

Peer review file

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Reviewer A

This group from China present a retrospective case series of small cell carcinoma of the esophagus. The authors "aimed to evaluate the outcomes of patients treated with different therapeutic methods and investigate the prognostic factors of PSCCE".

Even though the authors listed in the limitations of the study that there is a small number of patients, this series has actually a large number of patients with a rare disease. This data may provide interesting insights into the treatment of PSCCE; however, the manuscript is sometimes hard to follow specially when the authors deviated from the first aim of the study that was to evaluate outcomes based on different treatment modalities. Here are the points were the manuscript gets confusing:

Comment 1: It is hard to understand the type of treatments and how many patients were selected for each one. A flowchart is mandatory. Furthermore, radiotherapy alone cannot be compared to surgery. The authors should create for understandable groups and compare then.

Reply 1:

Thanks for your kind comments. After a detailed search from the medical records, each type of treatment and the number of patients with different treatments were recorded in the Table 1. In our study, treatments for PSCCE include surgery alone, chemotherapy, surgery and postoperative chemotherapy, palliative radiotherapy, chemoradiotherapy, and trimodality therapy, including surgery and postoperative

chemoradiotherapy. There is no consensus on the standard therapy modality of PSCCE [1]. Figure 1 shows a treatment flowchart, which was made by summarizing therapeutic experiences at our center. The number of patients who received various treatments was shown below.

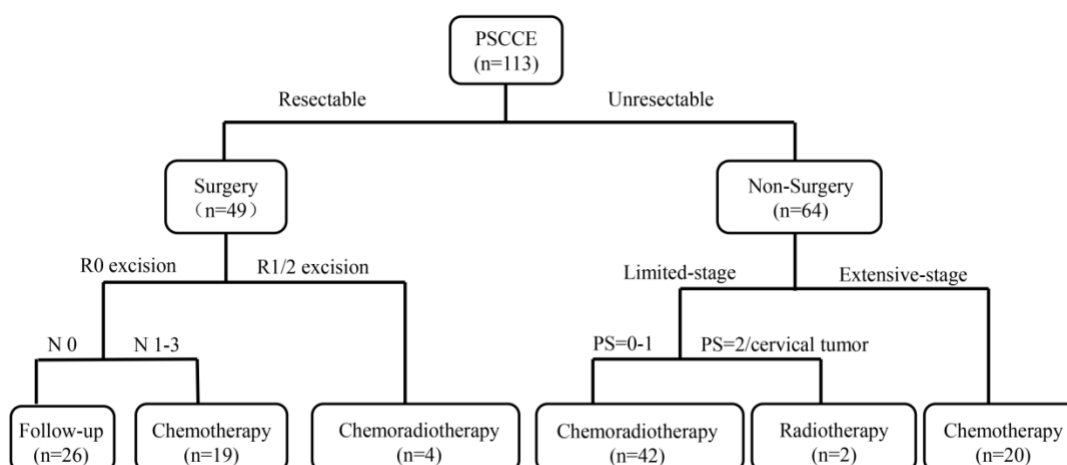


Figure 1. The treatment flowchart.

In our study, only two patients received palliative radiotherapy. Due to the limited number of patients who received radiotherapy alone, we could not compare the survival of patients who received radiotherapy alone to other treatment modalities in our study. The treatment of radiotherapy alone is only suitable for patients who cannot afford surgery or concurrent chemoradiotherapy, especially those with poor performance status. As suggested, the therapeutic effect of palliative radiotherapy alone cannot be compared to surgery directly. Therefore, we compared the effects of treatment modalities again in a reasonable way. In the new comparison, the treatment modalities were classified as single (surgery or chemotherapy alone) and combined treatment (surgery combined postoperative chemotherapy). The mean survival time (MST) of surgery/chemotherapy alone was shorter than that of surgery combined with

postoperative chemotherapy (10.4 versus 17.8 months; $p = 0.001$, Figure 5a). Based on the stratified data, the benefits of surgery combined with chemotherapy were observed in N1-3 patients (see Figure 5b).

The relative contents have been added in the Results (Page 8, line 9-13; Page 11, line 8-9, 11-14) and Discussion Section (Page 19, line 3-5) which are shown below for your convenience of reviewing.

