**Name of Journal:** *World Journal of Gastrointestinal Oncology*

**Manuscript NO:** 48635

**Manuscript Type:** ORIGINAL ARTICLE

***Retrospective Study***

**Differences in failure patterns of pT3-4N0-3M0 esophageal cancer with surgery *vs* surgery/radiotherapy**

Zeng Y *et al*. Failure pattern of ESCC after PORT

Ya Zeng, Wen Yu, Qi Liu, Wei-Wei Yu, Zheng-Fei Zhu, Wei-Xin Zhao, Jun Liu, Jia-Ming Wang, Xiao-Long Fu, Yuan Liu, Xu-Wei Cai

**Ya Zeng,** **Jun Liu, Jia-Ming Wang,** Department of Radiation Oncology, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai 200030, China

**Qi Liu,Zheng-Fei Zhu, Wei-Xin Zhao**, Department of Radiation Oncology, Fudan University Shanghai Cancer Center, Shanghai 200030, China

**Wei-Wei Yu,** Department of Radiation Oncology, Shanghai Jiao Tong University Affiliated Shanghai Sixth People’s Hospital, Shanghai 200030, China

**Wei-Wei Yu,** Department of Radiation Oncology, Fudan University Shanghai Cancer Center, Shanghai 200030, China

**Wen Yu, Xiao-Long Fu, Xu-Wei Cai,** Department of Radiation Oncology, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai 200030, China

**Wen Yu, Xiao-Long Fu, Xu-Wei Cai,** Department of Radiation Oncology, Fudan University Shanghai Cancer Center, Shanghai 200030, China

**Yuan Liu,** Department of Statistics, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai 200030, China

**ORCID number:** Ya Zeng (0000-0002-3524-5476); Wen Yu (0000-0002-2338-4663); Qi Liu (0000-0002-8770-5470); Wei-Wei Yu (0000-0002-8081-6418); Zheng-Fei Zhu (0000-0002-5516-039X); Wei-Xin Zhao (0000-0001-8553-7429); Jun Liu (0000-0002-8453-2957); Jia-Ming Wang (0000-0001-8842-7110); Xiao-Long Fu (0000-0001-8127-3884); Yuan Liu (0001-6842-9346); Xu-Wei Cai (0000-0001-9673-4188).

**Author contributions**: All authors participated in this research; Zeng Y and Cai XW manuscript writing, patient collection and data analysis; Yu W, Yu WW, Liu Qi, Wang JM, Liu J, Zhu ZF and Zhao WX patient collection and follow-up visit; Fu XL and Cai XW, patient collection and research design; and the statistical methods of this study were reviewed by Liu Y.

**Supported by** Emerging advanced technology joint research project of Shanghai Shenkang Hospital Development Center, No. SHDC12017103; and Shanghai Municipal Education Commission-Gaofeng Clinical Medicine Grant Support, No. 20161433.

**Institutional review board statement**: Approval was achieved from the Institute Research Ethics Committee of Shanghai Chest Hospital and Shanghai Cancer Center before the patients enrolled the relevant studies. So, there was no additional approval for this study.

**Informed consent statement:** Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

**Conflict-of-interest statement:** None of the authors have any conflict of interest to disclose.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

**Manuscript source:** Unsolicited manuscript

**Correspondence author:** **Xu-Wei Cai, MD, PhD, Chief Doctor,** Department of Radiation Oncology, Shanghai Chest Hospital, Shanghai Jiao Tong University, 241 West Huaihai Road, Shanghai 200030, China. cxw1802@shchest.org

**Received:** April 26, 2019

**Peer-review started:** May 9, 2019

**First decision:** July 31, 2019

**Revised:** August 8, 2019

**Accepted:** September 10, 2019

**Article in press:**

**Published online:**

**Abstract**

***Background***

There was no study comparing the difference in the failure patterns between patients with or without post-operative radiotherapy (PORT) after esophagectomy for pT3-4N0-3M0 esophageal squamous cell carcinoma (ESCC).

***Aim***

To investigate the differences in the failure patterns of stage pT3-4N0-3M0 ESCC patients with or without PORT.

***Methods***

Patients with stage pT3-4N0-3M0 ESCC, who underwent surgery with or without PORT, were enrolled in this study. The primary endpoint was to investigate the differences in the failure patterns between patients with or without PORT after esophagectomy. The secondary endpoint was to estimate whether patients with stage pT3-4 could achieve a disease-free survival (DFS) advantage after receiving adjuvant PORT. Statistical analyses were performed by the Kaplan-Meier method, Cox regression model and Chi-squared test or Fisher’s exact test.

