Thoracic Cancer

Open Access

Thoracic Cancer ISSN 1759-7706

STUDY PROTOCOL

Adjuvant radiotherapy, chemotherapy or surgery alone for high-risk histological node negative esophageal squamous cell carcinoma: Protocol for a multicenter prospective randomized controlled trial

Xufeng Guo[1], Wentao Fang[1], Zhigang Li[1], Zhengtao Yu[2], Tiehua Rong[3], Jianhua Fu[3], Yongtao Han[4], Lijie Tan[5], Chun Chen[6], Shuoyan Liu[7], Yongde Liao[8], Gaoming Xiao[9], Yucheng Wei[10], Chengchu Zhu[11], Hecheng Li[12], Jinhua Luo[13] & Wenqun Xing[14]

1 Department of Thoracic Surgery, Shanghai Chest Hospital, Shanghai Jiaotong University, Shanghai, China
2 Department of Esophageal Surgery, Tianjin Cancer Hospital, Tianjin Medical University, Tianjin, China
3 Department of Thoracic Surgery, Sun Yat-sen University Cancer Center, Guangzhou, China
4 Department of Thoracic Surgery, Sichuan Cancer Hospital, Chengdu, China
5 Department of Thoracic Surgery, Zhongshan Hospital, Fudan University, Shanghai, China
6 Department of Thoracic Surgery, Fujian Medical University Union Hospital, Fuzhou, China
7 Department of Thoracic Surgery, Fujian Cancer Hospital, Fuzhou, China
8 Department of Thoracic Surgery, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China
9 Department of Thoracic Surgery, Hunan Provincial Cancer Hospital, Changsha, China
10 Department of Thoracic Surgery, Affiliated Hospital of Qingdao University, Qingdao, China
11 Department of Cardiovascular Surgery, Taizhou Hospital affiliated to Wenzhou Medical University, Taizhou, China
12 Department of Thoracic Surgery, Ruijin Hospital, Shanghai Jiaotong University, Shanghai, China
13 Department of Thoracic and Cardiovascular Surgery, Jiangsu Province People's Hospital and the First Affiliated Hospital of Nanjing Medical University, Nanjing, China
14 Department of Thoracic Surgery, Henan Provincial Cancer Hospital, Henan Province, China

Keywords
Adjuvant chemotherapy; adjuvant radiotherapy; esophageal squamous cell carcinoma; randomized controlled trial.

Correspondence
Wentao Fang, Department of Thoracic Surgery, Shanghai Chest Hospital, Shanghai Jiaotong University, 241 West Huaihai Road, Shanghai, 200030, China.
Tel: +86 21 6282 1990
Fax: +86 21 6282 1109
Email: vwtfang@hotmail.com

Received: 14 August 2018;
Accepted: 29 August 2018.

doi: 10.1111/1759-7714.12882

Thoracic Cancer **9** (2018) 1801–1806

Abstract

Histologically node negative esophageal squamous cell carcinoma (pN0 ESCC) after radical resection still carries a significant risk of recurrence, especially in high-risk patients. Our previous study showed that the risk of recurrence was associated with tumor location and cell differentiation, as well as the presence of lymphovascular invasion. Most recurrence occurs within two years after surgery. There is still a lack of knowledge on the risks or potential benefits of postoperative adjuvant therapies for high-risk pN0 ESCC patients. This study was designed to evaluate the efficacy and toxicity of adjuvant therapies after radical surgery in high-risk patients with pN0 ESCC. This study is a multicenter, prospective, controlled randomized trial, which will compare the differences between either adjuvant chemotherapy or adjuvant radiotherapy and surgery alone for high-risk pN0 ESCC. Patients in group A will receive three cycles of adjuvant chemotherapy with paclitaxel and cisplatin, patients in group B will receive adjuvant radiotherapy with intensity-modulated radiation of 50 Gy, and patients in group C (the control) will receive surgery alone. The primary endpoint is three-year disease-free survival. Secondary endpoints include toxicity of adjuvant therapies and five-year overall survival. One hundred and sixty-two patients in each group are required and a total of 486 patients will finally be enrolled into the study. This will be the first randomized trial to investigate the necessity or potential benefit of postoperative adjuvant therapies for high-risk pN0 ESCC patients.

