

# A phase III, multicenter randomized controlled trial of neo-adjuvant chemotherapy paclitaxel plus cisplatin versus surgery alone for stage IIA–IIIB esophageal squamous cell carcinoma

Yan Zheng\*, Yin Li\*, Xianben Liu, Ruixiang Zhang, Zongfei Wang, Haibo Sun, Shilei Liu

Department of Thoracic Surgery, The Affiliated Cancer Hospital of Zhengzhou University, Henan Cancer Hospital, Zhengzhou 450008, China

**Contributions:** (I) Conception and design: Y Li, Y Zheng; (II) Administrative support: Y Li; (III) Provision of study materials or patients: Y Li, Y Zheng, X Liu, R Zhang; (IV) Collection and assembly of data: Y Li, Y Zheng, H Sun, Z Wang, S Liu; (V) Data analysis and interpretation: Y Zheng, H Sun, Z Wang, S Liu; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

\*These authors contributed equally to this work.

**Correspondence to:** Yin Li, MD, PhD. Department of Thoracic Surgery, The Affiliated Cancer Hospital of Zhengzhou University, Henan Cancer Hospital, Zhengzhou 450008, China. Email: liyin0825@hotmail.com.

**Background:** The survival benefits of neoadjuvant chemotherapy (NAC) for esophagus squamous cell carcinoma (ESCC) remains controversial. The surgical procedure was not well defined in NAC strategy, in past trials. The different surgical procedure and different levels of lymphadenectomy may decrease the survival benefits from NAC. The new chemotherapy regimen with paclitaxel is promising. The purpose of this study is to confirm the superiority of paclitaxel, cisplatin and McKeown esophagectomy with total two-field lymphadenectomy compared with surgery alone for ESCC.

**Methods:** A two-arm phase III trial was launched in June 2015. A total of 528 patients will be recruited from eight Chinese institutions within 2.5 years. The overall survival (OS) is the primary endpoint, and the secondary endpoints include disease-free survival (DFS), R0 resection rate, complication rate, perioperation mortality, days of hospitalization, quality of life (QOL), NAC response rate, pathologic response rate, toxicities of NAC, prognostic factors, predictive factors, progression-free survival (PFS), and adverse events.

**Discussion:** The study will provide the final conclusion of NAC for ESCC in China.

**Trial registration:** NCT02442440 (<https://register.clinicaltrials.gov/>).

**Keywords:** Esophageal cancer; preoperative chemotherapy; clinical trial; phase III

Submitted Oct 15, 2016. Accepted for publication Dec 07, 2016.

doi: 10.21037/jtd.2017.01.44

**View this article at:** <http://dx.doi.org/10.21037/jtd.2017.01.44>

## Introduction

In 2012, 286,700 new cases and 210,900 deaths made esophageal cancer the fifth most common cancer in China (1). The main histological subtypes include squamous cell carcinomas (SCCs) and adenocarcinomas (AC) (2). A characteristic trait for esophageal carcinoma (EC) is its regional distribution (2). SCC cases are more likely to occur in developing regions, such as Africa (3) and Eastern Asia (4). Greater than half of the global ESCC cases each year occur in China (53%, 210,000 cases) (5). EC was the third most common cancer in Henan province with an estimated

36,840 new cases every year (1). However, compared with Western countries and Japan, we are far behind the times and contributed minimal level A evidence. In the past 30 years, a series of multi-institutional clinical trials were conducted by the Japan Clinical Oncology Group (JCOG) (6-8). Based on trials (JCOG9204) (6) and (JCOG9907) (7), the current Japanese standard treatment for locally advanced EC is neoadjuvant chemotherapy (NAC). Based on Radiation Therapy Oncology Group (RTOG) 8911 (trial 8911 or USA Intergroup 113) (9) and the ChemoRadiotherapy for Oesophageal cancer

followed by Surgery Study (CROSS) (10) and Francophone de Cancérologie Digestive 9901 (FFCD 9901) (11) trials, Western countries have adopted neoadjuvant chemoradiotherapy (NACR) therapy as a standard treatment. What is the situation in China, where 53% of new cases are diagnosed every year (2)?

