

BMJ Open Comparative clinical studies of primary chemoradiotherapy versus S-1 and nedaplatin chemotherapy against stage IVb oesophageal squamous cell carcinoma: a multicentre open-label randomised controlled trial

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ABSTRACT

Introduction Oesophageal squamous cell carcinoma (OSCC) is one of the most commonly occurring devastating tumours worldwide, including in China. To date, the standard care of patients with stage IV OSCC is systemic chemotherapy and palliative care, which results in poor prognosis. However, no consensus has been established regarding the role of radiotherapy in targeting the primary tumour in patients with stage IVa OSCC. Thus, the aim of this study is to assess the effectiveness of primary radiotherapy combined with S-1 and nedaplatin (NPD) chemotherapy in the patients with stage IV OSCC.

Methods and analysis The study is a multicentre, open-label, randomised controlled trial. A total of 180 eligible patients with stage IV OSCC will be randomised into a study group (90 patients) and a control group (90 patients). Patients in the study group will receive radiotherapy to the primary tumour at a dose of 50.4 Gy combined with 4–6 cycles of S-1 and NPD chemotherapy. In the control group, patients will only receive 4–6 cycles of S-1 and NPD chemotherapy. The primary and secondary outcomes will be measured. The differences between the two groups will be statistically analysed with regard to overall survival, the progression-free survival and safety. All outcomes will be ascertained before treatment, after treatment and after the follow-up period.

The results of this study will provide evidence on the role of radiotherapy in patients with stage IV OSCC in China, which will show new options for patients with advanced oesophageal cancer.

Ethics and dissemination This study was approved by the Institutional Ethics Committee of The First Hospital Affiliated of Zhengzhou University (approval number: SS-2018–04).

Trial registration The trial has been registered at the Chinese Clinical Trial Registry (ChiCTR1800015765) on 1 November 2018; retrospectively registered, <http://www.chictr.org.cn/index.aspx>.

Strengths and limitations of this study

- The role of radiotherapy to target the primary tumours during the treatment of patients with stage IVa oesophageal squamous cell carcinoma (OSCC).
- The aim of this multicentre, open-label, randomised controlled trial is to ascertain the effectiveness of primary radiotherapy combined with S-1 and nedaplatin (NPD) chemotherapy in patients with stage IV OSCC.
- Strength of this study: radiotherapy in combination with S-1 NPD in patients with stage IV OSCC provides potent insights into the treatment standards for patients with advanced oesophageal cancer.
- Limitation of this study: small sample size for radiotherapy with S-1 and NPD chemotherapy.

INTRODUCTION

Oesophageal cancer (OSCC) is one of the most common malignant tumours and is the sixth leading cause of cancer-associated mortality.^{1–3} The incidence of OC is comparatively higher in China than in Western countries and its incidence is over a half of all newly diagnosed OCs.⁴ Among these cases, oesophageal squamous cell carcinoma (OSCC) accounts for ~95% of all cases.^{5–7} OSCC is a distinctive subtype of OC which predominantly observed in China, while the predominant histological subtype of OC is oesophageal adenocarcinoma in Europe and the USA.⁸ OSCC is highly responsive to chemoradiation, which takes up to over 90% of patients suffering from OC in China.⁹ For instance, the concurrent chemoradiotherapy



(cisplatin in combination with 5-fluorouracil (5-FU)) is an effective first-line treatment for stage II–III OSCC. Even though this combination enhances overall survival (OS), the clinical outcomes are constrained by the adverse toxicity including nausea, cardiotoxicity and nephrotoxicity.^{10–13} Nedaplatin (NPD) could be another potential second-generation platinum-based therapy against OC and the combinatorial regimen of docetaxel with ‘tegafur-gimeracil-oteracil potassium (S-1)’ has proven effective against OC when combined with the platinum-based therapeutic molecule, but this combination also conferred adverse toxicity with minimal OS.^{7 14–19}

