

Response to Reviewer 1:

Reviewer's code: 04761856

Conclusion: Major revision

Scientific Quality: Grade D (Fair)

Language Quality: Grade B (Minor language polishing)

This article is fairly well written with an interesting subject. Clinical experiences which this study based on seem valuable. However, contexts are generally too conclusive without suitable logic rationales, yielding several major issues to be solved. I can assume that the affiliation where authors work is a well-established one, and the skills and affections of surgeon are both quite strong. But I suggest that authors should be objective and discreet in academic field although they have excellent clinical experience and authorities. Major revisions Materials and method Statistics: "p<0.20 was considered to be significant." => I know that p-value based binary decisions should be careful especially for the studies with small case numbers. But I have never seen such approach, that consider significant p-value as <0.20 and proceed to do multivariate analysis. Well, if the authors mentioned p <0.1, I might have understand. But p <0.2 sounds strange. It somewhat looks like the authors choose the statistical method for your intended conclusion. Please explain sufficiently. Results "there were no grade IV or grade V postoperative complications." => You must investigate about complications in much more detail. This study is dealing with more intense surgery than that is commonly regarded as a standard. Intense therapy surely causes oncologic efficacy, but also worse complications. Standard treatment, including OP, CTx, RTx, is the treatment established in an optimized point between excessive complication and the best outcome. Grade 4 or 5 complications are extremely serious complication. At least the authors should investigate grade 3 complication rates, and also state which method you use for investigation (e.g. CTCAE). Discussion "If these pathological metastases had not been removed by LLND they may subsequently lead to local recurrence and

eventually mortality." => Are you sure? How can you say so conclusive? If you want to say like this, you need at least some references. Considering experiences as a clinical oncologist myself and academic evidences, 4 weeks interval after CCRT is established for adequate healing and to avoid delayed surgery, but not because the effect of CCRT is terminated within 4 weeks. Extrapolating from liver neoplasm, tumor response rate continued to rise until 1 year in recent studies after locoregional treatment including RTx. Hence, pathologically positive LNs after CCRT and surgery do not mean that will surely progress even to death. Of note, in your study, the pathologically positive LN rates were similar between patients underwent CCRT and no CCRT (41.3% vs 34.6%); however, we all know that adjuvant CCRT surely help the overall oncologic outcome, probably because they can control subclinical disease. Please deeply consider this advice and how can you upgrade your contexts throughout the manuscript. "In the 2-year follow up period, 2 (2.2%) patients developed local recurrence. Thus, our results suggest that there is an oncological benefit when performing LLND for patients with clinically suspected LLN metastasis after preoperative CRT. In addition, in the present study, after LLND 80.9% patients did not have systemic recurrence. Therefore, we believe that LLN metastasis can be regarded as locoregional disease rather than a systemic disease." => I can assume that you are quite confident about the oncologic outcome of your affiliation. Since this is an observational study, you should compare your oncologic outcomes with other comparative studies. You cannot conclude only with showing your excellent results. The whole paragraph "The performance of TME and LLND dates back to the 1970s when it was associated with favorable oncological results~": this paragraph should be adjusted. After further investigating the complication among your patients, please adjust the context by showing your result and compare with other studies quantitatively. The current paragraph is just a list of barely related studies. Minor revisions Abstract, background: wildly => widely Abstract, results: "TME and LLND was performed in patients who underwent NCRT with short axis (SA) of the lateral lymph node greater than 5mm and in patients without NCRT of the lateral lymph node SA greater than 10mm." => Difficult to understand meaning and structure of sentence. Please clarify. Introduction: "National Cancer

