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Reviewer A

Very interesting and well-prepared paper.

Reply: Thank you very much for the recognition of the design and results of our study.

Reviewer B

The authors have studied treatment options for small cell carcinoma of the esophagus (SCCE) using multi-center institutional data and the SEER database. The authors have included patients over a very long time frame. The time frame is 20 years for their institutional data and 46 years for the SEER database.

Comment 1: It is very difficult to compare esophageal cancer outcomes in 1975 with outcomes in 2020. There have been dramatic advances in surgical technique, perioperative care and neoadjuvant/adjuvant options. Even since 2001, there have been major advances in each of those areas related to esophageal cancer. I understand that a long time period is needed since SCCE is very rare. But did the authors consider shortening the time period for each group, especially the SEER patients? At the very least, it may be advisable to use the same time period for each study.

Reply 1: Thank you for your comments. We agree that surgical techniques have changed dramatically over time, but the basic principle of operation in the treatment of esophageal cancer have not changed significantly. The impact of differences in medical technologies on the prognosis of patients with SCCE over time, we therefore reselected 157 patients diagnosed with LS-SCCE from 2000 to 2020 in SEER databases (8 registries, 12 registries, and 17 registries) including 128 treated patients and 29 untreated patients, which were in the same time period as the 483 patients in China. We re-analyzed the data of patients from the Seer database and modified the content of the manuscript accordingly.

Changes in the text:

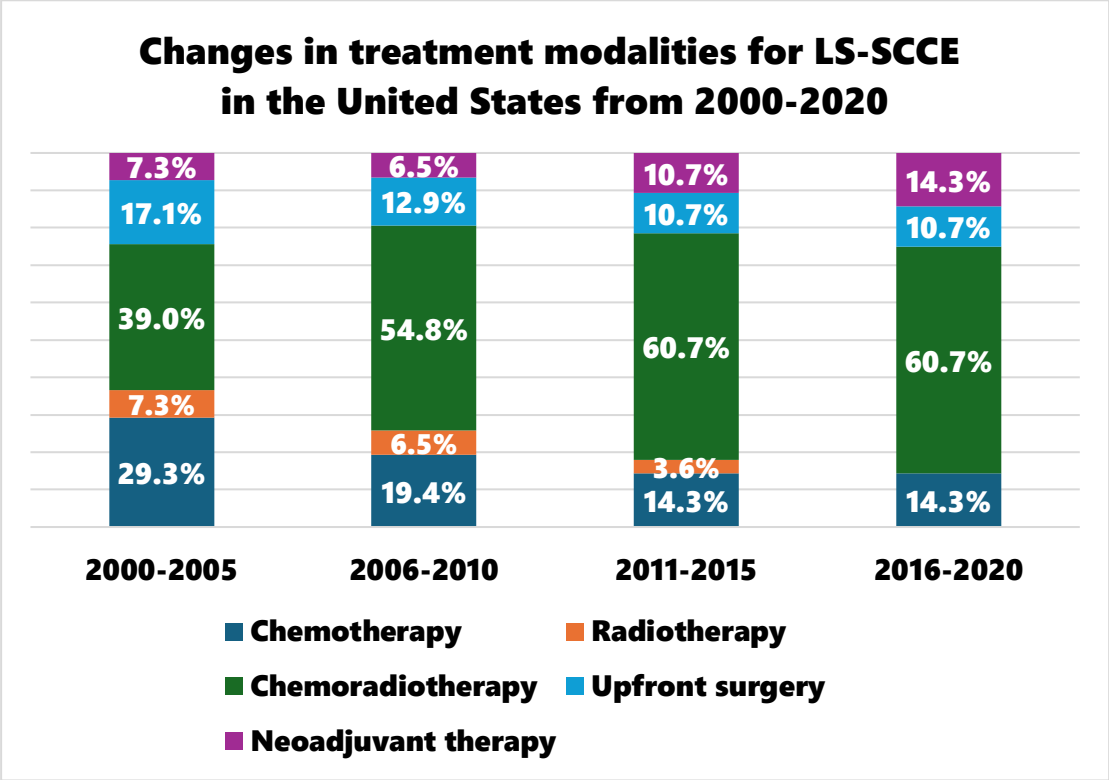
1. Page 6, line 175-178: “We analyzed the data of 483 patients from China and 157 patients from the SEER database. The median survival time of the patients in China was 25.3 months (95% CI, 21.2–29.4), while that of the patients in the SEER database was 16.0 months (95% CI, 12.3–19.7).”
2. Page 6-7, line 187-188: “The data from the SEER database showed that non-surgical treatment (99, 77.3%), including CRT (67, 52.3%), CT (26, 20.3%), and RT (6, 4.7%), was predominant in the United States.”
3. Page 7, line 199-201: “The results for the SEER patients database were similar (HR, 0.717; 95% CI: 0.440–1.169, P=0.18) (Table S1 and Figure S2).”
4. Table 1, Table S1, Figure 1, Figure S1, Figure S2 are modified based on the new