Based on the past multicenter randomized controlled clinical trials (MRCTs), we can draw a conclusion. The survival of EC could be prolonged by NACR (12,13); however, its side effects on ESCC cannot be neglected (14). In contrast, NAC is safe and feasible (14). The controversial part, however, is whether the NAC offers a survival benefit for ESCC. How should the best neoadjuvant method for ESCC be chosen in China based on contradictory level A evidence outside of China? We should answer this question on our own.

The other important factor that cannot be neglected in the NAC model is local control, namely the surgical strategy. In these trials, the survival rates of Western countries are typically poorer than those in Asia (15). We observed differences among these trials, such as the R0 resection rate, [the United Kingdom Medical Research Council (MRC) OEO2 58% *vs.* JCOG 9907 90%], surgical strategy [JCOG 9907 transthoracic esophagectomy (THE) 100% *vs.* RGOT 8911 transhiatal esophagectomy (TTE) acceptable] and region of lymphadenectomy (OEO2 missing *vs.* 9907 three-field 62.8%) (15). Some Asian surgeons believe that their THE with regional lymphadenectomy can achieve better local control as observed in gastric cancer (GC). From the results of the MAGIC trial, European countries implemented NAC plus D1 lymphadenectomy (16). Asian countries implemented D2 lymphadenectomy plus adjuvant chemotherapy based on ACTS-GC (17) and CLASSIC (18) trials. D0/D1 lymphadenectomy with adjuvant chemoradiotherapy was adopted in America based on the INT 0116 trial (19). Different types of lymphadenectomy defined the different combined therapies. We cannot exclude the surgical method when discussing the survival benefit of NAC. Different levels of lymphadenectomy may decrease the survival benefit achieved by NAC.

With all of this information in mind, we conducted a meta-analysis and a retrospective study in our center. In the light of past trials, our meta-analysis (HR =0.81; 95% CI, 0.65–1.00; P=0.053) revealed the potential survival benefit and also our retrospective study (P=0.054) (15). A phase III RCT (ClinicalTrials.gov identifier: NCT02395705, Neoadjuvant Chemotherapy Versus Surgery Alone for Esophageal Squamous Cell Carcinoma) was launched in China.

Thus, the first purpose of this trial is to investigate whether NAC and McKeown esophagectomy with complete two-field lymphadenectomy is effective and safe. In this trial, we emphasized the standard surgical procedure and the stations of lymphadenectomy.

Paclitaxel is a promising drug for the treatment of EC. A feasibility study was conducted by Hara *et al.* (20). The DCF regimen exhibited a good response rate (60.0%) in EC with no treatment-related deaths (20). In our retrospective study, the clinical effect of cisplatin and paclitaxel (TP) was promising. Sixteen (19.3%) patients achieved clinical complete responses (CCR), and clinical partial responses (CPR) occurred in 48 (57.8%) patients. The pathological response (PR) rate was 20.5%. Only 1 (1.2%) patient had grade 4 leukopenia. The side effects were tolerable. The second purpose of this trial is to investigate whether TP could achieve a high response rate for ESCC.

Based on these studies, “the Re-evaluation”, a phase III multicenter randomized controlled trial of neo-adjuvant chemotherapy paclitaxel plus cisplatin versus surgery alone for stage IIA–IIIB ESCC, was launched to confirm the superiority of TP and McKeown esophagectomy with total two-field lymphadenectomy.

This study protocol was approved by the Esophageal Cancer Professional Committee Protocol Review Committee in November 2014 and passed the Institutional Review Board (IRB) in the same month. The trial was launched in June 2015, and patient enrollment was initiated in the same month. Before beginning patient enrollment in sub-centers, the trial was approved by the IRBs of all the sub-centers. This trial was registered at ClinicalTrials.gov [identifier: NCT02395705 (<https://www.clinicaltrials.gov/ct2/show/NCT02395705>)].