***Results***

In total, 230 patients with stage pT3-4N0-3M0 were included in this study. Fifty-six patients who received PORT were screened from a prospective cohort (S + R arm). And 174 patients involving surgery alone were retrospectively selected from July 2006 to October 2014 (S arm). There were no significant differences in the clinical and pathological characteristics of patients between the two arms, except for the tumor location (*p* = 0.031). The failure patterns between two arms were significantly different (*p* < 0.001). Patients in the S arm had a significantly higher proportion of locoregional recurrence and a lower proportion of distant metastasis than those in the S + R arm [92.0% *vs* 35.7%, (*p* < 0.001) and 19.0% *vs* 75.0%, (*p* < 0.001), respectively]. The difference in the median DFS between two arms was statistically significant (12.7 *vs* 8 mo, *p* = 0.048). Univariate analysis and multivariate analysis both demonstrated that the number of lymph node metastases ≥ 3 (HR = 0.572, 95%CI: 0.430-0.762, *p* < 0.001) was an independent poor prognostic factor for DFS in patients with stage pT3-4N0-3M0.

***Conclusion***

PORT could improve DFS and local control of patients with stage pT3-4N0-3M0 ESCC. However, further studies need to be conducted to control hematogenous metastasis after PORT.

**Key words:** Esophageal squamous cell carcinoma; Post-operative radiotherapy; Failure patterns; Disease-free survival

**© The Author(s) 2019.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** This is the first study to compare the difference in the failure patterns for pT3-4N0-3M0 esophageal squamous cell carcinoma (ESCC) patients with or without post-operative radiotherapy (PORT) after esophagectomy. The result showed that PORT could improve disease-free survival and local control of patients with stage pT3-4N0-3M0 ESCC. However, distant metastasis was the main failure pattern after receiving PORT. Further studies need to be conducted to control hematogenous metastasis in the future.

Zeng Y, Yu W, Liu Q, Yu WW, Zhu ZF, Zhao WX, Liu J, Wang JM, Fu XL, Liu Y, Cai XW. Differences in failure patterns of pT3-4N0-3M0 esophageal cancer with surgery *vs* surgery/radiotherapy. *World J Gastrointest Oncol* 2019; In press

**Introduction**

Esophageal cancer is an aggressive malignancy with high morbidity and mortality[[1](#_ENREF_1)]. The guidelines of the National Comprehensive Cancer Network[[2](#_ENREF_2)] recommends that esophagectomy is still the primary choice for esophageal cancer. Neoadjuvant chemoradiotherapy followed by surgery is the standard care for patients with locally advanced esophageal squamous cell carcinoma (ESCC)[3]. Nevertheless, many patients tend to choose surgery as their primary treatment because of the traditional concept in China, although neoadjuvant therapy is recommended by surgeons. Furthermore, most patients who were clinically diagnosed as stage T1-2 were pathologically confirmed as stage T3-4 after surgery owing to the less frequent use of ultrasound endoscopy. However, with a poor survival and high rate of recurrence after esophagectomy[4,5], patients with pT3-4 are required for multidisciplinary adjuvant treatments. Additionally, the efficacy of post-operative radiotherapy (PORT) has been investigated widely. Based on a cancer registry database, patients with esophageal cancer could not benefit from PORT[[6](#_ENREF_6)]. However, many retrospective studies showed that post-operative radiotherapy could apparently improve the locoregional control rate and overall survival (OS) rate for patients with locally advanced ESCC (stage III or with positive lymph node)[[7](#_ENREF_8)-[9](#_ENREF_9)].

Locoregional recurrence is the most common pattern of failure after esophagectomy[[4](#_ENREF_3),[10](#_ENREF_4)]. Approximately 80% of recurrence sites of ESCC patients after curative esophagectomy are located in the supraclavicular and superior mediastinal lymph nodes, which is called the T-shape field[[11](#_ENREF_10)-[13](#_ENREF_12)]. Chen *et al*[7] reported that the locoregional recurrence rate for patients receiving PORT was significantly lower than that in those who had undergone surgery alone. However, no study had compared the difference of the failure patterns between stage pT3-4 patients with or without PORT after esophagectomy.

In that case, this study was administered with the intention of investigating the differences in the failure patterns of patients with stage pT3-4N0-3M0 ESCC after complete resection with or without PORT and estimating whether patients could obtain a DFS benefit from PORT.

**Materials and Methods**

***Patients***

Patients in this study were screened from two treatment centers that included 429 ESCC patients with stage pT1-4N0-3M0. Patients in the S + R arm were screened from a prospective cohort that included 124 ESCC patients with only stage pT3-T4, who had received radiotherapy after surgery[14]. Patients in the S arm were screened from a retrospective cohort including 305 patients who had undergone radical surgery alone[12]. The main eligible inclusion criteria were as follows: (A) a diagnosis of primary thoracic esophageal squamous cell carcinoma and pathologically confirmed stage T3-4N0-3M0; (B) aged 18-75 years; (C) integrated physical examination, contrast esophagography, enhanced computed tomography of chest and upper abdomen and external ultrasonography of the neck or positron emission tomography (PET/CT) conducted before surgery and radiotherapy; (D) adequate bone marrow, liver and renal functions for patients receiving radiotherapy; and (E) patients with any patterns of failure during following up. The excluded criteria were as follows: received chemotherapy or radiotherapy before surgery; no failure patterns occurred to the last follow up; patients with a secondary primary tumor after or during PORT. Additionally, patients who had received adjuvant chemotherapy was not considered in the study. The patient selection procedure is shown in Figure 1.

