

Dear Editor and reviewers:

Thank you very much for your kind letter of “75700-Notification on manuscript revision” on May 11, 2022.

We have seriously considered the reviewers' constructive comments and have made the corresponding changes in the revised manuscript which are highlighted in red in the paper. Point by point responses (in blue) to the reviewers' comments (in black) are listed below this letter. We hope the changes are satisfactory that we have a chance to publish the original article in the World Journal of Gastrointestinal Oncology. We are looking forward to hearing from you soon.

Thank you and best regards.

Sincerely yours,

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May 22, 2022.

Reply to the comments on 75700

Reviewer #1:

**Scientific Quality:** Grade C (Good)

**Language Quality:** Grade B (Minor language polishing)

**Conclusion:** Accept (General priority)

**Specific Comments to Authors:** Dear authors Thank you very much for your research and effort. The study has good design and the topic is new. The main concern, it is a retrospective study with a small number of patients in a single institute. So, the results are not universally reliable and can not be used as a reference. These are local results of your centre. The discussion section: You did not compare your results with the other studies and did not give explanation for any discrepancy in results.

**Reply:**

First of all, thank you very much for your recognition and encouragement of our research. And we thank you for pointing out the major limitation which also bothers us for a long time.

As mentioned above, this was a single retrospective study with small number of patients. However, our centre implements nearly 1200 cases of ESD each year including 430 cases of esophagus, 370 cases of stomach and 400 cases of colon, reaches the top level in domestic. Furthermore, the inclusion of our study was extremely rigid, only patients exceed the ESD relative indications and lose the opportunity of surgery can be enrolled. And the type of lesion must be protruding with no ulceration exist. On the basis of carrying out large number of ESD, we conduct some exploratory research on the treatment of selected ESCC patients. Clinicians perform EdR should be skilled in endoscopy therapy and must select patients strictly. The initial aim of our study was to remove the primary lesion, reduce tumor burden, and enhance the effect of CRT. This strategy was only a daring attempt, and the conclusions in our study need to be treated with caution.

As for the discussion section, we have made some changes and added discussion with discrepancies which are highlighted in red in the revised manuscript (Page 10, Line 25-30;

Page 11, Line 22-30; Page 12, Line 2-5).

Reviewer #2:

**Scientific Quality:** Grade D (Fair)

**Language Quality:** Grade B (Minor language polishing)

**Conclusion:** Rejection

**Specific Comments to Authors:** Dear Authors, I read with interest your paper. Really I' confused the purpose of the research. You remembered that only CRT therapy is indagated for advance inoperable esophageal squamous carcinoma. It sure is that the patients with CRT therapy have better results !!! Why submit the patients at the endoscopic debulking with possible complications ? ( bleending, esophageal stenosis , esophagealtracheal fistula). I think that it can be interesting compare two groups : debulking +CRT and CRT alone, to demonstrate the possible usefulness of debulking.

Reply:

We appreciate your acceptance of our manuscript review, and thank you for pointing out this issue.

Although dCRT is fairly safe for unresectable ESCC, this treatment does not show decent OS or PFS. As we described in the discussion part: Previous researches reported the 5-year OS of ESCC patients who received dCRT was only 20-30%, with a median survival of 14 months. Another randomized phase III trial enrolled 267 unresectable ESCC patients received dCRT showed a median PFS was merely 9.7 months. Besides, the incidence of local failure of dCRT was up to 50-70%, with worse life quality. Secondly, patients who receive dCRT always suffer complications such as hemorrhage, perforation, radiation esophagitis, pericarditis, pneumonia, and tracheal stenosis. It is reported that the rates of esophagealfistula in locally advanced ESCC patients who received dCRT are varied from 3.7% to 24%. Furthermore, in the clinical practice, there exist amount of inoperable patients unable to receive CRT either (contraindications of CRT). New alternative strategies are needed for those specific populations. As we all know, every brand new treatment should be improved by trial and error, and should not be strangled in the cradle by some complications. The initial aim of our study was to remove the primary lesion, reduce tumor burden, and enhance the effect of CRT. This strategy was

only a daring attempt, and we believe this treatment is workable for selected ESCC patients. However, it needs large number and long-term follow up studies to verify.

We couldn't agree more with your idea about compare two groups: debulking +CRT and CRT alone. However, our study was a retrospective research, and we selected patients that are refused to undergo surgery or dCRT. And this is one limitation of our research. The randomized comparative trial you designed is the direction we need to work on in the future.