Center is the largest colorectal cancer treatment hospital in China and data from 89 consecutive patients" => Do you really need to say that you are working in 'the largest hospital'? It seems like a newspaper article, but not a scientific one. What does it mean for your academic result? It can probably make many reviewers feel negatively, that the authors can be overly conclusive having too much pride. Remove it or, if you still want to say that, prove it (e.g. annual number of cases, admission capacity...) Materials and method Patients: "(the short axis of the lymph node in the NCRT patient ≥ 5 mm or ≥ 10 mm without NCRT)." => is it grammatically correct? Treatment strategy: "For the most part, patients received a short-course radiotherapy for a total dose of 25Gy or received 5-fluorouracil-based NCRT, with a total dose of 45Gy or 50.4Gy before surgery." => what do you mean by, 'for the most part'? Please clarify. Treatment strategy: "For patients without NCRT, if the lateral swollen lymph nodes with a SA ≥ 10 mm, TME plus LLND would be performed." => Why those patients did not undergo NCRT? Discussion "we suggest routine LLND should be performed for patients with LLN short axis diameter greater than 5mm after NCRT." => too conclusive. Please reconsider after revision. "Next, the rectal cancer patients received either short-course or long-course radiotherapy, this might cause heterogeneity in the pathological outcomes of the lateral lymph nodes." => You only have 3 patients who underwent short CCRT. This small heterogeneity does not seem to be a limitation. Conclusion Please re-write conclusion after performed all the other revisions. English editing: I recommend a round of formal English editing by professional English editors. There are some errors, though not so many, and sentences difficult to be understood. By the way, Dr. Jun Yu graduated Gannan Univ. in China and achieved PhD degree in Japan. Is he a native English speaker?

Response:

Thank you very much for your detailed suggestions.

1. I have read one manuscript that takes variables $p < 0.20$ for further evaluation in a multivariate analysis. (DOI: 10.1245/s10434-015-4565-5. Epub 2015 Apr 21.) Since in this study, we have gained every risk factor's P-value and to make our manuscript more rigorous we deleted "p < 0.20 was considered to be significant".

2. In the manuscript, we investigated the complication rates according to the Clavien-Dindo classification, and we highlighted them in the manuscript, and table 2 shows the postoperative complications.
3. We admire and thankful for your share of experiences, we changed our discussion and made a citation. As follow" If these pathological metastases had not been removed by LLND they may subsequently lead to local recurrence[28](DOI: 10.1097/SLA.0000000000002212.) ~~and eventually mortality"~~
4. We add some comparative studies as citations to compare oncological outcomes. And we highlighted our results in the "The performance of TME and LLND dates back to the 1970s when it was associated with favorable oncological results~" paragraph.
5. We revised wildly to widely.
6. We revised "TME and LLND was performed in patients who underwent NCRT with short axis (SA) of the lateral lymph node greater than 5mm and in patients without NCRT of the lateral lymph node SA greater than 10mm" => "In the NCRT group, TME plus LLND was performed in patients with short axis (SA) of the lateral lymph node greater than 5mm; in the non-NCRT group, TME and LLND was performed in patients with SA of the lateral lymph node greater than 10mm".
7. We revised " National Cancer Center is the largest colorectal cancer treatment hospital in China and data from 89 consecutive patients with mid or low rectal cancer who underwent TME plus LLND were collected in this study to investigate the therapeutic effect of preoperative CRT on lateral lymph node (LLN) metastasis and identify the risk factors associated" to "We collected data from 89 consecutive patients with mid or low rectal cancer who underwent TME plus LLND in this study to investigate the therapeutic effect of preoperative CRT on lateral lymph node (LLN) metastasis and identify the risk factors associated "

8. As has been described before" In the NCRT group, TME plus LLND was performed in patients with short axis (SA) of the lateral lymph node greater than 5mm; in the non-NCRT group, TME and LLND was performed in patients with SA of the lateral lymph node greater than 10mm." We deleted "~~the short axis of the lymph node in the NCRT patient ≥ 5 mm or ≥ 10 mm without NCRT~~".
9. We revised "For the most part" to" In the NCRT group".
10. "For patients without NCRT, if the lateral swollen lymph nodes with a SA ≥ 10 mm, TME plus LLND would be performed." => Why those patients did not undergo NCRT? As I mentioned before, "Treatment strategies for each patient were determined by a multidisciplinary meeting and the patient's wishes". In a few patients, they refused to take NCRT due to personal reasons.
11. To make it less conclusive, we revise "we suggest routine LLND should be performed for patients with LLN short axis diameter greater than 5mm after NCRT" to "Since the LLN metastatic rate in NCRT patients can be as high as 41.3%, we suggest selective LLND should be performed".
12. We re-write the conclusion.
13. This manuscript was edited carefully by Joseph R. Habib, M.D. and Jun Yu, M.D.