Introduction

Esophageal cancer is the eighth most common cause of cancer worldwide. Among the 500 000 new cases reported globally per year, nearly half occur in in China.[1] In 2013, the incidence and mortality of esophageal cancer ranked fifth and fourth, respectively, among all cancers in China.[1] Over 90% of patients in East Asia have squamous cell carcinoma located in the thoracic esophagus, in contrast to the increasing incidence of adenocarcinoma located in the gastroesophageal junction observed in Western countries.[2] Distinctive features in pathogenesis, clinical manifestations, treatment approaches, and prognosis exist between these two different histologies. The current available evidence to guide the management of esophageal cancers is mainly derived from studies on adenocarcinoma of gastroesophageal junction. Therefore, further understanding of esophageal squamous cell carcinoma (ESCC) is required to improve outcomes for this large population of patients.

For locally advanced esophageal cancer with obvious tumor invasion or regional lymph node metastasis, neoadjuvant treatment with chemotherapy or chemoradiation has been shown to increase resectability and improve long-term survival and thus, is accepted as the standard approach. For relatively early stage lesions, surgery still carries the best chance for cure;[3–6] however, the results are far from satisfactory, with five-year survival after radical resection of only 30–40%.[7] There is still a lack of knowledge of the necessity or potential benefit of postoperative adjuvant treatment, especially for patients with thoracic ESCC.

pN0 esophageal cancer refers to tumors histologically proven to be free of lymph node involvement after resection and account for nearly half of all completely resected squamous cell carcinomas located in the thoracic esophagus. However, even in this group of patients, long-term survival remains unsatisfactory. The five-year survival rate of pT2N0M0 and pT3N0M0 ESCC patients is < 50%.[8] Postoperative recurrence is the main cause of treatment failure. The recurrence rate of pN0 esophageal cancer is reported at 39.5%.[8] It is necessary to find a reasonable adjuvant therapy strategy to reduce local-regional recurrence and distant metastasis, and thereby improve survival. Unfortunately, few prospective randomized controlled studies of adjuvant therapy for ESCC have been conducted, and even fewer in patients with pN0 status. This study has immense clinical significance to guide rational postoperative adjuvant therapy for pN0 ESCC.

Methods

The proposed study is a multicenter, prospective, randomized and parallel controlled trial, which will compare the differences in outcomes among adjuvant chemotherapy, adjuvant radiotherapy, and surgery alone for high-risk pN0 ESCC after complete resection. Cervical esophageal cancer and adenocarcinoma of the gastroesophageal junction will be excluded. In China, cervical esophageal cancer is treated mainly with definitive chemoradiation.

Pathological staging will be based on the seventh edition Union for International Cancer Control (UICC) tumor node metastasis (TNM) staging for esophageal cancer.[9] To ensure accurate pathological staging and true pN0 status, all patients need to have undergone systemic lymphadenectomy, with at least thoracoabdominal two-field lymph node dissection according to the nodal stations described by the Society of Esophageal Tumor, Chinese Anti-Cancer Association.[10] These would include left and right recurrent laryngeal nerve nodes; upper, middle, and lower periesophageal nodes; subcarinal and left/right peribronchial nodes in the chest; and left and right pericardiac nodes, left gastric artery, and lesser curvature nodes in the abdomen. Three-field dissection is encouraged but is not considered mandatory in this study.

Only patients determined by pathological examination with pT1b–T4aN0M0 disease after radical resection, without nodal involvement, will be enrolled in the study. Patients will need to meet at least one of the following criteria to be classified as high risk for further randomization into one of the three study arms, which are based on the results of a previous retrospective risk factor study in pN0 patients: (i) primary tumor located in the middle or upper thoracic esophagus, (ii) presence of lymphovascular invasion (LVI) or submucosal metastasis (SM), and (iii) low differentiation.[11]

Patients will be divided into three groups. Group A patients will receive three cycles of adjuvant chemotherapy with paclitaxel and cisplatin. Group B patients will receive adjuvant radiotherapy with intensity-modulated radiation therapy (IMRT) of 50 Gy. Group C patients will undergo surgery alone without any additional treatment and are designated as the control group. A flowchart of the trial is shown in Figure 1.

