Phase I trial of intensity-modulated hyperfractionated radiotherapy boost with concurrent chemotherapy following standard chemoradiotherapy in patients primarily with advanced intra-thoracic/cervical esophageal squamous cell carcinoma

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1. Synopsis

Trial title	Phase I trial of intensity-modulated hyperfractionated radiotherapy (HFRT) boost with concurrent chemotherapy following standard chemoradiotherapy in advanced esophageal cancer
Clinical trials.gov ID	NCT03082586
Unique protocol ID	SGH201705
Approval number:	20170128
Trial manager	Tingfeng Chen, MD, PhD, Department of Radiation Oncology, Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China
Trial start	November 2016
Recruitment period	18 months
Type of study	A prospective, one-institutional, open, phase I trial
Treatment	**Standard chemoradiotherapy during weeks 1-5:** 50 Gy in 25 fractions of 2 Gy + concurrent weekly paclitaxel 45 mg/m^2, carboplatin AUC 1.5 **HFRT boost to gross tumor volume beginning on Week 6:** One of dose levels given as follows: 7.2 Gy, 14.4 Gy, 21.6 Gy (i.e., increments of 7.2 Gy delivered in 6 twice daily fractions of 1.2 Gy), concurrent with the same chemotherapy schedule
Endpoints	The primary objective: To define the maximum tolerated dose (MTD) of HFRT boost The second objective: To evaluate the efficacy, local control, and patterns of

	failure of this regimen
Number of patients	Thirty-one patients
Inclusion criteria	1. Histologically confirmed primary squamous cell carcinoma or adenocarcinoma of the esophagus. 2. Age 18-75. 3. Patients must be deemed unresectable disease or patient is not deemed operable due to medical reasons. 4. Patients with distant metastasis and life expectancy ≥ 4 months are eligible. 5. Zubrod performance status 0 to 2. 6. No prior radiation to the thorax that would overlap with the current treatment field. 7. Patients with nodal involvement are eligible. 8. Adequate bone marrow, renal and hepatic functions: hemoglobin ≥ 100.0 g/L, platelet count ≥ 100×10^9/L, absolute granulocyte count (AGC) ≥ 2×10^9 cells/L, bilirubin and aspartate transaminase ≤ 1.5 × upper limit of normal (ULN), creatinine ≤ 1.5 times ULN. 9. A signed informed consent must be obtained prior to therapy. 10. Induction chemotherapy is allowed.
Exclusion criteria	1. The presence of a fistula. 2. Prior radiotherapy that would overlap the radiation fields. 3. Lower thoracic esophageal cancer involving the stomach.

	4. Gastroesophageal junction cancer. 5. Uncontrolled concurrent illness including, but not limited to: chronic obstructive pulmonary disease(COPD) exacerbation or other respiratory illness, serious uncontrolled infection, symptomatic congestive heart failure (CHF), unstable angina pectoris, uncontrolled hypertension, or psychiatric illness/social situations that would limit compliance with the study requirements. 6. Known hypersensitivity to paclitaxel. 7. Any other condition or circumstance that would, in the opinion of the investigator, make the patient unsuitable for participation in the study. 8. Acquired immune deficiency syndrome. 9. Conditions precluding medical follow-up and protocol compliance.
Statistics / sample size calculation	Tumor response is evaluated according to RECIST 1.1 (Response Evaluation Criteria in Solid Tumors). A clinical CR (cCR) is defined as both the absence of tumor cells in the endoscopic biopsy and the complete disappearance of all measurable disease on imaging studies. Immediate local failure is defined as persistence of tumors, and failure patterns are documented using basic calculations. The time to event variables is calculated from the date of entering the study. Time to first local-regional failure is estimated using a cumulative incidence analysis with death as a competing risk. Kaplan-Meier method is used to estimate the survival rates. The HFRT boost dose after standard chemoradiotherapy is

	escalated in cohorts of 3 to 6 patients in increments of 7.2 Gy delivered in 6 twice daily fractions of 1.2 Gy at interval of ≥ 6 hours using a modified Fibonacci schema, with probability of dose escalation 91%, 71%, 49%, 31%, 17% and < 1% respectively at true DLT rates of 10%, 20%, 30%, 40%, 50% and 80%. Once the MTD is determined, it is given to a larger patient cohort (10 cases) to further determine the safety profile and efficacy. Based on these assumption, a total sample size of 31 evaluable patients will be required for this study.

2. Background and Rationale

2.1.1. Epidemiology

Esophageal cancer is a highly lethal disease, with an overall 5-year survival rate of 15-25%.[1] It is the eighth most common cancer, and sixth cause of cancer-related deaths in the world.[2] The total incidence of esophageal cancer is rising, mainly due to a dramatic rise in the incidence of adenocarcinoma.[3] In China, esophageal cancer is the fourth most common cancer and fourth cause of cancer-related deaths. About 477,900 new esophageal cancer patients were diagnosed in 2015 that account for more than 50% of the global morbidity and mortality, of which 95% have esophageal squamous cell carcinoma (ESCC).[4]

2.1.2. Curative treatment of esophageal cancer

Surgery is currently the standard of care for esophageal cancer with curative intent if a patient is fit enough to undergo surgery and the tumor is considered to be technically resectable without evidence of distant metastases (cT1-3 N0-1 M0).[5,6] However, when patients have an inoperable condition due to comorbid conditions, technically unresectable cancer (T4N2M0), or a desire not to undergo surgery, then definitive chemoradiotherapy is an appropriate alternative to surgery.[7-9] In addition, for individuals with cervical esophageal carcinoma and those with high thoracic squamous cell carcinoma, definitive chemoradiotherapy might be a preferred option,[7-9] considering potentially increased postoperative morbidity and mortality associated with surgical resection. Sometimes, physicians or patients will prefer to choose this treatment modality.[10] Increasingly, definitive chemoradiotherapy is being established as the standard of care in patients with esophageal squamous-cell carcinoma, because evidence suggests that outcomes are similar to those of surgical treatment.[11-13] A Patterns of Care analysis by the American College of Radiology for the period of 1996 - 1999 suggests that 56% of patients with esophageal cancer had received combined-modality therapy as definitive therapy.[14]

2.1.3. Chemoradiotherapy

The landmark RTOG 85-01 trial is the first to demonstrate a statistically significant survival benefit for radiation (50Gy in 25 fractions of 2 Gy) and concurrent chemotherapy compared with radiation therapy alone (64 Gy in 32 fractions of 2 Gy).

Following chemoradiotherapy, 5-year survival rates were 26%, compared with 0% with radiation alone.[15-17] Nevertheless, locoregional tumor control remains a major problem, with 25% of patients having persistence and 21% recurrence of locoregional disease after combined modality treatment (Table 1).

Table 1 Patterns of failure

First failure	Radiation therapy alone (N = 62)		Radiotherapy+ chemotherapy (N = 61)
Persistent	23 (37%)		15 (25%)
Local-regional	10 (16%)		8 (13%)
Distant only	9 (15%)		5 (8%)
Local, regional, and distant	9 (15%)		5 (8%)

As shown in table 1, local-regional persistence and relapse of disease account for the majority of treatment failures after concurrent chemoradotherapy, with the majority of local failures occuring within gross tumor volume.[15-18] It is not possible to cure patients with esophageal cancer without local disease control. Efforts to improve survival have frequently focused on strategies to improve local control.