## Methods

### Statement of ethics approval

This study obtained ethics approval from the ethics committee and IRB of Henan Cancer Hospital (ID: 2014ys38). All the participants will sign informed consent before taking part.

### Study design and setting

A phase III, multicenter, open label, randomized controlled study. The aim of this study is to confirm the superiority of TP and total two-field lymphadenectomy on overall survival

(OS) compared with surgery alone as the neoadjuvant therapy for ESCC.

### Participants

#### Inclusion criteria

- ❖ Histologic diagnosis of squamous cell thoracic EC stage IIA to IIIB, [7th Union for International Cancer Control (UICC)-TNM];
- ❖ Patients must not have received any prior anticancer therapy for EC;
- ❖ Aged 18 to 75 years old;
- ❖ Without operative contraindication;
- ❖ Absolute white blood cells count  $\geq 4.0 \times 10^9/L$ , neutrophil  $\geq 1.5 \times 10^9/L$ , platelets  $\geq 100.0 \times 10^9/L$ , hemoglobin  $\geq 90$  g/L, and normal liver and kidney functions, total bilirubin (TBIL)  $\leq 1.5$  N, aspartate aminotransferase (AST)  $\leq 2.5$  N, alanine aminotransferase (ALT)  $\leq 2.5$  N, prothrombin time (PT)  $\leq 1.5$  N, normal range of activated partial thromboplastin time (APTT), and endogenous creatinine clearance rate (CRE)  $\leq 1.5$  N;
- ❖ Patients must not have been diagnosed with other cancer and must not have received any prior anticancer therapy except for prostate cancer with greater than 5 years of disease-free survival (DFS);
- ❖ Expected R0 resection;
- ❖ ECOG 0–2;
- ❖ Signed informed consent document on file;
- ❖ No metastatic lymph node in cervical by color Doppler sonography.

#### Exclusion criteria

- ❖ Multiple primary cancer;
- ❖ The subject cannot understand and sign the informed consent form (ICF);
- ❖ Patients with concomitant hemorrhagic disease;
- ❖ Patients who cannot undergo the operation for any unexpected reason;
- ❖ Inability to use gastric conduit after esophagectomy due to a prior surgery;
- ❖ Pregnant or breast-feeding;
- ❖ Patients are diagnosed as or suspected to be allergic to cisplatin or paclitaxel.

### Randomization

The investigators took the responsibility to enroll the patients. First, the eligibility criteria are confirmed. Second,

patients are randomized to the NAC or surgery alone group.

### Randomization and masking

The randomization numbers were generated by a centrally located computer. Patients were randomly assigned (1:1). All the randomized numbers were sealed into envelopes and sent to local sites. After the patient signs the written consent form, the envelope is opened, and the randomized group is unsealed. The trial is unmasked.

### Treatment

#### Neo-adjuvant chemotherapy group (cisplatin and paclitaxel)

- (I) Paclitaxel, 175 mg/m<sup>2</sup>, d1, cisplatin, 25 mg/m<sup>2</sup>, d2–d4; 3 weeks, 2 cycles;
- (II) Paclitaxel, 87.5 mg/m<sup>2</sup>, d1, d8, cisplatin, 25 mg/m<sup>2</sup>, d2–d4; 3 weeks, 2 cycles;
- (III) Paclitaxel, 175 mg/m<sup>2</sup>, d1, cisplatin, 75 mg/m<sup>2</sup>, d1; 3 weeks, 2 cycles.

Two–six weeks after NAC, right thoracotomy esophagectomy and regional lymphadenectomy is performed. Thoracoscopic esophagectomy is accepted, whereas TTE is prohibited. The regional lymph nodes are defined as thoracic (left recurrent laryngeal nerve, right recurrent laryngeal nerve, paraesophageal, paratracheal, subcarinal, supradiaphragmatic and posterior mediastinal lymph nodes) lymph nodes and perigastric nodes (celiac, left gastric artery, common hepatic artery and splenic artery lymph nodes). The right and left recurrent laryngeal nerve lymph nodes must be included.