Over the past decade, many therapeutic regimens have been continuously examined for their efficacy as promising targeted therapeutics against OC. For instance, trastuzumab has been approved as it can target human epidermal growth factor receptor (HER2) for patients with HER2-positive OC as the first-line therapy.²⁰ The efficacy of newly developed targeted agents for OC is still limited with unsatisfying improvement in survival, and some potential targeted drugs are still in the preclinical trial stage.²¹ To date, 5-FU combined with platinum-based chemotherapy is still preferred in the management of OC, and this combinatorial regimen has delivered only a 20% 5-year OS rate.²² S-1 is a novel oral fluorouracil anticancer drug which has an enhanced effect if given in combination with radiotherapy and mitigates gastrointestinal toxicity.²³ NPD can foster antitumour effects by inhibiting DNA replication which exhibits nearly similar antitumour mechanisms as cisplatin but with the reduced nephrotoxicity and gastrointestinal toxicity. Yamashita *et al* performed a single-arm study on concurrent chemoradiotherapy with S-1 plus NPD in patients with stage I–IV OC. In this study, the overall remission rate was 85% and the 3-year OS was 39.8% at stage IV. About 70% patients were treated as outpatients, which shortens hospitalisation and reduces medical expenditure.²⁴ As a result, the concurrent chemoradiotherapy with S-1 in combination with NPD is effective and well tolerated, and has been adopted in our study. Thus, it would be of great interest to investigate the optimal regimen of chemoradiation as the treatment strategy for OSCC. In terms of a combined chemoradiation approach, a number of studies have compared the effect of sequential chemoradiation (SCR) and concurrent chemoradiation (CCR) against advanced OC in the patients unfit for surgery.^{25–27} The results confirmed that CCR could enhance local control and survival benefit when compared with SCR, which provides a positive reference for the chemoradiation combinatorial regimen in OC management. As a result, CCR is adopted as the standard regimen in this clinical trial. In addition, according to the Radiation Therapy Oncology Group (RTOG) 9405 regimen, a total dose of concurrent 50.4 Gy is proposed as the standard radiation dose for the patients with OSCC; however, a higher dose of 64.8 Gy previously has not generated significant survival advantages in patients with OSCC.²⁸

Approximately 30% of patients with OC are reported to exhibit distant metastases at their initial diagnosis, which refers to patients with stage IVb OC who generally have little chance to receive curative resection.²⁹ Thus, it would be remarkable to explore the optimal modality paradigm for the treatment of patients with stage IVb OC based on the current drugs and treatment. According to the latest National Comprehensive Cancer Network guidelines, systemic chemotherapy and palliative care are recommended for patients with OC accompanied by unresectable, local recurrence or metastasis; hence, the treatment of OC requires combinatorial doublet or triplet chemotherapeutic agents as first-line or second-line therapy.³⁰ Notably, the use of radiotherapy is not mentioned in this treatment regimen. The possible reason would be a lack of strong prospective results that demonstrate the explicit role of radiotherapy in the management of patients with stage IVb OC. At present, no consensus has been established regarding the role of radiotherapy to the primary tumour in the treatment of patients with OC, especially in patients with stage IVb OSCC. Therefore, a prospective randomised controlled study is urgently needed to provide the effective combinatorial modalities for patients with stage IVb OSCC. The current study is conducted to compare the effect of ‘primary radiotherapy in combination with concurrent chemotherapy’ with chemotherapy alone for the patients with stage IVb OSCC, to ascertain OS, local control rate and quality of life (QoL).

METHODS

Patient and public involvement

This study did not involve any patients or the public in the design, or conduct, or reporting, or dissemination plans of the research.

Study design

The current study is a multicentre, open-label, randomised controlled trial. This clinical trial is completely random, but not double-blind because the patients are divided into a chemotherapy group and a ‘concurrent radiotherapy with chemotherapy group’ according to the treatment plan. Such differences in treatment options cannot be double-blind. Therefore, masking was not executed for this protocol. Patients were enrolled from 1 June 2018 and the enrolment will be completed in July 2021; 14 hospitals will participate in the study (table 1). A total of 180 patients will be randomised, with 90 in each group (figure 1). After informed consent is obtained, eligible patients will be randomly assigned to one of the two groups in a ratio of 1:1. The randomised numbers will be generated by the block randomisation method using SAS software, version 9.4.

