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Comparison of paclitaxel in combination with cisplatin (TP), carboplatin (TC) or fluorouracil (TF) concurrent with radiotherapy for patients with local advanced esophageal squamous cell carcinoma: a three-arm phase III randomized trial (ESO-Shanghai 2)

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Key words: esophageal squamous cell carcinoma, concurrent chemoradiotherapy, paclitaxel, cisplatin, carboplatin, fluorouracil

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Abstract

Introduction: Concurrent chemoradiation is the standard therapy for patients with local advanced esophageal carcinoma unsuitable for surgery. Paclitaxel is an active agent against esophageal cancer and it has been proved as a potent radiation sensitizer. There have been multiple studies evaluating paclitaxel-based chemoradiation in esophageal cancer, the results of which are inspiring. However, which regimen, among paclitaxel in combination with cisplatin (TP), carboplatin (TC) and fluorouracil (TF) concurrent with radiotherapy, provides best prognosis with minimum adverse events is still considered far from resolved and very few studies focus on this field. The purpose of this study is to confirm the priority of TF to TP or TC concurrent with radiotherapy in terms of overall survival and propose a feasible and effective plan for patients with local advanced esophageal cancer.

Methods and analysis: ESO-Shanghai 2 is a three-arm, multicenter, open-labeled, randomized phase III clinical trial. The study was initiated in July 2015 and the duration of inclusion will be 4 years. The study compares two pairs of regimen: TF versus TP and TF versus TC concurrent with definitive radiotherapy for patients with esophageal squamous cell carcinoma (ESCC). Patients with histologically confirmed ESCC (clinical stage II, III or IVa based on the 6th UICC-TNM classification) and without any prior treatment of chemotherapy, radiotherapy or surgery against esophageal cancer will be eligible. A total of 321 patients will be randomized and allocated in a 1:1:1 ratio to the three treatment groups. Patients are stratified by lymph node status (N0, N1, M1a). The primary endpoint is overall survival and the secondary endpoint is progression-free survival and adverse events.

Ethics and dissemination:

This trial has been approved by the Fudan University Shanghai Cancer Center Institutional Review Board. Trial results will be disseminated via peer reviewed scientific journals and conference presentations.

Trial registration: Clinicaltrials.gov: NCT02459457

Strengths and limitations of this study

- First phase III randomized multi-centered study comparing these three regimens
- Stratification by lymph node status (N0, N1, M1a based on the 6th UICC-TNM classification)

Introduction

Worldwide, esophageal cancer is the eighth most common cancer, which is responsible for an estimated 455,800 new cases and 400,200 deaths in 2012.[1] Since its prognosis is dismal, much effort has been put into improving overall survival through multi-modality treatments, which consist of surgery, radiotherapy and chemotherapy.[2] Concurrent chemoradiation is the standard non-operative therapy for local advanced esophageal squamous cell carcinoma (ESCC).[3]

Paclitaxel is an active agent against esophageal cancer, with the response rate of 28% in ESCC, and it has been shown to be a potent radiation sensitizer.[4] There have been multiple studies evaluating paclitaxel-based chemoradiation in esophageal cancer, for instance, paclitaxel/fluorouracil (TF) developed at The University of Texas M.D. Anderson Cancer Center, and paclitaxel/cisplatin (TP) developed at Memorial Sloan-Kettering Cancer Center,[5,6] with paclitaxel/carboplatin (TC) from CROSS trial.[7] In many preoperative studies, paclitaxel-based chemoradiotherapy has achieved inspiring effect, the pathologic complete response rates of TP-based chemoradiotherapy were 19%-42%, [8-11] and of TC-based chemoradiotherapy was 49%.[7] However, which regimen, among TF, TP and TC-based definitive chemoradiotherapy, provides best prognosis with minimum adverse events is still considered far from resolved and very few studies focus on this field.

RTOG 0113[5] evaluated 2 different paclitaxel-based regimens (TP and TF). Eighty-four patients were accrued to this study. Patients in arm A (TF) received induction 5-FU, cisplatin, and paclitaxel followed by radiation and concurrent continuous infusion 5-FU and weekly paclitaxel. Patients in arm B (TP) received induction paclitaxel and cisplatin followed by radiation and concurrent weekly cisplatin and 96-hour infusion of paclitaxel. The median survival time was 28.7 months for patients in arm A (TF) and 14.9 months for patients in arm B (TP). Neither arm achieved the hypothesized 1-year survival rate of at least 77.5%. The main deficiency of this study is the small sample size, but the effect of TF group is still inspiring.

Another perspective multicenter randomize clinical trials from Europe[12] showed the overall survival of TC-based definitive chemoradiotherapy was comparable with cisplatin/5-FU(PF) as definitive concurrent chemoradiotherapy in esophageal cancer.

However, the toxicity rates were lower in the TC group together with higher treatment compliance.

Based on RTOG 0113 and other reports, we designed a multicenter randomized controlled phase III trial to confirm the priority of TF to TP and TF to TC concurrent with radiotherapy in terms of overall survival for patients with local advanced esophageal squamous cell carcinoma. Independent ethics committees of the participating centers approved the study protocol. This trial has been registered with ClinicalTrials.gov, number NCT02459457.

The trial is a three-arm, multicenter, open-labeled, randomized phase III clinical trial. The study was initiated in July 2015 and the duration of inclusion will be 4 years. The study compares two pairs of regimen: TF versus TP and TF versus TC concurrent with definitive radiotherapy in patients with esophageal squamous cell carcinoma.

Methods and analysis

Patient selection

To be eligible for this study, patient must fulfill all of the following criteria (Table 1):

Inclusion criteria
1. Histologically confirmed esophageal squamous cell carcinoma
2. Clinical stages II, III or IVa based on the 6th UICC-TNM classification
3. No prior treatment of chemotherapy, radiotherapy or surgery against esophageal cancer, except for non-curative resection by EMR/ESD.
4. Aged 18-75 years
5. Adequate organ functions for chemoradiation therapy
a) White blood cell (WBC) $\geq 3\times10^9$/L
b) Absolute neutrophil counts (ANC) $\geq 1.5\times10^9$/L
c) Hemoglobin (Hb) $\geq$10g/dl
d) Platelet (Plt) $\geq 100\times10^9$/L
e) Total bilirubin <1.5 upper limit of normal (ULN)
f) Aspartate transaminase (AST) $\leq$2.5 ULN
g) Alanine aminotransferase (ALT) $\leq$2.5 ULN

h) Creatinine ≤1.5 ULN

6. ECOG PS of 0-2
7. Life expectancy ≥3 months
8. Written informed consent

Patients fulfilling any of the following criteria are ineligible for this study (Table 2).

Exclusion criteria
1. Esophageal perforation or hematemesis
2. Synchronous or metachronous malignancies (except for cutaneous (non-melanomas) carcinoma, thyroid papillary carcinoma, phase I seminoma or cervical carcinoma in situ curatively treated and disease free for a minimum of 3 months)
3. Received thoracic, abdominal or craniocerebral surgery within 30 days
4. Enrolled in other clinical trials within 30 days
5. Unstable angina and/or congestive heart failure requiring hospitalization within 6 months
6. Severe psychiatric disease
7. Pregnancy, lactation or unwillingness to adopt contraception
8. Drug addiction
9. Acquired immune deficiency syndrome (AIDS) based upon current CDC definition
10. History of radiotherapy in the planning area
11. Other ineligible conditions according to researchers

Treatment

The treatment plan is shown in Figure 1. Patients receive radiotherapy combined with concurrent chemotherapy. Radiotherapy begins on day 1, concurrent with the beginning of cycle 1 of chemotherapy.

Same radiation therapy will be delivered in all three treatment groups. Radiotherapy is delivered with photons (≥6 MV) to a total dose of 61.2Gy in 34 fractions. Patients will be treated 5 days per week at 1.8Gy/d. Three-dimensional conformal radiotherapy or intensity modulated radiotherapy is required. All patient will be positioned in an individualized immobilization device in the treatment

position.

The definition of volumes will be in accordance with the 1993 ICRU Report #50 and 1999 ICRU Report #62.

The gross target volume (GTV) is defined as all known involved field, which detected by endoscopic ultrasound, barium swallow or CT scan (whichever is larger). The regional lymph nodes included in GTV is whose diameter more than 1cm (0.5cm for lymph nodes at tracheoesophageal groove) or histologically proven metastatic after puncture.

The superior and inferior borders of the clinical target volume (CTV) are 3cm beyond the primary tumor along the esophagus. The lateral, anterior and posterior borders of the field are the same as GTV.

The superior, inferior, anterior, posterior and lateral borders of planning target volume (PTV) are 1cm beyond CTV. Field next to the spinal cord could be slightly adjusted in order to reduce the exposure of spinal cord.

As for target volume, tissue inhomogeneity correction is adopted and it is required that more than 99% PTV receive 95% prescription dose and more than 95% PTV receive 99% or more prescription dose. Highest and lowest point dose inside PTV should be recorded.

When making the treatment plan, we should take normal organ dose restrictions into consideration as the following order: (Table 3)

Risk organ	Contour regulation	Dose restriction
Spinal cord	All the layers of CT scan have to be contoured and the margin of vertebra tube can be regarded as that of planning organ at risk volume.	Highest point dose less than 45Gy
Lung	It is allowed to use automatic tools in the delineation of margin of lungs. (Trachea and bronchia must be contoured manually)	The volume of lung (PTV excluded) receiving 20Gy or higher has to be less than 30% of the total lung volume, and the median

		dose has to be less than 15Gy.
Heart	The superior margin of heart consists of right atrium and right ventricle, pulmonary artery trunk, ascending main aorta and superior vena cava excluded. The inferior margin is at the level of heart apex.	The median dose has to be less than 40Gy.

Chemotherapy

Patients are randomly assigned to receive one of three therapies.

Arm A (TP)

Patients in arm A receive 4 courses of TP every 4 weeks. Details are as follows:

Paclitaxel: 175mg/m^2/d, ivgtt over 3 hours, d1; Cisplatin: 25mg/m^2/d, ivgtt, d1-3;

Arm B (TF)

Patients in arm B receive 6 courses of TF concurrent with radiotherapy every week and 2 courses of TF adjuvant chemotherapy every 4 weeks. Details are as follows:

Concurrent: paclitaxel 50mg/m^2/d, ivgtt over 3 hours, d1; 5-FU 300mg/m^2, civ 96h, d1-4

Adjuvant: paclitaxel 175 mg/m^2/d, ivgtt over 3 hours, d1; 5-FU 1800mg/m^2, civ 72h, d1-3

Arm C (TC)

Patients in arm C receive 6 courses of TC concurrent with radiotherapy every week and 2 courses of TC adjuvant chemotherapy every 4 weeks. Details are as follows:

Concurrent: paclitaxel 50mg/m^2/d, ivgtt over 3 hours, d1; carboplatin AUC=2, ivgtt, d1

Adjuvant: paclitaxel 175 mg/m^2/d, ivgtt over 3 hours, d1; carboplatin AUC=5, ivgtt, d1

Patients receive premedication to prevent allergic reaction and significant nausea or vomiting as indicated.

Dose modifications

Radiotherapy interruption

If following toxicity is observed, radiotherapy has to be delayed until toxicity is no more than grade 2.

- WBC<2.0×10^9/L or ANC<1.0×10^9/L
- Plt<50×10^9/L
- Grade 3 or higher non-hematological toxicity

If following toxicity is observed, radiotherapy has to be delayed until complete recovery.

- Mediastinal or thoracic infection with fever over 38.5□

It is allowed to suspend at most 2 weeks, or radiotherapy will be terminated.

Chemotherapy interruption and dose modifications

If following toxicity is observed on day 1, chemotherapy has to be delayed until toxicity is no more than grade 1.

- ANC<1.5×10^9/L
- Plt<100×10^9/L
- Grade 2 or higher non-hematological toxicity, except for nausea, vomiting and alopecia

It is allowed to delay at most 2 weeks, or chemotherapy will be terminated.

Chemotherapy dose modifications are based on the greatest toxicity during the last cycle. Any patients who need to make chemotherapy dose modifications will receive the modified dose in the following cycles.

