Aggressive surgical resection does not improve survival in operable esophageal squamous cell carcinoma with N2-3 status

Yu-Zhen Zheng, Wei Zhao, Yi Hu, Xiao-Xiao Ding-Lin, Jing Wen, Hong Yang, Qian-Wen Liu, Kong-Jia Luo, Qing-Yuan Huang, Jun-Ying Chen, Jian-Hua Fu

Yu-Zhen Zheng, Yi Hu, Hong Yang, Qian-Wen Liu, Kong-Jia Luo, Qing-Yuan Huang, Jun-Ying Chen, Jian-Hua Fu, Department of Thoracic Oncology, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangzhou 510060, Guangdong Province, China

Wei Zhao, Department of Medical Oncology, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangzhou 510060, Guangdong Province, China

Xiao-Xiao Ding-Lin, Department of Oncology, Sun Yat-sen Memorial Hospital, Guangzhou 510060, Guangdong Province, China

Jing Wen, Department of Experimental Research, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangzhou 510060, Guangdong Province, China

Yu-Zhen Zheng, Yi Hu, Jing Wen, Hong Yang, Qian-Wen Liu, Kong-Jia Luo, Qing-Yuan Huang, Jun-Ying Chen, Jian-Hua Fu, Guangdong Esophageal Cancer Institute, Guangzhou 510060, Guangdong Province, China

Author contributions: Zheng YZ and Zhao W contributed equally to this study; Fu JH conceived of and designed the experiments; Zheng YZ and Zhao W performed the experiments; Hu Y, Ding-Lin XX, Wen J, and Yang H analyzed the data; Liu QW, Luo KJ, Huang QY, and Chen JY contributed reagents/materials/analysis tools; and Zhao YZ wrote the paper.

Supported by: Chinese Ministry of Health Key Program, No. 179 and National Natural Science Foundation of China General Program, No. 81272635.

Institutional review board statement: The study was reviewed and approved by the Medical Ethics Committee of Sun Yat-sen University Cancer Center Institutional Review Board.

Informed consent statement: Informed written consent was obtained from all patients.

Conflict-of-interest statement: The authors have declared that no competing interests exist.

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at fujh_sysucc@163.com. Participants gave informed consent for data sharing.

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/

Correspondence to: Jian-Hua Fu, Professor, Department of Thoracic Oncology, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, No. 651, Dongfeng East Road, Guangzhou 510060, Guangzhou province, China. fujh_sysucc@163.com

Telephone: +86-20-87343258
Fax: +86-20-87343268

Received: February 27, 2015
Peer-review started: February 28, 2015
First decision: March 26, 2015
Revised: April 1, 2015
Accepted: May 2, 2015
Article in press: May 4, 2015
Published online: July 28, 2015
Abstract

AIM: To investigate the influence of nodal status on response and clarify the optimal treatment for operable esophageal squamous cell carcinoma (OSCC).

METHODS: We retrospectively analyzed 1490 OSCC patients who underwent transthoracic esophagectomy and lymphadenectomy between December 1996 and December 2009 at the Sun Yat-sen University Cancer Center. The surgical approach and the number of resected lymph nodes (LNs) were considered in the assessment of surgery. Patients were classified according to their nodal statuses (N0 vs N1 vs N2-3). Overall survival was defined as the time from the date of death or final follow-up. Survival analysis was performed using the Kaplan-Meier method and differences between curves were assessed by the log-rank test. Univariate and multivariate Cox regression analyses were used to identify factors associated with prognosis. Statistical significance was assumed at a P < 0.05.

RESULTS: With a median time from surgery to the last censoring date for the entire cohort of 72.2 mo, a total of 631 patients were still alive at the last follow-up and the median survival time was 35.5 mo. The surgical approach (left transthoracic vs Ivor-Lewis/tri-incisional) was verified as independent prognostic significance in patients with N0 or N1 status, but not in those with N2-3 status. Similar results were also observed with the number of resected LNs ($\leq 14$ vs $\geq 15$). Compared with surgery alone, combined therapy achieved better outcomes in patients with N1 or N2-3 status, but not in those with N0 status. For those with N2-3 status, neither the surgical approach nor the number of resected LNs reached significance by univariate analysis, with unadjusted HRs of 0.826 (95%CI: 0.644-1.058) and 0.849 (95%CI: 0.668-1.078), respectively, and aggressiveness of surgery did not influence the outcome; the longest survival was observed in those patients who received the combined therapy.