Objectives

The primary endpoint is to observe and compare disease-free survival (DFS) among the three arms. The secondary endpoints are to observe and compare overall survival (OS) among the three arms and to compare adverse events between adjuvant chemotherapy and adjuvant radiation.

Participating surgeons and hospitals

Surgeons with sufficient experience and skills in either open transthoracic esophagectomy or minimally invasive

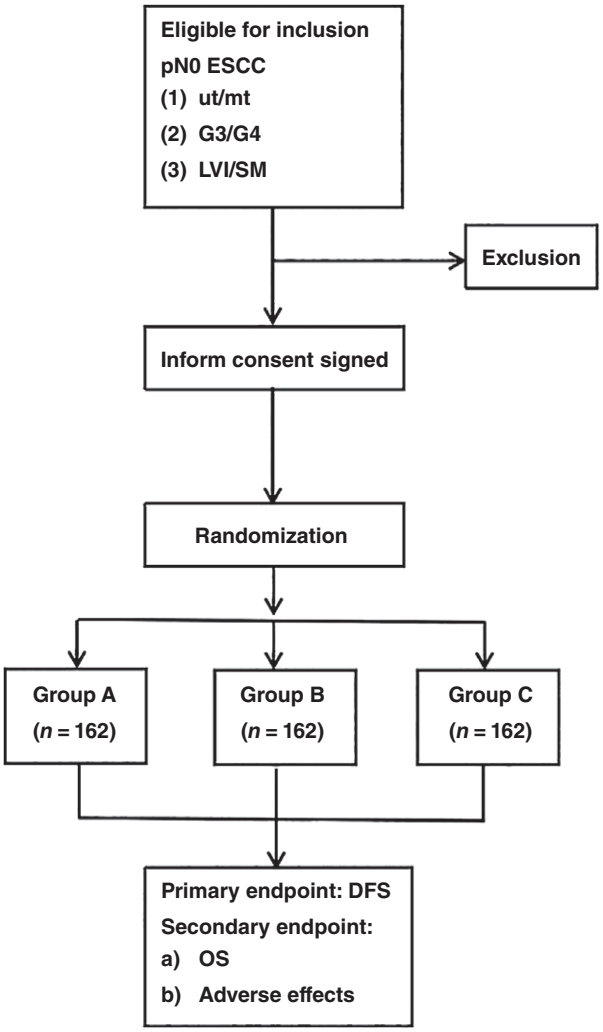

Figure 1 Flow chart of the study. DFS, disease-free survival; ESCC, esophageal squamous cell carcinoma; LVI, lymphovascular invasion; OS, overall survival; SM, submucosal metastasis; ut/mt, upper or middle thoracic.

thoracoscopic laparoscopic esophagectomy will perform all operations. All participating surgeons need to have adequate experience in performing thoracoabdominal two-field or cervico-thoraco-abdominal three-field lymphadenectomy. In order to prevent institution bias, only high-volume esophagectomy hospitals (> 200 cases annually) will participate in the study (Table 1).

Table 1 Hospitals participating in the study

No.	Province	Unit
1	Shanghai	Department of Thoracic Surgery, Shanghai Chest Hospital, Shanghai Jiaotong University
2	Tianjin	Department of Esophageal Surgery, Tianjin Cancer Hospital, Tianjin Medical University
3	Guangdong	Department of Thoracic Surgery, Sun Yat-sen University Cancer Center
4	Sichuan	Department of Thoracic Surgery, Sichuan Cancer Hospital
5	Shanghai	Department of Thoracic Surgery, Zhongshan Hospital, Fudan University
6	Fujian	Department of Thoracic Surgery, Fujian Medical University Union Hospital
7	Fujian	Department of Thoracic Surgery, Fujian Cancer Hospital
8	Hubei	Department of Thoracic Surgery, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology
9	Hunan	Department of Thoracic Surgery, Hunan Provincial Cancer Hospital
10	Shandong	Department of Thoracic Surgery, Affiliated Hospital of Qingdao University
11	Zhejiang	Department of Cardiothoracic Surgery, Taizhou Hospital, Affiliated to Wenzhou Medical University
12	Shanghai	Department of Thoracic Surgery, Ruijin Hospital, Shanghai Jiaotong University
13	Jiangsu	Department of Thoracic and Cardiovascular Surgery, Jiangsu Province People's Hospital and the First Affiliated Hospital of Nanjing Medical University
14	Henan	Department of Thoracic Surgery, Henan Provincial Cancer Hospital