If modifications are needed, dose of paclitaxel, cisplatin, carboplatin and 5-FU will decreased by 25% from the planned dose for the first time and 50% for the second time. It is allowed to make dose modifications at most twice, or chemotherapy will be terminated. Details are as follows:

Dose modification of paclitaxel

- Febrile neutropenia (ANC< 0.5×10^9/L and fever over 38.3□ or over 38.0□ for 1h)
- Grade 2 or higher peripheral neuropathy

Dose modification of cisplatin and carboplatin

- Febrile neutropenia (ANC< 0.5×10^9/L and fever over 38.3□ or over 38.0□ for 1h)
- Grade 2 or higher peripheral neuropathy
- Serum creatinine >3ULN

Dose modification of 5-FU

- Febrile neutropenia (ANC< 0.5×10^9/L and fever over 38.3□ or over 38.0□ for 1h)
- Grade 3 or higher mucositis

The adverse events will be evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE version 4.0). All adverse events, occurring during the course of the trial, which is from randomization until 28 days after end of treatment, regardless of relatedness to study medication, will be recorded. Adverse events occurring later than 28 days after the end of treatment will only be recorded if they are considered relevant.

Randomization

After the confirmation of eligibility criteria, patients will be randomly allocated in a 1:1:1 ratio to the three treatment groups by a central randomization center (Fudan University Shanghai Cancer Center, Shanghai, China). Patients will be stratified by lymph node status (N0, N1, M1a). The SAS was used to generate a random permutation sequence and produce patient randomization numbers. The data center registers the enrollment, assigns a unique identification number to every participant, and replies to the respective investigators.

Sample size calculation and statistical analysis

This three-arm randomized trial is designed to confirm whether TF is superior to TP or TC concurrent with radiotherapy in terms of overall survival. According to RTOG 0113 and other reports, median survival time of TF concurrent with radiotherapy for esophageal cancer is 28.7 months while TP 14.9 months[5] and TC 17.4 months[13]. According to the Schoenfeld and Richter's method, the sample size of 107 patients per arm (154 events in total) is required to warrant a power of 80% at a two-sided α

level of 0.025 for the comparison between TP and TF with relatively smaller difference, assuming an accrual period of 48 months, a minimum follow-up period of 24 months and a dropout rate of 10%[14 15]. The total sample size is planned as 321 patients (107 patients in each arm, a total of 231 events).

The median overall survival will be estimated with Kaplan-Meier method, and log-rank test will be used to compare the overall survival among treatment arms. We will conduct a subgroup analyze to test whether the treatment effects differ among subgroups (N0, N1, M1a).

Endpoints

The primary endpoint is overall survival in all randomized patients. Overall survival is defined as time from the date of randomization until death. The secondary endpoint is progression free survival (PFS) and adverse events. PFS is defined as the time from the date of randomization to the date of progression or to the date of death, whichever occurs first and disease progression will be evaluated according to RECIST Version 1.1. Adverse events will be evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE version 4.0).

Interim analysis

We plan to conduct two interim analyses. The first interim analysis will be conducted independently from the study group when half of the planned number of patients are enrolled and the second interim just after the planned patient accrual is completed. If the superiority of one of test arms is demonstrated with an adjusted α level, the study will be terminated.

In general, the interim reports will contain the following information:

1. Patient accrual rate with a projected completion date (while the study is still accruing)
2. Total patients accrued
3. Distributions of important pretreatment and prognostic baseline variables
4. The frequencies and severity of adverse events by treatment arm.
5. Compliance rates of treatment delivery
6. Observed results with respect to the primary and secondary endpoints

Ethics and dissemination

This trial has been approved by the Fudan University Shanghai Cancer Center Institutional Review Board (Ethics Committee of Fudan University Shanghai Cancer Center：No.1505146-13). Written informed consent will be obtained from all participants. Serious adverse events will be reported to the safety desk of the trial, the Data and Safety Monitoring Board and trial sites. Trial results will be disseminated via peer reviewed scientific journals and conference presentations.

Participating institutions (From east to west)

Fudan University Shanghai Cancer Center, Huadong Hospital Affiliated to Fudan University, Fudan University Shanghai Cancer Center Minhang Branch, Affiliated Hospital of Jiangnan University, Fujian Province Cancer Hospital, Jiangsu Province Cancer Hospital, The First Affiliated Hospital of Xiamen University, Jiangxi Province Cancer Hospital, Shanxi Province Cancer Hospital, Hainan Province People's Hospital, Gansu Province Cancer Hospital

Trial Status

The trial was initiated in July 2015 and is currently recruiting patients in all of the participating institutions above.

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Declarations

List of abbreviations

TP: Paclitaxel combined with cisplatin

TC: Paclitaxel combined with carboplatin

TF: Paclitaxel combined with fluorouracil

UICC: Union for International Cancer Control

ESCC: Esophageal squamous cell carcinoma

PF: Cisplatin combined with fluorouracil

AIDS: Acquired immune deficiency syndrome

RT: Radiotherapy

PTX: Paclitaxel

DDP: Cisplatin

CBP: Carboplatin

5-FU: Fluorouracil

W: Week

ICRU: International Commission on Radiation Units and Measurements

GTV: Gross Target Volume

CTV: Clinical Target Volume

PTV: Planning Target Volume

WBC: White Blood Cell

ANC: Absolute Neutrophil Counts

Hb: Hemoglobin

Plt: Platelet

ULN: Upper Limit of Normal

AST: Aspartate Transaminase

ALT: Alanine aminotransferase

Consent of publication

Not applicable

Declaration of interests

We declare no competing interests.

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Author's contributions

D Ai was responsible for drafting the manuscript. Y Chen, Q Liu, J Zhang, J Deng, H Zhu, W Ren, K Wu, M Fan, H Yang, Z Zhu, W Zhao, L Li were responsible for the collection of previous study and putting forward the conception. X Zheng, Y Li, J Ye, J Zhou, Q Lin, H Luo, J Cao, S Wei, J Fan, J Li, G Huang and H Badakhshi were responsible for designing the details of the study. K Zhao was responsible for all aspects of trial design, the protocol and trial conduct. All authors have read and approved this manuscript.

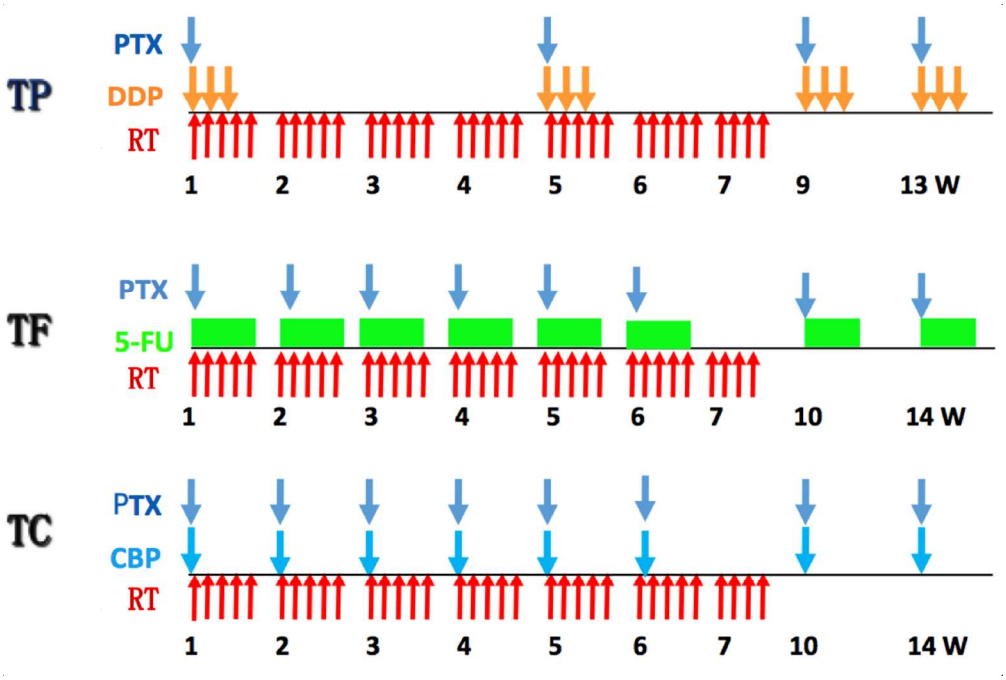

Fig1. Treatment design of the ESO-Shanghai 2 trial.
RT=radiotherapy, PTX=paclitaxel, DDP=cisplatin, 5-Fu=fluorouracil, CBP=carboplatin, W=Week.

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Keywords:	esophageal squamous cell carcinoma, concurrent chemoradiotherapy, paclitaxel, cisplatin, carboplatin, fluorouracil

Comparison of paclitaxel in combination with cisplatin (TP), carboplatin (TC) or fluorouracil (TF) concurrent with radiotherapy for patients with local advanced esophageal squamous cell carcinoma: a three-arm phase III randomized trial (ESO-Shanghai 2)

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Key words: esophageal squamous cell carcinoma, concurrent chemoradiotherapy, paclitaxel, cisplatin, carboplatin, fluorouracil

Word counts: 2,856 words

Abstract

Introduction: Concurrent chemoradiation is the standard therapy for patients with local advanced esophageal carcinoma unsuitable for surgery. Paclitaxel is an active agent against esophageal cancer and it has been proved as a potent radiation sensitizer. There have been multiple studies evaluating paclitaxel-based chemoradiation in esophageal cancer, the results of which are inspiring. However, which regimen, among paclitaxel in combination with cisplatin (TP), carboplatin (TC) and fluorouracil (TF) concurrent with radiotherapy, provides best prognosis with minimum adverse events is still considered far from resolved and very few studies focus on this field. The purpose of this study is to confirm the priority of TF to TP or TC concurrent with radiotherapy in terms of overall survival and propose a feasible and effective plan for patients with local advanced esophageal cancer.

Methods and analysis: ESO-Shanghai 2 is a three-arm, multicenter, open-labeled, randomized phase III clinical trial. The study was initiated in July 2015 and the duration of inclusion will be 4 years. The study compares two pairs of regimen: TF versus TP and TF versus TC concurrent with definitive radiotherapy for patients with esophageal squamous cell carcinoma (ESCC). Patients with histologically confirmed ESCC (clinical stage II, III or IVa based on the 6th UICC-TNM classification) and without any prior treatment of chemotherapy, radiotherapy or surgery against esophageal cancer will be eligible. A total of 321 patients will be randomized and allocated in a 1:1:1 ratio to the three treatment groups. Patients are stratified by lymph node status (N0, N1, M1a). The primary endpoint is overall survival and the secondary endpoint is progression-free survival and adverse events.

Ethics and dissemination:

This trial has been approved by the Fudan University Shanghai Cancer Center Institutional Review Board. Trial results will be disseminated via peer reviewed scientific journals and conference presentations.

Trial registration: Clinicaltrials.gov: NCT02459457

Strengths and limitations of this study

- First phase III randomized multi-centered study comparing these three regimens
- Stratification by lymph node status (N0, N1, M1a based on the 6th UICC-TNM classification)
- No stratification for different centers

Introduction

Worldwide, esophageal cancer is the eighth most common cancer, which is responsible for an estimated 455,800 new cases and 400,200 deaths in 2012.[1] Since its prognosis is dismal, much effort has been put into improving overall survival through multi-modality treatments, which consist of surgery, radiotherapy and chemotherapy.[2] Concurrent chemoradiation is the standard non-operative therapy for local advanced esophageal squamous cell carcinoma (ESCC).[3]

Paclitaxel is an active agent against esophageal cancer, with the response rate of 28% in ESCC, and it has been shown to be a potent radiation sensitizer.[4] There have been multiple studies evaluating paclitaxel-based chemoradiation in esophageal cancer, for instance, paclitaxel/fluorouracil (TF) developed at The University of Texas M.D. Anderson Cancer Center, and paclitaxel/cisplatin (TP) developed at Memorial Sloan-Kettering Cancer Center,[5,6] with paclitaxel/carboplatin (TC) from CROSS trial.[7] In many preoperative studies, paclitaxel-based chemoradiotherapy has achieved inspiring effect, the pathologic complete response rates of TP-based chemoradiotherapy were 19%-42%, [8-11] and of TC-based chemoradiotherapy was 49%.[7] However, which regimen, among TF, TP and TC-based definitive chemoradiotherapy, provides best prognosis with minimum adverse events is still considered far from resolved and very few studies focus on this field.

RTOG 0113[5] evaluated 2 different paclitaxel-based regimens (TP and TF). Eighty-four patients were accrued to this study. Patients in arm A (TF) received induction 5-FU, cisplatin, and paclitaxel followed by radiation and concurrent continuous infusion 5-FU and weekly paclitaxel. Patients in arm B (TP) received induction paclitaxel and cisplatin followed by radiation and concurrent weekly cisplatin and 96-hour infusion of paclitaxel. The median survival time was 28.7 months for patients in arm A (TF) and 14.9 months for patients in arm B (TP). Neither arm achieved the hypothesized 1-year survival rate of at least 77.5%. The main deficiency of this study is the small sample size, but the effect of TF group is still inspiring.