***Radiotherapy***

All the patients in S + R arm received radiotherapy within 8 wk after surgery. The patients underwent CT-based treatment simulation in the supine position with a thermoplastic mask for immobilization. Five-millimeter-thick images were obtained from the entire neck to the upper abdomen. Intensity-modulated radiotherapy with a 6 MV X-ray linear accelerator was used for external beam radiation. The delineation of the clinical tumor volume (CTV) was based on surgery procedure, CT imaging obtained before and after surgery and gastrointestinal endoscopy obtained before treatment. The CTV included the primary tumor bed and metastasis lymph nodes or plus bilateral supraclavicular and upper-middle mediastinal lymphatic drainage areas (T-shape field). The planning target volume was defined as CTV plus a 0.8 to 1.0 cm margin. The radiation dose to the primary tumor bed and metastatic lymph nodes was 63 Gy (2.25 Gy/day/fraction, 28 fractions) for patients with stage T4 or 60.2 Gy (2.15 Gy/day /fraction, 28 fraction) for patients with stage T3. The lymphatic drainage area was prescribed a dose of 50.4 Gy (1.8 Gy/day/fraction, 28 fractions). The prescription dose was delivered to the target volume mainly through the mediastinum. Normal tissue dose constraints met the usual requirements: (1) maximum spinal cord dose ≤ 45 Gy; (2) lung V20 ≤ 25% and mean lung dose ≤ 15 Gy; and (3) mean heart dose ≤ 30 Gy.

***Chemotherapy***

After surgery or radiotherapy was completed, chemotherapy was scheduled intravenously with cisplatin (25 mg/m2/d, d1–3) and 5-fluorouracil (5-Fu, 600 mg/m2/d, d1–5) or paclitaxel (135-175 mg/m2/d, d1) for four cycles with an interval of 3-4 wk.

***Follow up***

Follow-up visits were administered every 3 mo for the first two years after treatment, every 6 mo for the next three years, and then once a year thereafter. Patients in the S + R arm were followed to March 2017. Follow-up investigations include hematological examination, supraclavicular lymph node ultrasonography, contrast esophagography and enhanced computed tomography of the chest and upper abdomen. When necessary, PET/CT or bone emission computed tomography was required.

***Definitions of failure patterns***

This study analyzed the first failure pattern only. The discovery of relapse was mainly based on imaging features. Fine-needle aspiration biopsy and PET/CT were implemented only when necessary. Locoregional recurrence included the tumor bed area, anastomotic stoma relapse and regional lymph nodes, for which the short axis diameter was at least 1cm in the CT image, according to the tumor location. Distant metastasis was defined as neoplasms occurring in organs or non-regional lymph node metastasis. The definitions of failure patterns were described in detail in our previous report[12]. Recurrence comprising locoregional and distant failure simultaneously was classified as mixed failure.

***Statistical analysis***

Owing to the retrospective characteristics of the S arm, we did not have access to the OS information of over 10% patients. The primary endpoint of this study was to compare the differences in the failure patterns between the two arms. Secondary endpoint was to evaluate whether patients with locally advanced ESCC could achieve DFS benefit from PORT. DFS was calculated from the date of surgery to the date that any type of failure occurred or the date of the last follow-up. The difference in the failure patterns and clinical characteristics were calculated by Chi-squared test or Fisher’s exact test. The Kaplan-Meier method was used to evaluate the difference in DFS between the two arms. The log-rank test was used to determine the statistical significance of the difference. Univariate analysis and multivariate analysis (Cox proportional hazard regression model) were performed to evaluate the risk factors associated with the prognosis. A *P* value less than 0.05 (two sided) was considered to be statistically significant. All statistical analyses were calculated by SPSS (version 22.0 IBM Chicago, United States).

**Results**

This study included 230 patients. In the prospective cohort of 124 ESCC patients with stage pT3-T4 who underwent PORT, 66 patients lived with disease-free and 2 patients with secondary primary tumor were excluded. Finally, 56 patients who met the criteria were recruited as the S + R arm from April 2011 to February 2016. We retrospectively screened 305 patients who received surgery alone. Among them, 131 patients with stage pT1-2 were excluded and 174 patients with pT3-4 suffering failure were enrolled as the S arm from July 2006 and October 2014. Finally, 230 patients were included in this study. All patients in the S + R arm completed the intended radiotherapy treatment plan within 6 wk. There were 60.7% patients received sequential chemotherapy after radiotherapy completed. Others who declined or could not tolerate did not receive chemotherapy. There was no difference in receiving chemotherapy between S arm and S + R arm. The baseline clinical and pathologic characteristics of the two arms are shown as Table 1. Differences between the two cohorts in sex, age, pathological differentiation, number of lymph node dissection, lymph node involvement and chemotherapy were not significant, except for the tumor location (*p* = 0.031).