2.1.4. Attempts to improve local control

Three prior RTOG phase II or III trials examine the role of increasing the radiation dose in patients selected for a nonsurgical approach, with the arm of improving local control. RTOG 9207 conducted a phase I/II study of 50 Gy of external beam radiation (25 fractions given over 5 weeks) followed 2 weeks later by esophageal brachytherapy (either high-dose-rate 5 Gy during Weeks 8, 9, and 10, for 15 Gy total, or low-dose-rate 20 Gy during Week 8).[19-20]Chemotherapy was administered for the first 4 days of weeks 1, 5, 8, and 11, with cisplatin 75 mg/m^2 and 5-fluorouracil 1000 mg/m^2 /24 hours in a 96-hour infusion. Of the 49 eligible patients, forty-seven patients (96%) completed external beam radiation plus at least 2 courses of chemotherapy, whereas 34 patients (69%) were able to complete external beam radiation, esophageal brachytherapy, and at least 2 courses of chemotherapy. The estimated survival rate at 12 months was 49%, with an estimated median survival of 11 months. Life-threatening toxicity or treatment-related death occurred in 12 (24%)

and 5 (10%) cases, respectively. Treatment-related esophageal fistulas occurred in 6 cases (12% overall, 14% of patients starting esophageal brachytherapy) at 0.5– 6.2 months from the first day of brachytherapy, leading to death in 3 cases. The phase II intergroup trial 0122 entered 45 patients with squamous cell carcinoma who were treated with three cycles of neoadjuvant 5-FU and cisplatin followed by concurrent 5-FU, cisplatin, and 64.8 Gy.[21-22] With a median follow-up of 15 months in surviving patients, the incidence of total grade 3+ toxicity during the neoadjuvant chemotherapy segment was 61%, and during the combined modality segment was 72%. Of the 33 patients who started radiation therapy, 91% were able to complete the full course. There were six deaths during treatment, five of which (11 %), because of nadir sepsis and/or dehydration, were treatment-related. The local/regional failure rate was 39%, median survival was 20 months, and 3-year survival was 30%. The overall treatment-related mortality rate was 9%; however, 5% were the sole result of the neoadjuvant component of the treatment (i.e., chemotherapy-related). RTOG 9405 randomly assigned two hundred thirty-six patients with esophageal cancers not extending to within 2 cm of the gastroesophageal junction to combined-modality therapy arm treated with high-dose radiation (64.8 Gy) with four monthly cycles of 5-FU (1,000 mg/m^2 /24 hours for 4 days) and cisplatin (75 mg/m^2 bolus on day 1) or conventional-dose radiation arm (50.4 Gy) with the same chemotherapy schedule.[13] With the exception of a higher proportion of males in the standard dose arm (76% vs. 65%), the distribution of the baseline characteristics (weight loss, primary tumor size, performance status, age, and histology) were well balanced between the two arms. A planned interim analysis using a stochastic curtailment analysis after 230 patients were accrued revealed that the probability of the high dose arm having a statistically significant survival result was only 2.4%. Therefore, the trial was prematurely closed before reaching its planned accrual goal of 298. There was no significant difference in median survival (13.0 v 18.1 months), 2-year survival (31% v 40%), or local/regional failure and local/regional persistence of disease (56% v 52%) between the high-dose and standard-dose arms. Although 11 treatment-related deaths occurred in the high-dose arm compared with two in the standard-dose arm, seven of the 11 deaths occurred in patients who had received 50.4 Gy or less, indicating that it did not seem to be related to the higher radiation dose (i.e., not RT-related).

Another attempt was made to address persistent and recurrent locoregional esophageal tumor by using selective surgical resection after definitive chemoradiotherapy.[23-25]

Actually, salvage surgery after definitive chemoradiotherapy may salvage only a minority of patients with local failure. For example, Sudo K et al from the University of Texas MD Anderson Cancer Center reported that approximately 8% of 276 patients could undergo salvage surgical resection treatment in a retrospective study.[23] The patients with local relapse only who received salvage surgery had their median overall survival of 58.6 months compared with 9.5 months for those with local relapse who were unable to undergo surgery. However, a phase II prospective RTOG 0246 study testing the strategy of definitive chemoradiotherapy with selective surgical salvage in locoregionally advanced esophageal cancer, with the primary objective of an improvement in 1-year survival from 60% to 77.5%, did not reach the hypothesized 1-year RTOG survival rate (77.5%).[25] One-year survival rate was 71%, suggesting no improved overall survival with salvage surgery following definitive chemoradiotherapy.[25] Postoperative morbidity and mortality associated with salvage surgery are significant. Markar S. et al reported an in-hospital mortality and in-hospital morbidity rate of 8.4% (26/308) and 63.6% (196/308), respectively in a large retrospective study.[24]

Incorporation of new chemotherapeutical drugs or targeted agents (including paclitaxel, cetuximab) into definitive chemoradiotherapy was investigated in phase II or III prospective trial. Unfortunately, addition of these drugs to chemoradiotherapy have still failed to improve local control and overall survival for patients with locally advanced esophageal cancer.[26,27] Taken together, the use of either intensification of radiation therapy with either esophageal brachytherapy boost or higher radiation dose (64.8 Gy) conventional fractionated radiation therapy, salvage surgery after definitive chemoradiotherapy, or incorporation of new chemotherapeutical/targeted drugs have so far not improved significantly local disease control and overall survival. The issue of suboptimal local control remains unsettled and a novel strategy is urgently needed.

2.1.5. Evidence concerning improvement in local control with BED more than 100 Gy in cancer therapy

Over the last two decades, one of the most impressive achievements in radiation oncology has probably been to dramatically improve local control and survival of early-stage non-small cell lung cancer (NSCLC) with a biological effective dose (BED) more than 100 Gy using stereotactic body radiation therapy (SBRT).[28,29] A

local control rate increases from 30-40% with conventional radiotherapy of 60 Gy (calculated BED = 72 Gy), most commonly given in 20-30 outpatient treatments,[30-32] to more than 90% with a BED 100Gy or greater, and 2-3-year overall survival from 20-30% to 50-70%. [33,34]Theoretically, the established benefits of higher radiation dose or BED ≥ 100 Gy for early-stage NSCLC could potentially be extrapolated to treatment of locally advanced esophageal cancer. The currently accepted standard-dose of 50 Gy (calculated BED = 60 Gy, assuming $\alpha/\beta = 10$ for esophageal cancer) seems insufficient to offer optimal local control for esophageal cancer. Central is how higher radiation dose can be safely delivered to patients with esophageal cancer within normal tissue tolerances. Although SBRT can deliver a biologically potent, tumoricidal, hypofractionated dose to the tumor while using a variety of modern technologies and techniques to achieve rapid falloff limiting dose to innocent, surrounding normal tissues, it is potentially associated with severe late toxicity, resulting in catastrophic problems like dysfunction, necrosis, fistula and even death.[35] It should be noted that parallel-functioning organs such as lung and liver, which are composed of parenchymal tissues of which subdivisions perform a similar and independent function, allow damage or destruction of a small portion of the organ without clinically significant toxicity when using SBRT if they have a sufficient reserve of function. In contrast, serial-functioning organs such as esophagus (delivering a food bolus from the pharynx to the stomach), whose function depends on a cascade of events occurring along a pathway does not permit any position along the esophagus to be destroyed, otherwise, resulting in clinically severe toxicity including loss of the entire function and even death secondary to fistula and infection.[28,35] In addition, the increased morbidity, especially fistulas, and mortality associated with dose escalation as demonstrated in a series of the above-mentioned RTOG studies indicate that the use of SABR/hypofractionation and conventional fractionated radiation therapy techniques for dose escalation is obviously inappropriate in esophageal cancer.[13, 19-22,36,37]