Response to Reviewer 2:

Reviewer's code: 03664520

Conclusion: Major revision

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

This manuscript deals with an hot topic in rectal cancer treatment. It endorses a more aggressive surgical treatment when dealing with locally advanced mid and low rectal cancer. Nevertheless some issues should be addressed: Better define lateral lymph node dissection in the introduction. Please better define the methods: is it a retrospective observational study? If so, what for do patients had to sign a specific informed consent? If instead it was a prospective interventional study the CONSORT 2010 Statement should be applied instead of the STROBE statement. Why 26 patients with T3/4 or N1/2 were treated with TME plus LLND directly without receiving any NCRT ? Some results are reported referring to the 89 patients treated with LLND, some referring to the 63 patients that received NCRT. This confuses the interpretation of data. In the analysis of risk factors related to LLN metastasis after NCRT, the 3 patients who received a short course RT should be separated. The authors should better analyze the impact of NCRT on LLN metastasis by comparing the results of the two groups that received LLND: with or without NCRT. “In the 2-year follow up period, 2 (2.2%) patients developed local recurrence. Thus, our results suggest that there is an oncological benefit when performing LLND” Oncological benefit compared to what other data? “In addition, in the present study, after LLND 80.9% patients did not have systemic recurrence. Therefore, we believe that LLN metastasis can be regarded as locoregional disease rather than a systemic disease.” The follow up is too short to make this conclusion.

Response:

Thank you very much for your detailed suggestions.

1. We better defined the lateral lymph nodes according to the Japanese Classification of Colorectal, Appendiceal, and Anal Carcinoma: the 3d English Edition [Secondary Publication]. According to the Japanese Classification of Colorectal, Appendiceal, and Anal Carcinoma: the 3d English Edition, lateral lymph nodes are two groups of lymph nodes, one group along the internal iliac

arteries and the obturator vessels and nerves and the other along the common iliac external iliac and median sacral arteries.

2. This is a retrospective observational study. Patients signed informed consent before the surgery. And this study was approved by the IRB of Chinese Academy of Medical Sciences.
3. "Treatment strategies for each patient were determined by a multidisciplinary meeting and the patient's wishes". In a few patients, they refused to take NCRT due to personal reasons.
4. In this manuscript, all 89 patients underwent TME plus LLND, among them 63 underwent NCRT. This is described in the inclusion part.
5. Because of the small sample size, only 3 patients received the short course RT, we did not separate them from the other NCRT patients.
6. The main purpose of this manuscript is to demonstrate that NCRT cannot eradicate LN metastasis, selective LLND should be considered by surgeons. So we did not detailly analyze the impact of NCRT on LLN metastasis.
7. We have added some citations about the oncological results after rectal cancer surgery, and in the introduction part, we mentioned that the local recurrence after surgery is nearly 10%. So, we describe 2.2% is a satisfying result.
8. We realized this limitation and mentioned it at the end of the article.

Response to Reviewer 3:

Reviewer's code: 03036434

Conclusion: Accept (General priority)

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Thank you very much for giving me the opportunity to review and enjoy your manuscript. This is a single center retrospective study conducted in an high volume cancer center addressing an hot controversial topic : TME + LLND in mid and low rectal cancer. There are two strategy in WEst Countries and in East Countries especially in Korea and Japan. This paper contribute to present a balanced honestly results indicating selection creteria fo LLND.

Response:

Thank you very much for accepting our manuscript.

Answering Reviewer letter

Dear Reviewer and Editor,

Thank you very much for your efficient work in procession of our manuscript entitled "Selective Lateral Lymph Node Dissection After Neoadjuvant Chemoradiotherapy in Rectal Cancer" (Manuscript No: 54050). And we also really appreciate that the reviewer and editor spent time to review the manuscript, gave us precious advices and second chance to revise this manuscript to make it more rigorous and scientific.

We have carefully revised our paper based on the comments of reviewer, and the point-to-point responses to the reviewers' comments are presented below:

Comment 1:

This is the most important revision among my list, but you almost did nothing. What do you mean by, highlighting "Clavien-Dindo classification"? I asked you to re-assess complication including at least grade III, not only grade IV or V. Clavien Dindo classification also has grade III. Worse thing is, that the reference you added for Clavien Dindo classification is not an exact one (can you find complication table or scale in that manuscript?) This revision should be properly done again. Adding a complication table is **STRONGLY** recommended.