Changes in the text:

Results

In our study, treatments for PSCCE include surgery alone, chemotherapy, surgery and postoperative chemotherapy, palliative radiotherapy, chemoradiotherapy, and trimodality therapy, including surgery and postoperative chemoradiotherapy. Figure 1 shows a treatment flowchart, which was made by summarizing therapeutic experiences at our center (Page 8, line 9-13).

Also, the MST of surgery/chemotherapy alone was shorter than that of surgery combined with postoperative chemotherapy (10.4 versus 17.8 months; $p = 0.001$, Figure 5a). Based on the stratified data, the benefits of surgery combined with chemotherapy were observed in N1-3 patients (see Figure 5b), but systemic treatments did not show an obviously beneficial effect among N0 patients (see Figure S1) (Page 11, line 8-9, 11-14).

Discussion

The treatment of radiotherapy alone is only suitable for patients who cannot afford

surgery or concurrent chemoradiotherapy, especially those with poor performance status (Page 19, line 3-5).

Reference:

1. Krishnatreya M, Katak AC, Sharma JD, Borthakur BB, Kalita M. Epidemiology of primary small cell carcinoma of the esophagus: a retrospective study. South Asian J Cancer. 2014;3(4):231-2.

Comment 2: I could not learn from the authors how each modality was chosen.

Reply 2:

Thanks for your advice. As shown in Figure 1 (below), different modalities of PSCCE were chosen according to our experience.

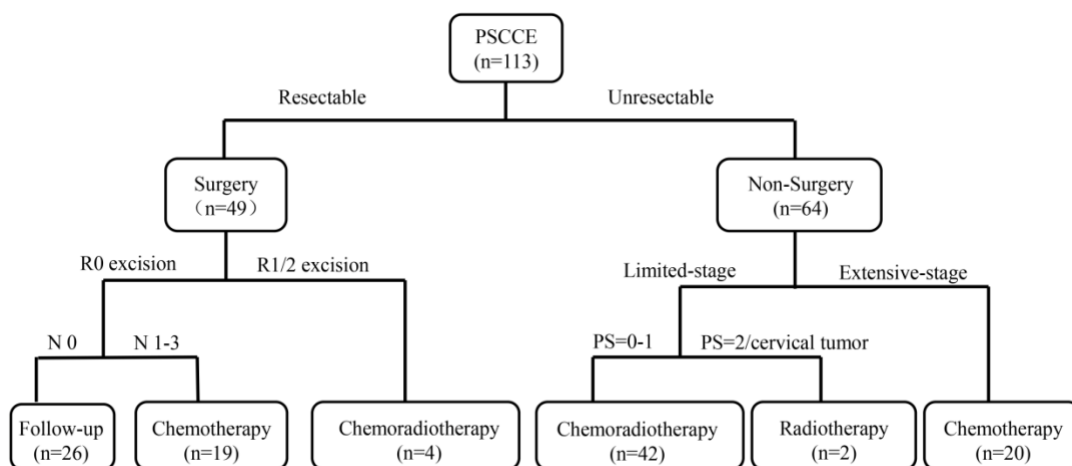


Figure 1. The treatment flowchart.

Briefly, we firstly divided the modalities of PSCCE into surgery and non-surgery treatment according to tumor respectability [1]. Different modalities were chosen

depending on the characteristics of the tumors and the physical condition of patients.

Surgery is highly recommended for patients with good performance status and resectable tumors [2]. To be eligible for surgery, PSCCE patients must meet the following criteria: 1) be at a TNM stage of I, II, or III; 2) a tumor stage of 1, 2, or 3 (T1, T2, or T3); 3) show no nodal involvement (N0), or the presence of tumor(s) in no more than 6 lymph nodes (N1-2); 4) and show no metastases (M0); 5) have esophageal cancer in the middle or lower third of the esophagus; 6) have a World Health Organization performance-status score of 0 or 1 (on a 5-point scale) [3]. Long-term follow-up examinations may be acceptable for patients without lymph node metastasis after an R0 excision.

In the present study, we explored the correlation between treatment methods and the prognosis of PSCCE and found that N1-3-stage (but not N0-stage) patients who were treated with surgery combined with chemotherapy had a better prognosis than those who underwent surgery or chemotherapy alone. Thus, combined with our data, we recommended that N1-N3-stage PSCCE patients receive adjuvant therapy after surgery. Due to chemotherapy's potential side effects, we do not recommend over-enthusiastic chemotherapy for early-stage PSCCE patients. Concerning patients who received an R1/2 excision, postoperative chemoradiotherapy is essential to eliminate the residual lesion.