CONCLUSION: Combined therapy has a positive role in OSCC with LN metastasis, and aggressive surgical resection does not improve survival in patients with N2-3 status.

Key words: Esophageal neoplasm; Lymph nodes; Prognosis; Surgery

© The Author(s) 2015. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Esophageal cancer is one of the most fatal malignant cancers worldwide, and survival is still unsatisfactory for locally advanced subjects. Until now, the optimal multimodality therapy has not yet been established. The assessment of nodal status might facilitate the selection of the most effective treatment for operable esophageal squamous cell carcinoma (OSCC). We retrospectively analyzed 1490 OSCC patients classified according to their nodal statuses (N0 vs N1 vs N2-3). Our results demonstrate the positive role of combined therapy in OSCC with lymph node metastasis, and further suggest that aggressive surgical resection does not improve survival in patients with N2-3 status.

INTRODUCTION

Esophageal cancer is a frequent cause of death worldwide, and the traditional management has always been surgical resection[1-3]. Over the previous decades, great improvements in preoperative examination and surgical technology have led to significantly enhanced long-term survival[1-3]. However, survival is still unsatisfactory for locally advanced esophageal cancer, which has prompted an evaluation of neoadjuvant (preoperative) and adjuvant (postoperative) combined-modality therapy[14-25]. Until now, the optimal multimodality therapy has not yet been established.

Lymph node metastasis (LNM) is one of the worst prognostic factors for localized esophageal cancer. Furthermore, LNM decreases the curative effects of surgery[13,8-11] and enhances the necessity of multimodality treatment[14-20,22]. Therefore, we speculated that the assessment of nodal status might facilitate the selection of the most effective treatment.

In this study, we recruited esophageal squamous cell carcinoma (OSCC) patients who had undergone surgery at a Chinese institution over a 13-year period. The aim of this study was to investigate the influence of nodal status on therapeutic response and attempt to clarify the optimal treatment for operable OSCC.

MATERIALS AND METHODS

Patient selection

This study was approved by the Medical Ethics Committee of Sun Yat-sen University Cancer Center. Informed written consent was obtained from all participants. Patients diagnosed with OSCC who underwent transthoracic esophagectomy and lymphadenectomy at the thoracic surgery department of Sun Yat-sen University Cancer Center from December 1996 to December 2009 were screened for study recruitment. Our institutional electronic medical record system was initiated in December 1996; therefore, this was considered the date after which
Surgical procedure

Surgical approaches applied in this study included left transthoracic, Ivor-Lewis, and tri-incisional procedures, which were mainly selected based on tumor location and preoperative inspection results. For patients with middle/lower thoracic OSCC with no evidence of superior mediastinum metastasis, we generally performed left transthoracic esophagectomies. For patients with middle/lower thoracic OSCC with evidence of superior mediastinum metastasis, we performed Ivor-Lewis/tri-incisional esophagectomies. In patients with upper thoracic OSCC, we only carried out tri-incisional procedures.

Lymphadenectomy extent was influenced by the surgical approach. For left transthoracic esophagectomy, we could not achieve upper mediastinal lymphadenectomy in most cases, and instead performed standard two-field lymphadenectomy, including subcarinal, lower mediastinal, and upper abdominal dissections. However, for Ivor-Lewis or tri-incisional esophagectomies, an additional upper mediastinal dissection was completed in most cases by so-called extended two-field lymphadenectomy. Cervical lymphadenectomy was not routinely carried out.

Adjuvant treatment

Because there were no standard guidelines for the adjuvant treatment of OSCC, treatment options were selected based on tumor stage, the doctor’s opinion, and the patient’s desires. In our hospital, adjuvant treatment was started at 4–6 wk after operation, mostly in patients with LNM. Chemotherapy was typically applied as platinum-based two-drug regimen for 4–6 cycles. Radiotherapy was mainly delivered to the position of the anastomosis, mediastinum, pericardium, and left epiploic lymphatic vessels, at a total dose of 50-60 Gy.