***Failure patterns***

All patients included in this study developed failure during the follow-up. We compared the differences in the constituent ratio of the failure patterns between the two arms. As shown in Table 2, the difference in the failure patterns between two arms was statistically significant (*p* < 0.001). Regarding patients with distant metastasis, locoregional recurrence and mixed failure, 64.3%, 25.0%, and 10.7%, respectively, were in the S + R arm and 8.0%, 81.0%, and 11.0%, respectively, were in the S arm. Patients in the S arm had a significantly higher proportion of locoregional recurrence than patients in the S + R arm (92.0% *vs* 35.7%, respectively, *p* < 0.001). However, patients in the S + R arm had a much higher proportion of distant metastasis than patients in the S arm (75.0% *vs* 19.0%, *p* < 0.001). The most common regions for locoregional recurrence were the supraclavicular and mediastinal lymph nodes (29.5% and 48.3%, respectively) for the surgery cohort. For the S + R arm, supraclavicular lymph node recurrence (9/17 patients) was the highest relapse region after PORT. The lung, liver and bone (41.7% (14/36 patients), 19.4% (7/36 patients) and 16.7% (6/36 patients), respectively) were the most common metastatic organs for the S + R arm. Distant metastasis mainly occurred in the lung (7/33), supraclavicular lymph node (16/33) and celiac lymph node (10/33) for the S arm (Figure 2).

***Disease-free survival***

Recurrence occurred almost within two years for both arms. The 1-year, 2-year and 3-year DFS of the S arm and S + R arm were 33.7%, 14.5%, 4.7% and 51.8%, 26.8%, 8.9%, respectively. The DFS was improved from 8 mo to 12.7 mo after receiving PORT. The difference in DFS for the two arms was marginally significant (*p* = 0.048, Figure 3).

Univariate analysis revealed only lymph node involvementwas associated with DFS for T3-4 patients (*p* < 0.001, Figure 4 and Table 3). Patients with the number of lymph node metastases fewer than 2 could achieve a better DFS (11.0 *vs* 8.0 mo). DFS was not statistically associated with age, sex, tumor location, pathological differentiation, lymph node dissection, number of lymph node dissection and adjuvant chemotherapy.

However, multivariate analysis indicated that the number of lymph node metastases ≥ 3 (HR = 1.843, 95%CI: 1.369-2.482; *p* < 0.001), post-operative radiotherapy (HR = 0.667, 95%CI: 0.487-0.915; *p* = 0.012), age (HR = 0.712, 95%CI: 0.530-0.957; *p* = 0.024) and chemotherapy (HR = 0.732, 95%CI: 0.552-0.971; *p* = 0.031) were independent prognostic factors for DFS in patients with stage pT3-4N0-3M0 (Table 3).

**Discussion**

Although many studies have investigated the characteristics of failure patterns for patients with thoracic esophageal carcinoma after esophagectomy, this study is the first to investigate the differences in the failure patterns for stage pT3-4 ESCC patients with or without PORT after radical surgery. Our study found that radiotherapy following esophagectomy was more effective in improving DFS and decreasing locoregional recurrence of patients with stage pT3-4 ESCC. Distant metastasis was the most common failure after receiving PORT. Lymph node involvement over 3, radiotherapy, age and chemotherapy were significantly associated with disease progression for patients with stage pT3-4.

It is known that neoadjuvant chemoradiotherapy is recommended as the standard care for locally advanced ESCC. However, many patients initially diagnosed as T1-2N0 before surgery were finally diagnosed as pT3-4N0-3M0 after surgery. Do these patients need to receive adjuvant treatment after surgery? Xiao *et al*[15] revealed that patients receiving PORT with a prescription dose of 60 Gy could obtain a local control benefit and a higher 5-year OS than patients receiving surgery alone. With the application of 3-dimentional conformality radiotherapy, PORT could bring both local control and OS benefit for patients with esophageal cancer of stage III, stage T3N0M0 or patients with positive lymph node[16-19]. Additionally, Schreiber *et al*[18] reported a survival benefit for patients with stage III of both ESCC and esophageal adenocarcinoma after receiving PORT. Our result also revealed better DFS for patients in the S + R arm than that in the S arm.

It is common for patients with esophageal cancer to develop relapse after treatment. Locoregional failure is the most common failure pattern for patients with surgery alone; and mediastinal lymph node recurrence, especially at the upper mediastinal lymph node and supraclavicular lymph node are the most common recurrence sites[11-13,20]. This study also showed that approximately 80% of locoregional failure occurred in the T-shape field. By comparing the constituent ratio of failure patterns for patients who underwent surgery with or without PORT, it showed that locoregional recurrence decreased and distant metastasis became the main failure pattern after receiving PORT for patients with stage T3-4, a finding that agrees with the previous study results[7,21]. Distant metastasis after receiving PORT is a new issue that leads to treatment failure. Considering no difference was found in the of patients receiving adjuvant chemotherapy, whether chemotherapy could further decrease the rate of metastasis needs further research. The reasons more patients showed distant metastasis may be due to the small number of patients, local control increase, or there were inherent factors making patients prone to distant metastasis. Our recent research identified a potential biomarker for metastasis of ESCC[22], and we will study this topic further to clarify the mechanism of increased distant metastasis after PORT.