For patients who were not suitable for surgery, we divided the non-surgery treatment into chemoradiotherapy, radiotherapy and chemotherapy modalities according to the tumor metastasis and the physical condition of patients [4]. Concurrent

chemoradiotherapy is recommended for patients who are in a good performance condition but not suitable for surgery [5]. Concurrent chemoradiotherapy could provide a radical treatment for patients without tumor metastasis. For patients with tumor metastasis, chemotherapy is the key treatment to destroy metastatic tumor cells and control disease progression [6]. Radiotherapy is an effective treatment for PSCCE, especially in patients with cervical esophageal cancer, which is sensitive to radiotherapy but not suitable for surgery [7]. Radiotherapy is often used as an adjuvant therapy pre- or post-surgery [8]. The treatment of radiotherapy alone is only suitable for patients who cannot afford surgery or concurrent chemoradiotherapy, especially those with poor performance status.

The relative contents have been supplemented in the Results Section of our manuscript (Page 16, line 2-3, 10-11, 13-19; Page 17, line 7-16; Page 19, line 1-5).

Changes in the text:

Discussion

Different modalities were chosen depending on the characteristics of the tumors and the physical condition of patients (Page 16, line 2-3).

In the present study, we divided the modalities of PSCCE into surgery and non-surgery treatment according to tumor resectability (Page 16, line 10-11).

Surgery is highly recommended for patients with good performance status and resectable tumors. To be eligible for surgery, PSCCE patients must meet the following criteria: 1) be at a TNM stage of I, II, or III; 2) a tumor stage of 1, 2, or 3 (T1, T2, or

T3); 3) show no nodal involvement (N0), or the presence of tumor(s) in no more than 6 lymph nodes (N1-2); 4) and show no metastases (M0); 5) have esophageal cancer in the middle or lower third of the esophagus; 6) have a World Health Organization performance-status score of 0 or 1 (on a 5-point scale) (Page 16, 13-19).

Long-term follow-up examinations may be acceptable for patients without lymph node metastasis after an R0 excision. In the present study, we explored the correlation between treatment methods and the prognosis of PSCCE and found that N1-3-stage (but not N0-stage) patients who were treated with surgery combined with chemotherapy had a better prognosis than those who underwent surgery or chemotherapy alone. Thus, combined with our data, we recommended that N1-3-stage PSCCE patients receive adjuvant therapy after surgery. Due to chemotherapy's potential side effects, we do not recommend over-enthusiastic chemotherapy for early-stage PSCCE patients. Concerning patients who received an R1/2 excision, postoperative chemoradiotherapy is essential to eliminate the residual lesion (Page 17, line 7-16).

For patients with tumor metastasis, chemotherapy is the key treatment to destroy metastatic tumor cells and control disease progression (Page 17, line 5-6).

Radiotherapy is an effective treatment for PSCCE, especially in patients with cervical esophageal cancer, which is sensitive to radiotherapy but not suitable for surgery. Radiotherapy is often used as an adjuvant therapy pre- or post-surgery. The treatment of radiotherapy alone is only suitable for patients who cannot afford surgery or concurrent chemoradiotherapy, especially those with poor performance status (Page 19, line 1-5).

Reference:

1. Wong AT, Shao M, Rineer J, Osborn V, Schwartz D, Schreiber D. Treatment and survival outcomes of small cell carcinoma of the esophagus: an analysis of the National Cancer Data Base. *Dis Esophagus*. 2017;30(2):1-5.
2. Xu L, Li Y, Liu X, Sun H, Zhang R, Zhang J, et al. Treatment Strategies and Prognostic Factors of Limited-Stage Primary Small Cell Carcinoma of the Esophagus. *J Thorac Oncol*. 2017;12(12):1834-44.
3. Mariette C, Markar SR, Dabakuyo-Yonli TS, Meunier B, Pezet D, Collet D, et al. Hybrid Minimally Invasive Esophagectomy for Esophageal Cancer. *N Engl J Med*. 2019 Jan 10;380(2):152-162.
4. Jeene PM, Geijsen ED, Muijs CT, Rozema T, Aleman BMP, Muller K, et al. Small cell carcinoma of the esophagus: a Nationwide analysis of treatment and outcome at patient level in Locoregional disease. *Am J Clin Oncol*. 2019;42(6):534-8.
5. Wang HH, Zaorsky NG, Meng MB, Wu ZQ, Zeng XL, Jiang B, et al. Multimodality therapy is recommended for limited-stage combined small cell esophageal carcinoma. *Onco Targets Ther*. 2015;8:437-44.
6. Raja S, Rice TW, Rajeswaran J, Zhong J, Blackstone EH. Esophageal small-cell cancer: study of a rare disease. *Dis Esophagus*. 2013;26(7):690-5.
7. Chen B, Yang H, Ma H, Li Q, Qiu B, Hu Y, et al. Radiotherapy for small cell carcinoma of the esophagus: outcomes and prognostic factors from a retrospective study. *Radiat Oncol*. 2019 Nov 21;14(1):210.
8. Pasquali S, Yim G, Vohra RS, Mocellin S, Nyanhongo D, Marriott P, Geh JI,

Griffiths EA. Survival After Neoadjuvant and Adjuvant Treatments Compared to Surgery Alone for Resectable Esophageal Carcinoma: A Network Meta-analysis. *Ann Surg.* 2017 Mar;265(3):481-491.

Comment 3: The authors concluded that surgery + adjuvant chemotherapy is the ideal treatment but I could not follow the rationale for that in the results and discussion.

Reply 3:

Thanks for your kind comments. After summarizing the experience at our center, we made a treatment flowchart in the Figure 1. We highly recommended surgery combined with or without adjuvant therapy for PSCCE patients with a resectable tumor [1]. The use of adjuvant therapy depends on the lymph node metastasis. Our study revealed that the mean survival time (MST) of surgery/chemotherapy alone was shorter than that of surgery combined with postoperative chemotherapy (10.4 versus 17.8 months; $p = 0.001$, Figure 5a). We explored the correlation between treatment methods and the prognosis of PSCCE and found that N1-3-stage (but not N0-stage) patients who were treated with surgery combined with chemotherapy had a better prognosis than those who underwent surgery or chemotherapy alone. Our treatment experience and survival data revealed that surgery combined adjuvant chemotherapy was the ideal treatment for limited-stage PSCCE patients, especially for those with lymph node stages N1-3.

The relative contents have been added in the Results and Discussion Section of the manuscript (Page 11, line 8-9; Page 17, line 8-11).

Changes in the text:

Results

Also, the MST of surgery/chemotherapy alone was shorter than that of surgery combined with postoperative chemotherapy (10.4 versus 17.8 months; $p = 0.001$, Figure 5a) (Page 11, line 8-9).

Discussion

In the present study, we explored the correlation between treatment methods and the prognosis of PSCCE and found that N1-3-stage (but not N0-stage) patients who were treated with surgery combined with chemotherapy had a better prognosis than those who underwent surgery or chemotherapy alone (Page 17, line 8-11).

Reference:

1. Xu L, Li Y, Liu X, Sun H, Zhang R, Zhang J, et al. Treatment Strategies and Prognostic Factors of Limited-Stage Primary Small Cell Carcinoma of the Esophagus. *J Thorac Oncol.* 2017;12(12):1834-44.

Minor comments:

Comment 1: The abstract does not reflect the manuscript.

Reply 1:

Thanks for your kind comments. In this study, we aimed to investigate the

prognostic factors and evaluate the outcomes of PSCCE patients treated with different therapeutic methods. We retrospectively evaluated 113 consecutive patients with PSCCE who received treatment in our center. The early lymph node stage, VALSG limited disease staging and multimodality treatment were identified as independent prognostic factors. Surgery combined adjuvant chemotherapy was necessary for limited-stage PSCCE patients, especially for those with lymph node stages N1-3.

As suggested, we have revised the abstract which could reflect the manuscript well according to the purpose and result of the research. The changes were labeled in red in the Abstract Section of the manuscript (Page 2, Line 1-20) and were shown below.

Changes in the text:

Abstract

Background: Primary small cell carcinoma of the esophagus (PSCCE) is a rare and aggressive malignancy. It has a poor survival rate, and there is no consensus as to a standard therapeutic modality. In this study, we aimed to investigate the prognostic factors and evaluate the outcomes of patients with PSCCE who had been treated with different therapeutic methods (Page 2, line 3-6).