2.1.6. Evidence that the tolerated dose of RT exceeds 50 Gy in esophageal cancer

The currently accepted standard-dose has been established as 50 Gy in 25 fractions of 2 Gy based on the results of the RTOG 9405 trial. It should be noted that the RTOG 9405 was not designed for defining the maximum tolerated radiation dose for esophageal cancer although it did not detect any advantage of high radiation dose

(64.8 Gy) compared with standard-dose (50 Gy).[13] Growing evidence suggests that the tolerated dose of RT for esophageal cancer exceeds 50 Gy. Yu et al.[38] and Chen et al.[39] reported that 66-70 Gy in 25-30 fractions can be safely delivered using a simultaneous integrated boost technique in esophageal cancer. Socinski et al [40]reported no dose-limiting esophageal toxicity at 78 Gy (range 70.9 to 90 Gy) of the average maximum dose to the esophagus in the treatment of stage IIIA and IIIB NSCLC. However, the maximum tolerated dose of RT has not so far been well defined in prospective dose-finding trials in esophageal cancer.

2.1.7. HFRT and modern radiation techniques

HFRT, which allows for delivering a higher total dose without increasing late toxicity,[41] may be used to further increase the total tumor dose after standard chemoradiotherapy. Moreover, advances in radiation planning, tumor imaging, and radiation delivery using image-guided radiotherapy (IGRT) have also enhanced the ability to deliver higher, more conformal doses to esophageal cancer.[42,43]

2.2. Rationale of the study

Although chemoradiotherapy has been established as the standard of care for advanced esophageal cancer, outcomes remains poor, with a 5-year overall survival of 20-25%. Local failure accounts for the major of treatment failure. Curing patients is not possible without local disease control. Effective approaches for control of local disease have so far been lacking. Based on the experiences of significantly improved local disease control with BED more than 100 Gy or greater as compared with conventional radiotherapy of 60 Gy in early-stage NSCLC, radiation dose escalation is potentially one strategy to improve local control and subsequent survival for patients with esophageal cancer. However, the maximum tolerated radiation dose has so far not been well defined in prospective dose-finding trials. It is felt that SBRT or conventional fractionated RT is inappropriate for dose escalation of RT for esophageal cancer because the esophagus is a serially functioning organ and more esophageal fistulas and deaths were noted with hypofractionated radiation boost in the RTOG 9207 trial and conventional fractionated dose escalation in the RTOG 9405 study.

The majority of local failures occur within gross tumor volume. We therefore design this phase I trial to define the maximum tolerated dose (MTD) of the HFRT boost to

gross tumor volume (the main sites of treatment failure after standard chemoradiotherapy) with concurrent weekly carboplatin and paclitaxel, immediately following standard dose chemoradiotherapy (SCRT) of 50 Gy with the same chemotherapy regimen which abides by the National Comprehensive Cancer Network guidelines, using modern image-guided intensity-modulated radiation therapy (IG-IMRT). Although the entire protocol (SCRT + HFRT boost) would need prolonged overall treatment time (more than 5weeks), potentially resulting in tumor repopulation. The rationale is that all patients will be treated with upfront standard chemoradiotherapy, ensuring that patients gain the established benefit from standard chemoradiotherapy. We hypothesize that the potential benefits gained from additional radiation dose after standard chemoradiotherapy may outweigh the detrimental effect of tumor repopulation due to prolongation of treatment time as the boost dose increases.

3. Objectives of the study

The primary objective:

To define the maximum tolerated dose (MTD) of the HFRT boost with concurrent weekly carboplatin/paclitaxel immediately following standard chemoradiotherapy of 50 Gy with the same chemotherapy regimen, using modern image-guided intensity-modulated radiation therapy.

The second objective :

To evaluate the efficacy, local control, and patterns of failure of the regimen.

4. Patient selection criteria

4.1. Eligibility criteria

1) Histologically confirmed primary squamous cell carcinoma or adenocarcinom of the esophagus.
2) Age 18-75.
3) Patients must be deemed unresectable disease or patient is not deemed operable due to medical reasons.
4) Life expectancy ≥ 4 months (T1-4N0-3M0-1).

5) Zubrod performance status 0 to 2.

6) No prior radiation to the thorax that would overlap with the current treatment field.

7) Patients with nodal involvement are eligible.

8) Adequate bone marrow, renal and hepatic functions:

   - ✓ Hemoglobin ≥100.0 g/L
   - ✓ Platelet count ≥ 100×10^9/L
   - ✓ Absolute granulocyte count (AGC) ≥ 2×10^9 cells/L
   - ✓ Bilirubin and Aspartate transaminase ≤ 1.5 × upper limit of normal (ULN),
   - ✓ Creatinine ≤ 1.5 times ULN

9) A signed informed consent must be obtained prior to therapy.

10) Induction chemotherapy is allowed.

4.2. Ineligibility criteria

1) The presence of a fistula.

2) Lower thoracic esophageal cancer involving the stomach.

3) Prior radiotherapy that would overlap the radiation fields.

4) Gastroesophageal junction cancer.

5) Uncontrolled concurrent illness including, but not limited to: chronic obstructive pulmonary disease(COPD) exacerbation or other respiratory illness, serious uncontrolled infection, symptomatic congestive heart failure (CHF),unstable angina pectoris, uncontrolled hypertension,or psychiatric illness/social situations that would limit compliance with the study requirements.

6) Known hypersensitivity to paclitaxel.

7) Any other condition or circumstance that would, in the opinion of the Investigator, make the patient unsuitable for participation in the study.

8) Acquired immune deficiency syndrome.

9) Conditions precluding medical follow-up and protocol compliance.

5. PRETREATMENT EVALUATION

1) Complete history and physical examination, including the patient's weight and height measurement, with an assessment of the patient's performance status within four weeks prior to study entry.

2) All patients must be reviewed by a multidisciplinary team consisting of a radiologist, an experienced surgical oncologist, a radiation oncologist, and a medical oncologist to determine operability prior to registration.

3) Laboratory studies (within 2 weeks prior to registration):

CBC, ANC, platelets; Chemistry including serum creatinine, electrolytes, ALT, AST, LDH, alkaline phosphatase (if alkaline phosphatase is ≥ 1.5 × upper limits of institutional normal, a bone scan is required), total bilirubin, total protein, albumin, uric acid, inorganic phosphorous, calcium, BUN, magnesium; calculated creatinine clearance (optional). A central venous access (a long line, subclavian catheter, or implantable device) should be established in all patients prior to beginning chemotherapy.

4) Imaging studies (within 4 weeks prior to registration):

- ✓ CT scan of the chest and abdomen (MRIs are acceptable).
- ✓ Upper GI endoscopy (endoscopic ultrasound is required; Double contrast upper GI radiographs are optional.
- ✓ PET scan (strongly encouraged); A PET scan suggestive of metastatic disease must have imaging studies or biopsies to prove that there is no metastatic disease.
- ✓ Bronchoscopy is required if the lesion is < 25 cm from the incisors to exclude TE fistula or invasion.

Data on T stage, N stage will be collected. Whenever possible, EUS/FNA of the nodes is highly desirable to improve accuracy.

5) Biopsy of supraclavicular node if clinically enlarged (i.e., palpable).