Both univariate and multivariate analysis demonstrated that lymph node involvement is significantly associated with the DFS of patients in stageT3-4. Adjuvant chemotherapy may be a favorable factor. Meanwhile, many studies have reported that adjuvant chemotherapy could improve local control and improve OS or DFS, especially for patients with positive lymph node[23,24]. Researchers also reported that post-operative chemoradiotherapy could decrease both locoregional and distant recurrence. However, it must be noted that combined chemoradiation therapy may lead to higher toxicity[25]. Thus, we supposed that combined radiation and chemotherapy sequentially may be effective in improving disease-free survival or even OS**.**

This study possessed some limitations. First, due to the retrospective nature of this study, it is inevitable that some information was uncontrolled or missed and it is difficult to address some biases. A perspective study should be conducted to answer these questions in the future. Second, patients in the S + R arm were fewer than those in the S arm, possibly influencing DFS; a longer follow-up and more enrolled patients are needed. Third, the study compared the constituent ratio of failure patterns because of the respective characteristics of patients.

In conclusion, PORT could improve DFS and decrease the locoregional recurrence of patients with stage pT3-4N0-3M0 ESCC. However, distant metastasis was the main failure pattern after receiving PORT. Further study needs to be conducted to evaluate how to control hematogenous metastasis.

**Article Highlights**

***Research background***

Post-operative radiotherapy is could improve local control of esophageal squamous cell carcinoma (ESCC) patients with T3-4 or lymph node positive. There was no study comparing the difference of failure patterns after surgery with or without post-operative radiotherapy (PORT) in such patients.

***Research motivation***

We want to investigate the difference of failure patterns in order to guide the following treatment for patients who suffered treatment relapse.

***Research objectives***

In order to define the differences between patients with stage pT3-4N0-3M0 ESCC with or without PORT after esophagectomy.

***Research methods***

Patients who underwent radical surgery and pathologically stage T3-4 were included in this study. And those who received adjuvant radiotherapy after surgery were S + R arm, otherwise were included in S arm. This study mainly investigated the differences of failure patterns between the two arms.

***Research results***

This study reported that post-operative radiotherapy could decrease locoregional relapse. However, the proportion of distant metastasis of S + R arm was much more than that in the S arm.

***Research conclusions***

PORT could improve local control for ESCC patients with stage pT3-4. Further studies need to be conducted to control hematogenous metastasis.

***Research perspectives***

The treatment of locally advanced ESCC is a hot topic. PORT could decrease locoregional lymph node relapse, but recurrence after PORT is the main reason that result in treatment failure. It’s urgent to find an effect treatment to control this situation. And now we should explain the main failure pattern after undergoing different treatment strategies.

**References**

1 **Chen W**, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, Jemal A, Yu XQ, He J. Cancer statistics in China, 2015. *CA Cancer J Clin* 2016; **66**: 115-132 [PMID: 26808342 DOI: 10.3322/caac.21338]

2 **National Comprehensive Cancer Network**. NCCN Clinical Practice Guidelines in Oncology: Esophageal and Esophagogastric Junction Cancers, 2017. Available from: URL: https://www.nccn.org/professionals/physician\_gls/default.aspx

3 **Shapiro J**, van Lanschot JJB, Hulshof MCCM, van Hagen P, van Berge Henegouwen MI, Wijnhoven BPL, van Laarhoven HWM, Nieuwenhuijzen GAP, Hospers GAP, Bonenkamp JJ, Cuesta MA, Blaisse RJB, Busch ORC, Ten Kate FJW, Creemers GM, Punt CJA, Plukker JTM, Verheul HMW, Bilgen EJS, van Dekken H, van der Sangen MJC, Rozema T, Biermann K, Beukema JC, Piet AHM, van Rij CM, Reinders JG, Tilanus HW, Steyerberg EW, van der Gaast A; CROSS study group. 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**: 1090-1098 [PMID: 26254683 DOI: 10.1016/S1470-2045(15)00040-6]

4 **Chen G**, Wang Z, Liu XY, Liu FY. Recurrence pattern of squamous cell carcinoma in the middle thoracic esophagus after modified Ivor-Lewis esophagectomy. *World J Surg* 2007; **31**: 1107-1114 [PMID: 17426905 DOI: 10.1007/s00268-006-0551-1]

5 **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**: 5062-5067 [PMID: 19770374 DOI: 10.1200/JCO.2009.22.2083]

6 **Bilimoria KY**, Stewart AK, Tomlinson JS, Gay EG, Ko CY, Talamonti MS, Bentrem DJ. Impact of adjuvant radiation on survival: a note of caution when using cancer registry data to evaluate adjuvant treatments. *Ann Surg Oncol* 2007; **14**: 3321-3327 [PMID: 17899285 DOI: 10.1245/s10434-007-9576-4]