Inclusion criteria

The inclusion criteria are as follows:

1 Patients: No pretreatment before surgery. Informed consent signed after screening.
2 Surgery: Complete (R0) resection of the tumor, with thoracoabdominal two-field or cervico-thoraco-abdominal three-field lymph node dissection through transthoracic esophagectomy. At least 12 stations and 12 lymph nodes should be harvested, including bilateral recurrent laryngeal nerve lymph nodes. Both open thoracotomy and minimally invasive thoracoscopic-laparoscopic approaches are allowed.
3 Histology: Thoracic ESCC, with no lymph node involvement (pN0) by pathological examination.
4 Staging: Pathological tumor stage T1b–T4a according to the seventh edition UICC esophageal cancer staging system.
5 Definition of high risk of recurrence: Patients must meet at least one of the following:
  i Primary tumor located in the middle or upper third thoracic esophagus,
  ii Presence of LVI or SM,
  iii Low differentiation.
6 Performance status: Eastern Cooperative Oncology Group score 0–2.

7 Cardiac function: New York Heart Association classification 1–2. Normal electrocardiogram.
8 Renal function: Normal serum creatinine level (SCr = 120 mol/L) and creatinine clearance rate (CCr = 60 mL/minute).
9 Hepatic function:
  i Serum aspartate aminotransferase and alanine aminotransferase level ≤ 2.0 times the upper limit of normal (ULN),
  ii Serum alkaline phosphatase level ≤ 4 times the ULN,
  iii Serum total bilirubin level ≤ 1.5 times the ULN.
10 Hematopoietic function:
  i White blood cell count ≥ 4000/μL,
  ii Neutrophil absolute count ≥ 1500/μL,
  iii Platelet count ≥ 100 000/μL,
  iv Hemoglobin ≥ 10.0 g/dL.

Exclusion criteria

The exclusion criteria are as follows:
1 Surgery through left thoracic or transhiatal approach, whereby complete lymphadenectomy cannot be achieved.
2 Patients experience severe postoperative complications and thus are unable to tolerate adjuvant therapy within three months after surgery.
3 Patients with other concomitant malignant tumors.
4 Patients with abnormal coagulation function, with bleeding tendencies (such as active peptic ulcer), or currently receiving thrombolysis or anticoagulation therapies.
5 Severe cardiac comorbidities, including congestive heart failure, uncontrolled cardiac arrhythmia, unstable angina pectoris, myocardial infarction within six months, severe heart valve disease, or intractable hypertension.
6 Severe hepatic or renal insufficiency.
7 Poor mental status or mental disorders, poor compliance.

Ethics

The trial will be conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice Guidelines, local laws, and regulations. The institutional ethics committees of all participating institutions have approved the study protocol. During the study, all modifications, extensions and updates of trial procedures will be reviewed and approved by the medical ethics committee in each participating center.

Randomization

Once the eligible patients have been confirmed and informed consent obtained, the researchers will login through the trial randomization system and input patient information. The patient will then be randomized to either the adjuvant radiotherapy, adjuvant chemotherapy, or surgery alone group through a group number produced by SPSS version 20.0 (IBM Corp., Armonk, NY, USA).