6) Bone scan (if alkaline phosphatase is elevated ≥ 1 .5 × upper limits of institutional normal).

7) Pulmonary function tests - including DLCO and FEV1.

8) Cardiac function test- including electrocardiogram and echocardiography.

9) Nutritional counseling will be offered to all patients.

6. Trial design

6.1. Overall design

A prospective, one-institutional, open, phase I trial.

6.2. Study schema

50 Gy (2 Gy/fraction) + concurrent weekly paclitaxel at 45 mg/m^2 and carboplatin AUC 1.5 over 5 weeks

Dose-Escalated HFRT Boost to GTV Beginning on Week 6

Dose level	Level 1	Level 2	Level 3	Level 4	Level 5	Level 6
Dose schema (1.2 Gy/f, bid)	1.2×6 Gy	1.2×12 Gy	1.2×18 Gy	1.2×24 Gy	1.2×30 Gy	1.2×36 Gy
Total boost dose	7.2 Gy	14.4 Gy	21.6 Gy	28.8 Gy	36 Gy	43.2 Gy
Cumulative dose	57.2 Gy	64.4 Gy	71.6 Gy	78.8 Gy	86 Gy	93.2 Gy
Cumulative BED*	68.1 Gy	76.1 Gy	84.2 Gy	92.3 Gy	100.3 Gy	108.4 Gy

Concurrent Chemotherapy	paclitaxel 45 mg/m^2 + carboplatin AUC 1.5 weekly

*BED = n × d× (1+d/α/β), assuming α/β = 10 for esophageal cancer with no time correction; GTV: gross tumor volume; AUC: area under the curve.

6.3. Duration of enrollment

The study starts on November 2016. Two patients will be recruited per month and the duration of inclusion will be appropriately 18 months.

6.4. Termination criteria for individual patients

The patient may terminate participation in the study at any time and without giving any reasons.

6.5. Termination criteria for the trial in general

The clinical trial can be stopped by the principal investigator Tingfeng Chen if unacceptable toxicities occur. A Data Safety Monitoring Board (DSMB) will decide every three months whether the trial may continue or not.

7. Treatment

7.1. Chemotherapy

7.1.1. Concurrent chemotherapy during radiotherapy

Paclitaxel 45 mg/m^2 and carboplatin AUC = 1.5 will be administered by intravenous infusion on days 1, 8, 15, 22, 29, 36, 43, concurrent with RT. Typically, the infusion of paclitaxxel and carboplatin will be initiated on Monday morning. Radiation therapy will be delivered 2 hours after completion of the chemotherapy infusion.

Administration of paclitaxel and carboplatin

Premedication procedures:

All patients who receive paclitaxel will receive half an hour prior to the receipt of paclitaxel infusion premedication as follows:

- ✓ Dexamethasone 20 mg IV,
- ✓ Ranitidine 50 mg IV,

- ✓ Diphenhydramine 50 mg IV

Two hours prior to RT, the total dose of paclitaxel calculated, diluted in 500 ml of 0.9% normal saline will be infused over one hour, immediately followed by the infusion of 100 ml 0.9% normal saline over half an hour, then followed by the infusion of carboplatin that is diluted in 500 ml glucose 5% over more than 1 hour. The total absolute dose of carboplatin will be calculated for the target AUC = 1.5 according to the following formula:

- ✓ The absolute dose of carboplatin = [target AUC] × (GFR + 25)
- ✓ Formula GFR = [((140 – age) × 1.23 × body weight) / serum creatinine × (0.85 (female) or 1.00 (male))]

Prophylactic antiemetics (ondansetron 8 mg infusion) and proton pump inhibitors will be prescribed in all cases, and best supportive care including nutritional support and red blood cell infusion is allowed as clinically indicated.

7.1.2. Adjuvant chemotherapy after completion of RT

Patients will be given 4-6 weeks after completion of the HFRT boost at the discretion of the treating physician, as reported previously.[44,45]

7.1.3. Dose modifications for chemotherapy during radiotherapy

Reduction of chemotherapy dose will be based on the degree of hematologic and nonhematologic toxicities as follows. Toxicity was graded according to the National Cancer Institute-Common Toxicity Criteria (NCI-CTC) Version 4.0.

Dose Modifications for Concurrent Chemotherapy during RT			
Toxicity	Grade	Drug	Modification
Leucopenia	Grade 3	Carboplatin	Reduction 33%
Leucopenia	Grade 4	Carboplatin/ Paclitaxel	Discontinue
Thrombocytopenia	Grade 3	Carboplatin	Reduction 33%

Thrombocytopenia	Grade 4	Carboplatin/ Paclitaxel	Discontinue
Febrile neutropenia	Second or third incidence despite G-CSF support administered after the first occurrence;	Carboplatin/ Paclitaxel	Discontinue
Hypersensitivity reaction	Grade 1 or worse	Paclitaxel	Discontinue
Liver (bilirubin and/or AST)	Grade 3 or worse	Paclitaxel/C arboplatin	Discontinue
Liver (bilirubin and/or AST)	Grade 2	Carboplatin/ Paclitaxel	Reduction 33%
Creatinine clearance	Between 40 and 59 ml/min	Carboplatin	Reduction 33%
Creatinine clearance	Less than 40 ml/min	Carboplatin	Discontinue
Esophagitis	Grade 3	Carboplatin/ Paclitaxel	Reduction 33%
Other non-hematologic toxicity	Grade 3	Carboplatin/ Paclitaxel	Discontinue

7.2. Radiotherapy

Image-guided three-dimensional conformal intensity modulated radiation therapy (IG-IMRT) is mandatory for all patients. The radiation field encompasses the gross primary tumor, clinically positive lymph nodes, and draining lymph nodes; Radiation

therapy will be administered via a linear accelerator (Clinic ix, Varian) with 6–15 MV photons.

7.2.1. Dose specifications:

- ✓ Treatment plans for patients on the protocol will include 2 phases: 1) the first phase will include inverse-planned IMRT-based therapy to the planning target volume for a total of 50 Gy in 2 Gy daily fractions over 5 weeks, and 2) the second phase will include a cone-down dose-escalating HFRT boost immediately following delivery of 50 Gy to the gross primary tumor beginning on week 6.
- ✓ The HFRT boost dose is determined based on the study dose level, escalated in cohorts of 3 to 6 patients in increments of 7.2 Gy delivered in 6 twice daily fractions of 1.2 Gy at interval of ≥ 6 hours (7.2 Gy, 14.4 Gy, 21.6 Gy, ……), using a modified Fibonacci schema (see section 9.2.2).
- ✓ Planning constraints are set for the planning target volume (PTV), the boost gross tumor volume (BGTV), as well as critical normal organs to be spared. Acceptable treatment plans will be generated from a DVH-based analysis of the volumetric dose to the PTV, BGTV, and critical normal organs to be sure that minimally acceptable constraints for each volume of interest have been met.

7.2.2. Localization, immobilization, and simulation:

- ✓ Patients are immobilized in a vacuum pad in a supine position followed by 4-dimensional images to track internal organ motion.
- ✓ 2.5-mm-thick treatment planning CT images are acquired on a CT simulator (Philips Medical Madison, WI).

7.2.3. Treatment planning/target volumes:

- ✓ Inverse-planning capable TPS software (Eclipse 11.0, Varian, Palo Alto, CA) is used.
- ✓ The IMRT plans are generated and optimized using commercial planning software. Every effort is taken to limit dose to the heart and lung.
- ✓ The primary tumor volume and clinically positive lymph nodes as determined by barium swallow, CT scan, EUS and PET (if available). Clinically positive lymph

nodes are defined as nodes sized ≥1 cm visualized on CT/PET scan and/or EUS (whichever is larger).