Reviewer #3:

**Scientific Quality:** Grade C (Good)

**Language Quality:** Grade A (Priority publishing)

**Conclusion:** Minor revision

**Specific Comments to Authors:** Dear Authors Thank you for giving me the nice opportunity to read this article. It is interesting to introduce a novel therapy called endoscopic debulking resection (EdR) followed by additive chemoradiotherapy (CRT) and evaluate its efficacy and safety, however it should describe the following queries. 1. Page 6, Line4 in PATIENTS AND METHODS; A mixture of saline solution diluted with methylthionine chloride and epinephrine was injected into the fundus of the lesion, ->For the elevation of lesion in endoscopic resection such as ESD which are often performed for large esophageal lesion, hyaluronic acid is commonly used for its efficiency and persistency. Please describe your intention about this point. 2. Page7, Line 8 in PATIENTS AND METHODS; The tumor was removed with a snare by fragment resection. ->For the prevention of perforation and the correct histopathological examination of resected specimen, ESD technique are considered to be tried on a priority basis. Please describe your intension, too. 3. Page 7, Line1-6 in PATIENTS AND METHODS; Chemoradiotherapy As for chemotherapy regimens, There should be some description about the indication of each regimen to the cases, because these assignment should have great influence on the treatment result. 4. Page8, Line 1-10 in Results; Baseline characteristics These data should be listed in one figure of Flow diagram, to make it easier to read. 5. Page 8, Line 11-18 in Results; Baseline characteristic, Table1 Table 1 should also contain the number %: percentage in each data column for easier recognition of digit data in the sentences. 6. Page 8, Line 19 - Page 9 Line 6; Outcomes and AEs of EDR and CRT These complicated data should be also described in one Table, for more smooth comprehension.

[Reply:](#)

[We thank the reviewer for the manuscript reviewing and pointing out these issues.](#)

Question 1. Page 6, Line4 in PATIENTS AND METHODS; A mixture of saline solution diluted with methylthionine chloride and epinephrine was injected into the fundus of the

lesion, ->For the elevation of lesion in endoscopic resection such as ESD which are often performed for large esophageal lesion, hyaluronic acid is commonly used for its efficiency and persistency. Please describe your intention about this point.

Answer 1. As the lesion in our study always deep than SM2, it was difficult to create submucosal fluid cushion and lift the lesion completely. Sometimes, we added hyaluronic acid in the mixture for its efficiency and persistency. We have added this point in the revised manuscript (Page 6, Line 7-10).

Question 2. Page7, Line 8 in PATIENTS AND METHODS; The tumor was removed with a snare by fragment resection. ->For the prevention of perforation and the correct histopathological examination of resected specimen, ESD technique are considered to be tried on a priority basis. Please describe your intension, too.

Answer 2. ER has the advantage of being able to evaluate the actual depth of tumor invasion and the presence or absence of lymphovascular invasion using the resected specimen. ESD, as one of ER technologies, can provide en-bloc resection, is considered as the first option to treat superficial cancers. However, the lesion in our study was deeper than SM2 so that it can't be resected en-bloc. In the procedure of our study, we always dissect superficial muscle propria, and resect lesions by piecemeal. So, we called this therapy endoscopic debulking resection, intended to reduce or remove the primary tumor.

Question 3. Page 7, Line1-6 in PATIENTS AND METHODS; Chemoradiotherapy As for chemotherapy regimens, There should be some description about the indication of each regimen to the cases, because these assignment should have great influence on the treatment result.

Answer 3. The regimens of ESCC chemotherapy in our study was 5-fluorouracil (5-FU), plus cisplatin or nedaplatin or docetaxel. Each patient has different tolerance to the same drug, such as marrow suppression, vomiting, diarrhea, and etc. Clinicians will choose different drugs to decrease the side effects, but the drug mechanism is similar. As you suggested, we have list the regimens of patients in supplemental Table 1.

Table S 1. Type of addictive CRT

Chemotherapy regimen	N
cisplatin plus 5-FU	15
nedaplatin plus 5-FU	6
docetaxel plus 5-FU	7

Question 4. Page 8, Line 1-10 in Results; Baseline characteristics These data should be listed in one figure of Flow diagram, to make it easier to read.

Answer 4. We have added the flow diagram of the enrollment in the revised manuscript (Page 8, Line 5-6, Fig 2).

Question 5. Page 8, Line 11-18 in Results; Baseline characteristic, Table 1 Table 1 should also contain the number %: percentage in each data column for easier recognition of digit data in the sentences.

Answer 5. We have added the number % in the revised Table 1.

Question 6. Page 8, Line 19 - Page 9 Line 6; Outcomes and AEs of EdR and CRT These complicated data should be also described in one Table, for more smooth comprehension.

Answer 6. We have added one Table described the outcomes and AEs of EdR, CRT in the revised manuscript.