Patients with stage IVb OSCC who meet the eligibility criteria of this study will be randomised into the synchronous radiotherapy group (study group) or chemotherapy group (control group). Screening tests will be performed to determine eligible patients, including a physical

Table 1 Participating unit

Institution (hospital)	City
The First Affiliated Hospital of Zhengzhou University	Zhengzhou
Henan Province People's Hospital	Zhengzhou
Henan Cancer Hospital	Zhengzhou
Anyang Cancer Hospital	Anyang
The First Affiliated Hospital of Xinxiang Medical College	Weihui
The First Affiliated Hospital of Henan University of Science and Technology	Luoyang
Nanyang Central Hospital	Nanyang
The General Hospital of Pingmei Shenma Medical Group	Pingdingshan
Linzhou People's Hospital	Linzhou
Linzhou Cancer Hospital	Linzhou
The First Affiliated Hospital of Nanyang Medical College	Nanyang
Xixia County People's Hospital	Xixia
Xinxiang Central Hospital	Xinxiang
Linying County People's Hospital	Linying

examination, Karnofsky Performance Status, ECG, laboratory examinations (blood routine, serum biochemistry and routine urine), and imaging examinations including oesophageal barium meal, oesophagoscopy or ultrasound endoscope, contrast-enhanced CT or MRI scans of the neck, chest and abdomen, and other CT or MRI based on metastases). Eligible patients will be enrolled according to the inclusion and exclusion criteria with informed consent as described below. The schedule of the whole study period is summarised in [table 2](#).

Patients in the study group will be treated with 'primary radiotherapy' combined with four to six cycles of S-1 and NPD chemotherapy. Patients in the control group will receive individual treatment modalities of four to six cycles of S-1 and NPD chemotherapy. After treatment, patients are followed up for 3 years and the differences between the two groups are statistically analysed regarding OS, progression-free survival (PFS) and safety. The study design is shown in the flow chart in [figure 1](#).

Patients and eligibility criteria

Patients with stage IVb OSCC will be enrolled in this study. The detailed *inclusion criteria* are as follows:

- ▶ Patients who are older than 18 years old, male or female, at least on a liquid diet
- ▶ Patients with the eastern US tumour cooperation group (ECOG) score 0–2
- ▶ Patients with histologically proven initial diagnosis of OSCC
- ▶ Patients with the clinical stage of cTxNxMI, IVb³¹
- ▶ Patients with baseline blood routine and biochemical indicators in accordance with the following criteria: haemoglobin greater than 80 g/L; absolute neutrophil count over $1.5 \times 10^9/L$; platelet count over $100 \times 10^9/L$; total bilirubin less than 1.5 times the upper limit of normal (ULN); alanine aminotransferase and aspartate aminotransferase less than 2.5 ULN; international normalised ratio of prothrombin time and partial thromboplastin time less than 1.5, in the normal range (1.2 times the normal limit to 1.2 times the ULN value); less than 1.5 ULN
- ▶ Patients with basically normal ECG in the first 4 weeks, and with no obvious clinical symptom of heart disease
- ▶ Patients with barium meal lesion length less than or equal to 10 cm
- ▶ Patients who signed informed consent.

The *exclusion criteria* are as follows:

- ▶ Patients with OC proven by histology
- ▶ Patients with known allergies to NPD or fluorouracil, or metabolic disorders
- ▶ Patients who received prior chemotherapy, radiotherapy or targeted therapy
- ▶ Patients who received prior experimental drugs in other clinical trials at the same time
- ▶ Patients with complete or incomplete digestive tract obstruction, digestive tract active bleeding, and perforation

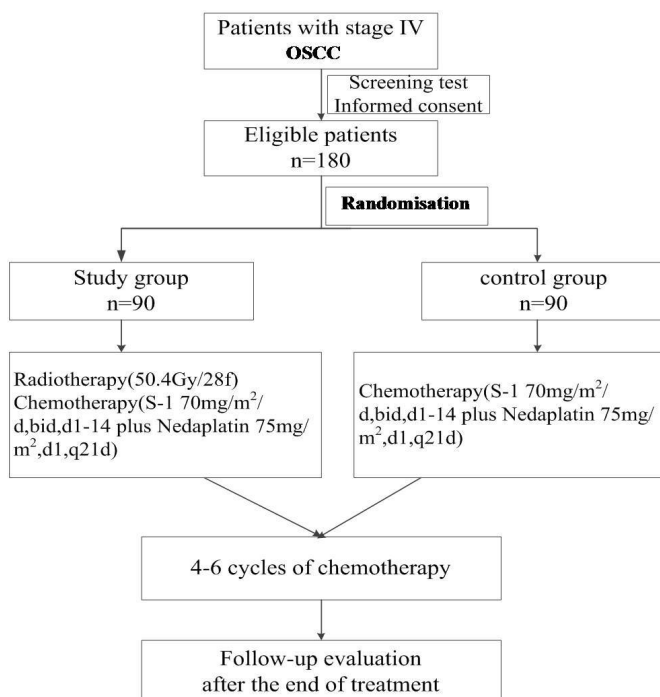


Figure 1 The current trial design including patient recruitment, inclusion criteria, randomisation of patient groups into study group and control group is depicted. A total of 180 patients randomised into the study group (n=90) and control group (n=90). OSCC, oesophageal squamous cell carcinoma.