results.

Comment 2: Related to the above comment, were there differences over time in treatment pattern and outcome? As an example, the authors say in lines 156-162 that "in China, surgery was the main treatment option" and that 29.2 percent of patients received upfront surgery. But did the rate of upfront surgery decrease over time? It is very likely that in both groups the rate of CRT increased significantly over time.

Reply 2: Thank you for your comments. Due to the limitations of retrospective studies and the iteration of information systems in five cancer centers, the specific treatment time of a proportion of the patients in this study is not available, and thus it is hard to accurately describe the trend of the treatment patterns of Chinese LS-SCCE patients over time by means of specific graphs and other forms. However, according to the clinical experience of frontline clinicians in five cancer centers, the proportion of Chinese patients with LS-SCCE who choose NCT is on an increasing trend, and the proportion of CRT treated patients is also increasing. The proportion of patients underwent upfront surgery has gradually declined in recent years. At the same time, they agree that the trend of change in treatment patterns in China is generally consistent with the trend presented in the Seer database. Cai et al. (doi: 10.1016/j.athoracsur.2021.08.059) described trends in Chinese treatment regimens over time, dominated by an increase in the proportion of neoadjuvant chemotherapy. Another retrospective study with a larger sample size, in which we are participating, is currently underway to provide a more detailed description of trends in treatment regimens for LS-SCCE in China.

The percentage of patients in the Seer database with different treatment modalities over time is shown in the Figure below. The proportion of patients with LS-SCCE in the SEER database who chose the CRT regimen increased from 39% in 2000-2005 to 60.7% in 2016-2020, while the proportion of patients underwent neoadjuvant therapy increased from 7.3% in 2000-2005 to 14.3% in 2016-2020, and the proportion of patients underwent upfront surgery decreased from 17.1% in 2000-2005 to 10.7% in 2016-2020.



Comment 3: Do the authors have any ideas about the chemotherapy regimen(s) used? It would be helpful to reference that in the methods, even if just a broad description.

Reply 3: Thank you for your suggestions. The chemotherapy regimens used in China: etoposide, 120 mg/m^2 by intravenous (IV) bolus on days 1-3, and cisplatin, 75 mg/m^2 by IV on day 1, every 3 weeks for 2-4 cycles; or irinotecan, 130 mg/m^2, and cisplatin, 75 mg/m^2, by IV on day 1, every 3 weeks for 2-4 cycles. The Seer database does not give specific chemotherapy regimens for each patient.

Changes in the text: We have added a description of the chemotherapy regimens used in China (see Page 5, line 140-144): "The chemotherapy regimens used in China: etoposide, 120 mg/m^2 by intravenous (IV) bolus on days 1-3, and cisplatin, 75 mg/m^2 by IV on day 1, every 3 weeks for 2-4 cycles; or irinotecan, 130 mg/m^2, and cisplatin, 75 mg/m^2, by IV on day 1, every 3 weeks for 2-4 cycles."

Comment 4: Did any patients receive immunotherapy as part of their treatment regimen?

Reply 4: Thank you for your comment. None of the Chinese patients in this study underwent immunotherapy, and the SEER database does not provide information about receiving immunotherapy.