Follow-up

After completion of primary treatment, the patients were asked to participate in outpatient follow-up every 3 mo for the first 2 years, every 6 mo for years 3-5, and every 12 mo thereafter. Regular assessment included physical examination, blood test, endoscopy, chest X-ray, and ultrasound testing. CT scans of the chest, abdomen, and cervical region were performed at least once a year. For those who could not afford regular follow-up visits, a telephone follow-up was performed. Survival status was reclassified using the best available methods in March 2014. The median time from surgery to the last censoring date for the entire cohort was 72.2 mo.

Statistical analysis

Statistical analysis was performed using SPSS 19.0 software package (IBM Corp., Armonk, NY, United States). We defined death as the event and overall...
survival (OS) as the time from the date of surgery to the date of death or final follow-up. Survival analysis was performed using the Kaplan-Meier method and differences between curves were assessed by the log-rank test. Univariate and multivariate Cox regression analyses were used to identify factors associated with prognosis. Statistical significance was assumed at a $P < 0.05$. The statistical methods of this study were reviewed by Yin Guo from Sun Yat-sen University Cancer Center.

### Table 2 Influence of surgical parameters on survival for patients with N0, N1, and N2-3 status

| Factors | Surgical approach | Resected lymph nodes ($n$) |
|---------|------------------|---------------------------|
|         | Left transthoracic | Ivor-Lewis/tri-incisional | ≤ 14 | ≥ 15 |
| In patients with N0 status ($n = 727$) |
| No. at risk | 445 | 282 | 391 | 336 |
| No. of events | 204 | 106 | 215 | 95 |
| aHR (95%CI) | 1 | 0.632 (0.499-0.801) | 1 | 0.478 (0.375-0.609) |
| $P$ value | < 0.001 | < 0.001 |
| In patients with N1 status ($n = 419$) |
| No. at risk | 254 | 165 | 219 | 200 |
| No. of events | 183 | 97 | 174 | 106 |
| aHR (95%CI) | 1 | 0.661 (0.516-0.847) | 1 | 0.464 (0.364-0.592) |
| $P$ value | < 0.001 | < 0.001 |
| In patients with N2-3 status ($n = 344$) |
| No. at risk | 218 | 126 | 154 | 190 |
| No. of events | 170 | 99 | 127 | 142 |
| uHR (95%CI) | 1 | 0.826 (0.644-1.058) | 1 | 0.849 (0.668-1.078) |
| $P$ value | 0.130 | 0.179 |

1Multivariate analysis adjusted for sex (male/female), age ($\leq 58/> 58$ years), tumor location (upper/mid/lower), pathologic T status (T1/T2/T3/T4a), and tumor cell differentiation (well/moderate/poor); 2Univariate analysis. aHR: Adjusted hazard ratio; uHR: Unadjusted hazard ratio.
RESULTS

Patient characteristics
A total of 1490 patients were enrolled as the target population. There were 1150 male and 340 female patients with a median age of 58 years (range: 30-88 years). In this study, 4.1% (61/1490) of the patients were pathologically diagnosed as stage I, 48.6% (724/1490) as stage II, and 47.3% (705/1490) as stage III. The most frequently applied approach was left transthoracic esophagectomy (917/1490; 61.5%), and the median number of resected lymph nodes (LNs) was 14 (range: 1-91). Combined therapy was used for 319 patients, including 194 who received adjuvant chemotherapy, 91 who received adjuvant chemoradiotherapy, and 34 who received adjuvant radiotherapy. The patient characteristics are listed in Table 1.

Influence of nodal status on therapeutic response
A total of 631 patients were still alive at the last follow-up, and the median survival time was 35.5 mo. To investigate the influence of nodal status on therapeutic response, we divided the entire cohort based on their nodal status (N0 vs N1 vs N2-3).