Methods: We retrospectively evaluated 113 consecutive patients with PSCCE who received treatment at our center from 2003 to 2016. The primary endpoint was overall survival (OS). The Cox regression model was used to analyze the prognostic factors. The survival analysis was calculated using the Kaplan-Meier and log-rank methods.

Results: The 12- and 36-month OS rates of all 113 enrolled patients were 45% and 12%, respectively. A significantly prolonged OS rate was associated with lymph node stages N0-N1 ($p = 0.022$), the Veterans' Administration Lung Study Group (VALSG) system limited-disease staging ($p = 0.040$), and multimodality treatments ($p = 0.047$). Patients with regional lymph node metastasis benefited more from surgery combined with chemotherapy than surgery or chemotherapy alone ($p = 0.046$). Concerning chemotherapy, cisplatin plus etoposide was the regimen most commonly used to treat PSCCE patients (67.5%) (Page 2, line 14-16).

Conclusions: An early lymph node stage, the VALSG limited-disease stages, and multimodality treatments were identified as independent prognostic factors of PSCCE. Surgery combined with adjuvant chemotherapy was especially necessary for limited-disease stage PSCCE patients with lymph node stages N1-3 (Page 2, line 18-19).

Comment 2: Some abbreviations in the tables are not explained.

Reply 2: Thanks for your helpful suggestions. Abbreviations in all tables were checked again and detailed explanation was provided.

Changes in the text:

Table 1: EP: etoposide and cisplatin chemotherapy, TP: paclitaxel and cisplatin chemotherapy;

Table 3: Syn: synaptophysin, P63: tumor protein P63;

Table 4: VALSG: Veterans' Administration Lung Study Group, LD: limited-stage disease, ED: extensive-stage disease.

Comment 3: Language needs review.

Reply 3: Thanks for your kind comments. The language of the article has been further modified and polished by a professional scientific editing agency—AME Editing Service.

Reviewer B

This is an impressive case-series of a rare disease that has many merits, and can be a good addition to the world literature. The authors have provided a strobe statement which is quite valuable. The manuscript does require a fair amount of editing, and I have the following comments and question to the authors:

Comment 1: It does not seem that a PET SCAN or EUS were performed in the work up of patients. I think this is a significant deficiency in the staging of patients with esophageal small cell cancer. Was there any brain imaging?

Reply 1: We appreciate your kind suggestions. As you mentioned, PET SCAN is an essential preoperative auxiliary examination to exclude distant metastasis [1-2]. And endoscopic ultrasonography (EUS) could evaluate the extent of the lesion and the regional lymph node condition, especially for patients who prepare to receive surgery treatment [1-2]. To assess PSCCE staging accurately, we recommend that all PSCCE patients undergo PET scans and EUS examinations. However, not all patients could

afford the cost of the two examinations, especially for patients who were diagnosed as PSCCE ten years ago, when the PET SCAN was expensive and not widely used.

Among 113 PSCCE patients in our study, 34 patients (34/113, 30.1%) received a PET SCAN examination. For patients who did not receive a PET SCAN, the brain imaging was recommended to exclude brain metastasis [3]. All patients in our study have received a brain imaging or PET SCAN and the brain metastases in six patients were found. Among 49 patients who were conducted surgery, 40 patients (40/49, 81.6%) received a EUS examination before surgery. Combined with contrast-enhanced computed tomography (CT), the EUS provided the detailed information of the extent of the lesion and the regional lymph node metastasis condition.

The relative contents have been added in the Materials and Methods Section (Page 5, line 19-20; Page 6, line 1-3) and Discussion Section (Page 14, line 17-20; Page 15, line 1) which are shown below for your convenience of reviewing.

Changes in the text:

Materials and Methods

Preoperative auxiliary examination

The routine workup included barium esophagography, endoscopic biopsy, brain imaging, and contrast-enhanced computed tomography (CT) scans of the neck, chest, and upper abdomen. A positron emission tomography (PET) scan is recommended to exclude distant metastasis. Endoscopic ultrasonography (EUS) evaluates the extent of the lesion and the condition of regional lymph nodes (Page 5, line 19-20; Page 6, line

1-3).