- ✓ The boost GTV (BGTV) is defined as the GTV with cranio-caudal margins of 2 cm and radial margins of 0.5 cm.
- ✓ The clinical target volume (CTV) includes the GTV with cranio-caudal margins of 5 cm and radial margins of 1 cm. For tumors of the cervical and upper third thoracic esophagus, the supraclavicular lymph nodes are also included. The anatomic boundaries with surrounding critical organs must be respected.
- ✓ The planning tumor volume (PTV) is the CTV plus a 0.5 cm margin in all directions to account for daily patient set-up variation and potential internal organ motion.

7.2.4. PTV and BGTV dose-volume constraints:

- ✓ 100% of the PTV and BGTV receive ≥ 95% of the prescribed dose.
- ✓ ≥ 95% of the PTV and BGTV receive 100% of the prescribed dose.
- ✓ ≤ 10% of the PTV and BGTV receive ≥ 105% of the prescribed dose.
- ✓ ≤ 5% of the PTV and BGTV receive ≥ 110% of the prescribed dose.
- ✓ None of the PTV or BGTV is to receive ≥ 115% of the prescribed dose.

7.2.5. Critical structures (IMRT planning constraints)

Normal-tissue dose-volume constraints:

Lung	≤ 30% of the lung to receive 20 Gy
Spinal cord	Max dose ≤ 54Gy
Brachial plexus	Max dose ≤ 66 Gy
Heart	≤ 50% of the heart to receive 40 Gy

7.2.6. Identification and correction of setup errors

Image-guided RT is performed using KV-cone-beam CT scans at least twice-weekly, more frequently if clinically indicated, prior to treatment delivery. The results are registered to the planning CT scans in order to identify setup errors; In case of errors ≥3 mm, the patient's position is corrected immediately.

7.2.7. Compliance criteria

Each treatment will be reviewed for quality assurance of target volumes and critical structures and ensuring that dose-volume goals and constraints are met. The following criteria will be utilized to assess compliance and/or deviation.

- ✓ PTV and BGTV

A. Per protocol if the prescription criteria are fulfilled.

B. Variation acceptable if not to meet constraints but can meet the following constraints:

1) 100% of the PTV and BGTV receive ≥ 93% of the prescribed dose.
2) ≥ 95% of the PTV and BGTV receive ≥ 97% of the prescribed dose.
3) ≤ 13% of the PTV and BGTV receive ≥ 105% of the prescribed dose.
4) ≤ 7% of the PTV and BGTV receive ≥ 110% of the prescribed dose.

A. Variation unacceptable if not to meet any of the above criteria.

Lung

A. Per protocol if the prescription criteria are fulfilled.
B. Variation acceptable: ≤ 33% of the lung to receive 20 Gy.
C. Variation unacceptable: Dose limits for variation acceptable are exceeded.

Spinal cord

A. Per protocol if the prescription criteria are fulfilled.
B. Variation acceptable: Max is > 54 Gy but dose ≤ 56 Gy.
C. Dose limits for variation acceptable are exceeded.

7. 2.8. RT quality assurance reviews

Quality assurance is required with matrix, chamber, and daily orthogonal films.

The imaging and dosimetry plans must be reviewed and approved prior to the start of treatment by the Principal Investigator Tingfeng, Chen MD.

7.2.9. Radiation treatment interruptions and dose modifications

No dose modifications are planned for radiation therapy; every effort must be made to administer the target dose to all patients at a given dose level.

Treatment breaks are strongly not encouraged. However, they may be necessary because of grade 3 or greater acute toxicities (e.g., pneumonitis). Every effort must be made to minimize the duration of treatment breaks. In case of grade ≥ 3 non-hematological or grade IV hematological toxicity, radiation treatment will be allowed to delay until these symptoms resolve to no worse than grade 1 for non-hematological toxicity or no worse than grade 2 for hematological toxicity. Treatment breaks longer than 4 days will be discussed. The reasons for any length of any such interruption must be recorded. If irradiation is delayed more than 2 weeks, patients will drop off the study.

7.3. Supportive treatment

If estimated caloric intake is < 1500 kilo-calories or if weight loss is > 5% of pretreatment weight, oral, enteral and/or intravenous alimentation should be provided. Nasogastric feeding tubes may be set to ensure adequate caloric intake. Prophylactic medication to inhibit peptic ulceration, antiemetics, antacid, anti-diarrheal agents, and other aggressive supportive care are allowed to avoid irradiation interruptions to a minimum. Kangfuxin liquid, a Chinese medicine extracted from periplaneta americana dried worms, which can promotes tissue regeneration and has long been used for the clinical treatment of burns, wounds and ulcers,[46] is permitted with the goal of mitigate irradiation-induced esophagitis.

8. Patients evaluation

8.1. Study parameters

Evaluation	4 weeks prior to study	Weekly during chemo-RT	4 weeks after RT
History	×	×	×

Physical exam, Zubrod	×	×	×
CBC, AGC,platelets	×	×	×
Chemistry panel (TP,Alb, Ca,Phos, Glu, BUN,Uric acid, Cr, T. Bili, Alk Phos, LDH, SGPT,SGOT) electrolytes	×	×	×
CEA	×		×
EKG	×		×
UGI radiographs	×		×
Abdomen and chest and pelvis CT	×		×
Endoscopic biopsy	×		×
Endoscopic ultrasound	×		×
Bone scan	×		
PET/CT	×*		
Nutritional evaluation	×	×	×
Adverse event evaluation	×	×	×

* strongly recommended

Follow-up evaluation	3 months after RT	6 months after RT	9 months after RT	12 months after RT	15 months after RT
History and physical	×	×	×	×	×
CBC, AGC, platelets	×	×	×	×	×
Chemistry (liver and renal functions, electrolytes,)	×	×	×	×	×
CEA	×	×	×	×	×
UGI radiographs	×		×		×
Abdomen and chest and pelvis CT	×	×	×	×	×
Endoscopic biopsy		×		×	

Follow-up evaluation	18 months after RT	21 months after RT	24 months after RT	then every 6 months until year 5
History and physical	×	×	×	×
CBC, AGC, platelets	×	×	×	×
Chemistry (liver and renal functions, electrolytes,)	×	×	×	×

CEA	×	×	×	×
UGI radiographs		×		×
Abdomen and chest and pelvis CT	×	×	×	×
Endoscopic biopsy	×		×	×

8.2. Criteria for acute toxicity

Any toxicity occurring within 6 weeks of completing RT is considered acute, otherwise late. The NCI Common Toxicity Criteria (CTC) Version 4.0 will be utilized to score chemotherapy and acute radiation (≤ 90 days) toxicities. A serious adverse event is defined as any adverse drug event (experience) occurring at any dose and any time that result in any of the following outcomes (see section 10.2.1.):

- ✓ Death.
- ✓ A life-threatening adverse drug/RT experience.
- ✓ Inpatient hospitalization or prolongation of existing hospitalization.
- ✓ A persistent or significant disability/incapacity.
- ✓ A medically significant event, as judged by the treating investigator.

8.3. Criteria for late toxicity

Any toxicity occurring more than 6 weeks after completing RT is considered late. Late radiation toxicities are documented according to the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer Late Radiation Morbidity Scoring Schema.