Reviewer C

The investigators of "Treatment strategies for limited-stage small cell carcinoma of the esophagus: evidence from a Chinese multicenter cohort study and the American SEER database" compare outcomes following upfront surgery (S), neoadjuvant chemotherapy plus surgery (NCT) and chemoradiation (CRT) for this condition. One major criticism I have of this study is that you are constantly switching between comparisons: S + NCT vs CRT, S vs NCT, NCT vs CRT. I think you need to be consistent with the comparison. Depending on the rate of adjuvant therapy in the S group, I would consider just analyzing S vs NCT vs CRT rather than combining the S and NCT groups. If the rate of adjuant therapy My comments/questions below:

Comment 1: "Aggressive treatment" (line 28) is a term that is used multiple times in the manuscript. It is not clear what this means. Please reword. Please apply this to the other times that this terminology is used in the manuscript.

Reply 1: Thank you for your comment. We would like to emphasize that taking therapeutic measures (including upfront surgery, NCT, CRT, CT, RT, etc.) in the limited stage can significantly prolong the survival time of the patients compared with no treatment at all, so we think that "aggressive treatment" can be used here.

Comment 2: "Ranging from death within 2 years" (lines 55-56) does not make sense. Please delete.

Reply 2: Thank you for your comment. We have deleted "Ranging from death within 2 years" in the manuscript.

Changes in the text:

Page 3, line 82-85: "Patients with SCCE have an extremely poor prognosis, with a median overall survival (mOS) of 8–13 months and a 5-year overall survival (OS) rate of approximately 6.7–18% (3,8,11-14)."

Comment 3: The term "limited-stage" (line 92) needs to be defined.

Reply 3: Thank you for your suggestion. We added the definition of limited stage in the third paragraph (See Page 4, line 88-91).

Changes in the text: We added the definition of limited stage in the third paragraph (See Page 4, line 88-91): "The VALSG system classifies SCCE into limited-stage disease (LS) and extensive-stage disease (ES). LS is defined as tumor confined to the esophagus and surrounding tissues with or without regional lymph node involvement."

Comment 4: The abbreviations for treatment groups is a bit misleading. I would recommend a different abbreviation for NCT, as these patients (to my knowledge) all underwent surgery also.

Reply 4: Thank you for your comment. We conducted a literature search and found that the use of the abbreviation "neoadjuvant chemotherapy + surgery" as "NCT" appeared in several studies. The meaning of the abbreviation is also explained in the article. So we believe that NCT does not create ambiguity in this paper.

The following are the references:

1. Xu L, Li Y, Liu X, Sun H, Zhang R, Zhang J, Zheng Y, Wang Z, Liu S, Chen X. Treatment Strategies and Prognostic Factors of Limited-Stage Primary Small Cell Carcinoma of the Esophagus. J Thorac Oncol. 2017 Dec;12(12):1834-1844. doi: 10.1016/j.jtho.2017.09.1966. Epub 2017 Oct 9. PMID: 29024756.
2. Wang H, Tang H, Fang Y, Tan L, Yin J, Shen Y, Zeng Z, Zhu J, Hou Y, Du M, Jiao J, Jiang H, Gong L, Li Z, Liu J, Xie D, Li W, Lian C, Zhao Q, Chen C, Zheng B, Liao Y, Li K, Li H, Wu H, Dai L, Chen KN. Morbidity and Mortality of Patients Who Underwent Minimally Invasive Esophagectomy After Neoadjuvant Chemoradiotherapy vs Neoadjuvant Chemotherapy for Locally Advanced Esophageal Squamous Cell Carcinoma: A Randomized Clinical Trial. JAMA Surg. 2021 May 1;156(5):444-451. doi: 10.1001/jamasurg.2021.0133. PMID: 33729467; PMCID: PMC7970392.
3. Tang H, Wang H, Fang Y, Zhu JY, Yin J, Shen YX, Zeng ZC, Jiang DX, Hou YY, Du M, Lian CH, Zhao Q, Jiang HJ, Gong L, Li ZG, Liu J, Xie DY, Li WF, Chen C, Zheng B, Chen KN, Dai L, Liao YD, Li K, Li HC, Zhao NQ, Tan LJ. Neoadjuvant chemoradiotherapy versus neoadjuvant chemotherapy followed by minimally invasive esophagectomy for locally advanced esophageal squamous cell carcinoma: a prospective multicenter randomized clinical trial. Ann Oncol. 2023 Feb;34(2):163-172. doi: 10.1016/j.annonc.2022.10.508. Epub 2022 Nov 15. PMID: 36400384.