Discussion

To assess PSCCE staging accurately, we recommend that all PSCCE patients undergo PET scans and EUS examinations. Combined with contrast-enhanced computed tomography (CT), EUS examinations provide detailed information about the extent of the lesion, and the condition of regional lymph node metastasis. A PET scan is an essential preoperative auxiliary examination that can be used to exclude distant metastasis (Page 14, line 17-20; Page 15, line 1).

Reference:

1. Jeong DY, Kim MY, Lee KS, Choi JY, Kim SJ, Chung MJ, et al. Surgically resected T1- and T2-stage esophageal squamous cell carcinoma: T and N staging performance of EUS and PET/CT. *Cancer Med.* 2018 Aug;7(8):3561-3570.
2. Manoharan P, Salem A, Mistry H, Gornall M, Harden S, Julyan P, et al. 18F-Fludeoxyglucose PET/CT in SCLC: Analysis of the CONVERT Randomized Controlled Trial. *J Thorac Oncol.* 2019 Jul;14(7):1296-1305.
3. Li Q, Deng M, Xi M, Zhu Y, Hu Y. Characteristics and Treatment of Brain Metastases from Esophageal Squamous Cell Carcinoma. *J Cancer.* 2018 Feb 25;9(5):901-905.

Comment 2: I am not aware that the VALSG is applicable for esophageal small cell cancers. The staging system was developed for small cell lung cancers, and the limited vs. extended disease based on whether or not the disease is limited to one

hemithorax. The esophagus is a midline structure, I am not sure how we can apply that staging system to this organ. How was the local region defined to determine if patients had limited disease anyhow?

Reply 2: Thanks for your kind suggestions. TNM staging system of the American Joint Committee on Cancer (AJCC) is the best staging system for primary small cell carcinoma of the esophagus (PSCCE) [1-2]. In this study, the PSCCEs were staged according to the AJCC TNM Classification of Carcinoma of the esophagus and the results were displayed in Table 1. Moreover, PSCCE has a tendency toward early development of widespread metastasis which is similar to the characteristics of small cell lung cancer (SCLC) [3]. The Veterans' Administration Lung Study Group (VALSG) system, which was originally applied in SCLC, has been widely used in PSCCE staging [4-6].

VALSG comprises two staging categories: limited disease (LD) and extensive disease (ED). As we known, the limited-stage SCLC was confined to a single radiation port, the ipsilateral mediastinum, the ipsilateral mediastinal or supraclavicular lymph nodes. Unlike SCLC, esophagus is a midline structure organ, which could invade the bilateral mediastinum. LD-stage PSCCE is characterized by limited tumoral involvement to the bilateral mediastinum (with or without local extension) and no distant extra-thoracic metastatic disease. Bilateral hilar, abdominal trunk, bilateral cervical paraoesophageal lymph nodes are considered as esophageal regional lymph nodes. However, regardless of the primary tumor location, bilateral supraclavicular lymph nodes are defined as distant metastases. All other cases, including features, such

as malignant pleural and pericardial effusions, are classified as ED-stage PSCCE.

The relative description was added in the Results Section (Page 6, line 9-16).

Changes in the text:

Staging

LD-stage PSCCE is characterized by limited tumoral involvement to the bilateral mediastinum (with or without local extension) and no distant extra-thoracic metastatic disease. Bilateral hilar, abdominal trunk, bilateral cervical paraoesophageal lymph nodes are considered as esophageal regional lymph nodes. However, regardless of the primary tumor location, bilateral supraclavicular lymph nodes are defined as distant metastases. All other cases, including features, such as malignant pleural and pericardial effusions, are classified as ED-stage PSCCE (Page 6, line 9-16).

Reference:

1. Rice TW, Ishwaran H, Ferguson MK, Blackstone EH, Goldstraw P. Cancer of the esophagus and esophagogastric junction: an 8 edition staging primer. *J Thorac Dis.* 2017;9(3):E282-4.
2. Wang SY, Mao WM, Du XH, Xu YP, Zhang SZ. The 2002 AJCC TNM classification is a better predictor of primary small cell esophageal carcinoma outcome than the VALSG staging system. *Chin J Cancer.* 2013 Jun;32(6):342-52.
3. Sun KL, He J, Cheng GY, Chai LX. Management of primary small cell carcinoma of the esophagus. *Chin Med J (Engl).* 2007;120(5):355-8.