Trial intervention (arms and assigned interventions)

1 *Experimental groups:*
  i Adjuvant chemotherapy group: Surgery followed by three four-week cycles of adjuvant chemotherapy with 175 mg/m^2 paclitaxel and 75 mg/m2 cisplatin via intravenous glucose tolerance test for three hours each on day 1 of every cycle.
  ii Adjuvant radiotherapy group: Surgery followed by adjuvant radiotherapy. Target: the upper mediastinum and bilateral supraclavicular region (upper bound of cricothyroid and lower bound of 3 cm lower than tracheal carina). IMRT 50 Gy. Conventional segmentation of 2 Gy/day.
2 *Control group:* Surgery alone, without any adjuvant therapy.

Postoperative follow-up

The follow-up period will commence one month after surgery or at the conclusion of adjuvant therapy once every three months in the first two years, and once every six months thereafter until disease progression, patient death, or the end of the study. Follow-up will include neck ultrasound, enhanced computed tomography scans of the chest and abdomen, and blood tumor markers. Esophagoscopy is recommended at least once a year.

Treatment-related side effects, and DFS and OS, including the site and time of recurrence or metastasis and cause of death will be recorded during the follow-up period.

Sample size calculation

This is a multicenter clinical study with a unilateral significance level of $\alpha = 0.025$ and a power of $\beta = 0.8$. DFS is expected to improve 15%; Groups A, B, and C are estimated at a ratio of 1:1:1. Accounting for a 10% sample loss, 162 patients are required for each group, for a total of 486 patients enrolled into the study.

Statistical analysis

Statistical analyses will be performed using SPSS version 20.0. Continuous variables will be presented as mean ± standard deviation and compared using a Student's *t*-test or analysis of variance. Categorical variables will be

reported as absolute numbers (frequency, percentages) and analyzed using χ^2 or Fisher's exact tests as appropriate. Survival will be estimated by using Kaplan–Meier curves and compared using a log-rank test. A two-tailed P value of < 0.05 is considered statistically significant.

Dissemination policy

The results, whether positive, negative, or inconclusive, will be published in a peer-reviewed international journal.

Discussion

According to our previous retrospective study on the recurrence pattern of pN0 ESCC, the primary reason for treatment failure is postoperative recurrence and metastasis.[11] Our results showed that 40.2% of pN0 ESCC patients developed recurrence and metastasis within two years after esophagectomy, and the median time to recurrence and metastasis was 17.4 months. Locoregional recurrence, especially locoregional lymph node metastasis, was the most common recurrence pattern, accounting for 84.4% of all treatment failure. The main sites of lymph node metastasis were the cervicothoracic junction and the superior mediastinum (79%). Recurrence was closely correlated with tumor location, cell differentiation, and depth of invasion of the primary tumor (pT). Multivariate analysis revealed that tumor location at the upper and/or middle thoracic esophagus and pT3-4a stage were independent risk factors for postoperative locoregional recurrence. Moreover, the recurrence rate in patients with LVI or SM was also very high. Thus, these patients should be considered at high risk of developing recurrence after resection. Effective adjuvant therapies are needed to improve the long-term outcomes in this high-risk group.

The results of postoperative adjuvant chemotherapy for locally advanced esophageal cancer are not satisfactory, probably because of the low response rate of squamous cell carcinoma to traditional regimens.[12] In recent years, chemotherapy agents, such as paclitaxel, have shown higher response rates, exhibiting better results in neoadjuvant chemotherapy for locally advanced esophageal cancer. An overall clinical response rate of up to 70%, with a 12% pathological complete response, has been reported when combining paclitaxel with carboplatin in neoadjuvant chemotherapy for stage III resectable esophageal cancer.[13] However, the toxicity profile was less significant, making this regimen more appealing in an adjuvant setting.