Comment 5: This study appears to encompass two very different patient groups – one multicenter trial on Chinese patients, and one SEER database study (US patients). This is an unusual structure – would consider eliminating the SEER group or explaining the justification for including the SEER group in more detail.

Reply 5: Thank you for your constructive comments. In this study, by comparing the mOS of Chinese patients with that of patients in SEER database, we found that the mOS of Chinese cohorts was 25.3 months (95% CI, 21.2-29.4), and the mOS of American cohorts was 16.0 months (95% CI: 12.3-19.7). The difference in mOS between the two

cohorts suggests to some extent that the Chinese treatment regimen may be superior in the treatment of LS-SCCE, and thus we focused on the Chinese cohort during the subsequent analysis. It also provides a reference basis for extending the Chinese treatment regimen to other regions. So we consider it's necessary to keep the SEER cohort.

Comment 6: What did the evaluation of these patients consist of?

Reply 6: Thank you for your question. Clinicians decide to conduct adjuvant chemotherapy if patients had an R1 or R2 resection. It is important to note that in 2015-2020, although the criteria for whether or not a patient underwent adjuvant therapy were basically the same as before, an MDT team approach to treatment was introduced within this phase, and therefore whether or not a patient underwent adjuvant chemotherapy within this phase is a joint decision of the MDT team.

Changes in the text:
Page 5, line 140-143: After surgery, clinicians decide to conduct adjuvant chemotherapy if patients had an R1 or R2 resection.
Page 5, line 145-147: After surgery, the attending physician decided whether each patient would receive adjuvant therapy according to the same criteria as above.

Comment 7: What variables were used in the propensity matching?
Comment 8: What does "upper middle third" mean (line 152)? Do you mean upper third or middle third? Or both upper AND middle third?
Comment 9: What does "early T stage" (line 154) mean?

Reply 7-9:
Variables used for propensity score matching include: Gender, Age, Tumor location, T stage, N stage.

The "upper middle third" means both upper third and middle third.

The "early T stage" means T1/2 stage.

Comment 10: Percentages should be provided in the "All" columns in Table 1.

Reply 10: Thank you for your comment. Since the table is labeled with the percentage of each treatment modality for each clinical characteristic (e.g., female, male, etc.) out

of the total number of people in that clinical characteristic, labeling the data in the "All" column with a percentage would cause confusion and ambiguity in the table. So we avoided labeling percentages in the "All" column.

Comment 11: What percent of patients in the upfront surgery group received adjuvant therapy (chemotherapy, radiation, or both chemotherapy and radiation)? These percentages should be provided; they are very important to understand the conclusions of the study.

Reply 11: Thank you for your question. After surgery, clinicians decide to conduct adjuvant chemotherapy if patients had an R1 or R2 resection. It is important to note that in 2015-2020, although the criteria for whether or not a patient underwent adjuvant therapy were basically the same as before, an MDT team approach to treatment was introduced within this phase, and therefore whether or not a patient underwent adjuvant chemotherapy within this phase is a joint decision of the MDT team. Due to some missing information on adjuvant therapy in the second half of the section, we couldn't to make precise statistics on the percentage of patients who underwent adjuvant therapy in the upfront surgery cohort. However, we calculated that the percentage is roughly 30%. This is similar to the proportions in Cai's study (doi: 10.1016/j.athoracsur.2021.08.059).

Comment 12: I do not think extended-stage patients (ES disease line 214) needs to be mentioned in this manuscript.