7 **Chen G**, Wang Z, Liu XY, Zhang MY, Liu FY. Clinical study of modified Ivor-Lewis esophagectomy plus adjuvant radiotherapy for local control of stage IIA squamous cell carcinoma in the mid-thoracic esophagus. *Eur J Cardiothorac Surg* 2009; **35**: 1-7 [PMID: 18926712 DOI: 10.1016/j.ejcts.2008.09.002]

8 **Xu Y**, Liu J, Du X, Sun X, Zheng Y, Chen J, Li B, Liu W, Jiang H, Mao W. Prognostic impact of postoperative radiation in patients undergoing radical esophagectomy for pathologic lymph node positive esophageal cancer. *Radiat Oncol* 2013; **8**: 116 [PMID: 23656920 DOI: 10.1186/1748-717X-8-116]

9 **Chen J**, Zhu J, Pan J, Zhu K, Zheng X, Chen M, Wang J, Liao Z. Postoperative radiotherapy improved survival of poor prognostic squamous cell carcinoma esophagus. *Ann Thorac Surg* 2010; **90**: 435-442 [PMID: 20667325 DOI: 10.1016/j.athoracsur.2010.04.002]

10 **Mariette C**, Balon JM, Piessen G, Fabre S, Van Seuningen I, Triboulet JP. Pattern of recurrence following complete resection of esophageal carcinoma and factors predictive of recurrent disease. *Cancer* 2003; **97**: 1616-1623 [PMID: 12655517 DOI: 10.1002/cncr.11228]

11 **Liu J**, Cai X, Liu Q, Li H, Cheng Y, Fu X. Characteristics of the local recurrence pattern after curative resection and values in target region delineation in postoperative radiotherapy for lower thoracic esophageal squamous cell cancer. *Thorac Cancer* 2017; **8**: 630-633 [PMID: 28941320 DOI: 10.1111/1759-7714.12499]

12 **Liu Q**, Cai XW, Wu B, Zhu ZF, Chen HQ, Fu XL. Patterns of failure after radical surgery among patients with thoracic esophageal squamous cell carcinoma: implications for the clinical target volume design of postoperative radiotherapy. *PLoS One* 2014; **9**: e97225 [PMID: 24820177 DOI: 10.1371/journal.pone.0097225]

13 **Cai WJ**, Xin PL. Pattern of relapse in surgical treated patients with thoracic esophageal squamous cell carcinoma and its possible impact on target delineation for postoperative radiotherapy. *Radiother Oncol* 2010; **96**: 104-107 [PMID: 20605246 DOI: 10.1016/j.radonc.2010.04.029]

14 **Cai XW**, Zeng Y, Feng W, Liu MN, Yu W, Zhang Q, Liu J, Wang JM, Lv CX, Fu XL. Randomized phase II trial comparing tumor bed alone with tumor bed and elective nodal postoperative radiotherapy in patients with locoregionally advanced thoracic esophageal squamous cell carcinoma. *Dis Esophagus* 2019; [PMID: 30855089 DOI: 10.1093/dote/doz013]

15 **Xiao ZF**, Yang ZY, Liang J, Miao YJ, Wang M, Yin WB, Gu XZ, Zhang DC, Zhang RG, Wang LJ. Value of radiotherapy after radical surgery for esophageal carcinoma: a report of 495 patients. *Ann Thorac Surg* 2003; **75**: 331-336 [PMID: 12607634 DOI: 10.1016/S0003-4975(02)04401-6]

16 **Hsu PK**, Huang CS, Wang BY, Wu YC, Hsu WH. Survival benefits of postoperative chemoradiation for lymph node-positive esophageal squamous cell carcinoma. *Ann Thorac Surg* 2014; **97**: 1734-1741 [PMID: 24612702 DOI: 10.1016/j.athoracsur.2013.12.041]

17 **Chen J**, Pan J, Zheng X, Zhu K, Li J, Chen M, Wang J, Liao Z. Number and location of positive nodes, postoperative radiotherapy, and survival after esophagectomy with three-field lymph node dissection for thoracic esophageal squamous cell carcinoma. *Int J Radiat Oncol Biol Phys* 2012; **82**: 475-482 [PMID: 20934269 DOI: 10.1016/j.ijrobp.2010.08.037]

18 **Schreiber D**, Rineer J, Vongtama D, Wortham A, Han P, Schwartz D, Choi K, Rotman M. Impact of postoperative radiation after esophagectomy for esophageal cancer. *J Thorac Oncol* 2010; **5**: 244-250 [PMID: 20009774 DOI: 10.1097/JTO.0b013e3181c5e34f]

