival 79.1% vs 82.9%, P = 0.442 and overall survival 87.5% vs 78.2%, P = 0.667 in the chemo group and non-chemo group, respectively.
The authors also show that cT, preoperative chemo treatment, and number of retrieved lymph nodes were prognostic factors for DFS. In a multi-variant analysis cT4 was shown to be an independent risk factor for OS and DFS. In addition, the authors highlight improvement in DFS with preoperative consolidation chemotherapy with Capeox or FOLFOX after neoadjuvant chemoradiation.
Overall this is an important topic, despite that sample size is small and it is a single institutional retrospective study. It still provide data that is relevant to clinical practice and adds to previous published results. The manuscript is well written and clear except for minor grammatical and punctuation errors, the sciences is logical and the tables are clear.

Specific questions:

1. There are multiple inconsistency in the data reported. The abstract reflects 90 patients in the chemo group and 31 patient in the non-chemo group. However, the text (line 82) shows 91 patients receiving adjuvant chemotherapy after surgery and 30 patients without adjuvant chemotherapy. Also, the abstract description shows the 31 patients in the non-chemo group receiving less than 3 cycles, however as the text notes, the 30 patients who did not receive

chemotherapy 15 patients did not get adjuvant therapy because of favorable pathology, 8 patients were in poor performance status, 4 patients refused and 3 patient suffer from postoperative complication. The information is a bit conflicting and not very clear. It is important to clarify whether these patients did or did not receive chemotherapy, and what are the specification of each of the 2 cohorts.

Reply: We thank the reviewer for the positive comments and valuable advice. There were 90(74.4%) and 31(25.6%) patients in the chemo group and non-chemo group, respectively. The specification of the two cohorts were adjusted as "The adjuvant chemo group comprised 90 patients (74.4%) including: (i) oral capecitabine (n = 22); (ii) CapeOx (n = 59); (iii) FOLFOX (n = 9). The non-chemo group comprised 31 (25.6%) patients, including 8 patients who received fewer than 3 cycles of chemotherapy due to poor performance status, the other 23 patients in the non-chemo group did not receive adjuvant chemotherapy including 15 patients who had favorable pathology, 5 patients who refused chemotherapy, and 3 patients who experienced postoperative complications"(line 140-147, page 8-9).

2. 25 patients (20%) were treated with radiotherapy only, however, it is not clear in what arm where those patients. The data from table 1 does not reflect any patient receiving radiation only…

Reply: We thank the reviewer for the suggestions. We followed up the 25 patients mentioned in the original manuscript with radiotherapy only before operation again. After confirmation by the patient or family members, we found that these 25 patients took capecitabine orally while taking radiotherapy. These drugs were purchased outside the hospital, so there is no record in the hospital's medical system. And we delete the sentence "There were 25 patients treated with radiotherapy alone before surgery." in the results part.

3. Out of 90 patients 48 receive NCRT and 40 NCRT+chemo in the chemo cohort. In the non-chemo cohort 18 received NCRT and 13 received NCRT+chemo. It is clear that the addition of chemotherapy to radiation enhance local response as well as overall survival, therefore, it would be imperative to disclose what group/s these patients were in, as they are a significant number of the evaluated patients.

Reply: We agree with the reviewer that the number of combined therapy should be explained in each group. We add the following contents into the results part: "In the chemotherapy group(the chemo group), 48 patients underwent NCRT alone and 42 patients underwent combined chemotherapy. In the non-chemotherapy group (the non-chemo group), NCRT alone and combined chemotherapy was received by 18 and 13 patients, respectively" (line 128-131, page 8).

4. The text on line 122 showed 24 patients relapsed of which 3 were local recurrence and 21 were distance metastases. 19 cases of recurrence in the chemo group of which 16 cases were

distant metastases in 3 with pelvic recurrences. The comparative data in table 2 only shows recurrence in 17 patients. Again showing discrepancies in data reporting.

Reply: We thank the reviewer for the suggestions. During follow-up, a total of 24 patients relapsed, of which three were local recurrences, 21 were distant metastases, and the median relapse time was 37.5 (range, 5.3-113.1). However, in table 2, the relapse of 17 patients was the number within 5 years instead of during the whole follow up. To avoid confusion, the number of events at the time of five years involved in Table 2 has been deleted.

5. Table 2 last line adjuvant chemotherapy shows that 31 patient received adjuvant chemotherapy and 19 did not this is most likely an error.

Reply: We thank the reviewer for the suggestions and we acknowledge that this is an error in table 2. 90 patients received chemotherapy, and 31 patients did not .This number is corrected in the table 2 correspondingly.

6. The data was collected between 2010 and 2018 and clinical staging have significantly evolved. What was the modality for staging the patients clinically? Rectal MRIs versus EUS?

Reply: Thank you very much for your advice. For preoperative clinical staging assessment, we used pelvic enhanced MRI.

7. With regards to the authors conclusions that postoperative ypT0-2N0 patients did not benefit significantly from adjuvant chemotherapy, this may be misrepresented. This is a small single institute data with a control of 30 patients, who 50% of them did not receive chemotherapy due to favorable pathology.

Reply: We thank the reviewer for the advice. We acknowledge that this is a single-center retrospective study. According to the current guidelines, patients with locally advanced rectal cancer require chemotherapy after surgery, so there are few patients without chemotherapy after surgery. So the number of cases in the non-chemo group is small. 50% of these 31 patients did not received chemotherapy because of favourable pathology. And this limitation is indicated in the discussion part (line 283-289, page 15). The following contents about the randomized clinical trials was inserted into the discussion part as well: “As ypT0-2N0 patients represent a large proportion of patients with rectal cancer after neoadjuvant chemoradiotherapy, randomized clinical trials should be performed in the future”(line 289-291, page 15).

8. It is definitely reasonable that clinical staging is not as prognostic as pathological staging, however the CAO/ARO/AIO-94 Trial concluded that even in patient with good response to treatment, hence ypT1-2 had more than 20% of patients with residual lymph node metastases. Even in ypT0 treated with TME, the risk of lymph node positive disease or mesorectal deposits is as high as 12% (Stipa F et al. Ann Surg Oncol. 2004;11(2):187, Zmora O et al. Dis Colon Rectum. 2004;47(10):1607).

Reply: Thank you very much for the comments. We agreed that residual lymph nodes metastasis and tumor deposits will influence the prognosis. So our study only included patients with ypT0~2N0M0 stage, excluding patients with residual lymph node metastases and tumor deposits. The sentence “or (4) pathological results showed tumor deposits” was added to the exclusion criteria in the methods part.

9. The authors own data show that clinical T4 is an independent risk factor for DFS and OS. Data also highlights the importance of preoperative consolidation chemotherapy after NCRT, which was noted to improve DFS. A growing number of studies now reflect improved PCR rates with total neoadjuvant treatment.

Reply: There are now more and more studies showing that preoperative consolidation chemotherapy can increase the PCR rates, but whether consolidation chemotherapy can improve DFS was not the direct focus of these studies. Our study found that consolidation chemotherapy can improve patients' DFS as well. So we inserted the following contents into the discussion part “However, finding out if consolidation chemotherapy can improve DFS was not the direct focus of these studies” (line 279-281, page 15).