Comment 13: I do not agree with stating that the "use of surgery as the primary treatment option for patients with LS disease .. (has) been accepted by most researchers" (lines 212-215). Your own manuscript refers to the fact that CRT is the dominant choice of therapy in the US.

Reply 12-13: Thank you for your comment. We have deleted the content related to ES disease treatment. At the same time, we revised our formulation of surgery as the dominant choice of therapy for patients with LS-SCCE (see Page 8, line 246-248): "Second, the use of surgery as the primary treatment option for patients with LS disease have been accepted by most researchers in China."

Changes in the text:

Page 8, line 246-248: "Second, the use of surgery as the primary treatment option for patients with LS disease have been accepted by most researchers in China."

Comment 14: Lines 255-258 are confusing. Please reword.

Reply 14: Thank you for your comment. Because Zhu's study only compared the survival differences between patients who underwent CRT and patients who underwent chemotherapy and surgery, but did not differentiate between the sequences of chemotherapy and surgery for the surgical population. Our results suggest that there is a statistically significant difference between upfront surgery and neoadjuvant chemotherapy + surgery in OS for patients with LS-SCCE. Therefore, we believe that Zhu's conclusion that the two treatment modalities have the same efficacy has some limitations, and we need to further differentiate between neoadjuvant chemotherapy + surgery and upfront surgery.

Changes in the text:

Page 9-10, line 287-290: "However, it should be noted that patients in the CT + radical surgery group were not further stratified into those receiving neoadjuvant therapy and upfront surgery, which might have reduced the efficacy of the neoadjuvant treatment."

Comment 15: Is the statement that NCT "enables patients to achieve a longer survival time" (lines 267-269) true? Your study did not demonstrate a difference in survival for patients in the NCT group, compared to the CRT group. Would revise.

Reply 15: Thank you for your comment. We agreed that NCT does not prolong patient survival time compared to CRT, and therefore we emphasized in the manuscript that NCT prolongs survival compared to upfront surgery, not compared to CRT.

Comment 16: The limitations section of the manuscript is perfunctory; more thoughtful, extensive discussion of the limitations of the study is justified.

Reply 16: Thank you for your comment. We complement the limitations of this study (see Page 10, lines 315-321).

Changes in the text:

We added the limitations of this study (see Page 10, lines 315-321): "Third, limitations of the data resulted in some cohorts still having mismatched clinical characteristics after PSM, which may have influenced the study conclusions. Finally, we only compared the OS of the three treatment modality cohorts and were unable to obtain other end points of the patients, such as progression-free survival, quality of life, side effects, etc. We hope that more prospective studies in the future will allow a more detailed comparison of the above parameters."

Comment 17: I would consider creating three groups, not two, for the propensity matched study: S, NCT, and CRT, instead of S + NCT and CRT. For Figure 2, this would mean that there are three survival curves rather than 2.

Reply 17: Thank you for your suggestion. We also tried to perform PSM on the three groups of patients. However, we found that there were still statistical differences in the two characteristics of T-stage and N-stage after performing PSM on the three groups of patients (See Table 1 below). So we chose another way of comparing the three groups of patients: 1. Compare the difference in efficacy between patients with surgical treatments and those with non-surgical treatments after performing PSM; 2. S vs. NCT, NCT vs. CRT, S vs. S vs. CRT respectively to compare the difference in efficacy after PSM. After performing PSM on S vs. CRT, we found that there was still a statistical difference between the two groups in tumor location (See Table 2 below), while the number of patients included in each group after PSM was only 105. Meanwhile, we have found that the efficacy of NCT was superior to that of S, while there was no statistically significant difference in OS between NCT and CRT. Therefore, we did not further compare the difference in efficacy between S and CRT.