8.4. Criteria for response

Tumor response will be assessed using the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1.

- ✓ Clinical Complete Response (cCR): Absence of tumor cells in the endoscopic biopsy and the complete disappearance of all measurable or assessable disease on imaging studies.
- ✓ Partial Response (PR): a ≥ 30% regression in the greatest dimension of all measurable or assessable disease on imaging studies.
- ✓ Progressive Disease (PD): an increase of ≥20% in the greatest dimension of all measurable or assessable disease or the appearance of any new lesion on imaging studies.
- ✓ Stable Disease(SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

8.5. Documentation of incidence and patterns of recurrence

- ✓ Local failure: recurrence or persistence of disease within GTV of RT.
- ✓ Regional failure: recurrence or persistence of disease within PTV of RT.
- ✓ Distant failure: distant metastases to sites beyond those specified as locoregional.

8.6. Criteria for dropping off protocol treatment

- ✓ Delays in protocol treatment > 2 weeks.
- ✓ The development of dose-limiting toxicity, which is defined as grade ≥ 4 esophatitis, any other grade ≥ 3 non-hematological toxicity (except nausea and vomiting), or grade ≥ 4 hematological toxicity lasting more than 7 days.
- ✓ Patient's refusal to continue study participation or non compliance with protocol requirements.

If protocol treatment is discontinued, follow-up and data collection will continue according to the protocol.

9. Ethical considerations

The principles enunciated in the Declaration of Helsinki (HELSINKI, 1986) will be respected. Patients will be informed about the background and present knowledge on the drugs and RT under study with special attention to known activity and toxicity. It must be emphasized that the patient is allowed to refuse the treatment either prior to or at any time during the study. The study must be approved by the institutional review board of the Shanghai General Hospital. All patients are required to provide written informed consent prior to study enrollment. Informed consent form includes the following items:

- ✓ Diagnosis of disease and stage.
- ✓ The currently accepted standard of care and expected outcomes.
- ✓ Rationale for this study and objectives of the study.
- ✓ Study design and treatment protocol – RT, drugs, schedule, duration of study, etc.
- ✓ Anticipated efficacy of the treatment protocol (e.g., to potentially improve local disease control).
- ✓ Expected increased risk of severe acute/late radiation-related toxicity, including, but not limited to, fistulas/ perforation, massive hemorrhage, esophageal stricture, pneumonitis, even treatment-related death.
- ✓ Alternative treatment –the efficacies and toxicities of the alternatives.
- ✓ Freedom of refusal and withdrawal from the study.
- ✓ Strict privacy protection.

10. Statistical considerations

10.1. Endpoint of the study

- ✓ The primary endpoint of this study is to determine the maximum tolerated dose of HFRT boost immediately following standard-dose chemoradiotherapy in patients with advanced esophageal cancer.
- ✓ The second objective was to evaluate the efficacy, local control, and patterns of failure of this regimen.

10.2. Sample size

10.2.1. Dose limiting toxicity (DLT)

The DLT, which are possibly, probably or definitely associated with HFRT boost occurring during and after completion of the HFRT boost treatment, was defined as follows:

- ✓ Grade ≥ 4 esophatitis.
- ✓ Any other grade ≥ 3 non-hematological toxicity (except nausea and vomiting), including radiation pneumonitis, fistulas/perforation, esophageal stricture.
- ✓ Grade ≥ 4 hematological toxicity lasting more than 7 days.

10.2.2. HFRT boost dose escalation

The HFRT boost dose is escalated in cohorts of 3 to 6 patients in increments of 7.2 Gy delivered in 6 twice daily fractions of 1.2 Gy at interval of ≥ 6 hours, using a modified Fibonacci schema. If none of three patients treated at a given dose level has a dose-limiting toxicity (DLT), patients are enrolled at the next dose level. If one of the initial three patients experiences a DLT, then three additional patients are entered at that dose level. If no additional DLT occurs, patients proceed to the next dose level, and if two or more of the total six patients experience a DLT, dose escalation is stopped and the previous dose level is considered MTD. Once the MTD is determined, it is given to a larger patient cohort to further determine the safety profile and efficacy. The patients who leave the trial before completion of HFRT (except for toxicity reasons) are not considered for determining MTD.

A minimum of 6-week follow-up is required after completion of RT before proceeding to the next dose. Since 6 weeks is a short period to evaluate RT-induced toxicity, the assessment is continued after the initial follow-up, and any subsequent late toxicity is also considered in defining the MTD.

The number of evaluable patients that will be needed depends on the number of times the dose is escalated, the number of patients enrolled at a given dose level, and the number of additional patient enrolled in the MTD expansion cohort for further determining the safety and efficacy. If the escalation continues up through dose level

6 with 3 additional patients enrolled at a given dose level due to the occurrence of DLT and 10 additional patients are enrolled in the MTD expansion cohort, 31 evaluable patients will be required.

With a modified Fibonacci design, the probability of dose escalation 91%, 71%, 49%, 31%, 17% and < 1% respectively at true DLT is rates of 10%, 20%, 30%, 40%, 50% and 80%, respectively.

10.3. Statistics analysis

Immediate local failure is defined as persistence of tumors, and failure patterns are documented using basic calculations. The time to event variables are calculated from the date of entering the study. Time to first local-regional failure is estimated using a cumulative incidence analysis with death as a competing risk. Kaplan-Meier method is used to estimate the survival rates.

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Appendix I

Eastern Cooperative Oncology Group (ECOG) – Performance Status

Grade	ECOG performance status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

APPENDIX II

ESOPHAGUS, AJCC 7th Edition, 2010

DEFINITION OF TNM

Primary Tumor (T)

TX Primary tumor cannot be assessed

T0 No evidence of primary tumor

Tis High-grade dysplasia

T1 Tumor invades lamina propria, muscularis mucosae, or submucosa

T1a Tumor invades lamina propria or muscularis mucosae

T1b Tumor invades submucosa

T2 Tumor invades muscularis propria

T3 Tumor invades adventitia

T4 Tumor invades adjacent structures

T4a Resectable tumor invading pleura, pericardium, or diaphragm

T4b Unresectable tumor invading other adjacent structures, such as aorta, vertebral body, trachea, etc.

Regional Lymph Nodes (N)

NX Regional lymph nodes cannot be assessed

N0 No regional lymph node metastasis

N1 Metastasis in 1-2 regional lymph nodes

N2 Metastasis in 3-6 regional lymph nodes

N3 Metastasis in 7 or more regional lymph nodes

Distant Metastasis (M)

M0 No distant metastasis

M1 Distant metastasis

Histopathologic G (G)

GX Grade cannot be assessed—stage grouping as G1

G1 Well differentiated

G2 Moderately differentiated

G3 Poorly differentiated

G4 Undifferentiated—stage grouping as G3 squamous

Squamous Cell Carcimona					
Stage	**T**	**N**	**M**	**G**	**Location**
0	Tis (HGD)	N0	M0	1,X	Any
IA	T1	N0	M0	1,X	Any
IB	T1	N0	M0	2–3	Any
	T2–3	N0	M0	1,X	Lower, X
IIA	T2–3	N0	M0	1,X	Upper, middle
	T2–3	N0	M0	2–3	Lower, X
IIB	T2–3	N0	M0	2–3	Upper, middle
	T1–2	N1	M0	Any	Any
IIIA	T1–2	N2	M0	Any	Any
	T3	N1	M0	Any	Any
	T4a	N0	M0	Any	Any
IIIB	T3	N2	M0	Any	Any
IIIC	T4a	N1–2	M0	Any	Any
	T4b	Any	M0	Any	Any
	Any	N3	M0	Any	Any
IV	Any	Any	M1	Any	Any