The influence of nodal status on surgery is shown in Table 2. The patients with a status of N0 or N1 who underwent the Ivor-Lewis/tri-incisional procedure presented with significantly better survival compared with those who underwent left transthoracic esophagectomy, with adjusted hazard ratios (HRs) of 0.632 (95%CI: 0.499-0.801) and 0.661 (95%CI: 0.516-0.847), respectively (P < 0.05) (Figure 1). Similar results were also observed for the number of resected LNs (Figure 2). For the patients with an N2-3 status, neither the surgical approach nor the number of resected LNs reached significance by univariate analysis, with unadjusted HRs of 0.826 (95%CI: 0.644-1.058) and 0.849 (95%CI: 0.668-1.078), respectively. The results indicate the poor curative effect of surgery in the patients with an N2-3 status.

The influence of nodal status on combined therapy is shown in Table 3. Compared with surgery alone, the

---

Table 3 Influence of combined therapy on survival for patients with N0, N1, or N2-3 status

| Factors | Surgery alone | Combined therapy |
|---------|--------------|------------------|
| In patients with N0 status (n = 727) | | |
| No. at risk | 644 | 83 |
| No. of events | 275 | 35 |
| uHR (95%CI) | 1 | 0.878 (0.617-1.249) |
| P value<sup>1</sup> | 0.469 | |
| In patients with N1 status (n = 419) | | |
| No. at risk | 313 | 106 |
| No. of events | 217 | 63 |
| aHR (95%CI) | 1 | 0.712 (0.537-0.944) |
| P value<sup>2</sup> | 0.018 | |
| In patients with N2-3 status (n = 344) | | |
| No. at risk | 214 | 130 |
| No. of events | 169 | 100 |
| aHR (95%CI) | 1 | 0.672 (0.521-0.867) |
| P value<sup>3</sup> | 0.002 | |

<sup>1</sup>Univariate analysis; <sup>2</sup>Multivariate analysis adjusted for sex (male/female), age (< 58/> 58 years), tumor location (upper/mid/lower), pathologic T status (T1/T2/T3/T4a), and tumor cell differentiation (well/moderate/poor); <sup>3</sup>Multivariate analysis adjusted for sex, age, tumor location, pathologic T status, nodal status (N2/N3), and tumor cell differentiation.

aHR: Adjusted hazard ratio; uHR: Unadjusted hazard ratio.

---

Figure 2 Overall survival curves stratified by resected lymph nodes for esophageal squamous cell carcinoma patients. A: Patients with N0 status; B: Patients with N1 status; C: Patients with N2-3 status (Log-rank test).
combined therapy did not generate better outcomes in the patients with N0 status (unadjusted HR = 0.878, 95%CI: 0.617-1.249). For those with an N1 or N2-3 status, survival benefits were observed in those who received the combined therapy, with adjusted HRs of 0.712 (95%CI: 0.537-0.944) and 0.672 (95%CI: 0.521-0.867), respectively (Figure 3). These data supported the use of combined therapy to treat OSCC with LNM.
Searching for optimal treatment for patients with N0, N1, and N2-3 statuses

To search for an optimal treatment, extensive surgery was defined as Ivor-Lewis/tri-incisional procedure with resection of $\geq 15$ LNs, and limited surgery as the other procedures assessed. Therefore, patients were classified into four groups based on their therapeutic regimens, including Group A (limited surgery alone), Group B (extensive surgery alone), Group C (limited surgery followed by adjuvant treatment), and Group D (extensive surgery followed by adjuvant treatment). The prognosis of patients with N0 status who underwent surgery alone was comparable to that of the combined therapy, and the longest survival times were observed in Group B and Group D (Figure 4A). The optimal treatment for the patients with N1 status was extensive surgery followed by adjuvant treatment (Group D) (Figure 4B). The outcomes of limited surgery for the patients with an N2-3 status were similar to those of extensive surgery, and the best curative effects were observed in Group C and Group D (Figure 4C).

DISCUSSION

In this study, we investigated the influence of nodal status on therapeutic responses to different treatments for operable OSCC. Based on the results, adopting combined therapy improved the outcomes of the nodal-positive patients, except for those with N0 status. Furthermore, aggressive surgical resection did not improve survival in patients with an N2-3 status.