Table 1 Clinical and tumor characteristics of patients with LS-SCCE receiving upfront surgery, NCT and CRT

Characteristics	Before matching					After matching			
	Upfront surgery (n=141)	NCT (n=171)	CRT (n=171)	P		Upfront surgery (n=139)	NCT (n=139)	CRT (n=139)	P
Sex, n (%)				0.80					0.50
Female	41 (29.1)	50 (29.2)	45 (26.3)			40 (28.8)	41 (29.5)	33 (23.7)	
Male	100 (70.9)	121 (70.8)	126 (73.7)			99 (71.2)	98(70.5)	106 (76.3)	
Age, years, n (%)				0.01					0.23
≤60	61 (43.3)	89 (52.0)	62 (36.3)			60 (43.2)	62 (44.6)	49 (35.3)	
>60	80 (56.7)	82 (48.0)	109 (63.7)			79 (56.8)	77 (55.4)	90 (64.7)	
Tumor location, n (%)				0.45					0.33

Proximal/middle third	101 (71.6)	111 (64.9)	117 (68.4)			100 (71.9)	89 (64.0)	91 (65.5)	
Distal third	40 (28.4)	60 (35.1)	54 (31.6)			39 (28.1)	50 (36.0)	48 (34.5)	
T, n (%)				<0.001					<0.0
T1/2	74 (52.5)	78 (45.6)	50 (29.2)			72 (51.8)	73 (52.5)	32 (23.0)	
T3/4	67 (47.5	93 (54.4)	121 (70.8)			67 (48.2)	66 (47.5)	107 (77.0)	
N, n (%)				<0.001					<0.0
N0	57 (40.4)	76 (44.4)	41 (24.0)			57 (41.0)	58 (41.7)	23 (16.5)	
N+	84 (59.6)	95 (55.6)	130 (76.0)			82 (59.0)	81 (58.3)	116 (83.5)	

Table 2 Clinical and tumor characteristics of patients with LS-SCCE receiving upfront surgery and CRT

Characteristics	Before matching				After matching		
	upfront surgery (n=141)	CRT (n=171)	P		upfront surgery (n=105)	CRT (n=105)	P
Sex, n (%)			0.67				>0.99
Female	41 (29.1)	45 (26.3)			31 (29.5)	31 (29.5)	
Male	100 (70.9)	126 (73.7)			74(70.5)	74 (70.5)	
Age, years, n (%)			0.25				>0.99
≤60	61 (43.3)	62 (36.3)			43 (41.0)	43 (41.0)	
>60	80 (56.7)	109 (63.7)			62 (59.0)	62 (59.0)	
Tumor location, n (%)			0.62				0.01
Proximal/middle third	101 (71.6)	117 (68.4)			75 (71.4)	91(86.7)	

Distal third	40 (28.4)	54 (31.6)			30 (28.6)	14 (13.3)	
T, n (%)			<0.001				>0.99
T1/2	74 (52.5)	50 (29.2)			45 (42.9)	45 (42.9)	
T3/4	67 (47.5	121 (70.8)			60(57.1)	60 (57.1)	
N, n (%)			0.003				>0.99
N0	57 (40.4)	41 (24.0)			36 (34.3)	36 (34.3)	
N+	84 (59.6)	130 (76.0)			69(65.7)	69(65.7)	

Comment 18: The colors in the two pie charts for Figure 1 should "match". In Figure 1A, the S group is green, but in Figure 1B, CRT is green. This is confusing.

Comment 19: Is the survival analysis performed on propensity matched groups or not? This should be clarified in the legends.

Comment 20: The univariate Cox analyses can be omitted from the paper (ex. Figures 3 AC, Figure S2A, C, E).

Comment 21: I do not think Figures S3-S5 are needed.

Comment 22: In Figures 3 and S2, the treatment groups differ in each Forest plot which is confusing. In Figure 3B, for instance, the treatment groups are S and NCT, while in Figure 3D, they are S + NCT vs CRT. Also, it should be more apparent in the labeling which plots refer to the multicenter study vs SEER database (can consider splitting into different Figures completely)

Reply 18-22: Thank you for your suggestion.

We have modified the colors in the pie charts to make the two match.

We have labeled in the KM curve legends if survival analysis is performed on propensity matched groups.
We retained univariate Cox analyses in order to make the analytical process more rigorous.