19 **Yang J**, Zhang W, Xiao Z, Wang Q, Zhou Z, Zhang H, Chen D, Feng Q, He J, Gao S, Sun K, Liu X, Fang D, Mu J, Wang D, Li Y. The Impact of Postoperative Conformal Radiotherapy after Radical Surgery on Survival and Recurrence in Pathologic T3N0M0 Esophageal Carcinoma: A Propensity Score-Matched Analysis. *J Thorac Oncol* 2017; **12**: 1143-1151 [PMID: 28411098 DOI: 10.1016/j.jtho.2017.03.024]

20 **Wang X**, Luo Y, Li M, Yan H, Sun M, Fan T. Recurrence pattern of squamous cell carcinoma in the midthoracic esophagus: implications for the clinical target volume design of postoperative radiotherapy. *Onco Targets Ther* 2016; **9**: 6021-6027 [PMID: 27785048 DOI: 10.2147/OTT.S116348]

21 **Zhang W**, Liu X, Xiao Z, Zhang H, Chen D, Feng Q, Zhou Z, Lv J, Liang J, Hui Z, Wang L, Yin W, Cheng G, Sun K, Liu X, Fang D, He J. Postoperative intensity-modulated radiotherapy improved survival in lymph node-positive or stage III thoracic esophageal squamous cell carcinoma. *Oncol Res Treat* 2015; **38**: 97-102 [PMID: 25792080 DOI: 10.1159/000375391]

22 **Cai XW**, Yu WW, Yu W, Zhang Q, Feng W, Liu MN, Sun MH, Xiang JQ, Zhang YW, Fu XL. Tissue-based quantitative proteomics to screen and identify the potential biomarkers for early recurrence/metastasis of esophageal squamous cell carcinoma. *Cancer Med* 2018; **7**: 2504-2517 [PMID: 29683265 DOI: 10.1002/cam4.1463]

23 **Qin RQ**, Wen YS, Wang WP, Xi KX, Yu XY, Zhang LJ. The role of postoperative adjuvant chemotherapy for lymph node-positive esophageal squamous cell carcinoma: a propensity score matching analysis. *Med Oncol* 2016; **33**: 31 [PMID: 26922662 DOI: 10.1007/s12032-016-0746-8]

24 **Zou B**, Pang J, Liu Y, Xu Y, Li L, Zhou L, Zhu J, Huang M, Wang J, Ren L, Gong Y, Lu Y, Chen L, Peng F. Postoperative chemoradiotherapy improves survival in patients with stage II-III esophageal squamous cell carcinoma: An analysis of clinical outcomes. *Thorac Cancer* 2016; **7**: 515-521 [PMID: 27766781 DOI: 10.1111/1759-7714.12355]

25 **Wong RK**, Malthaner R. Withdrawn. Combined chemotherapy and radiotherapy (without surgery) compared with radiotherapy alone in localized carcinoma of the esophagus. *Cochrane Database Syst Rev* 2010; CD002092 [PMID: 20091530 DOI: 10.1002/14651858.CD002092.pub3]

**P-Reviewer:** Tarnawski as **S-Editor:** Zhang L **L-Editor:** **E-Editor:**

**Specialty type:** Oncology

**Country of origin:** China

**Peer-review report classification**

Grade A (Excellent): 0

Grade B (Very good): 0

Grade C (Good): C

Grade D (Fair): 0

Grade E (Poor): 0



**Figure 1 Patient selection flow chart.**ESCC: Esophageal squamous cell carcinoma; PORT: Post-operative radiotherapy.



**Figure 2 Details of the failure patterns for the two arms.** Vertical -Y axis represents number of patients. The highest regions for locoregional recurrence were the supraclavicular and mediastinal lymph node (29.5% and 48.3%, respectively) for the surgery cohort. For the S + R arm, supraclavicular lymph node recurrence (9 of 17 patients) was the highest relapse region after post-operative radiotherapy.



**Figure 3 Disease-free survival (174 *vs* 56) of patients in the two arms who were T3-4 with failure occurred.** Vertical -Y axis represents disease-free survival (DFS) rate. The median DFS of the S and S + R arm were 8.0 and 12.7 mo, respectively.



**Figure 4 Univariate analysis: Vertical -Y axis represents disease-free survival rate.** Patients with fewer than 2 lymph nodes involvement could achieve a better disease-free survival in stage T3-4 patients with failure.