Surgical resection has long been applied as a mainstay treatment for esophageal cancer[6,26,27]. Previous studies have shown that performing aggressive surgical resection is very important to achieving long-term survival[1,4,5,10,11]. However, recent studies have indicated that the curative effects of surgical resection might be invalid for patients with multiple LNs. For instance, Tabire et al[9] concluded that the five-year survival rate for patients with $\geq 5$ LNs is merely 9.1% even after McKeown esophagectomy and three-field lymphadenectomy, which is in accordance with Mariette et al[13]. Likewise, Nishimaki et al[9] investigated the outcomes of extended radical esophagectomy in 190 patients and observed that no patients with $\geq 5$ LNs survive beyond five years. Thus, in this study, we first grouped the nodal status according to LNM number (0 vs 1-2 vs 3-4 vs 5-6 vs $\geq 7$). We found that the positive effect of aggressive surgery on survival is insignificant in patients with 3-4, 5-6, and $\geq 7$ LNs (data not shown), which led us to adopt our current grouping program (N0 vs N1 vs N2-3). Our finding indicated that prognosis could not be improved in patients with an N2-3 status solely by performing more aggressive surgery.

In recent years, there have been many research studies performed in search of an effective multidisciplinary treatment for esophageal cancer[14,15,17-22,24,25,28-30]. In this study, we observed that combined therapy generated better outcomes only in nodal-positive patients compared with surgery alone, which is quite similar with previous studies[14-17]. For example, Ando et al[14] enrolled 242 patients with localized OSCC and found that adjuvant chemotherapy prevents recurrence in patients with LNM, which was further supported by additional studies[15,17]. Further, Lyu et al[16] supported the positive role of adjuvant chemotherapy in enhancing long-term survival in OSCC with LNM.

Recent studies have also reported that neoadjuvant chemoradiotherapy is associated with better outcomes than surgery alone for esophageal cancer, especially in patients with LNM[18-20,22,25,28-30]. Additionally, in the final analysis of the randomized controlled phase III trial FFCD 9901, Mariette et al[21] negated the value of neoadjuvant chemoradiotherapy for stage I or II esophageal cancer. Notably, most of these patients were clinically staged with an N0 status (74.2%). Recently, Okumura et al[22] found that neoadjuvant chemoradiotherapy improves the outcomes of patients with $\geq 4$ LNs, similar to those with 1-3 LNs treated with surgery alone. Thus, we also support the positive role of neoadjuvant treatment for esophageal cancer with LNM. However, because we did not include patients who underwent neoadjuvant treatment, our results are inconclusive in this regard.

Based on our results, we recommend intraoperative frozen sectioning of suspicious LNs and oppose excessively aggressive surgery for patients with $\geq 3$ LNM (at least N2 status), because conservative surgical procedure would decrease perioperative morbidity[12]. In addition, the pathologic stage of OSCC with $\geq 3$ LNM is at least IIIA according to the 7th American Joint Committee on Cancer staging system[24], supporting the use of multimodality treatment suggested by our study and previous investigations[14-17]. Although a more aggressive lymphadenectomy might facilitate the acquisition of more accurate staging information in theory[31-34], it would not alter the treatment choice. Furthermore, long-term survival did not differ between the limited dissection and aggressive lymphadenectomy groups in this study.

These finding should be considered in the context of certain weaknesses in our study design. First, the study is retrospective in nature. Second, heterogeneities, including those associated with the basic characteristics of patients or the determination of treatment, were unavoidable due to the long study period, though we conducted subgroup and multivariate analyses to minimize these confounders. However, we believe it is this nonselective and nonmatching population that results in a more generalized significance of this study. Third, because patients who received neoadjuvant treatment were not investigated, further studies are critical to validate our results.
The results presented here indicate the positive role of combined therapy in OSCC with LNM and further suggest that aggressive surgical resection does not improve survival in patients with an N2-3 status.

COMMENTS

Background
Esophageal cancer is a frequent cause of death worldwide, and the traditional management has always been surgical resection. In previous decades, great improvements in preoperative examination and surgical technology have led to significantly enhanced long-term survival. However, survival is still unsatisfactory for locally advanced esophageal cancer, which has prompted an evaluation of neoadjuvant (preoperative) and adjuvant (postoperative) combined-modality therapy. Until now, the optimal multimodality therapy has not yet been established.