Another retrospective multicenter randomize clinical trials from Europe[12] showed the overall survival of TC-based definitive chemoradiotherapy was comparable with cisplatin/5-FU (PF) as definitive concurrent chemoradiotherapy in

esophageal cancer. However, the toxicity rates were lower in the TC group together with higher treatment compliance.

Based on RTOG 0113 and other reports, we designed a multicenter randomized controlled phase III trial to confirm the priority of TF to TP and TF to TC concurrent with radiotherapy in terms of overall survival for patients with local advanced esophageal squamous cell carcinoma. Independent ethics committees of the participating centers approved the study protocol. This trial has been registered with ClinicalTrials.gov, number NCT02459457.

The trial is a three-arm, multicenter, open-labeled, randomized phase III clinical trial. The study was initiated in July 2015 and the duration of inclusion will be 4 years. The study compares two pairs of regimen: TF versus TP and TF versus TC concurrent with definitive radiotherapy in patients with esophageal squamous cell carcinoma.

Methods and analysis

Patient selection

To be eligible for this study, patient must fulfill all of the following criteria (Table 1):

Inclusion criteria
1. Histologically confirmed esophageal squamous cell carcinoma
2. Clinical stages II, III or IVa based on the 6th UICC-TNM classification
3. No prior treatment of chemotherapy, radiotherapy or surgery against esophageal cancer, except for non-curative resection by EMR/ESD.
4. Aged 18-75 years
5. Adequate organ functions for chemoradiation therapy
a) White blood cell (WBC) $\geq 3\times10^9$/L
b) Absolute neutrophil counts (ANC) $\geq 1.5\times10^9$/L
c) Hemoglobin (Hb) $\geq$10g/dl
d) Platelet (Plt) $\geq 100\times10^9$/L
e) Total bilirubin <1.5 upper limit of normal (ULN)
f) Aspartate transaminase (AST) $\leq$2.5 ULN
g) Alanine aminotransferase (ALT) $\leq$2.5 ULN

h) Creatinine ≤1.5 ULN
6. ECOG PS of 0-2
7. Life expectancy ≥3 months
8. Written informed consent

Table 1. Inclusion criteria

Patients fulfilling any of the following criteria are ineligible for this study (Table 2).

Exclusion criteria
1. Esophageal perforation or hematemesis
2. Synchronous or metachronous malignancies (except for cutaneous (non-melanomas) carcinoma, thyroid papillary carcinoma, phase I seminoma or cervical carcinoma in situ curatively treated and disease free for a minimum of 3 months)
3. Received thoracic, abdominal or craniocerebral surgery within 30 days
4. Enrolled in other clinical trials within 30 days
5. Unstable angina and/or congestive heart failure requiring hospitalization within 6 months
6. Severe psychiatric disease
7. Pregnancy, lactation or unwillingness to adopt contraception
8. Drug addiction
9. Acquired immune deficiency syndrome (AIDS) based upon current CDC definition
10. History of radiotherapy in the planning area
11. Other ineligible conditions according to researchers

Table 2. Exclusion criteria

Treatment

The treatment plan is shown in Figure 1. Patients receive radiotherapy combined with concurrent chemotherapy. Radiotherapy begins on day 1, concurrent with the beginning of cycle 1 of chemotherapy.

Same radiation therapy will be delivered in all three treatment groups. Radiotherapy is delivered with photons (≥6 MV) to a total dose of 61.2Gy in 34 fractions. Patients will be treated 5 days per week at 1.8Gy/d. Three-dimensional

conformal radiotherapy or intensity modulated radiotherapy is required. All patient will be positioned in an individualized immobilization device in the treatment position.

The definition of volumes will be in accordance with the 1993 ICRU Report #50 and 1999 ICRU Report #62.

The gross target volume (GTV) is defined as all known involved field, which detected by endoscopic ultrasound, barium swallow or CT scan (whichever is larger). The regional lymph nodes included in GTV is whose diameter more than 1cm (0.5cm for lymph nodes at tracheoesophageal groove) or histologically proven metastatic after puncture.

The superior and inferior borders of the clinical target volume (CTV) are 3cm beyond the primary tumor along the esophagus. The lateral, anterior and posterior borders of the field are the same as GTV.

The superior, inferior, anterior, posterior and lateral borders of planning target volume (PTV) are 1cm beyond CTV. Field next to the spinal cord could be slightly adjusted in order to reduce the exposure of spinal cord.

As for target volume, tissue inhomogeneity correction is adopted and it is required that more than 99% PTV receive 95% prescription dose and more than 95% PTV receive 99% or more prescription dose. Highest and lowest point dose inside PTV should be recorded.

When making the treatment plan, we should take normal organ dose restrictions into consideration as the following order: (Table 3)

Risk organ	Contour regulation	Dose restriction
Spinal cord	All the layers of CT scan have to be contoured and the margin of vertebra tube can be regarded as that of planning organ at risk volume.	Highest point dose less than 45Gy
Lung	It is allowed to use automatic tools in the delineation of margin of lungs. (Trachea and	The volume of lung (PTV excluded) receiving 20Gy or higher has to be less

	bronchia must be contoured manually)	than 30% of the total lung volume, and the mean dose has to be less than 15Gy.
Heart	The superior margin of heart consists of right atrium and right ventricle, pulmonary artery trunk, ascending main aorta and superior vena cava excluded. The inferior margin is at the level of heart apex.	The mean dose has to be less than 40Gy.

Table 3. Contour regulation and dose restriction of risk organs

Chemotherapy

Patients are randomly assigned to receive one of three therapies.

Arm A (TP)

Patients in arm A receive 4 courses of TP every 4 weeks. Details are as follows:

Paclitaxel: 175mg/m^2/d, ivgtt over 3 hours, d1; Cisplatin: 25mg/m^2/d, ivgtt, d1-3;

Arm B (TF)

Patients in arm B receive 6 courses of TF concurrent with radiotherapy every week and 2 courses of TF consolidation chemotherapy every 4 weeks. Details are as follows:

Concurrent: paclitaxel 50mg/m^2/d, ivgtt over 3 hours, d1; 5-FU 300mg/m^2, civ 96h, d1-4

Consolidation: paclitaxel 175 mg/m^2/d, ivgtt over 3 hours, d1; 5-FU 1800mg/m^2, civ 72h, d1-3

Arm C (TC)

Patients in arm C receive 6 courses of TC concurrent with radiotherapy every week and 2 courses of TC consolidation chemotherapy every 4 weeks. Details are as follows:

Concurrent: paclitaxel 50mg/m^2/d, ivgtt over 3 hours, d1; carboplatin AUC=2, ivgtt, d1

Consolidation: paclitaxel 175 mg/m^2/d, ivgtt over 3 hours, d1; carboplatin AUC=5,

ivgtt, d1

Patients receive premedication to prevent allergic reaction and significant nausea or vomiting as indicated.

Dose modifications

Radiotherapy interruption

If following toxicity is observed, radiotherapy has to be delayed until toxicity is no more than grade 2.

- WBC<2.0×10^9/L or ANC<1.0×10^9/L
- Plt<50×10^9/L
- Grade 3 or higher non-hematological toxicity

If following toxicity is observed, radiotherapy has to be delayed until complete recovery.

- Mediastinal or thoracic infection with fever over 38.5□

It is allowed to suspend at most 2 weeks, or radiotherapy will be terminated.

Chemotherapy interruption and dose modifications

If following toxicity is observed on day 1, chemotherapy has to be delayed until toxicity is no more than grade 1.

- ANC<1.5×10^9/L
- Plt<100×10^9/L
- Grade 2 or higher non-hematological toxicity, except for nausea, vomiting and alopecia

It is allowed to delay at most 2 weeks, or chemotherapy will be terminated.

Chemotherapy dose modifications are based on the greatest toxicity during the last cycle. Any patients who need to make chemotherapy dose modifications will receive the modified dose in the following cycles.

If modifications are needed, dose of paclitaxel, cisplatin, carboplatin and 5-FU will decreased by 25% from the planned dose for the first time and 50% for the second time. It is allowed to make dose modifications at most twice, or chemotherapy will be terminated. Details are as follows:

Dose modification of paclitaxel

- Febrile neutropenia (ANC< 0.5×10^9/L and fever over 38.3□ or over 38.0□ for

1h)

- Grade 2 or higher peripheral neuropathy

Dose modification of cisplatin and carboplatin

- Febrile neutropenia (ANC< 0.5×10^9/L and fever over 38.3□ or over 38.0□ for 1h)
- Grade 2 or higher peripheral neuropathy
- Serum creatinine >3ULN

Dose modification of 5-FU

- Febrile neutropenia (ANC< 0.5×10^9/L and fever over 38.3□ or over 38.0□ for 1h)
- Grade 3 or higher mucositis

The adverse events will be evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE version 4.0). All adverse events, occurring during the course of the trial, which is from randomization until 28 days after end of treatment, regardless of relatedness to study medication, will be recorded. Adverse events occurring later than 28 days after the end of treatment will only be recorded if they are considered relevant.

Randomization

After the confirmation of eligibility criteria, patients will be randomly allocated in a 1:1:1 ratio to the three treatment groups by a central randomization center (Fudan University Shanghai Cancer Center, Shanghai, China). Patients will be stratified by lymph node status (N0, N1, M1a). The SAS was used to generate a random permutation sequence and produce patient randomization numbers. The data center registers the enrollment, assigns a unique identification number to every participant, and replies to the respective investigators.

Sample size calculation and statistical analysis

This three-arm randomized trial is designed to confirm whether TF is superior to TP or TC concurrent with radiotherapy in terms of overall survival. According to RTOG

0113 and other reports, median survival time of TF concurrent with radiotherapy for esophageal cancer is 28.7 months while TP 14.9 months[5] and TC 17.4 months[13]. According to the Schoenfeld and Richter's method, the sample size of 107 patients per arm (154 events in total) is required to warrant a power of 80% at a two-sided α level of 0.025 for the comparison between TP and TF with relatively smaller difference, assuming an accrual period of 48 months, a minimum follow-up period of 24 months and a dropout rate of 10%[14 15]. The total sample size is planned as 321 patients (107 patients in each arm, a total of 231 events).

The median overall survival will be estimated with Kaplan-Meier method, and log-rank test will be used to compare the overall survival among treatment arms. We will conduct a subgroup analyze to test whether the treatment effects differ among subgroups (N0, N1, M1a).

Endpoints

The primary endpoint is overall survival in all randomized patients. Overall survival is defined as time from the date of randomization until death. The secondary endpoint is progression free survival (PFS) and adverse events. PFS is defined as the time from the date of randomization to the date of progression or to the date of death, whichever occurs first and disease progression will be evaluated according to RECIST Version 1.1. Adverse events will be evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE version 4.0).

Data collection

Participants will be seen at hospital or contacted by telephone, letters from randomization to the end of treatment cycle, then at Month 3, 6, 9, 12, 15, 18, 21, 24, 30, 36, 42, 48, 54 and 60 after last treatment. Research staff at the hospitals will be expected to complete trial CRFs which record evidence of primary and secondary out-come measures.

Interim analysis

We plan to conduct two interim analyses. The first interim analysis will be conducted independently from the study group when half of the planned number of patients are

enrolled and the second interim just after the planned patient accrual is completed. If the superiority of one of test arms is demonstrated with an adjusted α level, the study will be terminated.

In general, the interim reports will contain the following information:

1. Patient accrual rate with a projected completion date (while the study is still accruing)
2. Total patients accrued
3. Distributions of important pretreatment and prognostic baseline variables
4. The frequencies and severity of adverse events by treatment arm.
5. Compliance rates of treatment delivery
6. Observed results with respect to the primary and secondary endpoints

Patient and Public Involvement

Patients in this study will be recruited from the outpatient of participant centers. After diagnosis and necessary clinical assessment, this clinical trial will be introduced to the patients to get their approval. All the recruitment and conduct of this study will be the responsible for doctors and other staffs. The only obligation of patients is to report any discomfort during the process of this study. Trial results will be disseminated via peer reviewed scientific journals and conference presentations rather than specifically notified to a single patient. No extra financial burden for patients if they are enrolled in this trial because standard cost of three treatment plans are similar if patients covered by the same insurance.