Table 2. Outcomes and AEs of EdR and CRT

Procedure details and outcomes of EdR	
Technical success (n, %)	
Success	41 (100%)
Failure	0 (0%)
R0 resection	
Yes	10 (24.4%)
No	31 (75.6%)
Procedure time [mean ± SD(range)] (min)	
	65 ± 29 (range, 25-150)
Intraoperative complications	
Mild subcutaneous emphysema	1 (2.4%)
None	40 (97.6%)

Post-operative complications	
Delayed bleeding	2 (4.9%)
Esophageal stenosis	19 (46.3%)
Esophagotracheal fistula	2 (4.9%)
None	18 (43.9%)
Complications of CRT after EdR (n, %)	
Myelosuppression	7 (25%)
Radiation pneumonia	3 (10.7%)
Mucous toxicity	3 (10.7%)
None	15 (53.6%)
Follow-up period [median (range)] (month)	36 (1-83)

Reviewer #4:

**Scientific Quality:** Grade C (Good)

**Language Quality:** Grade C (A great deal of language polishing)

**Conclusion:** Rejection

**Specific Comments to Authors:** Comments to the author I am grateful for the opportunity to review this interesting manuscript entitled: "Endoscopic debulking resection with additive chemoradiotherapy: Optimal management of advanced inoperable esophageal squamous cell carcinoma". This report is interesting because it focused on EdR with additive CRT for inoperable ESCC patients which has not been previously reported yet. However, your manuscript has low priority for acceptance of this journal by reason of the following. Firstly, the number of patients was too small to evaluate the long-term outcomes which should prove the feasibility of this method. Secondly, I think this method is not safe for patients with advanced ESCC, because there was high frequency of complications after EdR (stenosis 19/41; 46%, esophago-tracheal fistula 2/41; 5%). Your results did not suggest that this method was more suitable for patients with advanced inoperable ESCC than dCRT which was a present standard treatment for them. It may be safe and feasible for only inoperable patients with SM3 ESCC, in any case it should be evaluated with larger number of patients.

Reply:

We thank the reviewer for reviewing our manuscript and pointing out the issue.

Firstly, as you pointed out, the number of patients was small. However, our centre implements nearly 1200 cases of ESD each year including 430 cases of esophagus, 370 cases of stomach and 400 cases of colon, reaches the top level in domestic. On the basis of carrying out large number of ESD, we conduct some exploratory research on the treatment of selected ESCC patients. The inclusion of our study was extremely rigid, only patients exceed the ESD relative indications and lose the opportunity of surgery can be enrolled. And the type of lesion must be protruding with no ulceration exist. Within the constraints of these stringent conditions, the enrolled number was small. Clinicians perform EdR should be skilled in endoscopy therapy and must select patients strictly.

Secondly, although the standard treatment for unresectable ESCC is dCRT, it does not

show decent OS or PFS in previous studies. Researchers reported the 5-year OS of ESCC patients who received dCRT was only 20-30%, with a median survival of 14 months. Another randomized phase III trial enrolled 267 unresectable ESCC patients received dCRT showed a median PFS was merely 9.7 months. Besides, the incidence of local failure of dCRT was up to 50-70%, with poor life quality. Complications such as hemorrhage, perforation, radiation esophagitis, pericarditis, pneumonia, and tracheal stenosis are not scarce for patients who receive dCRT. It is reported that the rates of esophagealfistula in locally advanced ESCC patients who received dCRT are varied from 3.7% to 24%. Esophageal stenosis usually occurred late in radiotherapy, and there were few viable treatments. Once the radiation esophagitis and stenosis occurred, the risk of endoscopic therapy (bleeding, perforation) was extremely high. In conclusion, new alternative strategies are needed for inoperable ESCCs. In our study, the immediate intraoperative and delayed postoperative complications rate was low (two delayed bleeding, and one mild subcutaneous emphysema), and were all manageable through conservative treatment. Although the complication of stenosis in our study was 46% (19/41), it can be managed by endoscopic therapy, and all of them intake semi-fluid smoothly. As we all know, every brand new treatment should be improved by trial and error, and should not be strangled in the cradle by some complications. This strategy was only a daring attempt, and we believe this treatment is workable for selected ESCC patients. However, it needs large number and long-term follow up studies to verify.

Thirdly, as our study was a retrospective research, and we selected patients that are refused to undergo surgery or dCRT, we did not compare debulking +CRT and CRT alone, and can't concluded that this method was more suitable for patients with advanced inoperable ESCC than dCRT. The initial aim of our study was to remove the primary lesion, reduce tumor burden, and enhance the effect of CRT, not negate dCRT. The randomized comparative trial and large number of patients are needed in the future.