Figure S3 suggests that there was no statistical difference in OS among patients with different clinical characteristics except for the difference in treatment regimen, suggesting that the treatment regimen may play a major role in prolonging OS of patients. Figure S4 further compares the difference between the OS of patients treated with surgical and non-surgical treatments under each clinical characteristic, helping us to further search for the preferred treatment modality for the patients with different clinical characteristics. Figure S5 A,B emphasizes the advantage of NCT over upfront surgery for patients aged ≤60 years and male patients. Figure S5 C, D emphasizes the advantage of CRT over NCT for patients aged >60 years and female patients. Therefore, Figures S3-S5 are important in helping us to find the important factors for improving the prognosis of patients with LS-SCCE and the preferred treatment regimen for people with different clinical characteristics, so we would like to keep Figures S3-S5 in the article.

We have revised the headings in the forest plots to make the grouping and sources of each forest plot clearer.

Changes in the text: Figure 1，2，3，S2, S3, S4, S5.

Comment 23: Why did propensity matching not result in more similar age groups (Table S5)?

Reply 23: Thank you for your question. We also found a statistical difference in age group after performing PSM on NCT and CRT, which may be due to the limitation of the data. Considering the limited number of patients with LS-SCCE, we were unable to solve this problem by enlarging the sample size; therefore, we performed Cox regression analysis on the data after performing PSM in order to reduce the effect of the difference in age group on the conclusions. We add this issue to the limitations of this paper and look forward to other larger prospective studies in the future comparing the difference in efficacy between NCT and CRT while better balancing the differences in other variables between groups.

Comment 24: Tables S2 and S4 should include p values.

Comment 25: Table S7 is confusing and the abbreviations need to be specified. Please reformat.

Reply 24-25: Thank you for your suggestion.
We have added p-values to Tables S2, S4, S6.
We have added explanations for the abbreviations in Table S7.

Changes in the text: Tables S2, S4, S6, S7.

Reviewer D

Comment 1: A large cohort of NSCC of esophagus (a rare disease)
the SEER cohort does not add anything given the missing data so i think can be omitted.

Reply 1: Thank you for your comment. In this study, by comparing the mOS of Chinese patients with that of patients in SEER database, we found that the mOS of Chinese cohorts was 25.3 months (95% CI, 21.2-29.4), and the mOS of American cohorts was 16.0 months (95% CI: 12.3-19.7). The difference in mOS between the two cohorts suggests to some extent that the Chinese treatment regimen may be superior in the treatment of LS-SCCE, and thus we focused on the Chinese cohort during the subsequent analysis. It also provides a reference basis for extending the Chinese treatment regimen to other regions. So we consider it's necessary to keep the SEER cohort.

Comment 2: You state that CRT vs those who got surgery (does this incldue both surgery upfront and those with NCT and surgery) - CRT had better survival -- please clarify, also you said CRT is definteily better for age > 60 but no different than NCT (with f.u surgery) even in < 60.So, should the treatment in less than 60 be also CRT and avoid surgery completely or are there CRT morbidity which would sawy us towards NCT plus surgery.

Reply 2: Thank you for your questions. We compared the survival differences between surgical and non-surgical patients in a Chinese cohort, where surgical patients were those who underwent upfront surgery and neoadjuvant chemotherapy and surgery, and non-surgical patients were those who underwent CRT. For patients ≤60 years, we agree with your question about the preferred treatment regimen for this group and think that our existing formulation is flawed, so we have revised it (see Page 2, line 42): "Upfront surgery is not recommended for LS-SCCE patients aged ≤60 years." Based on the available findings, we were only able to determine that there was an advantage of CRT and NCT over upfront surgery in terms of OS, but we were unable to make any further

comparisons of the advantages and disadvantages of CRT versus NCT because there was no statistically significant difference between CRT and NCT in OS. We hope more studies can compare the differences between CRT and NCT in other parameters (e.g., PFS, quality of life, side effects, etc.) to better determine the preferred treatment regimen for patients ≤60 years in the future.

Changes in the text:

Page 2, line 42, Highlight box: “ Upfront surgery is not recommended for LS-SCCE patients aged ≤60 years, while CRT is recommended for LS-SCCE patients aged >60 years.”