Table 2 The entire schedule of proposed study

Study period	Screening D-21-D0	Treatment period										End of treatment		Follow-ups (every 3 months in the first year, every 4 months in the second year, and every 6 months in the third year)			
		First cycle					Second cycle					Dropout	Dn				
		First week D1	Second week D8	Third week D15	Fourth week D1	Fifth week D8	Sixth week D15	Third–sixth cycles	Seventh–eighteenth weeks								
Informed consent	✓																
General profiles and medical history	✓																
General condition and physical examination	✓	✓															✓
histology	✓																
ECOG Score	✓	✓															✓
Blood routine	✓	✓	✓														✓
Routine urine	✓	✓															✓
Serum biochemistry	✓	✓															✓
ECG	✓	✓															✓
Urine pregnancy test	✓																
Oesophageal barium meal	✓																✓
Esophagoscopy/ultrasound endoscopy	✓																✓
Contrast-enhanced CT or MRI scans of the neck, chest and abdomen	✓																✓
CT or MRI of the pelvic region																	
CT or MRI of the head																	
Radionuclide bone imaging																	
CEA																	
Chemotherapy																	
Radiotherapy (study group)																	
Tumour evaluation (RECIST 1.1)	✓																✓
QoL assessment	✓																✓

Continued

Table 2 Continued

Study period	Treatment period										End of treatment		Follow-ups (every 3 months in the first year, every 4 months in the second year, and every 6 months in the third year)
	First cycle					Second cycle					Dropout	Dn	
	Screening	First week	Second week	Third week	Fourth week	Fifth week	Sixth week	Third–sixth cycles	Seventh–eighteenth weeks				
Time of each cycle (day)	D-21-D0	D1	D8	D15	D1	D8	D15	D15	D8	D15	Dn		
CTC AE version.4.0	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Radiation-induced side effects (RTOG)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Survival data													
Concomitant medication	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	

AE, adverse event; CEA, Cost-Effectiveness Analysis; CTCAE, Common Terminology Criteria for Adverse Event; ECOG, Eastern Cooperative Oncology Group; QoL, quality of life; RECIST, Response Evaluation Criteria in Solid Tumors; RTOG, Radiation Therapy Oncology Group.

- ▶ Patients with serious liver disease (such as cirrhosis), kidney disease, respiratory disease or uncontrolled diabetes, hypertension, and other chronic systemic disease, patients with congestive heart failure, symptoms of coronary heart disease, drug refractory arrhythmia, or patients who have a myocardial infarction, or heart failure within 6 months
- ▶ Patients with a disorder of the peripheral nervous system or with a history of obvious mental disorders or central nervous system disorders
- ▶ Patients with an activity period of severe infection higher than level 2 of the common adverse event evaluation standard (Common Terminology Criteria for Adverse Event (CTCAE))
- ▶ Patients who are suffering from cancers other than OC during the first 5 years of treatment, which excludes cervical carcinoma in situ, basal cell carcinoma and bladder epithelial tumour (including Ta and Tis)
- ▶ Patients with a history of organ transplantation (eg, autologous bone marrow transplantation and peripheral stem cell transplantation) or long-term systemic steroid therapy (short-term users stop taking drugs for >2 weeks)
- ▶ Patients with a second primary tumour
- ▶ Patients who are pregnant, breastfeeding mothers and women of childbearing age, and their spouses refusing effective contraception
- ▶ People without legal capacity, medical or ethical reasons to involve in this current research.

Patients will be withdrawn from the study based on the following *dropout criteria*:

- ▶ Disease progression at any stage of the treatment
- ▶ Occurrence of adverse events (AEs) or serious adverse events (SAEs) which result in stopping the trial based on medical judgement or at the request of patients and their relatives
- ▶ Patients who cannot tolerate the treatment according to the trial protocol after dosage adjustment when grade 3/4 AEs occur
- ▶ Patients who have other complications and report to discontinue participating in the study based on medical judgement
- ▶ Patients who reject participation in the study
- ▶ Patients who are unable to follow the trial protocol with poor compliance
- ▶ Patients prescribed other anticancer treatment which affects the outcome
- ▶ Pregnant patients
- ▶ Patients who died
- ▶ Patients lost to follow-up.