Ethics and dissemination

This trial has been approved by the Fudan University Shanghai Cancer Center Institutional Review Board (Ethics Committee of Fudan University Shanghai Cancer Center：No.1505146-13). Written informed consent will be obtained from all participants. Serious adverse events will be reported to the safety desk of the trial, the Data and Safety Monitoring Board and trial sites. Trial results will be disseminated via peer reviewed scientific journals and conference presentations.

Participating institutions (From east to west)

Fudan University Shanghai Cancer Center, Huadong Hospital Affiliated to Fudan University, Fudan University Shanghai Cancer Center Minhang Branch, Affiliated Hospital of Jiangnan University, Fujian Province Cancer Hospital, Jiangsu Province Cancer Hospital, The First Affiliated Hospital of Xiamen University, Jiangxi Province Cancer Hospital, Shanxi Province Cancer Hospital, Hainan Province People's Hospital, Gansu Province Cancer Hospital

Trial Status

The trial was initiated in July 2015 and is currently recruiting patients in all of the participating institutions above.

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Declarations

List of abbreviations

TP: Paclitaxel combined with cisplatin

TC: Paclitaxel combined with carboplatin

TF: Paclitaxel combined with fluorouracil

UICC: Union for International Cancer Control

ESCC: Esophageal squamous cell carcinoma

PF: Cisplatin combined with fluorouracil

AIDS: Acquired immune deficiency syndrome

RT: Radiotherapy

PTX: Paclitaxel

DDP: Cisplatin

CBP: Carboplatin

5-FU: Fluorouracil

W: Week

ICRU: International Commission on Radiation Units and Measurements

GTV: Gross Target Volume

CTV: Clinical Target Volume

PTV: Planning Target Volume

WBC: White Blood Cell

ANC: Absolute Neutrophil Counts

Hb: Hemoglobin

Plt: Platelet

ULN: Upper Limit of Normal

AST: Aspartate Transaminase

ALT: Alanine aminotransferase

Consent of publication

Not applicable

Declaration of interests

We declare no competing interests.

Funding

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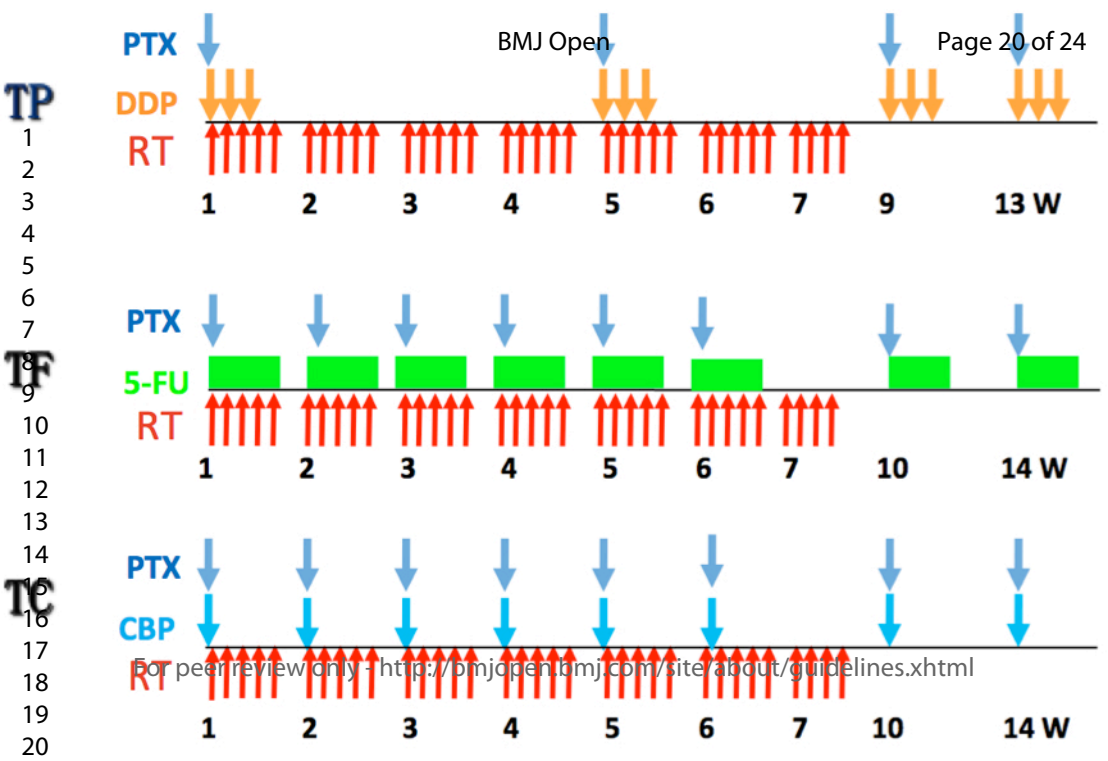
Author's contributions

D Ai was responsible for drafting the manuscript. Y Chen, Q Liu, J Zhang, J Deng, H Zhu, W Ren, K Wu, M Fan, H Yang, Z Zhu, W Zhao, L Li were responsible for the collection of previous study and putting forward the conception. X Zheng, Y Li, J Ye, J Zhou, Q Lin, H Luo, J Cao, S Wei, J Fan, J Li, G Huang and H Badakhshi were responsible for designing the details of the study. K Zhao was responsible for all aspects of trial design, the protocol and trial conduct. All authors have read and approved this manuscript.

Fig1. Treatment Design of the ESO-Shanghai 2 trial.

TP (arm A), TF (arm B) and TC (arm C) are TP-, TF- and TC-based definitive chemoradiotherapy, respectively.

RT=radiotherapy, PTX=paclitaxel, DDP=cisplatin, 5-Fu=fluorouracil, CBP=carboplatin, W=Week.



SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	____1_____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	____3_____
	2b	All items from the World Health Organization Trial Registration Data Set	__None_____
Protocol version	3	Date and version identifier	__None_____
Funding	4	Sources and types of financial, material, and other support	____17_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	____17_____
	5b	Name and contact information for the trial sponsor	____17_____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	__ None _____
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	__ None _____

Introduction

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5
	6b	Explanation for choice of comparators	6
Objectives	7	Specific objectives or hypotheses	6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	13
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6-7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	10
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	None
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	12
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	12

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	____12_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	____ None ___
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	____11_____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	____11_____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	____11_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	____ None ___
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	____ None ___
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	____ 11_____
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	____ None ___

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	____ None ___
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	_____12_____
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	_____12 _____
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	____ None ____
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	____ None ____
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	_____12_____
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	_____11_____
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	____ None ____
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	_____13_____
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	____ None ____

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	____ None ____
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	____ None ____
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	____ None ____
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	_____17 _____
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	____ None ____
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	____ None ____
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	____ None ____
	31b	Authorship eligibility guidelines and any intended use of professional writers	____ None ____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	____ None ____
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	____ None ____
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	____ None ____

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Comparison of paclitaxel in combination with cisplatin (TP), carboplatin (TC) or fluorouracil (TF) concurrent with radiotherapy for patients with local advanced esophageal squamous cell carcinoma: a three-arm phase III randomized trial (ESO-Shanghai 2)

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Primary Subject Heading:	Oncology
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Comparison of paclitaxel in combination with cisplatin (TP), carboplatin (TC) or fluorouracil (TF) concurrent with radiotherapy for patients with local advanced esophageal squamous cell carcinoma: a three-arm phase III randomized trial (ESO-Shanghai 2)

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Key words: esophageal squamous cell carcinoma, concurrent chemoradiotherapy, paclitaxel, cisplatin, carboplatin, fluorouracil

Word counts: 2,856 words

Abstract

Introduction: Concurrent chemoradiation is the standard therapy for patients with local advanced esophageal carcinoma unsuitable for surgery. Paclitaxel is an active agent against esophageal cancer and it has been proved as a potent radiation sensitizer. There have been multiple studies evaluating paclitaxel-based chemoradiation in esophageal cancer, the results of which are inspiring. However, which regimen, among paclitaxel in combination with cisplatin (TP), carboplatin (TC) and fluorouracil (TF) concurrent with radiotherapy, provides best prognosis with minimum adverse events is still considered far from resolved and very few studies focus on this field. The purpose of this study is to confirm the priority of TF to TP or TC concurrent with radiotherapy in terms of overall survival and propose a feasible and effective plan for patients with local advanced esophageal cancer.

Methods and analysis: ESO-Shanghai 2 is a three-arm, multicenter, open-labeled, randomized phase III clinical trial. The study was initiated in July 2015 and the duration of inclusion will be 4 years. The study compares two pairs of regimen: TF versus TP and TF versus TC concurrent with definitive radiotherapy for patients with esophageal squamous cell carcinoma (ESCC). Patients with histologically confirmed ESCC (clinical stage II, III or IVa based on the 6th UICC-TNM classification) and without any prior treatment of chemotherapy, radiotherapy or surgery against esophageal cancer will be eligible. A total of 321 patients will be randomized and allocated in a 1:1:1 ratio to the three treatment groups. Patients are stratified by lymph node status (N0, N1, M1a). The primary endpoint is overall survival and the secondary endpoint is progression-free survival and adverse events.

Ethics and dissemination:

This trial has been approved by the Fudan University Shanghai Cancer Center Institutional Review Board. Trial results will be disseminated via peer reviewed scientific journals and conference presentations.

Trial registration: Clinicaltrials.gov: NCT02459457

Strengths and limitations of this study

- First phase III randomized multi-centered study comparing these three regimens
- Stratification by lymph node status (N0, N1, M1a based on the 6th UICC-TNM classification)
- No stratification for different centers

Introduction

Worldwide, esophageal cancer is the eighth most common cancer, which is responsible for an estimated 455,800 new cases and 400,200 deaths in 2012.[1] Since its prognosis is dismal, much effort has been put into improving overall survival through multi-modality treatments, which consist of surgery, radiotherapy and chemotherapy.[2] Concurrent chemoradiation is the standard non-operative therapy for local advanced esophageal squamous cell carcinoma (ESCC).[3]

Paclitaxel is an active agent against esophageal cancer, with the response rate of 28% in ESCC, and it has been shown to be a potent radiation sensitizer.[4] There have been multiple studies evaluating paclitaxel-based chemoradiation in esophageal cancer, for instance, paclitaxel/fluorouracil (TF) developed at The University of Texas M.D. Anderson Cancer Center, and paclitaxel/cisplatin (TP) developed at Memorial Sloan-Kettering Cancer Center,[5,6] with paclitaxel/carboplatin (TC) from CROSS trial.[7] In many preoperative studies, paclitaxel-based chemoradiotherapy has achieved inspiring effect, the pathologic complete response rates of TP-based chemoradiotherapy were 19%-42%, [8-11] and of TC-based chemoradiotherapy was 49%.[7] However, which regimen, among TF, TP and TC-based definitive chemoradiotherapy, provides best prognosis with minimum adverse events is still considered far from resolved and very few studies focus on this field.

RTOG 0113[5] evaluated 2 different paclitaxel-based regimens (TP and TF). Eighty-four patients were accrued to this study. Patients in arm A (TF) received induction 5-FU, cisplatin, and paclitaxel followed by radiation and concurrent continuous infusion 5-FU and weekly paclitaxel. Patients in arm B (TP) received induction paclitaxel and cisplatin followed by radiation and concurrent weekly cisplatin and 96-hour infusion of paclitaxel. The median survival time was 28.7 months for patients in arm A (TF) and 14.9 months for patients in arm B (TP). Neither arm achieved the hypothesized 1-year survival rate of at least 77.5%. The main deficiency of this study is the small sample size, but the effect of TF group is still inspiring.

Another retrospective multicenter randomize clinical trials from Europe[12] showed the overall survival of TC-based definitive chemoradiotherapy was comparable with cisplatin/5-FU (PF) as definitive concurrent chemoradiotherapy in

esophageal cancer. However, the toxicity rates were lower in the TC group together with higher treatment compliance.

Based on RTOG 0113 and other reports, we designed a multicenter randomized controlled phase III trial to confirm the priority of TF to TP and TF to TC concurrent with radiotherapy in terms of overall survival for patients with local advanced esophageal squamous cell carcinoma. Independent ethics committees of the participating centers approved the study protocol. This trial has been registered with ClinicalTrials.gov, number NCT02459457.

The trial is a three-arm, multicenter, open-labeled, randomized phase III clinical trial. The study was initiated in July 2015 and the duration of inclusion will be 4 years. The study compares two pairs of regimen: TF versus TP and TF versus TC concurrent with definitive radiotherapy in patients with esophageal squamous cell carcinoma.