Response:

I appreciate this advice. Lateral lymph node dissection is more intense surgery, we should discuss and highlight the postoperative complications. After checking the medical records, we added a complication table as suggested. And we changed a citation that can better illustrate the Clavien Dindo classification (DOI:10.1097/01.sla.0000133083.54934.ae). We added this to the result section of the manuscript.

"Fifteen patients (16.8%) had postoperative complications reported after LLND (Table 3). According to the Clavien-Dindo classification, most of the patients developed to Grade II or Grade III complications, there were no grade IV or grade V postoperative

complications. Four (4.5%) patients suffered an anastomotic leakage, three of which received an ileostomy while the fourth recovered after conservative treatment. Two (15.4%) out of thirteen bilateral LLND patients were discharged from the hospital with an indwelling catheter due to urinary retention. In both cases, after four weeks of bladder training, the catheter was successfully removed. Tissue liquefaction occurred in three (3.4%) patients, after a careful dressing change, the wound finally healed well. Four (4.5%) patients had small bowel obstruction, and they all recovered with conservative medical treatment.”

Table 3. Postoperative complications (n=89)

Variables	Value (n %)
Anastomotic leakage	4 (4.5)
Urinary retention	2 (2.2)
Wound infection	3 (3.4)
Bowel obstruction	4 (4.5)
Lymphatic Leakage	1 (1.1)
Pelvic hemorrhage	1 (1.1)

Comment 2:

Do you really think this revision is solved? I told you that "adjust the context by SHOWING YOUR RESULT and COMPARE with other studies quantitatively. " please DO THAT as INDICATED. In direct words, your revision answer seems effortless and might be completed in less than an hour. I have never seen that revision answer is shorter than revision query itself. As I am telling you again, your study is talking about the more rigorous surgical method than current standard. Hence, comprehensive review of complication is CRUCIAL.

Response:

I am very sorry that we failed to correct this suggestion at the first time. As you wrote, the lateral lymph node dissection is a more rigorous surgical procedure, a

comprehensive review of the complication is crucial. After reviewing the relevant literature, we added the following paragraph to the manuscript.

“Laparoscopic lateral lymph node dissection for rectal cancer patients after neoadjuvant chemoradiotherapy is a challenging procedure because of the complicated anatomy of the pelvic sidewall. The JCOG0212 study showed that the operation time was significantly longer in the TME + LLND group compare with TME along group (360 min vs 254 min, $p < 0.0001$), and also the blood loss was significantly higher in the TME + LLND group (576 ml vs 337 ml, $p < 0.0001$). And the overall postoperative complication in the LLND + TME group is higher than that of TME along group, but without statistical difference (22% vs 16%, $p=0.007$).[31] In our study, the most common postoperative complications were anastomotic leakage (4.5%) and bowel obstruction (4.5%), and the overall postoperative complication rate was 16.8%, this proportion was similar with the previously reported study(18%).[32]”

As lateral lymph node dissection may influence the urinary functions, the urinary function was highlighted below. We added the following to the manuscript.

“Georgious *et al.* conducted a meta-analysis investigating the outcomes of an extended lymphadenectomy versus conventional surgery for rectal cancer. Their results suggested that LLND was associated with increased urinary and sexual dysfunction incidence, as one of its included studies suggested that the urinary retention happened in the LLND + TME and TME along group were 16% and 4%, respectively.” AND

“In our study, two (2.2%) patients experienced urinary retention, both received bilateral lymph node metastasis and after four weeks of bladder practice, their catheters were successfully removed. These acceptable functional results might be explained by the relatively mature nerve-preserving techniques in the laparoscopic rectal cancer surgeries.”

And because of the poor medical records, we did not study how LLND affects sexual functions, this was mentioned in the limitation part.

“Fourth, we did not study the effect of LLND on sexual functions because of poor medical records.”

Finally, thanks again for your time and work, your suggestions made my article more scientific.

Best regards,

Qian Liu

E-mail: fcwpumch@163.com

4-16-2020