Research frontiers
Lymph node metastasis (LNM) is one of the worst prognostic factors for localized esophageal cancer. Furthermore, LNM decreases the curative effects of surgery and enhances the necessity of multimodality treatment. Therefore, we speculated that the assessment of nodal status might facilitate the selection of the most effective treatment.

Innovations and breakthroughs
With a median follow-up time of 72.2 mo, a total of 1490 patients were analyzed for survival and the median survival time was 35.5 mo. The surgical approach (left transthoracic or Ivor-Lewis/tri-incisional) was verified as independent prognostic significance in patients with an N0 or N1 status, but not in those with an N2-3 status. Similar results were also observed with the number of resected LNs (≤14 vs ≥15). Compared with surgery alone, combined therapy achieved better outcomes in patients with N1 or N2-3 status, but not in those with an N0 status. For those with N2-3 status, neither the surgical approaches nor the number of resected LNs was significant, and aggressiveness of surgery did not influence the outcome; the longest survival was observed in those patients who received the combined therapy.

Applications
Our results demonstrate the positive role of combined therapy in esophageal squamous cell carcinoma with LNM, and that aggressive surgical resection does not improve survival in patients with an N2-3 status.

Peer-review
This retrospective study with a large cohort of patients with esophageal squamous cell carcinoma (n = 1490) contributes to the existing literature regarding surgical therapy of esophageal cancer. It adds relevant data and concludes that aggressive surgery is not justified at an advanced tumor stage. The limitations of this study are clear and declared by the authors. The aspect of a neoadjuvant therapy is not included but discussed and answered in other studies.