Adenocarcimona				
Stage	**T**	**N**	**M**	**G**
0	Tis (HGD)	N0	M0	1,X
IA	T1	N0	M0	1–2,X
IB	T1	N0	M0	3
	T2	N0	M0	1–2,X
IIA	T2	N0	M0	3
IIB	T3	N0	M0	Any
	T1–2	N1	M0	Any
IIIA	T1–2	N2	M0	Any
	T3	N1	M0	Any
	T4a	N0	M0	Any
IIIB	T3	N2	M0	Any
IIIC	T4a	N1–2	M0	Any
	T4b	Any	M0	Any
	Any	N3	M0	Any
IV	Any	Any	M1	Any

APPENDIX III　Case Report Forms (CRFs)

Patient and Disease Characteristics (病人和疾病特性)

Initials of Name and Surname（姓名）_____

Date of Birth（出生日期） _____ /_____ / _____

Age（年龄） _____ Gender（性别） _____

Blood Pressure（血压） _____ mmHg Heart Rate（心率）_____

Weight（体重）_____kg Height（身高）

_____cm

Smoke（吸烟史）_____ Alcohol（饮酒史）

_____

ECOG（体力状况评分） _____

Past History（既往史）_____

CBC（血常规）

WC_____ (N…….;L……) RC_____HB_____PLT_____

Comprehensive Chemistry Profile（生化）_____

CT / MRI / PET_____

Tumor Location（肿瘤位置）: Cervical（颈段）_____Upper Thoracic（胸上段）

_____ Middle Thoracic（胸中段）_____Lower Thoracic（胸下段）

_____

Histology（病理类型）: Squamous Cell Carcinomas（鳞癌）_____

Adenocarcinoma（腺癌）_____

Upper GI Endoscopy and Biopsy（内镜和组织活检）_____

Clinical Stage（临床分期）

T_____; N_____; M _____ Stage_____

Signed Informed Consent（知情同意）No____; Yes_____

Radiotherapy (放疗)

Start Date（开始日期）_____ /____ / ____End Date（结束日期）___ /___ / _____

Dose Level (剂量水平)_____ Total Dose（放疗剂量）_____

Total Days of Interruption for Toxicity and Motivation（因毒性中断治疗的时间）

_____

Chemotherapy (化疗)

Paclitaxel 45 mg/m^2 and Carboplatin AUC = 1.5

Start date（开始日期）_____ /_____ / _____;

Treatment Number (治疗次数):_____

Interruption（有无治疗中断）Yes/No _____Dose Reduction（有无减量）

Yes/No _____ Modification（剂量调整）_____

Maximum Degree of Toxicity（毒副反应）:

Esophagitis (食管炎): Grade (分级)_____; Pneumonitis (肺炎): Grade (分级)_____ Fistula (瘘): Grade (分级): _____;

Hematological: WC_____ HB_____BPC_____

Others (其它): _____

Toxicity Attribution: _____1 Not, 2 Unlikely, 3 Possibly, 4 Likely, 5 Definitively related to treatment.

Treatment Completion (Last Day of RT)(放疗治疗结束及日期)

Date（治疗结束日期）_____ /_____ / _____

Weight（体重）_____Response Evaluation（疗效评估） _____

Treatment Response (2 month) (疗效)

Date（复查日期）_____ /_____ / _____

Response Valuation（疗效评估） CR_____PR_____SD____PD_____

Treatment Failure(治疗失败): No(无)____ Yes/Date（是/日期）_____ Failure Sites（失败部位）: LF（局部）_____LRF（区域）_____DF（远处）_____

Date: _____

Signature_____

APPENDIX IV Informed Consent Form (ICF)

Trial Title： Phase I Trial of Intensity-Modulated Hyperfractionated Radiotherapy Boost with Concurrent Chemotherapy Immediately Following Standard Chemoradiotherapy in Patients Primarily with Advanced Intra-thoracic/Cervical Esophageal Squamous Cell Carcinomas

Research unit: Shanghai General Hospital

We invite you to participate in a **Phase I Trial of Intensity-Modulated Hyperfractionated Radiotherapy Boost with Concurrent Chemotherapy Immediately Following Standard Chemoradiotherapy in Patients Primarily with Advanced Intra-thoracic/Cervical Esophageal Squamous Cell Carcinomas**. Before deciding to participate in this study, please read this Informed Consent in detail. If you have any questions that you do not understand, you can ask the investigator or member of the trial working group to explain any terms or information that you do not understand.

一、 Research background and purpose

1、Background

The current treatment modality for patients with unresectable, locally advanced esophageal cancer (LAEC) is standard chemoradiotherapy (SCRT) with radiation dose of 50-50.4 Gy. However, the clinical outcomes are still poor, with a dismal 5-year overall survival (OS) rate of 15-25%. Local-regional persistence and relapse of disease account for the

majority of treatment failures after SCRT, with local failure of 44-58% versus distant failure of 8-26%. Curing patients is not possible in patients with esophageal cancer without local disease control. Current efforts to improve survival of LAEC patients by enhancing local tumor control have not yielded encouraging results. For example, a brachytherapy boost following SCRT resulted in increased fistula and treatment-related mortality without improvement in local control and survival. Similarly, high-dose (64.8 Gy) conventionally fractionated radiotherapy (RT) also lead to negative outcomes compared to standard dose treatment. Salvage surgery after CRT has benefitted only a minority of patients with local failure and not significantly improved overall survival, while novel chemotherapeutical and/or targeted drugs have also failed to improve outcomes in prospective randomized trials.

In the last two decades, RT has dramatically increased local control and survival rates of non-small cell lung cancer (NSCLC) with a biological effective dose (BED) $\geq$ 100 Gy as compared with conventional radiation therapy of 60 Gy (calculated BED = 72 Gy). Thus, radiation dose escalation is potentially one strategy to improve local control and subsequent survival for patients with esophageal cancer. However, the maximum tolerated radiation dose has so far not been well defined in prospective dose-finding trials.

Given the high radio-sensitivity of the esophagus resulting in life-threatening fistulas and other morbidities, as well as the high mortality rates associated with dose escalation, hypo- or conventional fractionated RT techniques are inappropriate for LAEC. Hyperfractionated RT (HFRT) allows a higher total radiation dose without increasing late toxicity, and can be used after SCRT to increase the cumulative dose to the tumor. Furthermore, advances in radiation planning, tumor imaging, and radiation delivery using image-guided radiotherapy (IGRT) have also enhanced the ability to deliver higher, more conformal doses to esophageal tumors.

The majority of local failures occur within the gross tumor volume (GTV). We therefore design a phase I trial to define the maximum tolerated dose (MTD) of the HFRT boost to GTV with concurrent weekly carboplatin and paclitaxel immediately following SCRT of 50 Gy with the same chemotherapy regimen, using image-guided intensity-modulated RT (IG-IMRT). The duration of treatment protocol (SCRT + HFRT boost) is more than 5 weeks. The rationale is that all patients would be treated with upfront standard chemoradiotherapy, ensuring that they gain the established benefits from standard chemoradiotherapy. The second objective is to evaluate the efficacy, local control, and patterns of failure of this regimen.