Previous studies on postoperative prophylactic radiotherapy had heterogeneous results. Xiao *et al.* found that adjuvant radiation might improve survival in esophageal cancer patients with positive lymph node metastasis and in patients with stage III disease compared to those not administered radiation therapy.[14] It is worth noting that most patients in that study had esophagectomy through the left thoracotomy (Sweet procedure), where lymph node dissection in the upper mediastinum is difficult, if not completely impossible. In most adjuvant radiation studies with negative results, the target area was set to the esophageal bed where the primary tumor was located. Our previous study showed that the main sites of lymph node recurrence after esophagectomy were the cervicothoracic junction and the upper mediastinum.[11] Lymph node metastasis occurred earlier than hematogenous dissemination, making it the most important prognostic factor after radical esophagectomy. Wu *et al.* also confirmed that regional lymph node metastasis was the most common recurrence pattern in pN0 ESCC patients.[15] Therefore, it is necessary to adjust the target area of adjuvant radiotherapy to the cervicothoracic junction to ensure that treatment is more effective and reduces the local recurrence rate.

In conclusion, patients with pN0 ESCC remain at risk of recurrence even after radical esophagectomy and systemic lymph node dissection. Based on our previous retrospective study, we have identified a group of patients at high risk of developing recurrence. This study will be carried out selectively in high-risk patients to determine if adjuvant chemotherapy or radiation is beneficial for this specific group. Hopefully the results of this study will help to decrease recurrence and improve long-term outcomes for pN0 ESCC patients.

Trial status

Patient recruitment began in December 2016. All centers have been enrolling patients since January 2017. Patient recruitment is expected to end in December 2019.

Disclosure

No authors report any conflict of interest.

References

1 Rustgi AK, El-Serag HB. Esophageal carcinoma. *N Engl J Med* 2014; **371**: 2499–509.
2 Chen W, Zheng R, Baade PD *et al.* Cancer statistics in China, 2015. *CA Cancer J Clin* 2016; **66**: 115–32.
3 Shapiro J, van Lanschot JJ, Hulshof MC *et al.* Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): Long-term results of a randomised controlled trial. *Lancet Oncol* 2015; **16**: 1090–8.
4 van Hagen P, Hulshof MC, van Lanschot JJ *et al.* Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med* 2012; **366**: 2074–84.

5 Sjoquist KM, Burmeister BH, Smithers BM *et al*. Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: An updated metaanalysis. *Lancet Oncol* 2011; **12**: 681–92.
6 Allum WH, Stenning SP, Bancewicz J, Clark PI, Langley RE. Long-term results of a randomized trial of surgery with or without preoperative chemotherapy in esophageal cancer. *J Clin Oncol* 2009; **27**: 5062–7.
7 Matsuda S, Takeuchi H, Kawakubo H *et al*. Current advancement in multidisciplinary treatment for resectable cStage II/III esophageal squamous cell carcinoma in Japan. *Ann Thorac Cardiovasc Surg* 2016; **22**: 275–83.
8 Rice TW, Chen L-Q, Hofstetter WL *et al*. Worldwide Esophageal Cancer Collaboration: Pathologic staging data. *Dis Esophagus* 2016; **29**: 724–33.
9 Edge SB, Byrd DR, Compton CC *et al*. *American Joint Committee on Cancer. Cancer Staging Manual*, 7th edn. Springer-Verlag, New York 2010.
10 Li H, Fang W, Yu Z *et al*. Chinese expert consensus on mediastinal lymph node dissection in esophagectomy for esophageal cancer (2017 edition). *J Thorac Dis* 2018; **10**: 2481–9.
11 Guo XF, Mao T, Gu ZT *et al*. Clinical study on postoperative recurrence in patients with pN0 esophageal squamous cell carcinoma. *J Cardiothorac Surg* 2014 Aug 28; **9**: 150.
12 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.
13 Urschel JD, Vasan H, Blewett CJ. A meta-analysis of randomized controlled trials that compared neoadjuvant chemotherapy and surgery to surgery alone for resectable esophageal cancer. *Am J Surg* 2002; **183**: 274–9.
14 Xiao ZF, Yang ZY, Liang J *et al*. Value of radiotherapy after radical surgery for esophageal carcinoma: A report of 495 patients. *Ann Thorac Surg* 2003; **75**: 331–6.
15 Wu SG, Dai MM, He ZY *et al*. Patterns of regional lymph node recurrence after radical surgery for thoracic esophageal squamous cell carcinoma. *Ann Thorac Surg* 2016; **101**: 551–7.