### Study endpoint

The primary outcome is the 5-year OS of all randomized patients. The survival time is defined as the number of days from randomization to death from any cause, and the last alive day of the patient is censored.

The secondary outcomes include the OS rate, DFS, R0 resection rate, complication rate, perioperation mortality, days of hospitalization, thoracic drainage days, perioperation bleeding, quality of life (QOL) (ECOG, KPS, NRS-2002, EORTC QLQ-ST018, EORTC QLQ-C30), NAC response rate criteria [(Response Evaluation Criteria in Solid Tumors (RECIST)], pathologic complete response rate, pathologic response rate, NAC toxicities [National Cancer Institute Common Terminology Criteria for

Adverse Event (CTCAE) v3.0], the complete rate for the protocol, prognostic factors, and predictive factors.

We define progression-free survival (PFS) as the number of days from randomization to death or progression. The patients receive R0/R1 resection, and disease progression during preoperative therapy is not included in PFS events. However, if the R2 resection is conducted, radiologically progression after surgery is defined as a PFS event.

### *Follow-up*

The analysis of primary endpoints will be performed 5 years after the recruitment. The surveillance studies after surgery include chest CT scan and abdominal, cervical color Doppler ultrasonography performed every 3 months for the first 2 years. Over the next 3 years, the patients will receive follow-up every 6 months.

### *Statistical analysis*

This two-arm randomized trial is designed to confirm the superiority of NAC followed by McKeown esophagectomy with complete two-field lymphadenectomy. We assumed a 5-year survival with a 12% increase for the NAC group. The sample size was calculated as 264 patients in each arm with a two-sided alpha level of 5%, a power of 80% for comparison, an expectation of 2 years for accrual and a 5-year follow-up period. The total sample size was set at 528 patients considering that 10% of patients will be lost to follow-up.

### *Interim analysis and monitoring*

We plan to conduct two interim analyses. The first analysis will be performed before half of the planned patient accrual is complete. After the planned patient accrual is complete, the second interim analysis will be conducted. IRB and good clinical practice (GCP) of the HCH will evaluate patient safety, data integrity and study progress.

### *Participating institutions*

#### **Main site**

Henan Cancer Hospital/The affiliated Cancer Hospital of Zhengzhou University. Principal investigator: Yin Li, MD & PhD.

#### **Sub-centers**

Cancer Institute and Hospital, Chinese Academy of Medical

Sciences. Principal investigator: Yousheng Mao, MD.

Beijing Cancer Hospital. Principal investigator: Keneng Chen, MD.

Sun Yat-sen University Cancer Center. Principal investigator: Peng Lin, MD & PhD.

Hunan Province Tumor Hospital. Principal investigator: Gaoming Xiao, MD.

Tianjin Medical University Cancer Institute and Hospital. Principal investigator: Zhentao Yu, MD.

Fujian Medical University Union Hospital. Principal investigator: Chun Chen, MD.

Fudan University Shanghai Cancer Center. Principal investigator: Jiaqing Xiang.

### **Acknowledgements**

None.

### **Footnote**

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

*Ethical Statement:* This study obtained ethics approval from the ethics committee and institutional review board of Henan Cancer Hospital (ID: 2014ys38). All the participants will sign informed consent before taking part.

### **References**

1. Chen W, Zheng R, Zuo T, et al. National cancer incidence and mortality in China, 2012. *Chin J Cancer Res* 2016;28:1-11.
2. Arnold M, Soerjomataram I, Ferlay J, et al. Global incidence of oesophageal cancer by histological subtype in 2012. *Gut* 2015;64:381-7.
3. Somdyala NI, Bradshaw D, Gelderblom WC, et al. Cancer incidence in a rural population of South Africa, 1998-2002. *Int J Cancer* 2010;127:2420-9.
4. Lin Y, Totsuka Y, He Y, et al. Epidemiology of esophageal cancer in Japan and China. *J Epidemiol* 2013;23:233-42.
5. Siegel R, Desantis C, Jemal A. Colorectal cancer statistics, 2014. *CA Cancer J Clin* 2014;64:104-17.
6. Ando N, Iizuka T, Ide H, et al. Surgery plus chemotherapy compared with surgery alone for localized squamous cell carcinoma of the thoracic esophagus: a Japan Clinical Oncology Group Study--JCOG9204. *J Clin Oncol* 2003;21:4592-6.