2、**Purpose**

Local persistence and relapse of disease in the gross tumor volume (GTV) account for the majority of treatment failures after standard chemoradiation therapy. The primary objective of this phase 1 trial is to define the maximum tolerated dose (MTD) of a hyperfractionated radiation therapy (HFRT) boost to the GTV with concurrent weekly paclitaxel and carboplatin after standard-dose chemoradiation therapy, using image guided intensity modulated radiation therapy techniques.

二、 **Methods**

1、**Eligibility**

11) Histologically confirmed primary squamous cell carcinoma or adenocarcinom of the esophagus.
12) Age 18-75.
13) Patients must be deemed unresectable disease or patient is not deemed operable due to medical reasons.
14) Life expectancy ≥ 4 months (T1-4N0-3M0-1).
15) Zubrod performance status 0 to 2.
16) No prior radiation to the thorax that would overlap with the current treatment field.
17) Patients with nodal involvement are eligible.
18) Adequate bone marrow, renal and hepatic functions:
    - ✓ Hemoglobin ≥100.0 g/L

- ✓ Platelet count ≥ 100×10^9/L
- ✓ Absolute granulocyte count (AGC) ≥ 2×10^9 cells/L
- ✓ Bilirubin and Aspartate transaminase ≤ 1.5 × upper limit of normal (ULN),
- ✓ Creatinine ≤ 1.5 times ULN

19) A signed informed consent must be obtained prior to therapy.

20) Induction chemotherapy is allowed.

2、**Ineligibility criteria**

10) The presence of a fistula.

11) Lower thoracic esophageal cancer involving the stomach.

12) Prior radiotherapy that would overlap the radiation fields.

13) Gastroesophageal junction cancer.

14) Uncontrolled concurrent illness including, but not limited to: chronic obstructive pulmonary disease(COPD) exacerbation or other respiratory illness, serious uncontrolled infection, symptomatic congestive heart failure (CHF),unstable angina pectoris, uncontrolled hypertension,or psychiatric illness/social situations that would limit compliance with the study requirements.

15) Known hypersensitivity to paclitaxel.

16) Any other condition or circumstance that would, in the opinion of the Investigator, make the patient unsuitable for participation in the study.

17) Acquired immune deficiency syndrome.

18) Conditions precluding medical follow-up and protocol compliance.

3、Study Treatment and Trial Design

Eligible patients are given weekly doses of paclitaxel (45 mg/m2) and carboplatin (area under the curve 1.5) for 5 weeks with concurrent radiation therapy (50 Gy), immediately followed by an HFRT boost to the GTV with the same chemotherapy regimen. The boost doses are escalated in increments of 7.2 Gy delivered in 6 twice-daily fractions of 1.2 Gy using a modified Fibonacci design. MTD is defined as the highest dose at which ≤ 1 patients experience dose limiting toxicity (DLT). Once the MTD is established, additional patients are treated at that dose to determine the safety。

4、Statistical analysis

The primary endpoint of this trial is to determine the MTD of HFRT boost with concurrent paclitaxel and carboplatin immediately following standard chemoradiotherapy in patients with advanced esophageal cancer. The dose-escalation regimen is based on a modified Fibonacci design, with probability of dose escalation 91%, 71%, 49%, 31%, 17% and < 1% respectively at true DLT rates of 10%, 20%, 30%, 40%, 50% and 80%. Tumor response is evaluated according to RECIST 1.1 (Response Evaluation Criteria in Solid Tumors). A clinical CR (cCR) is defined as both the absence of tumor cells in the endoscopic biopsy and the complete disappearance of all measurable disease on imaging studies.

Immediate local failure is defined as persistence of tumors, and failure patterns are documented using basic calculations. The time to event variables is calculated from the date of entering the study. Time to first local-regional failure is estimated using a cumulative incidence analysis with death as a competing risk. Kaplan-Meier method is used to estimate the survival rates.

三、 Research risks and benefits

1、Research risks

The dose limiting toxicities (DLTs), which are possibly, probably or definitely associated with the HFRT boost occurring during and after completion of the HFRT boost treatment, include:

- Grade ≥ 4 esophatitis.
- Any other grade ≥ 3 non-hematological toxicity (except nausea and vomiting), including radiation pneumonitis, esophageal fistulas/perforation, esophageal stricture, cardiac events.
- Grade ≥ 4 hematological toxicity lasting more than 7 days.

Nevertheless, we will still do our utmost to reduce treatment-related risks.

2、**Benefits**

You may not directly benefit from this trial, but your participation will be helpful to determine the MTD of the hyperfractionated radiotherapy boost for the primary tumor after the SCRT of esophageal cancer, and it will be

beneficial for humans to finally overcome this lethal disease and address the clinical problem of high local tumor recurrence rate , the main cause of death.

四、 Your rights

You have the right to decide whether to participate in this trial. If you cannot make a decision immediately, you have sufficient time to consider. If necessary, you can discuss with relatives, friends and other people you trust before making a decision. If you decide not to participate in this trial, it will not affect your relationship with the researchers and sponsors, you will not be discriminated against or retaliated against, and your treatment and rights will not be affected. If you decide to participate in this trial, if there is no special reason, we hope you can complete the trial, but you have the right to withdraw at any time during the trial. If you decide to withdraw, please be able to tell the researcher in time.

During the study, you can always know the information related to you in this study.

五、 Privacy protection

The personal information you provide to the researcher (such as name, gender, contact information, questionnaire, etc.), in addition to the needs of normal research, may be informed with the following persons or units:

- Staff members (inspectors, etc.) related to this experiment in the research funding institution;
- National and local Food and Drug Administration and other administrative agencies.

However, no one can disclose your personal information to others or other institutions without your permission. Except for the researchers and administrative institutions, no other person or unit has the right to take the initiative to contact you about the trial. Or provide you with information about this experiment directly.

The results of this experiment may be published in the form of academic papers, but your personal information will not appear in any publicly published documents.

六、 Other

1. When the following conditions occur, for your health, the researcher may withdraw you from this trial without your consent:

- Continue to participate in this test, may cause your risk outweigh the benefit;
- You do not follow the guidance of the investigator and participate in the trial according to the research plan;
- The study is terminated early.

2. This informed consent is in duplicate, and the researcher and you each keep one copy.

七、 Compensation for injury incurred in the test

If your injury is directly caused by participating in this trial, you do not need to pay the medical expenses borne by the treatment at all, the expenses will be borne by the researcher.

八、 Contact details

1. Office of Medical Ethics Committee of Shanghai General Hospital

Contact: 63240090-6424

2. Researcher's name: Tingfeng Chen

Contact: 18701777598

[The following is the signature page of informed consent]

Informed Consent Page

Agree to declare:

1. I have carefully read the instructions of the subject and understand the relevant background of this experiment. The researchers have explained me in detail about the characteristics of the study and possible adverse reactions, and answered my questions.

2. I know that if I refuse to participate in this trial, my treatment and rights will not be affected. After understanding all the contents of the subject and fully considering it, I volunteer to participate in this trial.

3. I am willing to follow the researcher's instructions and participate in the experiment according to the research protocol. During the experiment, I have the right to withdraw at any time, but before withdrawing, I need to tell the researchers in time.

4. During the test, if any discomfort occurs, I will tell the researcher in time.

Subject signature:

/ /

Name	Signature	Date of signature

Researcher signature:

/ /

Name	Signature	Date of signature

Subject Agent / Guardian (if any) signature::

Why the subject could not sign this page:

The relationship between the agent / guardian and the subject:

/ /

Name Signature Date of signature