Sample size

A total of 180 patients will be enrolled in this study and segregated into two groups with 90 in each group. The sample size in this study will be calculated using a log-rank test. It is assumed that the estimated OS is 8 months for the chemotherapy group and 11 months for the synchronous radiotherapy group. The estimated duration of

this study includes 2 years of recruitment and 3 years of follow-up. The desired level of HR at 95% CI is 0.75 with a statistical power of 0.8 at a two-sided value of $p=0.05$ ($\alpha=0.05$, $\beta=0.8$). Therefore, assuming approximately 10% dropouts, the minimum sample size required for both groups is taken as 90 patients.

Randomisation

A simple random method is used in this study. After informed consent is obtained, all the eligible patients will be randomly assigned to one of the two groups in a ratio of 1:1. Randomised numbers will be generated using the method of block randomisation using SAS software, version 9.4.

Interventions

Radiotherapy

Three-dimensional conformal radiation therapy or intensity-modulated radiation therapy will be given using a 6MV X-ray with a linear accelerator. The gross tumour volume (GTV) includes the primary tumour lesion defined by oesophageal barium meal and contrast-enhanced CT. The clinical tumour volume (CTV) is constructed by expanding the margin of GTV to 3cm superiorly and inferiorly, and 0.8cm laterally, which does not include regional lymph node drainage. The planning target volume (PTV) is produced by expanding CTV with 0.5cm in all directions. Organs at risks (OAR) including lung, spinal cord and heart will also be contoured. A total of 50.4Gy for PTV will be irradiated with 1.8Gy per fraction and delivered as 28 reactions every 5 days per week. Dose constraints of OAR are defined as follows: for lung, V20 Gy should be less than 25%; for liver, V30 Gy should be less than 30% and mean dose should be less than 20Gy; for spinal cord, the maximum dose should be less than 45 Gy.

Chemotherapy

All the enrolled patients will receive S-1 and NPD chemotherapy. S-1 will be administered orally twice daily at a dose of 70mg/m²/day for 14 consecutive days. NPD will be given on day 1 of every cycle at a dose of 75mg/m². The regimen will be repeated every 3 weeks. Physicians will perpetually evaluate the patients' tolerance and clinical outcomes during the treatment. Patients who attain good tolerance will receive six cycles of chemotherapy whereas the patients with poor tolerance will receive at least four cycles of chemotherapy.

Dosage adjustment and toxicity criteria

The predicted common adverse effect in this study could be myelosuppression, which is accompanied by clinical manifestations such as leucopenia, neutropenia, thrombocytopenia and neutropenia with fever. Patients will receive supportive treatment if they suffer myelosuppression. For instance, PEG-G-CSF will be used as a prophylactic during radiotherapy. Besides, antiemetics will be prescribed as prophylactics in order to relieve vomiting and anorexia caused by gastrointestinal toxicity. Chemotherapy will be

postponed to 28 days per cycle during severe toxicity such as myelosuppression that affects the normal process of treatment. Dosage will be properly adjusted when severe toxicity occurs during concurrent chemoradiotherapy. The anticipated dose levels of S-1 include 60mg/m²/day and 40mg/m²/day. For NPD, the dose reduced by 20% in each adjustment is one dose level. The toxicity testing will be applied in patients who have more than twice of the dosage adjustment.

Follow-up

Follow-ups include a physical examination, ECG, serum biochemistry, oesophageal barium meal, contrast-enhanced CT or MRI scans of the neck, chest and abdomen, and other CT or MRI based on metastasis. All patients will be followed up for 3 years, specifically, 1 month after the end of treatment, every 3 months for the first year, every 4 months for the second year and every 6 months for the third year. The survival of patients will be followed up by telephone or WeChat. If AEs have not been alleviated, the follow-up will continue.