4. Carter BW, Glisson BS, Truong MT, Erasmus JJ. Small cell lung carcinoma: staging, imaging, and treatment considerations. *Radiographics*. 2014 Oct;34(6):1707-21.
5. Xu L, Li Y, Liu X, Sun H, Zhang R, Zhang J, et al. Treatment Strategies and Prognostic Factors of Limited-Stage Primary Small Cell Carcinoma of the Esophagus. *J Thorac Oncol*. 2017 Dec;12(12):1834-1844.
6. Chen WW, Wang F, Chen S, Wang L, Ren C, Luo HY, et al. Detailed analysis of prognostic factors in primary esophageal small cell carcinoma. *Ann Thorac Surg*. 2014 Jun;97(6):1975-81.

Comment 3: Small cell cancer of the esophagus is a rare disease, and it would be most useful if the authors give their opinion in terms of management, based on their experience. For instance, can they comment in more details which patients underwent surgery alone, and how can they justify that. To extrapolate from the lung small cell lung cancer literature, when we operate on patients with limited disease, we invariably recommend adjuvant chemotherapy and even prophylactic brain radiation. What would be their management in patients with localized disease or loco-regional disease? Do they advocate neoadjuvant CRT followed by surgery? On that note, it is interesting that only 5 patients underwent trimodality therapy.

I suggest the authors try to focus on how to make their experience and results clinically relevant for authors from around the world, in terms of management of this very rare and aggressive disease.

Reply 3: Thanks for your helpful suggestions. Our center has abundant experience in the treatment of the small cell carcinoma of the esophagus (PSCCE). Different modalities were chosen depending on the characteristics of the tumors and the physical condition of patients. According to our experience, we divided the modalities

of PSCCE into surgery and non-surgery treatment according to tumor resectability [1].

Surgery is highly recommended for patients with localized or loco-regional disease [2]. Long-term follow-up examinations may be acceptable for patients without lymph node metastasis after an R0 excision. In the present study, we explored the correlation between treatment methods and the prognosis of PSCCE and found that N1-3-stage (but not N0-stage) patients who were treated with surgery combined with chemotherapy had a better prognosis than those who underwent surgery or chemotherapy alone. Thus, combined with our data, we recommended that N1-3-stage PSCCE patients receive adjuvant therapy after surgery.

Due to chemotherapy's potential side effects, we do not recommend over-enthusiastic chemotherapy for early-stage PSCCE patients. Concerning patients who received an R1/2 excision, postoperative chemoradiotherapy is essential to eliminate the residual lesion. For patients with tumor metastasis, chemotherapy is the key treatment to destroy metastatic tumor cells and control disease progression [3-5]. Radiotherapy is an effective treatment for PSCCE, especially in patients with cervical esophageal cancer, which is sensitive to radiotherapy but not suitable for surgery. Radiotherapy is often used as an adjuvant therapy pre- or post-surgery [6]. The treatment of radiotherapy alone is only suitable for patients who cannot afford surgery or concurrent chemoradiotherapy, especially those with poor performance status.

In recent years, more oncologists at our center have chosen neoadjuvant chemoradiotherapy (CRT) followed by surgery to treat PSCCE [7]. However, the

prognosis of patients with neoadjuvant CRT is not clear yet. For patients with a T4 tumor, we recommend a neoadjuvant CRT to shrink the tumor before surgery. With the development of immunotherapy, immunotherapy combined with chemotherapy can treat PSCCE patients, especially those with unresectable tumors, recurrence, or distal metastasis. Many ongoing clinical trials are being conducted at our center, and the results could provide useful insights into PSCCE treatments in the future. However, immunotherapy's side effects, including myocarditis, pneumonitis, hepatitis, and encephalitis, need to be considered [8].

Our opinion and experience have been shared in the Discussion Section (Page 16-19) with the clinically relevant authors from around the world, in terms of management of PSCCE which is a very rare and aggressive disease.

Changes in the text:

Discussion

Surgery is highly recommended for patients with good performance status and resectable tumors. To be eligible for surgery, PSCCE patients must meet the following criteria: 1) be at a TNM stage of I, II, or III; 2) a tumor stage of 1, 2, or 3 (T1, T2, or T3); 3) show no nodal involvement (N0), or the presence of tumor(s) in no more than 6 lymph nodes (N1-2); 4) and show no metastases (M0); 5) have esophageal cancer in the middle or lower third of the esophagus; 6) have a World Health Organization performance-status score of 0 or 1 (on a 5-point scale) (Page 16, line 13-19).

