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Joo Young Cho, MD, PhD

Bing Hu, MD,

Anastasios Koulaouzidis, MD, PhD

Sang Chul Lee, MD, PhD

Editors-in-Chief

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Dear Editors and Reviewers:

We appreciate the editor and reviewers for their insightful comments, which have helped us to significantly improve the manuscript.

<Answering Reviewers>

Responses to Reviewer #1:

>Very important topic. However, retrospective design and small sample size make it difficult to come with solid conclusion. Also, I think radiotherpay may cause fibrosis more than chemotherapy alone.

Response:

We really agree with you. As pointed out, the sample size was small for a retrospective study, which makes it difficult to evaluate. The reason for the small sample size is that this study was prospective and new data collection was done along the clinical course. Therefore, we would like to modify that this was an exploratory prospective observational study. We explored the relationship between the degree of muscle layer detect and the depth of residual tumor by retrospective imaging analysis. We have added the following text to ABSTRACT, Core Tip, and MATERIAL AND METHODS. **“exploratory prospective observational study”**. We have added the following text to Statistical analysis. **“prospectively collected data”**.

As pointed out, radiation therapy causes more fibrosis compared to chemotherapy alone. As a result, study 1 showed that residual tumor borders were irregular in all patients, and echogenicity was mixed type after chemoradiation therapy (CRT). However, there was no significant difference in the echo measurements of muscle layer. In the patient characteristics of Study 2, there was no difference in the preoperative treatment method. Furthermore, there was no difference between MDA factors and preoperative treatment

methods. Therefore, we thought that the MDA measurements could be used even if the preoperative treatment methods were different. We have added a table about the patients characteristics in study 2 (**Table5**) and a figure about the relationship between MDA measurements and preoperative treatment (**Figure5**).

Responses to Reviewer #2:

>Thank you for the opportunity to review this article. According to the content of the article, I believe this is a diagnostic study. However, the sample size of this study is too small to produce any reliable results. In addition, the results of the study were not reported in accordance with general diagnostic research standards, such as Standards for Reporting of Diagnostic Accuracy (STARD).

Response:

Thank you for your suggestion, and we agree that sample size is too small. We consider this study as an observational study, not a diagnostic study. Therefore, we reported it according to the STROBE statement. We have added the following text to the cover, and we can submit those documents anytime soon. **“STROBE statement: The authors have read the STROBE Statement—a checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—a checklist of items.”**

Responses to Reviewer #3:

>1. As the author puts forward, the number of cases in this study is too small, resulting in insufficient reliability and rigor of the results. 2. Different from neoadjuvant chemotherapy, different changes (tissue> fibrosis) after neoadjuvant chemoradiotherapy will have different effects on endoscopic ultrasonography. Therefore, it is necessary to separate the above two.3. The study is not sufficient to prove this conclusion.

Response:

We agree with your assessment. Sorry for the same answer as above, but we collected data prospectively and thus had a limited sample size. Therefore, we would like to modify that this was an exploratory prospective observational study. We have added the following text to METHODS, Core Tip, and MATERIAL AND METHODS. **“exploratory prospective observational study”** We have added the following text to Statistical analysis. **“prospectively collected data”**.

We also showed in study1 that there is a difference in echo image depending on the preoperative treatment method. However, there was no significant difference in the echo measurements of muscle layer. We have added a table about the patients characteristics in study 2 (**Table5**), a figure about the relationship between MDA measurements and preoperative treatment (**Figure5**).

Again, thank you for giving us the opportunity to strengthen our manuscript with your valuable comments and queries. We have endeavored to incorporate your feedback and hope that these revisions persuade you to accept our submission.

Sincerely,

Masaya Uesato, MD, PhD,
Department of Frontier Surgery, Graduate School of Medicine,
Chiba University. 1-8-1 Inohana, Chuo-ku,
Chiba 260-8670, Japan.
Telephone: +81-43-226-2110
Facsimile: +81-43-226-2113
E-mail: uesato@faculty.chiba-u.jp

Table 5 Patients' characteristics in study 2

	pT0/1 n=10	pT2/3 n=10	P
Age (years)			
Median (range)	73 (52-79)	72 (43-81)	0.94
Sex			
Male/Female	9/1	7/3	0.582
Tumor location			
Ut, Mt, Lt/ Ae	10/0	8/2	0.473
Clinical T stage			
cT2, 3/cT4a, b	6/4	6/4	1
Preoperative treatment			
NAC/CRT	6/4	6/4	1
Chemo regimen			
CF/DCF	9/1	9/1	1
Total irradiation dose			
38-40Gy/60Gy	2/2	4/0	0.429
Time of EUS after therapy (days)			
Median (range)	37 (21-49)	29 (14-50)	0.172
Time of surgery after therapy (days)			
Median (range)	41 (34-57)	37 (31-61)	0.471

Ut, upper thoracic esophagus; Mt, middle thoracic esophagus; Lt, lower thoracic esophagus; Ae, abdominal esophagus; CF, cisplatin plus 5-fluorouracil; DCF, docetaxel plus cisplatin plus 5-fluorouracil

Figure 5 Relationship between MDA measurements and clinicopathological factors

- (a) Pre-MDA not correlated with preoperative treatment (NAC vs. CRT).
- (b) Post-MDA not correlated with preoperative treatment (NAC vs. CRT).
- (c) MDA reduction rate not correlated with preoperative treatment (NAC vs. CRT).
- (d) Pre-MDA correlated with pT (pT0/1 vs. pT2/3).
- (e) Post-MDA correlated with pT (pT0/1 vs. pT2/3).

(f) MDA reduction rate correlated with pT (pT0/1 vs. pT2/3).