Ethics and dissemination

The current trial is planned and will be executed in accordance with the Declaration of Helsinki. This study was approved by the Institutional Ethical Committee (IEC) of The First Affiliated Hospital of Zhengzhou University (approval number: SS-2018-04) and the trial has been registered at the Chinese Clinical Trial Registry (ChiCTR1800015765). A timely intimation will be given to both IEC and registry centre if there will be any anticipated changes in the clinical research protocol. Prior to enrolment of patients, the researchers will inform treatment strategies and the risks anticipated in the study, followed by their power to withdraw from the study. Free medical advice and guidance will be given to all the patients throughout the duration of the study.

Trial status

The present trial is currently in the recruitment stage and the protocol was registered on 19 April 2018. The anticipated date for the completion of the trial will be 1 November 2023.

Outcome

Primary and secondary outcome measures

OS is the primary outcome measure and it is the time interval from the start of treatment to death due to any reason. Secondary outcome measures are PFS, 3-year PFS, 3-year OS, and objective response rate (ORR), QoL and adverse reactions. PFS indicates the interval of time from the first date of treatment to the first reported disease progression in the first time. Three-year PFS and 3-year OS refer to the rate of patients with PFS and OS at 3 years since the end of the treatment.

QoL refers to the scale of EORTCQLQ-C30 and EORTCQLQ-OES18. EORTCQLQ-C30 is a core scale for all patients with cancer with 30 items comprising five functional domains (body, role, cognition, emotion

and society), three symptomatic domains (fatigue, pain, nausea and vomiting), one QoL domain and six single items (dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial difficulties).³² EORTCQLQ-C18 will be applied for patients with OC with 18 items.³³

ORR is defined as the sum of complete response and partial response according to the Response Evaluation Criteria in Solid Tumors version 1.1.³⁴

Safety evaluation

Safety evaluation is based on CTCAE version 4.0.³⁵ Radiation-induced side effects will be evaluated according to the scoring criteria of the RTOG or the European Organisation for Research and Treatment of Cancer.³⁶ During the entire course of the study, any AE, including occurrence time, severity, duration and treatment measures, will be significantly reported and documented objectively in the case report form (CRF). SAEs should be reported to the First Affiliated Hospital of Zhengzhou University Ethics Committee within 24 hours. The association between AEs and treatment will be assessed according to the relevance evaluation standard between AE and investigational drugs, the judgements of which include definite relevance, probable relevance, difficult to determine, probable irrelevance, and definite irrelevance. Timely countermeasures would be taken when AEs or SAEs occur and patients followed up until normalisation or stabilisation.

Data management and analysis

Medical records of the enrolled patients will be considered as the original data in this clinical trial and will be kept in the hospital. Authors will have access to the information that could identify individual participants during or after data collection. Data will be documented in an accurate manner into CRFs in accordance with the original observations of patients, which cannot be altered or overwritten. All files including medical records, CRFs and informed consents will be sent to the corresponding project investigators and signed before archiving.

Statistical analysis of collected data will be conducted using SPSS V.19.0 statistical software by professional statisticians. The count data will be described as frequencies and percentages, and the measurement data will be described as the mean and SD. For the count data, *Pearson's χ^2 test* or *Fisher's exact test* will be used for analysis. *Student's t-test* or *Wilcoxon rank-sum tests* will be used for the measurement data. The *Kaplan-Meier method* will be used for survival analysis and differences between survival curves will be analysed using the log-rank test. Cox regression analysis will be used for prediction analysis. The significance level is at 0.05 with a CI of 95%. A two-sided value of $p < 0.05$ can be regarded as statistically significant.

Quality control

All the researchers will be significantly requested to accept complete training and they must be fully aware of the current study. During this study, the principal investigator

will check the CRFs on a weekly basis. Grouping, data collection and clinical analysis of the collected data will be executed by specific members. AEs that might occur during the study will be recorded clearly in detail. The participant's data will be recorded by the researcher and kept as confidential.

DISCUSSION

The majority of the patients who diagnosed for 'OC with advanced stage' failed to deliver a good OS rate and the disease is incurable by surgery.³⁷ It is to be noted that about 20%–30% of patients with OC are newly diagnosed with stage IVb OC which is generally unresectable, leading to a very poor prognosis. Palliative chemotherapy with doublet or triplet agents is recommended as standard practice for patients with stage IVb OC; the main goal of this therapy is to alleviate the symptoms, control tumour growth and improve QoL.³⁸ However, the role of primary radiotherapy in those patients remains unclear.