REFERENCES

1. Altorki N, Kent M, Ferrara C, Port J. Three-field lymph node dissection for squamous cell and adenocarcinoma of the esophagus. Ann Surg 2002; 236: 177-183 [PMID: 12170022 DOI: 10.1097/01.SLA.0000021583.51164.F4]
2. Natsugoe S, Yoshinaka H, Shimada M, Sakamoto F, Morinaga T, Nakano S, Kusano C, Baba M, Takao S, Akiou T. Number of lymph node metastases determined by presurgical ultrasound and endoscopic ultrasound is related to prognosis in patients with esophageal carcinoma. Ann Surg 2001; 234: 613-618 [PMID: 11685023 DOI: 10.1097/00000658-200110000-00005]
3. Ma GW, Situ DR, Ma QL, Long H, Zhang LJ, Lin P, Rong TH. Three-field vs two-field lymph node dissection for esophageal cancer: a meta-analysis. World J Gastroenterol 2014; 20: 18022-18030 [PMID: 25248502 DOI: 10.3748/wjg.v20.i47.18022]
4. Altorki NK, Zhou XK, Stiles B, Port JL, Paul S, Lee PC, Mazumdar M. Total number of resected lymph nodes predicts survival in esophageal cancer. Ann Surg 2008; 248: 221-226 [PMID: 18650631 DOI: 10.1097/SLA.0b013e31817be5e9]
5. Greenstein AJ, Little VV, Swanson SJ, Divino CM, Packer S, Wisnivesky JP. Effect of the number of lymph nodes sampled on postoperative survival of lymph node-negative esophageal cancer. Cancer 2008; 112: 1239-1246 [PMID: 18224663 DOI: 10.1002/cncr.23309]
6. Tabira Y, Yasunaga M, Tanaka M, Nakano K, Sakaguchi T, Nagamoto N, Ogi S, Kitamura N. Recurrent nerve nodal involvement is associated with cervical nodal metastasis in thoracic esophageal carcinoma. J Am Coll Surg 2000; 191: 232-237 [PMID: 10989896]
7. Ando N, Ozawa S, Kitagawa Y, Shinozawa Y, Kitajima M. Improvement in the results of advanced treatment of advanced squamous esophageal carcinoma during 15 consecutive years. Ann Surg 2000; 232: 225-232 [PMID: 10903602 DOI: 10.1097/00000658-200008000-00013]
8. Müller JM, Erasmis M, Stelzner M, Zieren U, Pichlmaier H. Surgical therapy of esophageal cancer. Br J Surg 1990; 77: 845-857 [PMID: 2203505 DOI: 10.1002/bs.1800770804]
9. Nishimaki T, Suzuki T, Suzuki S, Kuwabara S, Hatakeyama K. Outcomes of extended radical esophagectomy for thoracic esophageal cancer. J Am Coll Surg 1998; 186: 306-312 [PMID: 9510261]
10. Huberch JB, van Sandick JW, de Boer AG, Wijnhoven BP, Tijssen JG, Fockens P, Stamenie PF, van Katho DJ, van Deenck H, Obertop H, Tilanus HW, van Lanschot JJ. Extended transthoracic resection compared with limited transternal resection for adenocarcinoma of the esophagus. N Engl J Med 2002; 347: 1662-1669 [PMID: 12444180 DOI: 10.1056/NEJMoa022343]
11. Lenit T, Nafteux P, Moonis J, Coosman W, Decker G, De Leys P, Van Raemdonck D, Giudicelli R, Fuentes PA, Thomas PA. Transthoracic esophagectomy for adenocarcinoma of the esophagus: standard versus extended two-field mediastinal lymphadenectomy? Eur J Cardiothorac Surg 2005; 27: 697-704 [PMID: 15784377 DOI: 10.1016/j.ejcts.2004.12.022]
12. D’Journo XB, Dedolli C, Mischelet P, Loundou A, Trousse D, Giudicelli C, Ruentes PA, Thomas PA. Transthoracic esophageectomy for adenocarcinoma of the esophagus: standard versus extended two-field mediastinal lymphadenectomy? Eur J Cardiothorac Surg 2005; 27: 697-704 [PMID: 15784377 DOI: 10.1016/j.ejcts.2004.12.022]
13. Mariette C, Piessen G, Briez N, Triboulet JP. The number of metastatic lymph nodes and the ratio between metastatic and examined lymph nodes are independent prognostic factors in esophageal cancer regardless of neoadjuvant chemoradiation or lymphadenectomy extent. Ann Surg 2008; 247: 365-371 [PMID: 18216546 DOI: 10.1097/SLA.0b013e31815aaad00000658-200800000-00024]
14. Ando N, Iizuka T, Ide H, Ishida K, Shinoda M, Nishimaki T, Kiyatani W, Watanabe H, Isokon K, Aoyama N, Makushki H, Tanaka O, Yamana H, Ikeuchi S, Kabuto T, Nagai K, Shimada Y, Kinjo Y, Fukuda H. Surgery plus chemotherapy compared with surgery alone for localized squamous cell carcinoma of the esophagus: standard versus extended two-field mediastinal lymphadenectomy? Eur J Cancer 2008; 44: 365-371 [PMID: 18216546 DOI: 10.1097/SLA.0b013e31815aaad00000658-200800000-00024]
15. Zhang SS, Yang H, Xie X, Luo KJ, Wen J, Bella AE, Hu Y, Yang F, Fu JH. Adjuvant chemotherapy versus surgery alone for esophageal squamous cell carcinoma: a meta-analysis of randomized controlled trials and nonrandomized studies. Dis Esophagus 2014; 27: 574-584 [PMID: 23621199 DOI: 10.1111/dote.12073]
16. Lu X, Huang J, Mao Y, Liu Y, Feng Q, Shao K, Gao S, Jiang Y, Wang J, He J. Adjuvant chemotherapy after esophagectomy: is there a role in the treatment of the lymph node positive thoracic esophageal squamous cell carcinoma? J Surg Oncol 2014; 110: 864-868 [PMID: 24976079 DOI: 10.1002/jso.23716]
17 Lee J, Lee KE, Im YH, Kang WK, Park K, Kim K, Shim YM. Adjuvant chemotherapy with 5-fluorouracil and cisplatin in lymph node-positive thoracic esophageal squamous cell carcinoma. *Ann Thorac Surg* 2005; **80**: 1170-1175 [PMID: 16181835 DOI: 10.1016/j.athoracsur.2005.03.058]