Methods and analysis

Patient selection

To be eligible for this study, patient must fulfill all of the following criteria (Table 1):

Inclusion criteria
1. Histologically confirmed esophageal squamous cell carcinoma
2. Clinical stages II, III or IVa based on the 6th UICC-TNM classification
3. No prior treatment of chemotherapy, radiotherapy or surgery against esophageal cancer, except for non-curative resection by EMR/ESD.
4. Aged 18-75 years
5. Adequate organ functions for chemoradiation therapy
a) White blood cell (WBC) $\geq 3\times10^9$/L
b) Absolute neutrophil counts (ANC) $\geq 1.5\times10^9$/L
c) Hemoglobin (Hb) $\geq$10g/dl
d) Platelet (Plt) $\geq 100\times10^9$/L
e) Total bilirubin <1.5 upper limit of normal (ULN)
f) Aspartate transaminase (AST) $\leq$2.5 ULN
g) Alanine aminotransferase (ALT) $\leq$2.5 ULN

h) Creatinine ≤1.5 ULN
6. ECOG PS of 0-2
7. Life expectancy ≥3 months
8. Written informed consent (Supplementary material)

Table 1. Inclusion criteria

Patients fulfilling any of the following criteria are ineligible for this study (Table 2).

Exclusion criteria
1. Esophageal perforation or hematemesis
2. Synchronous or metachronous malignancies (except for cutaneous (non-melanomas) carcinoma, thyroid papillary carcinoma, phase I seminoma or cervical carcinoma in situ curatively treated and disease free for a minimum of 3 months)
3. Received thoracic, abdominal or craniocerebral surgery within 30 days
4. Enrolled in other clinical trials within 30 days
5. Unstable angina and/or congestive heart failure requiring hospitalization within 6 months
6. Severe psychiatric disease
7. Pregnancy, lactation or unwillingness to adopt contraception
8. Drug addiction
9. Acquired immune deficiency syndrome (AIDS) based upon current CDC definition
10. History of radiotherapy in the planning area
11. Other ineligible conditions according to researchers

Table 2. Exclusion criteria

Treatment

The treatment plan is shown in Figure 1. Patients receive radiotherapy combined with concurrent chemotherapy. Radiotherapy begins on day 1, concurrent with the beginning of cycle 1 of chemotherapy.

Same radiation therapy will be delivered in all three treatment groups. Radiotherapy is delivered with photons (≥6 MV) to a total dose of 61.2Gy in 34 fractions. Patients will be treated 5 days per week at 1.8Gy/d. Three-dimensional

conformal radiotherapy or intensity modulated radiotherapy is required. All patient will be positioned in an individualized immobilization device in the treatment position.

The definition of volumes will be in accordance with the 1993 ICRU Report #50 and 1999 ICRU Report #62.

The gross target volume (GTV) is defined as all known involved field, which detected by endoscopic ultrasound, barium swallow or CT scan (whichever is larger). The regional lymph nodes included in GTV is whose diameter more than 1cm (0.5cm for lymph nodes at tracheoesophageal groove) or histologically proven metastatic after puncture.

The superior and inferior borders of the clinical target volume (CTV) are 3cm beyond the primary tumor along the esophagus. The lateral, anterior and posterior borders of the field are the same as GTV.

The superior, inferior, anterior, posterior and lateral borders of planning target volume (PTV) are 1cm beyond CTV. Field next to the spinal cord could be slightly adjusted in order to reduce the exposure of spinal cord.

As for target volume, tissue inhomogeneity correction is adopted and it is required that more than 99% PTV receive 95% prescription dose and more than 95% PTV receive 99% or more prescription dose. Highest and lowest point dose inside PTV should be recorded.

When making the treatment plan, we should take normal organ dose restrictions into consideration as the following order: (Table 3)

Risk organ	Contour regulation	Dose restriction
Spinal cord	All the layers of CT scan have to be contoured and the margin of vertebra tube can be regarded as that of planning organ at risk volume.	Highest point dose less than 45Gy
Lung	It is allowed to use automatic tools in the delineation of margin of lungs. (Trachea and	The volume of lung (PTV excluded) receiving 20Gy or higher has to be less

	bronchia must be contoured manually)	than 30% of the total lung volume, and the mean dose has to be less than 15Gy.
Heart	The superior margin of heart consists of right atrium and right ventricle, pulmonary artery trunk, ascending main aorta and superior vena cava excluded. The inferior margin is at the level of heart apex.	The mean dose has to be less than 40Gy.

Table 3. Contour regulation and dose restriction of risk organs

Chemotherapy

Patients are randomly assigned to receive one of three therapies.

Arm A (TP)

Patients in arm A receive 4 courses of TP every 4 weeks. Details are as follows:

Paclitaxel: 175mg/m^2/d, ivgtt over 3 hours, d1; Cisplatin: 25mg/m^2/d, ivgtt, d1-3;

Arm B (TF)

Patients in arm B receive 6 courses of TF concurrent with radiotherapy every week and 2 courses of TF consolidation chemotherapy every 4 weeks. Details are as follows:

Concurrent: paclitaxel 50mg/m^2/d, ivgtt over 3 hours, d1; 5-FU 300mg/m^2, civ 96h, d1-4

Consolidation: paclitaxel 175 mg/m^2/d, ivgtt over 3 hours, d1; 5-FU 1800mg/m^2, civ 72h, d1-3

Arm C (TC)

Patients in arm C receive 6 courses of TC concurrent with radiotherapy every week and 2 courses of TC consolidation chemotherapy every 4 weeks. Details are as follows:

Concurrent: paclitaxel 50mg/m^2/d, ivgtt over 3 hours, d1; carboplatin AUC=2, ivgtt, d1

Consolidation: paclitaxel 175 mg/m^2/d, ivgtt over 3 hours, d1; carboplatin AUC=5,

ivgtt, d1

Patients receive premedication to prevent allergic reaction and significant nausea or vomiting as indicated.

Dose modifications

Radiotherapy interruption

If following toxicity is observed, radiotherapy has to be delayed until toxicity is no more than grade 2.

- WBC<2.0×10^9/L or ANC<1.0×10^9/L
- Plt<50×10^9/L
- Grade 3 or higher non-hematological toxicity

If following toxicity is observed, radiotherapy has to be delayed until complete recovery.

- Mediastinal or thoracic infection with fever over 38.5□

It is allowed to suspend at most 2 weeks, or radiotherapy will be terminated.

Chemotherapy interruption and dose modifications

If following toxicity is observed on day 1, chemotherapy has to be delayed until toxicity is no more than grade 1.

- ANC<1.5×10^9/L
- Plt<100×10^9/L
- Grade 2 or higher non-hematological toxicity, except for nausea, vomiting and alopecia

It is allowed to delay at most 2 weeks, or chemotherapy will be terminated.

Chemotherapy dose modifications are based on the greatest toxicity during the last cycle. Any patients who need to make chemotherapy dose modifications will receive the modified dose in the following cycles.

If modifications are needed, dose of paclitaxel, cisplatin, carboplatin and 5-FU will decreased by 25% from the planned dose for the first time and 50% for the second time. It is allowed to make dose modifications at most twice, or chemotherapy will be terminated. Details are as follows:

Dose modification of paclitaxel

- Febrile neutropenia (ANC< 0.5×10^9/L and fever over 38.3□ or over 38.0□ for

1h)

- Grade 2 or higher peripheral neuropathy

Dose modification of cisplatin and carboplatin

- Febrile neutropenia (ANC< 0.5×10^9/L and fever over 38.3□ or over 38.0□ for 1h)
- Grade 2 or higher peripheral neuropathy
- Serum creatinine >3ULN

Dose modification of 5-FU

- Febrile neutropenia (ANC< 0.5×10^9/L and fever over 38.3□ or over 38.0□ for 1h)
- Grade 3 or higher mucositis

The adverse events will be evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE version 4.0). All adverse events, occurring during the course of the trial, which is from randomization until 28 days after end of treatment, regardless of relatedness to study medication, will be recorded. Adverse events occurring later than 28 days after the end of treatment will only be recorded if they are considered relevant.

Randomization

After the confirmation of eligibility criteria, patients will be randomly allocated in a 1:1:1 ratio to the three treatment groups by a central randomization center (Fudan University Shanghai Cancer Center, Shanghai, China). Patients will be stratified by lymph node status (N0, N1, M1a). The SAS was used to generate a random permutation sequence and produce patient randomization numbers. The data center registers the enrollment, assigns a unique identification number to every participant, and replies to the respective investigators.

Sample size calculation and statistical analysis

This three-arm randomized trial is designed to confirm whether TF is superior to TP or TC concurrent with radiotherapy in terms of overall survival. According to RTOG

0113 and other reports, median survival time of TF concurrent with radiotherapy for esophageal cancer is 28.7 months while TP 14.9 months[5] and TC 17.4 months[13]. According to the Schoenfeld and Richter's method, the sample size of 107 patients per arm (154 events in total) is required to warrant a power of 80% at a two-sided α level of 0.025 for the comparison between TP and TF with relatively smaller difference, assuming an accrual period of 48 months, a minimum follow-up period of 24 months and a dropout rate of 10%[14 15]. The total sample size is planned as 321 patients (107 patients in each arm, a total of 231 events).

The median overall survival will be estimated with Kaplan-Meier method, and log-rank test will be used to compare the overall survival among treatment arms. We will conduct a subgroup analyze to test whether the treatment effects differ among subgroups (N0, N1, M1a).

Endpoints

The primary endpoint is overall survival in all randomized patients. Overall survival is defined as time from the date of randomization until death. The secondary endpoint is progression free survival (PFS) and adverse events. PFS is defined as the time from the date of randomization to the date of progression or to the date of death, whichever occurs first and disease progression will be evaluated according to RECIST Version 1.1. Adverse events will be evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE version 4.0).

Data collection

Participants will be seen at hospital or contacted by telephone, letters from randomization to the end of treatment cycle, then at Month 3, 6, 9, 12, 15, 18, 21, 24, 30, 36, 42, 48, 54 and 60 after last treatment. Research staff at the hospitals will be expected to complete trial CRFs which record evidence of primary and secondary out-come measures.

Interim analysis

We plan to conduct two interim analyses. The first interim analysis will be conducted independently from the study group when half of the planned number of patients are

enrolled and the second interim just after the planned patient accrual is completed. If the superiority of one of test arms is demonstrated with an adjusted α level, the study will be terminated.

In general, the interim reports will contain the following information:

1. Patient accrual rate with a projected completion date (while the study is still accruing)
2. Total patients accrued
3. Distributions of important pretreatment and prognostic baseline variables
4. The frequencies and severity of adverse events by treatment arm.
5. Compliance rates of treatment delivery
6. Observed results with respect to the primary and secondary endpoints

Patient and Public Involvement

Neither patients nor public will be involved in the design, recruitment, outcome measures and conduct of the study. Trial results will be disseminated via peer reviewed scientific journals and conference presentations rather than specifically notified to a single patient.

Ethics and dissemination

This trial has been approved by the Fudan University Shanghai Cancer Center Institutional Review Board (Ethics Committee of Fudan University Shanghai Cancer Center：No.1505146-13). Written informed consent will be obtained from all participants. Serious adverse events will be reported to the safety desk of the trial, the Data and Safety Monitoring Board and trial sites. Trial results will be disseminated via peer reviewed scientific journals and conference presentations.

Participating institutions (From east to west)

Fudan University Shanghai Cancer Center, Huadong Hospital Affiliated to Fudan University, Fudan University Shanghai Cancer Center Minhang Branch, Affiliated Hospital of Jiangnan University, Fujian Province Cancer Hospital, Jiangsu Province Cancer Hospital, The First Affiliated Hospital of Xiamen University, Jiangxi Province Cancer Hospital, Shanxi Province Cancer Hospital, Hainan Province People's Hospital, Gansu Province Cancer Hospital

Trial Status

The trial was initiated in July 2015 and is currently recruiting patients in all of the participating institutions above.

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Declarations

List of abbreviations

TP: Paclitaxel combined with cisplatin

TC: Paclitaxel combined with carboplatin

TF: Paclitaxel combined with fluorouracil

UICC: Union for International Cancer Control

ESCC: Esophageal squamous cell carcinoma

PF: Cisplatin combined with fluorouracil

AIDS: Acquired immune deficiency syndrome

RT: Radiotherapy

PTX: Paclitaxel

DDP: Cisplatin

CBP: Carboplatin

5-FU: Fluorouracil

W: Week

ICRU: International Commission on Radiation Units and Measurements

GTV: Gross Target Volume

CTV: Clinical Target Volume

PTV: Planning Target Volume

WBC: White Blood Cell

ANC: Absolute Neutrophil Counts

Hb: Hemoglobin

Plt: Platelet

ULN: Upper Limit of Normal

AST: Aspartate Transaminase

ALT: Alanine aminotransferase

Consent of publication

Not applicable

Declaration of interests

We declare no competing interests.