Long-term follow-up examinations may be acceptable for patients without lymph

node metastasis after an R0 excision. In the present study, we explored the correlation between treatment methods and the prognosis of PSCCE and found that N1-3-stage (but not N0-stage) patients who were treated with surgery combined with chemotherapy had a better prognosis than those who underwent surgery or chemotherapy alone. Thus, combined with our data, we recommended that N1-N3-stage PSCCE patients receive adjuvant therapy after surgery. Due to chemotherapy's potential side effects, we do not recommend over-enthusiastic chemotherapy for early-stage PSCCE patients. Concerning patients who received an R1/2 excision, postoperative chemoradiotherapy is essential to eliminate the residual lesion (Page 17, line 7-16).

Radiotherapy is an effective treatment for PSCCE, especially in patients with cervical esophageal cancer, which is sensitive to radiotherapy but not suitable for surgery. Radiotherapy is often used as an adjuvant therapy pre- or post-surgery. The treatment of radiotherapy alone is only suitable for patients who cannot afford surgery or concurrent chemoradiotherapy, especially those with poor performance status.

In recent years, more oncologists at our center have chosen neoadjuvant chemoradiotherapy (CRT) followed by surgery to treat PSCCE. However, the prognosis of patients with neoadjuvant CRT is not clear yet. For patients with a T4 tumor, we recommend a neoadjuvant CRT to shrink the tumor before surgery. With the development of immunotherapy, immunotherapy combined with chemotherapy can treat PSCCE patients, especially those with unresectable tumors, recurrence, or distal metastasis. Many ongoing clinical trials are being conducted at our center, and the

results could provide useful insights into PSCCE treatments in the future. However, immunotherapy's side effects, including myocarditis, pneumonitis, hepatitis, and encephalitis, need to be considered (Page 19, line 1-14).

Reference:

1. Wong AT, Shao M, Rineer J, Osborn V, Schwartz D, Schreiber D. Treatment and survival outcomes of small cell carcinoma of the esophagus: an analysis of the National Cancer Data Base. *Dis Esophagus*. 2017;30(2):1-5.
2. Xu L, Li Y, Liu X, Sun H, Zhang R, Zhang J, et al. Treatment Strategies and Prognostic Factors of Limited-Stage Primary Small Cell Carcinoma of the Esophagus. *J Thorac Oncol*. 2017;12(12):1834-44.
3. Jeene PM, Geijsen ED, Muijs CT, Rozema T, Aleman BMP, Muller K, et al. Small cell carcinoma of the esophagus: a Nationwide analysis of treatment and outcome at patient level in Locoregional disease. *Am J Clin Oncol*. 2019;42(6):534-8.
4. Wang HH, Zaorsky NG, Meng MB, Wu ZQ, Zeng XL, Jiang B, et al. Multimodality therapy is recommended for limited-stage combined small cell esophageal carcinoma. *Onco Targets Ther*. 2015;8:437-44.
5. Raja S, Rice TW, Rajeswaran J, Zhong J, Blackstone EH. Esophageal small-cell cancer: study of a rare disease. *Dis Esophagus*. 2013;26(7):690-5.
6. Chen B, Yang H, Ma H, Li Q, Qiu B, Hu Y, et al. Radiotherapy for small cell carcinoma of the esophagus: outcomes and prognostic factors from a retrospective study. *Radiat Oncol*. 2019 Nov 21;14(1):210.

7. Pasquali S, Yim G, Vohra RS, Mocellin S, Nyahongo D, Marriott P, et al. Survival After Neoadjuvant and Adjuvant Treatments Compared to Surgery Alone for Resectable Esophageal Carcinoma: A Network Meta-analysis. *Ann Surg.* 2017 Mar;265(3):481-491.
8. Martins F, Sofiya L, Sykiotis GP, Lamine F, Maillard M, Fraga M, et al. Adverse effects of immune-checkpoint inhibitors: epidemiology, management and surveillance. *Nat Rev Clin Oncol.* 2019 Sep;16(9):563-580.