**Table 1 Clinical and pathological characteristics of patients for the two arms, *n* (%)**

|  |  |  |  |
| --- | --- | --- | --- |
| **Variables** | **S arm *(n* = 174)** | **S + R arm *(n* = 56)** | ***p* value** |
| Sex |  |  | 0.656 |
| Male | 159 (91.4) | 49 (87.5) |  |
| Female | 15 (8.6) | 7 (12.5) |  |
| Age |  |  | 0.056 |
| < 60 | 106 (60.9) | 42 (75.0) |  |
| ≥ 60 | 68 (39.1) | 14 (25.0) |  |
| Pathological differentiation |  |  | 0.586 |
| Poorly | 66 (37.5) | 1 (1.8) |  |
| Moderately | 97 (55.7) | 33 (58.9) |  |
| Well | 10 (5.7) | 22 (39.3) |  |
| Tumor location |  |  | 0.031a |
| Upper | 15 (8.6) | 3 (5.4) |  |
| Middle | 98 (56.3) | 22 (39.3) |  |
| Lower | 61 (35.1) | 31 (55.4) |  |
| Lymph node dissection |  |  | 0.448 |
| 2-field resection | 139 (79.9) | 49 (87.5) |  |
| 3-field resection | 28 (16.1) | 7 (12.5) |  |
| LN involved |  |  | 0.740 |
| ≤ 2 | 113 (64.9) | 35 (62.5) |  |
| ≥ 3 | 61 (35.1) | 21 (37.5) |  |
| No. of LN dissection |  |  | 0.569 |
| < 12 | 2 (1.1) | 1 (1.8) |  |
| ≥ 12 | 172 (98.9) | 55 (98.2) |  |
| T stage |  |  | 0.075 |
| T3 | 164 (94.3) | 48 (85.7) |  |
| T4 | 10 (5.7) | 8 (14.3) |  |
| Chemotherapy |  |  | 0.978 |
| Yes | 106 (60.9) | 34 (60.7) |  |
| No | 68 (39.1) | 22 (39.3) |  |

a*p* < 0.05. S arm: Surgery alone arm; S + R arm: Surgery + post-operative radiotherapy arm; LN: Lymph node.

**Table 2 Comparison for the two arms, *n* (%)**

|  |  |  |  |
| --- | --- | --- | --- |
| **Type of failure** | **S arm *(n* = 174)** | **S + R arm *(n* = 56)** | ***p* value** |
| **Comparison of patterns of failure for the two arms** |  |  | < 0.001 |
| Distant metastasis | 14 (8.0) | 36 (64.3) |  |
| Locoregional recurrence | 141 (81.0) | 14 (25.0) |  |
| Mixed failure | 19 (11.0) | 6 (10.7) |  |
| **Comparison of distant metastasis for two arms** |  |  | < 0.001 |
| Distant metastasis | 33 (19.0) | 42 (75.0) |  |
| Others | 141 (81.0) | 14 (25.0) |  |
| **Comparison of locoregional failure for two arms** |  |  | < 0.001 |
| Locoregional recurrence | 160 (92.0) | 20 (78.3) |  |
| Others | 14 (8.0) | 36 (21.7) |  |

S arm: Surgery alone arm; S + R arm: Surgery+ post-operative radiotherapy arm; LN: Lymph node.

**Table 3 Univariate and multivariate analyses for patients with stage pT3-4**

|  |  |  |
| --- | --- | --- |
|  | **Univariate analysis** | **Multivariate analysis** |
| **Median DFS (mo)** | ***χ*2 value** | ***P* value** | **HR (95%CI)** | ***P* value** |
| Sex |  |  |  | 0.841 (0.532-1.328) | 0.457 |
| Male | 9.5 | 0.309 | 0.579 |  |  |
| Female | 8 |  |  |  |  |
| Age (yr) |  |  |  | 0.712 (0.530-0.957) | 0.024 |
| < 60 | 9 | 1.023 | 0.312 |  |  |
| ≥ 60 | 9.5 |  |  |  |  |
| Pathological differentiation |  |  |  | 1.128 (0.094-1.934) | 0.071 |
| Poorly | 8 | 6.377 | 0.095 |  |  |
| Moderately | 10.4 |  |  |  |  |
| Well | 9.5 |  |  |  |  |
| Tumor location |  |  |  | 1.423 (0.849-2.386) | 0.363 |
| Upper | 6.6 | 3.277 | 0.194 |  |  |
| Middle | 9.9 |  |  |  |  |
| Lower | 8.8 |  |  |  |  |
| Lymph node dissection |  |  |  | 0.531 (0.222-1.186) | 0.107 |
| 2-Field resection | 9 | 3.462 | 0.177 |  |  |
| 3-Field resection | 8 |  |  |  |  |
| LN involved |  |  |  | 1.843 (1.369-2.482) | < 0.001 |
| ≤ 2 | 11 | 13.483 | < 0.001a |  |  |
| ≥ 3 | 8 |  |  |  |  |
| No. of LN dissection |  |  |  | 1.460 (0.459-4.644) | 0.522 |
| < 12 | 7 | 0.656 | 0.418 |  |  |
| ≥ 12 | 9.5 |  |  |  |  |
| Chemotherapy |  |  |  | 0.732 (0.552-0.971) | 0.031 |
| Yes | 8 | 1.769 | 0.183 |  |  |
| No | 10 |  |  |  |  |
| T stage |  |  |  | 0.697 (0.441-1.124) | 0.132 |
| T3 | 9 | 0.087 | 0.767 |  |  |
| T4 | 8 |  |  |  |  |
| Radiotherapy | - | - | - | 0.667 (0.487-0.915) | 0.012a |

a*p* < 0.05. S arm: Surgery alone arm; S + R arm: Surgery + postoperative radiotherapy arm; LN: Lymph node.