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Author's contributions

D Ai was responsible for drafting the manuscript. Y Chen, Q Liu, J Zhang, J Deng, H Zhu, W Ren, K Wu, M Fan, H Yang, Z Zhu, W Zhao, L Li were responsible for the collection of previous study and putting forward the conception. X Zheng, Y Li, J Ye, J Zhou, Q Lin, H Luo, J Cao, S Wei, J Fan, J Li, G Huang and H Badakhshi were responsible for designing the details of the study. K Zhao was responsible for all aspects of trial design, the protocol and trial conduct. All authors have read and approved this manuscript.

Data Sharing Statement

No additional unpublished data from the study are available.

Fig1. Treatment Design of the ESO-Shanghai 2 trial.

TP (arm A), TF (arm B) and TC (arm C) are TP-, TF- and TC-based definitive chemoradiotherapy, respectively.

RT=radiotherapy, PTX=paclitaxel, DDP=cisplatin, 5-Fu=fluorouracil, CBP=carboplatin, W=Week.

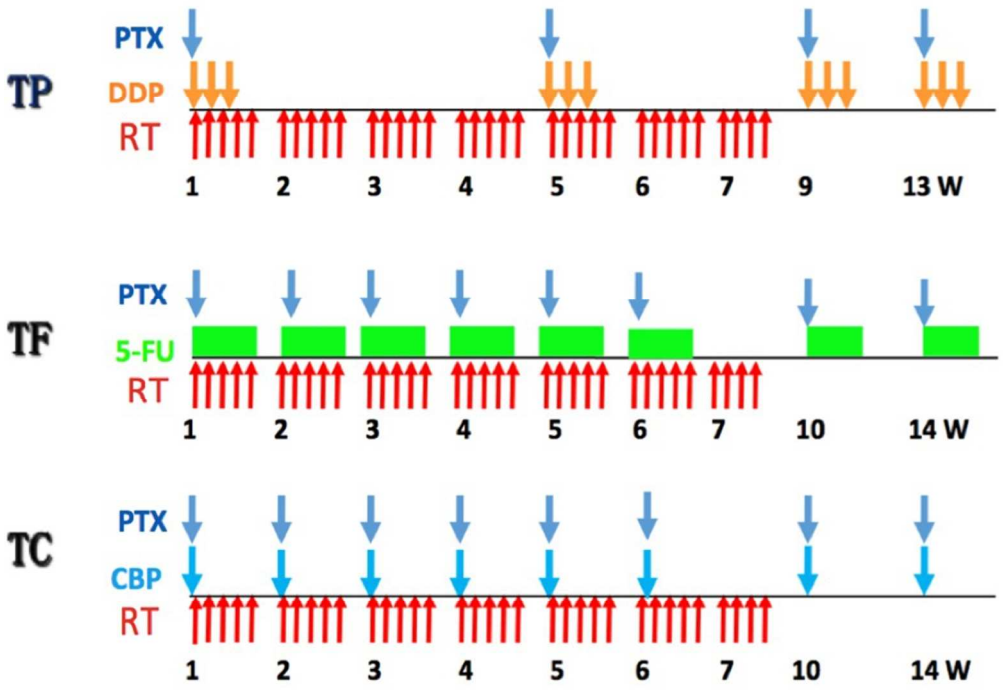

Fig1. Treatment design of the ESO-Shanghai 2 trial. ┣┳ RT=radiotherapy, PTX=paclitaxel, DDP=cisplatin, 5-Fu=fluorouracil, CBP=carboplatin, W=Week.┣┳

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Informed Consent Form

Comparison of paclitaxel in combination with cisplatin (TP), carboplatin (TC) or fluorouracil (TF) concurrent with radiotherapy for patients with local advanced esophageal squamous cell carcinoma: a three-arm phase III randomized trial (ESO-Shanghai 2)

You are being asked to take part in a clinical study. **Please take your time to make your decision about taking part. If you have any questions, you can ask your study doctor for more explanation.**

You are being asked to take part in this study because you have local advanced esophageal squamous cell carcinoma.

Why is this study being done?

Concurrent chemoradiation is the standard therapy for patients with local advanced esophageal carcinoma unsuitable for surgery. Paclitaxel is an active agent against esophageal cancer and it has been proved as a potent radiation sensitizer. There have been multiple studies evaluating paclitaxel-based chemoradiation in esophageal cancer, the results of which are inspiring. However, which regimen, among paclitaxel in combination with cisplatin (TP), carboplatin (TC) and fluorouracil (TF) concurrent with radiotherapy, provides best prognosis with minimum adverse events is still considered far from resolved and very few studies focus on this field. The purpose of this study is to confirm the priority of TF to TP or TC concurrent with radiotherapy in terms of overall survival and propose a feasible and effective plan for patients with local advanced esophageal cancer.

How many people will take part in the study?

About 321 people will take part in this study.

What will happen if I take part in this research study?

You will be randomized and allocated in a 1:1:1 ratio to the three treatment groups (TF, TP or TC). You will receive radiotherapy combined with concurrent chemotherapy. Radiotherapy will begin on day 1, concurrent with the beginning of cycle 1 of chemotherapy.

Radiation therapy

Same radiation therapy will be delivered in all three treatment groups. Radiotherapy will be delivered with photons (≥6 MV) to a total dose of 61.2Gy in 34 fractions. You will be treated 5 days per week at 1.8Gy/d.

Chemotherapy

Arm A (TP)

If you are in arm A, you will receive 4 courses of TP every 4 weeks. Details are as follows:

Paclitaxel: 175mg/m^2/d, ivgtt over 3 hours, d1; Cisplatin: 25mg/m^2/d, ivgtt, d1-3;

Arm B (TF)

If you are in arm B, you will receive 6 courses of TF concurrent with radiotherapy every week and 2 courses of TF adjuvant chemotherapy every 4 weeks. Details are as follows:

Concurrent: paclitaxel 50mg/m^2/d, ivgtt over 3 hours, d1; 5-FU 300mg/m^2, civ 96h, d1-4

Adjuvant: paclitaxel 175 mg/m^2/d, ivgtt over 3 hours, d1; 5-FU 1800mg/m^2, civ 72h, d1-3

Arm C (TC)

If you are in arm C, you will receive 6 courses of TC concurrent with radiotherapy every week and 2 courses of TC adjuvant chemotherapy every 4 weeks. Details are as follows:

Concurrent: paclitaxel 50mg/m^2/d, ivgtt over 3 hours, d1; carboplatin AUC=2, ivgtt, d1

Adjuvant: paclitaxel 175 mg/m^2/d, ivgtt over 3 hours, d1; carboplatin AUC=5, ivgtt, d1

During each treatment, blood tests will be performed to monitor blood counts, kidney function, liver function and electrolyte levels. Ultrasound, barium swallow and CT scan with contrast will be performed to evaluate the status of disease.

How long will I be in the study?

After your treatment is completed, you will be seen in follow-up visits with your doctor every 3 months in years 1-2, every 6 months in years 3-5 and then once a year for your lifetime.

Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so he or she can evaluate any risks from the treatment. Another reason to tell your study doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest, if you do not follow the study rules, or if the study is stopped.

What side effects or risks can I expect from being in the study?

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. There also is a risk of death.

Risks and side effects related to the chemoradiotherapy

- Soreness in throat or esophagus
- Cough
- Vomiting
- Nausea
- Fatigue
- Anorexia (loss of appetite)
- Diarrhea
- Numbness in arms and legs
- Allergic reaction
- Hair loss
- Redness of irritation of the skin in the treatment area
- Decrease in white blood cell counts and high risk of infection
- Renal insufficiency,

Are there benefits to taking part in the study?

Taking part in this study may or may not make your health better. While researchers hope these treatment regimens will be more useful against cancer compared to the usual treatment, there is no proof of this yet. We do know that the information from this study will help researchers learn more about these combinations of drugs as a treatment for cancer. This information could help future cancer patients.

Will my medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

What happens if I am injured because I took part in this study?

It is important that you tell your study doctor if you feel that you have been injured because of taking part in this study. You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our center.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

WHO CAN ANSWER MY QUESTIONS ABOUT THE STUDY?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor, Kuaile Zhao, at 021-64175590.

Signature

I have been given a copy of all 5 pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Participant:

_____	_____	_____
Name of Participant	Signature	Date

Researcher:

_____	_____	_____
Name of Participant	Signature	Date

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	____1_____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	____3_____
	2b	All items from the World Health Organization Trial Registration Data Set	__None_____
Protocol version	3	Date and version identifier	__None_____
Funding	4	Sources and types of financial, material, and other support	____17_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	____17_____
	5b	Name and contact information for the trial sponsor	____17_____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	__ None _____
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	__ None _____

Introduction

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5
	6b	Explanation for choice of comparators	6
Objectives	7	Specific objectives or hypotheses	6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	13
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6-7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	10
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	None
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	12
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	12

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	____12_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	____ None ___
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	____11_____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	____11_____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	____11_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	____ None ___
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	____ None ___
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	____ 11_____
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	____ None ___

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	____ None ___
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	_____12_____
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	_____12 _____
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	____ None ____
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	____ None ____
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	_____12_____
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	_____11_____
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	____ None ____
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	_____13_____
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	____ None ____

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	____ None ____
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	____ None ____
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	____ None ____
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	_____17 _____
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	____ None ____
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	____ None ____
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	____ None ____
	31b	Authorship eligibility guidelines and any intended use of professional writers	____ None ____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	____ None ____
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	____ None ____
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	____ None ____

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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Secondary Subject Heading:	Oncology
Keywords:	esophageal squamous cell carcinoma, concurrent chemoradiotherapy, paclitaxel, cisplatin, carboplatin, fluorouracil

Comparison of paclitaxel in combination with cisplatin (TP), carboplatin (TC) or fluorouracil (TF) concurrent with radiotherapy for patients with local advanced esophageal squamous cell carcinoma: a three-arm phase III randomized trial (ESO-Shanghai 2)

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Key words: esophageal squamous cell carcinoma, concurrent chemoradiotherapy, paclitaxel, cisplatin, carboplatin, fluorouracil

Word counts: 3,044 words

Abstract

Introduction: Concurrent chemoradiation is the standard therapy for patients with local advanced esophageal carcinoma unsuitable for surgery. Paclitaxel is an active agent against esophageal cancer and it has been proved as a potent radiation sensitizer. There have been multiple studies evaluating paclitaxel-based chemoradiation in esophageal cancer, of which the results are inspiring. However, which regimen among cisplatin(TP), carboplatin(TC) or fluorouracil(TF) in combination with paclitaxel) concurrent with radiotherapy, provides best prognosis with minimum adverse events is still unknown and very few studies focus on this field. The purpose of this study is to confirm the priority of TF to TP or TC concurrent with radiotherapy in terms of overall survival and propose a feasible and effective plan for patients with local advanced esophageal cancer.

Methods and analysis: ESO-Shanghai 2 is a three-arm, multicenter, open-labeled, randomized phase III clinical trial. The study was initiated in July 2015 and the duration of inclusion is expected to be 4 years. The study compares two pairs of regimen: TF versus TP and TF versus TC concurrent with definitive radiotherapy for patients with esophageal squamous cell carcinoma (ESCC). Patients with histologically confirmed ESCC (clinical stage II, III or IVa based on the 6th UICC-TNM classification) and without any prior treatment of chemotherapy, radiotherapy or surgery against esophageal cancer will be eligible. A total of 321 patients will be randomized and allocated in a 1:1:1 ratio to the three treatment groups. Patients are stratified by lymph node status (N0, N1, M1a). The primary endpoint is overall survival and the secondary endpoint is progression-free survival and adverse events.

Ethics and dissemination:

This trial has been approved by the Fudan University Shanghai Cancer Center Institutional Review Board. Trial results will be disseminated via peer reviewed scientific journals and conference presentations.

Trial registration: Clinicaltrials.gov: NCT02459457

Strengths and limitations of this study

- Strength - This clinical trial is the first phase III randomized multi-centered study comparing these three regimens.
- Strength - In the randomization session, patients were stratified by lymph node status (N0, N1, M1a based on the 6th UICC-TNM classification).
- Limitation - There's no stratification for different participation centers.