7. Ando N, Kato H, Igaki H, et al. A randomized trial comparing postoperative adjuvant chemotherapy with cisplatin and 5-fluorouracil versus preoperative chemotherapy for localized advanced squamous cell carcinoma of the thoracic esophagus (JCOG9907). *Ann Surg Oncol* 2012;19:68-74.
8. Nakamura K, Kato K, Igaki H, et al. Three-arm phase III trial comparing cisplatin plus 5-FU (CF) versus docetaxel, cisplatin plus 5-FU (DCF) versus radiotherapy with CF (CF-RT) as preoperative therapy for locally advanced esophageal cancer (JCOG1109, NExT study). *Jpn J Clin Oncol* 2013;43:752-5.
9. Kelsen DP, Winter KA, Gunderson LL, et al. Long-term results of RTOG trial 8911 (USA Intergroup 113): a random assignment trial comparison of chemotherapy followed by surgery compared with surgery alone for esophageal cancer. *J Clin Oncol* 2007;25:3719-25.
10. van Heijl M, van Lanschot JJ, Koppert LB, et al. Neoadjuvant chemoradiation followed by surgery versus surgery alone for patients with adenocarcinoma or squamous cell carcinoma of the esophagus (CROSS). *BMC Surg* 2008;8:21.
11. Mariette C, Dahan L, Mornex F, et al. Surgery alone versus chemoradiotherapy followed by surgery for stage I and II esophageal cancer: final analysis of randomized controlled phase III trial FFCD 9901. *J Clin Oncol* 2014;32:2416-22.
12. Sjoquist KM, Burmeister BH, Smithers BM, et al. Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis. *Lancet Oncol* 2011;12:681-92.
13. Gebski V, Burmeister B, Smithers BM, et al. Survival benefits from neoadjuvant chemoradiotherapy or chemotherapy in oesophageal carcinoma: a meta-analysis. *Lancet Oncol* 2007;8:226-34.
14. Kumagai K, Rouvelas I, Tsai JA, et al. Meta-analysis of postoperative morbidity and perioperative mortality in patients receiving neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal and gastro-oesophageal junctional cancers. *Br J Surg* 2014;101:321-38.
15. Zheng Y, Li Y, Liu X, et al. Reevaluation of Neoadjuvant Chemotherapy for Esophageal Squamous Cell Carcinoma: A Meta-Analysis of Randomized Controlled Trials Over the Past 20 Years. *Medicine (Baltimore)* 2015;94:e1102.
16. Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med* 2006;355:11-20.
17. Sakuramoto S, Sasako M, Yamaguchi T, et al. Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. *N Engl J Med* 2007;357:1810-20.
18. Bang YJ, Kim YW, Yang HK, et al. Adjuvant capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): a phase 3 open-label, randomised controlled trial. *Lancet* 2012;379:315-21.
19. Macdonald JS, Smalley SR, Benedetti J, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. *N Engl J Med* 2001;345:725-30.
20. Hara H, Tahara M, Daiko H, et al. Phase II feasibility study of preoperative chemotherapy with docetaxel, cisplatin, and fluorouracil for esophageal squamous cell carcinoma. *Cancer Sci* 2013;104:1455-60.

**Cite this article as:** Zheng Y, Li Y, Liu X, Zhang R, Wang Z, Sun H, Liu S. A phase III, multicenter randomized controlled trial of neo-adjuvant chemotherapy paclitaxel plus cisplatin versus surgery alone for stage IIA–IIIB esophageal squamous cell carcinoma. *J Thorac Dis* 2017;9(1):200–204. doi: 10.21037/jtd.2017.01.44