In a study of stage IV non-small cell lung cancer (NSCLC), 29 patients with oligometastasis NSCLC were enrolled.³⁹ The results of this study demonstrated that definitive dose radiotherapy combined with chemotherapy improved local control and survival in comparison to chemotherapy alone in the patients with oligometastatic tumours of NSCLC. The median time to local failure was significantly longer in the patient group receiving 'thoracic radiation combined with chemotherapy' than the patient group receiving chemotherapy alone, which shows the survival advantages of thoracic radiotherapy in patients with stage IV NSCLC.⁴⁰ In a phase III clinical trial, a total 498 patients with extensive stage small-cell lung cancer were randomly assigned to the thoracic radiotherapy group and the control group. The results showed that the patients who received thoracic radiotherapy exhibited higher median survival than those who did not receive thoracic radiotherapy.⁴¹ Similar results were identified in the patients with metastatic prostate cancer, in which local radiotherapy can improve survival in patients with a low metastatic burden, suggesting the potential survival advantages of radiotherapy for metastatic prostate cancer.⁴² These findings illustrate a survival benefit of the use of radiotherapy for targeting primary tumours for advanced malignancies, which provides a new treatment strategy for patients with stage IVb OC. Previously a meta-analysis by Zhang *et al* depicted the efficacy of NDP-based regimens accompanied by higher clinical efficacy, limited toxicity and enhanced tolerability in patients with OSCC than the cisplatin-based regimens.⁴³ Furthermore, a phase-I/II study of patients with OC were recommended with 50 mg/m² NDP administration twice every 3 weeks, concomitantly administered 5-FU and radiotherapy; this therapeutic modality produced an ORR of 85.5%.⁴⁴ The current study can delineate the efficacy of primary radiotherapy combined with S-1 and NPD chemotherapy in patients with stage IVa OSCC and this regimen may

improve OS and clinical outcomes. Ikeda *et al* evaluated the role of palliative chemoradiotherapy in patients with stage IVb OC with dysphagia. In this retrospective study, radiotherapy of 40 Gy to the oesophageal primary tumour combined with concurrent chemotherapy effectively relieved the symptoms of dysphagia with favourable clinical outcomes.⁴⁵ Similarly, Guttman *et al* also conducted an observational cohort study to assess the efficiency of radiotherapy in the patients with newly diagnosed metastatic OC. They found that an aggressive definitive radiotherapy dose of over '50.4 Gy' to the primary tumour was associated with improved OS compared with the palliative dose. These conclusions are consistent with previous findings that radiotherapy to the primary tumour confers a survival benefit. On the other hand, dose escalation may improve survival in patients with stage IV OC.⁴⁶ With regard to the underlying mechanisms of the potential role of radiotherapy in stage IV OC, there are several possible explanations. Primarily, to some extent, the radiotherapy to target the primary tumour can alleviate the symptoms of dysphagia or reduce the development of dysphagia, consequently fostering both nutritional status and psychological status.⁴⁷ Second, it is known that radiation can induce a bystander effect, including cell death, gene mutation and chromosome instability. In this scenario, non-irradiated normal cells have similar biological effects due to the release of molecular signals from the irradiated neighbouring cells.⁴⁸ This radiation-induced bystander effect has been confirmed in many metastatic solid tumours, including NSCLC, breast cancer and thymoma.⁴⁹ Furthermore, radiotherapy is reported to induce immunogenic tumour cell death and convert tumour cells into *in situ* vaccine to activate antitumour immune response.⁵⁰ Tumour cells inside and outside of the field of radiation can be killed by T cell-mediated immune response, which may be triggered by 'high-mobility group box 1 protein (HMGB1)' activity that can foster the processing and cross-presentation of tumour antigens taken up by dendritic cells.⁵¹

There are still some limitations of primary radiotherapy in the current anticipated research. Primarily, the sample size in these studies is very minimal, which will lead to inconclusive and unrepresentative results. Moreover, most studies on OC are single-arm trials without the set-up of a control group, and conclusions are not comparative. In summary, consensus has not been reached in respect to the impact on survival of primary radiotherapy in the patients with stage IVb OC. Therefore, further exploration and investigation is needed to focus on this issue. In this study, all the enrolled patients will receive chemotherapy with S-1 in combinatorial regimen with NPD. Additionally, patients in the study group will also receive synchronous radiotherapy to target primary oesophageal tumours. The prospective multicentre data in this study will assess the role of radiotherapy in patients with stage IV OSCC in China, which will provide potent insights into the treatment standards for patients with advanced OC.

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