Introduction

Worldwide, esophageal cancer is the eighth most common cancer, which is responsible for an estimated 455,800 new cases and 400,200 deaths in 2012.[1] Since its prognosis is dismal, much effort has been put into improving overall survival through multi-modality treatments, which consist of surgery, radiotherapy and chemotherapy.[2] Concurrent chemoradiation is the standard non-operative therapy for local advanced esophageal squamous cell carcinoma (ESCC).[3]

Paclitaxel is an active agent against esophageal cancer, with the response rate of 28% in ESCC, and it has been shown to be a potent radiation sensitizer.[4] There have been multiple studies evaluating paclitaxel-based chemoradiation in esophageal cancer, for instance, paclitaxel/fluorouracil (TF) developed at The University of Texas M.D. Anderson Cancer Center, and paclitaxel/cisplatin (TP) developed at Memorial Sloan-Kettering Cancer Center,[5,6] with paclitaxel/carboplatin (TC) from CROSS trial.[7] In many preoperative studies, paclitaxel-based chemoradiotherapy has achieved inspiring effects, the pathologic complete response rates of TP-based chemoradiotherapy were 19%-42%, [8-11] and of TC-based chemoradiotherapy was 49%.[7] However, which regimen, among TF, TP and TC-based definitive chemoradiotherapy, provides best prognosis with minimum adverse events is still unknown and very few studies focus on this field.

RTOG 0113[5] evaluated 2 different paclitaxel-based regimens (TP and TF). Eighty-four patients were accrued to this study. Patients in arm A (TF) received induction 5-FU, cisplatin, and paclitaxel followed by radiation and concurrent continuous infusion 5-FU and weekly paclitaxel. Patients in arm B (TP) received induction paclitaxel and cisplatin followed by radiation and concurrent weekly cisplatin and 96-hour infusion of paclitaxel. The median survival time was 28.7 months for patients in arm A (TF) and 14.9 months for patients in arm B (TP). Neither arm achieved the hypothesized 1-year survival rate of at least 77.5%. The main deficiency of this study is the small sample size, but the effect of TF group is still inspiring.

Another retrospective multicenter randomize clinical trials from Europe[12] showed the overall survival of TC-based definitive chemoradiotherapy was comparable with cisplatin/5-FU (PF) as definitive concurrent chemoradiotherapy in

esophageal cancer. However, the toxicity rates were lower in the TC group together with higher treatment compliance.

Based on RTOG 0113 and other reports, we designed a clinical trial to confirm the priority of TF to TP and TF to TC concurrent with definitive radiotherapy in terms of overall survival for patients with local advanced esophageal squamous cell carcinoma. The trial is a three-arm, multicenter, open-labeled, randomized phase III clinical trial.

Methods and analysis

Patient selection

To be eligible for this study, patient must fulfill all of the following criteria (Table 1):

Inclusion criteria
1. Histologically confirmed esophageal squamous cell carcinoma
2. Clinical stages II, III or IVa based on the 6th UICC-TNM classification
3. No prior treatments of chemotherapy, radiotherapy or surgery against esophageal cancer, except for non-curative resection by EMR/ESD.
4. Aged 18-75 years
5. Adequate organ functions for chemoradiation therapy
a) White blood cell (WBC) $\geq 3\times10^9$/L
b) Absolute neutrophil counts (ANC) $\geq 1.5\times10^9$/L
c) Hemoglobin (Hb) $\geq$10g/dl
d) Platelet (Plt) $\geq 100\times10^9$/L
e) Total bilirubin <1.5 upper limit of normal (ULN)
f) Aspartate transaminase (AST) $\leq$2.5 ULN
g) Alanine aminotransferase (ALT) $\leq$2.5 ULN
h) Creatinine $\leq$1.5 ULN
6. ECOG PS of 0-2
7. Life expectancy $\geq$3 months, based on the judgment of doctors
8. Written informed consent (Supplementary material)

Table 1. Inclusion criteria

Patients fulfilling any of the following criteria are ineligible for this study (Table 2).

Exclusion criteria
1. Esophageal perforation or hematemesis
2. Synchronous or metachronous malignancies (except for cutaneous (non-melanomas) carcinoma, thyroid papillary carcinoma, phase I seminoma or cervical carcinoma in situ curatively treated and disease free for a minimum of 3 months)
3. Received thoracic, abdominal or craniocerebral surgery within 30 days
4. Enrolled in other clinical trials within 30 days
5. Unstable angina and/or congestive heart failure requiring hospitalization within 6 months
6. Severe psychiatric disease
7. Pregnancy, lactation or unwillingness to adopt contraception
8. Drug addiction
9. Acquired immune deficiency syndrome (AIDS) based upon current CDC definition
10. History of radiotherapy in the planning area
11. Other ineligible conditions according to researchers

Table 2. Exclusion criteria

Treatment

The treatment plan is shown in Figure 1. Patients receive radiotherapy combined with concurrent chemotherapy. Radiotherapy begins on day 1, concurrent with the beginning of cycle 1 of chemotherapy.

Same radiation therapy will be delivered in all three treatment groups. According to current clinical practice in China, radiotherapy is delivered with photons (≥6 MV) to a total dose of 61.2Gy in 34 fractions. Patients will be treated 5 days per week at 1.8Gy/d. Three-dimensional conformal radiotherapy or intensity modulated radiotherapy is required. All patient will be positioned in an individualized immobilization device in the treatment position.

The definition of volumes will be in accordance with the 1993 ICRU Report #50 and 1999 ICRU Report #62.

The gross target volume (GTV) is defined as all known involved field, which

detected by endoscopic ultrasound, barium swallow or CT scan (whichever is larger). The regional lymph nodes that have diameters more than 1cm (0.5cm for lymph nodes at tracheoesophageal groove) or that have been histologically proven metastatic after puncture are included in GTV.

The superior and inferior borders of the clinical target volume (CTV) are 3cm beyond the primary tumor along the esophagus. The lateral, anterior and posterior borders of the field are the same as GTV.

The superior, inferior, anterior, posterior and lateral borders of planning target volume (PTV) are 1cm beyond CTV. Field next to the spinal cord could be slightly adjusted in order to reduce the exposure of spinal cord.

As for target volume, tissue inhomogeneity correction is adopted and it is required that more than 99% PTV receive 95% prescription dose and more than 95% PTV receive 99% or more prescription dose. Highest and lowest point dose inside PTV should be recorded.

When making the treatment plan, we should take normal organ dose restrictions into consideration as the following order: (Table 3)

Risk organ	Contour regulation	Dose restriction
Spinal cord	All the layers of CT scan have to be contoured and the margin of vertebra tube can be regarded as that of planning organ at risk volume.	Highest point dose less than 45Gy
Lung	It is allowed to use automatic tools in the delineation of margin of lungs. (Trachea and bronchia must be contoured manually)	The volume of lung (PTV excluded) receiving 20Gy or higher has to be less than 30% of the total lung volume, and the mean dose has to be less than 15Gy.
Heart	The superior margin of heart consists of right atrium and	The mean dose has to be less than 40Gy.

	right ventricle, pulmonary artery trunk, ascending main aorta and superior vena cava excluded. The inferior margin is at the level of heart apex.

Table 3. Contour regulation and dose restriction of risk organs

Chemotherapy

Patients are randomly assigned to receive one of three therapies.

Arm A (TP)

Patients in arm A receive 4 courses of TP every 4 weeks. Details are as follows:
Paclitaxel: 175mg/m^2/d, ivgtt over 3 hours, d1; Cisplatin: 25mg/m^2/d, ivgtt, d1-3;

Arm B (TF)

Patients in arm B receive 6 courses of TF concurrent with radiotherapy every week and 2 courses of TF consolidation chemotherapy every 4 weeks. Details are as follows:
Concurrent: paclitaxel 50mg/m^2/d, ivgtt over 3 hours, d1; 5-FU 300mg/m^2, civ 96h, d1-4
Consolidation: paclitaxel 175 mg/m^2/d, ivgtt over 3 hours, d1; 5-FU 1800mg/m^2, civ 72h, d1-3

Arm C (TC)

Patients in arm C receive 6 courses of TC concurrent with radiotherapy every week and 2 courses of TC consolidation chemotherapy every 4 weeks. Details are as follows:
Concurrent: paclitaxel 50mg/m^2/d, ivgtt over 3 hours, d1; carboplatin AUC=2, ivgtt, d1
Consolidation: paclitaxel 175 mg/m^2/d, ivgtt over 3 hours, d1; carboplatin AUC=5, ivgtt, d1

Patients receive premedication to prevent allergic reaction and significant nausea or vomiting as indicated.

Dose modifications

Radiotherapy interruption

If following toxicity is observed, radiotherapy has to be delayed until toxicity is no more than grade 2.

- WBC<2.0×10^9/L or ANC<1.0×10^9/L
- Plt<50×10^9/L
- Grade 3 or higher non-hematological toxicity

If following toxicity is observed, radiotherapy has to be delayed until complete recovery.

- Mediastinal or thoracic infection with fever over 38.5□

It is allowed to suspend at most 2 weeks, or radiotherapy will be terminated.

Chemotherapy interruption and dose modifications

If following toxicity is observed on day 1, chemotherapy has to be delayed until toxicity is no more than grade 1.

- ANC<1.5×10^9/L
- Plt<100×10^9/L
- Grade 2 or higher non-hematological toxicity, except for nausea, vomiting and alopecia

It is allowed to delay at most 2 weeks, or chemotherapy will be terminated.

Chemotherapy dose modifications are based on the greatest toxicity during the last cycle. Any patients who need to make chemotherapy dose modifications will receive the modified dose in the following cycles.

If modifications are needed, dose of paclitaxel, cisplatin, carboplatin and 5-FU will decreased by 25% from the planned dose for the first time and 50% for the second time. It is allowed to make dose modifications at most twice, or chemotherapy will be terminated. Details are as follows:

Dose modification of paclitaxel

- Febrile neutropenia (ANC< 0.5×10^9/L and fever over 38.3□ or over 38.0□ for 1h)
- Grade 2 or higher peripheral neuropathy

Dose modification of cisplatin and carboplatin

- Febrile neutropenia (ANC< 0.5×10^9/L and fever over 38.3□ or over 38.0□ for 1h)
- Grade 2 or higher peripheral neuropathy
- Serum creatinine >3ULN

Dose modification of 5-FU

- Febrile neutropenia (ANC< 0.5×10^9/L and fever over 38.3□ or over 38.0□ for 1h)
- Grade 3 or higher mucositis

The adverse events will be evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE version 4.0). All adverse events, occurring during the course of the trial, which is from randomization until 28 days after end of treatment, regardless of relatedness to study medication, will be recorded. Adverse events occurring later than 28 days after the end of treatment will only be recorded if they are considered relevant.

Randomization

After the confirmation of eligibility criteria, patients will be randomly allocated in a 1:1:1 ratio to the three treatment groups by a central randomization center (Fudan University Shanghai Cancer Center, Shanghai, China). Patients will be stratified by lymph node status (N0, N1, M1a). The SAS was used to generate a random permutation sequence and produce patient randomization numbers. The data center registers the enrollment, assigns a unique identification number to every participant, and replies to the respective investigators.

Sample size calculation and statistical analysis

This three-arm randomized trial is designed to confirm whether TF is superior to TP or TC concurrent with radiotherapy in terms of overall survival. According to RTOG 0113 and other reports, median survival time of TF concurrent with radiotherapy for esophageal cancer is 28.7 months while TP 14.9 months[5] and TC 17.4 months[13]. According to the Schoenfeld and Richter's method, the sample size of 107 patients per arm (154 events in total) is required to warrant a power of 80% at a

two-sided α level of 0.025 for the comparison between TP and TF with relatively smaller difference, assuming an accrual period of 48 months, a minimum follow-up period of 24 months and a dropout rate of 10%[14 15]. The total sample size is planned as 321 patients (107 patients in each arm, a total of 231 events).

The median overall survival will be estimated with Kaplan-Meier method, and log-rank test will be used to compare the overall survival among treatment arms. We will conduct a subgroup analyze to test whether the treatment effects differ among subgroups (N0, N1, M1a).

Endpoints

The primary endpoint is overall survival in all randomized patients. Overall survival is defined as time from the date of randomization until death. The secondary endpoint is progression free survival (PFS) and adverse events. PFS is defined as the time from the date of randomization to the date of progression or to the date of death, whichever occurs first and disease progression will be evaluated according to RECIST Version 1.1. Adverse events will be evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE version 4.0).

Data collection

Participants will be seen at hospitals or contacted by telephone and letters from randomization to the last treatment cycle, then at Month 3, 6, 9, 12, 15, 18, 21, 24, 30, 36, 42, 48, 54 and 60 after last treatment. Research staffs at the hospitals will be expected to complete trial CRFs.

Interim analysis

We plan to conduct two interim analyses. The first interim analysis will be conducted independently from the study group when half of the planned number of patients are enrolled and the second interim just after the planned patient accrual is completed. If the superiority of one of test arms (TF arm superior to TP arm or TC arm) is demonstrated with an adjusted α level, the study will be terminated.

In general, the interim reports will contain the following information:

1. Patient accrual rate with a projected completion date (while the study is still accruing)
2. Total patients accrued
3. Distributions of important pretreatment and prognostic baseline variables
4. The frequencies and severity of adverse events by treatment arm.
5. Compliance rates of treatment delivery
6. Observed results with respect to the primary and secondary endpoints

Patient and Public Involvement

Neither patients nor public will be involved in the design, recruitment, outcome measures and conduct of the study. Trial results will be disseminated via peer reviewed scientific journals and conference presentations rather than specifically notified to a single patient.

Ethics and dissemination

This trial has been approved by all participating centers including Fudan University Shanghai Cancer Center Institutional Review Board (Ethics Committee of Fudan University Shanghai Cancer Center: No.1505146-13). Written informed consent will be obtained from all participants. Serious adverse events will be reported to the safety desk of the trial, the Data and Safety Monitoring Board and trial sites. Trial results will be disseminated via peer reviewed scientific journals and conference presentations.

Participating institutions (From east to west)

Fudan University Shanghai Cancer Center, Huadong Hospital Affiliated to Fudan University, Fudan University Shanghai Cancer Center Minhang Branch, Affiliated Hospital of Jiangnan University, Fujian Province Cancer Hospital, Jiangsu Province Cancer Hospital, The First Affiliated Hospital of Xiamen University, Jiangxi Province Cancer Hospital, Shanxi Province Cancer Hospital, Hainan Province People's Hospital, Gansu Province Cancer Hospital

Trial Status

The trial was initiated in July 2015 and is currently recruiting patients in all of the participating institutions above.

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Declarations

List of abbreviations

TP: Paclitaxel combined with cisplatin

TC: Paclitaxel combined with carboplatin

TF: Paclitaxel combined with fluorouracil

UICC: Union for International Cancer Control

ESCC: Esophageal squamous cell carcinoma

PF: Cisplatin combined with fluorouracil

AIDS: Acquired immune deficiency syndrome

RT: Radiotherapy

PTX: Paclitaxel

DDP: Cisplatin

CBP: Carboplatin

5-FU: Fluorouracil

W: Week

ICRU: International Commission on Radiation Units and Measurements

GTV: Gross Target Volume

CTV: Clinical Target Volume

PTV: Planning Target Volume

WBC: White Blood Cell

ANC: Absolute Neutrophil Counts

Hb: Hemoglobin

Plt: Platelet

ULN: Upper Limit of Normal

AST: Aspartate Transaminase

ALT: Alanine aminotransferase

Consent of publication

Not applicable

Declaration of interests

We declare no competing interests.

Funding

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Author's contributions

D Ai was responsible for drafting the manuscript. Y Chen, Q Liu, J Zhang, J Deng, H Zhu, W Ren, K Wu, M Fan, H Yang, Z Zhu, W Zhao, L Li were responsible for the collection of previous study and putting forward the conception. X Zheng, Y Li, J Ye, J Zhou, Q Lin, H Luo, J Cao, S Wei, J Fan, J Li, G Huang and H Badakhshi were responsible for designing the details of the study. K Zhao was responsible for all aspects of trial design, the protocol and trial conduct. All authors have read and approved this manuscript.

Data Sharing Statement

No additional unpublished data from the study are available.

Fig1. Treatment Design of the ESO-Shanghai 2 trial.

TP (arm A), TF (arm B) and TC (arm C) are TP-, TF- and TC-based definitive chemoradiotherapy, respectively.

RT=radiotherapy, PTX=paclitaxel, DDP=cisplatin, 5-Fu=fluorouracil, CBP=carboplatin, W=Week.

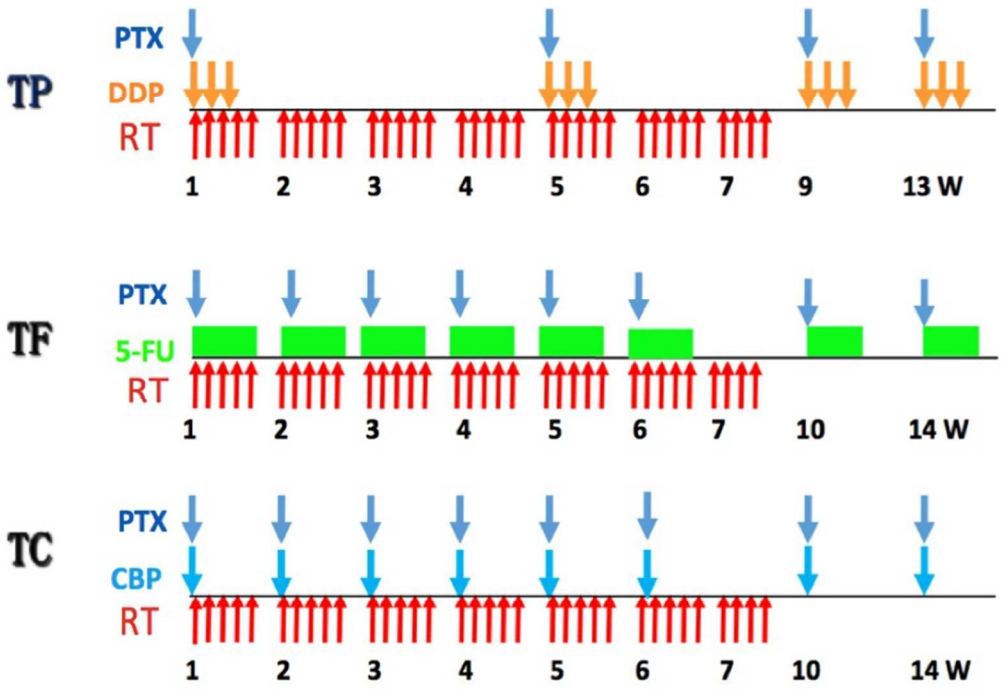

Fig1. Treatment design of the ESO-Shanghai 2 trial. ┣┳ RT=radiotherapy, PTX=paclitaxel, DDP=cisplatin, 5-Fu=fluorouracil, CBP=carboplatin, W=Week.┣┳

80x56mm (300 x 300 DPI)

Informed Consent Form

Comparison of paclitaxel in combination with cisplatin (TP), carboplatin (TC) or fluorouracil (TF) concurrent with radiotherapy for patients with local advanced esophageal squamous cell carcinoma: a three-arm phase III randomized trial (ESO-Shanghai 2)

You are being asked to take part in a clinical study. **Please take your time to make your decision about taking part. If you have any questions, you can ask your study doctor for more explanation.**

You are being asked to take part in this study because you have local advanced esophageal squamous cell carcinoma.

Why is this study being done?

Concurrent chemoradiation is the standard therapy for patients with local advanced esophageal carcinoma unsuitable for surgery. Paclitaxel is an active agent against esophageal cancer and it has been proved as a potent radiation sensitizer. There have been multiple studies evaluating paclitaxel-based chemoradiation in esophageal cancer, the results of which are inspiring. However, which regimen, among paclitaxel in combination with cisplatin (TP), carboplatin (TC) and fluorouracil (TF) concurrent with radiotherapy, provides best prognosis with minimum adverse events is still considered far from resolved and very few studies focus on this field. The purpose of this study is to confirm the priority of TF to TP or TC concurrent with radiotherapy in terms of overall survival and propose a feasible and effective plan for patients with local advanced esophageal cancer.

How many people will take part in the study?

About 321 people will take part in this study.

What will happen if I take part in this research study?

You will be randomized and allocated in a 1:1:1 ratio to the three treatment groups (TF, TP or TC). You will receive radiotherapy combined with concurrent chemotherapy. Radiotherapy will begin on day 1, concurrent with the beginning of cycle 1 of chemotherapy.

Radiation therapy

Same radiation therapy will be delivered in all three treatment groups. Radiotherapy will be delivered with photons (≥6 MV) to a total dose of 61.2Gy in 34 fractions. You will be treated 5 days per week at 1.8Gy/d.

Chemotherapy

Arm A (TP)

If you are in arm A, you will receive 4 courses of TP every 4 weeks. Details are as follows:

Paclitaxel: 175mg/m^2/d, ivgtt over 3 hours, d1; Cisplatin: 25mg/m^2/d, ivgtt, d1-3;

Arm B (TF)

If you are in arm B, you will receive 6 courses of TF concurrent with radiotherapy every week and 2 courses of TF adjuvant chemotherapy every 4 weeks. Details are as follows:

Concurrent: paclitaxel 50mg/m^2/d, ivgtt over 3 hours, d1; 5-FU 300mg/m^2, civ 96h, d1-4

Adjuvant: paclitaxel 175 mg/m^2/d, ivgtt over 3 hours, d1; 5-FU 1800mg/m^2, civ 72h, d1-3

Arm C (TC)

If you are in arm C, you will receive 6 courses of TC concurrent with radiotherapy every week and 2 courses of TC adjuvant chemotherapy every 4 weeks. Details are as follows:

Concurrent: paclitaxel 50mg/m^2/d, ivgtt over 3 hours, d1; carboplatin AUC=2, ivgtt, d1

Adjuvant: paclitaxel 175 mg/m^2/d, ivgtt over 3 hours, d1; carboplatin AUC=5, ivgtt, d1

During each treatment, blood tests will be performed to monitor blood counts, kidney function, liver function and electrolyte levels. Ultrasound, barium swallow and CT scan with contrast will be performed to evaluate the status of disease.

How long will I be in the study?

After your treatment is completed, you will be seen in follow-up visits with your doctor every 3 months in years 1-2, every 6 months in years 3-5 and then once a year for your lifetime.

Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so he or she can evaluate any risks from the treatment. Another reason to tell your study doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest, if you do not follow the study rules, or if the study is stopped.

What side effects or risks can I expect from being in the study?

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. There also is a risk of death.

Risks and side effects related to the chemoradiotherapy

- Soreness in throat or esophagus
- Cough
- Vomiting
- Nausea
- Fatigue
- Anorexia (loss of appetite)
- Diarrhea
- Numbness in arms and legs
- Allergic reaction
- Hair loss
- Redness of irritation of the skin in the treatment area
- Decrease in white blood cell counts and high risk of infection
- Renal insufficiency,

Are there benefits to taking part in the study?

Taking part in this study may or may not make your health better. While researchers hope these treatment regimens will be more useful against cancer compared to the usual treatment, there is no proof of this yet. We do know that the information from this study will help researchers learn more about these combinations of drugs as a treatment for cancer. This information could help future cancer patients.

Will my medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

What happens if I am injured because I took part in this study?

It is important that you tell your study doctor if you feel that you have been injured because of taking part in this study. You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our center.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

WHO CAN ANSWER MY QUESTIONS ABOUT THE STUDY?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor, Kuaile Zhao, at 021-64175590.

Signature

I have been given a copy of all 5 pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Participant:

_____	_____	_____
Name of Participant	Signature	Date

Researcher:

_____	_____	_____
Name of Participant	Signature	Date

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	____1_____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	____3_____
	2b	All items from the World Health Organization Trial Registration Data Set	__None_____
Protocol version	3	Date and version identifier	__None_____
Funding	4	Sources and types of financial, material, and other support	____17_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	____17_____
	5b	Name and contact information for the trial sponsor	_ _None_____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	__ None _____
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	__ None _____

Introduction

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5
	6b	Explanation for choice of comparators	6
Objectives	7	Specific objectives or hypotheses	6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	13
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6-7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7-9
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	10
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	None
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	12
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	13

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	____11-12___
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	____ None ___
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	____11_____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	____11_____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	____11_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	____ None ___
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	____ None ___
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	____ 11_____
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	____ 12 ___

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	____ None ___
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	_____12_____
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	_____12 _____
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	____ None ____
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	____ None ____
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	_____12-13____
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	_____11_____
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	____ None ____
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	_____13_____
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	____ None ____

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	____ None ____
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	____ None ____
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	____ None ____
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	_____17 _____
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	____ None ____
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	____ None ____
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	____ None ____
	31b	Authorship eligibility guidelines and any intended use of professional writers	____ None ____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	____ None ____
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	__Supplementary material____
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	____ None ____

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.