18 van Hagen P, Hulshof MC, van Lanschot JJ, Steyerberg EW, van Berge Henegouwen MJ, Wijnhoven BP, Michel DJ, Nieuwenhuijzen GA, Hospers GA, Bonenkamp JJ, Cuesta MA, Blaesse RJ, Busch OR, ten Kate FJ, Creemers GJ, Punt CJ, Plukker JT, Verheul HM, Spilleran Bilgen EJ, van Dekken H, van der Sangen MJ, Rozema T, Biermann K, Beukema JC, Piet AH, van Rij CM, Reinders JG, Tilanus HW, van der Gaast A. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med* 2012; **366**: 2074-2084 [PMID: 22646630 DOI: 10.1056/NEJMoa112088]

19 Allum WH, Stenning SP, Bancewicz J, Clark PI, Langley OR, ten Kate FJ, Mabrut JY, Triboulet JP, Bedenne L, Seitz JF. Surgery alone versus 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]

20 Berger AC, Farma J, Scott WJ, Freedman G, Weiner L, Cheng JD, Wang H, Goldberg M. Complete response to neoadjuvant chemoradiation therapy in esophageal carcinoma is associated with significantly improved survival. *J Clin Oncol* 2005; **23**: 4330-4337 [PMID: 15781882 DOI: 10.1200/JCO.2005.05.017]

21 Mariette C, Dahan L, Mornex F, Maillard E, Thomas PA, Meunier B, Boige V, Pezet D, Robb WB, Le Brun-Ly V, Bosset JF, Mabrut JY, Triboulet JP, Bedenne L, Seitz JF. Surgery alone versus chemoradiation followed by surgery for stage I and II esophageal cancer: final analysis of randomized controlled phase III trial [FRCCD 9901]. *J Clin Oncol* 2014; **32**: 2416-2422 [PMID: 24982463 DOI: 10.1200/JCO.2013.53.6532]

22 Urba SG, Orringer MB, Turrisi A, Iannettoni M, Forastiere A, Strawderman M. Randomized trial of preoperative chemoradiation versus surgery alone in patients with locoregional esophageal carcinoma. *J Clin Oncol* 2001; **19**: 305-313 [PMID: 11208820]

23 Okumura H, Uchikado Y, Omoto I, Kita Y, Sasaki K, Arigami T, Uenosono Y, Matsushita D, Hiraki Y, Owaki T, Ishigami S, Natsugoe S. The usefulness of neoadjuvant chemoradiation therapy for locally advanced esophageal cancer with multiple lymph-node metastases. *Ann Surg Oncol* 2014; **21**: 2845-2849 [PMID: 24728820 DOI: 10.1245/s10434-014-3688-4]

24 Liu HC, Hung SK, Huang CJ, Chen CC, Chen MJ, Chang CC, Tai CJ, Tzen CY, Lu LH, Chen YJ. Esophagectomy for locally advanced esophageal cancer, followed by chemosurgery and adjuvant chemotherapy. *World J Gastroenterol* 2005; **11**: 5367-5372 [PMID: 16149148]

25 Jin HL, Zhu H, Ling TS, Zhang HJ, Shi RH. Neoadjuvant chemoradiotherapy for resectable esophageal carcinoma: a meta-analysis. *World J Gastroenterol* 2009; **15**: 5983-5991 [PMID: 20014464 DOI: 10.3748/wjg.v15.i9.5983]

26 Edge S, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A. American joint committee on cancer (AJCC) cancer staging manual.7th ed. Chicago: Springer 2010: 67-72

27 Hofstetter W, Swisher SG, Correa AM, Hess K, Putnam JB, Ajani JA, Dolormente M, Francisco R, Komaki RR, Lara A, Martin F, Rice DC, Sarabia AJ, Smythe WR, Vapourcyian AA, Walsh GL, Roth JA. Treatment outcomes of resected esophageal cancer. *Ann Surg 2002*; **236**: 376-84; discussion 384-5 [PMID: 12192324 DOI: 10.1097/01.sla.0000027925.23604.5c]

28 Schena M, La Rovere E, Solerio D, Bustreo S, Barone C, Daniele L, Buffoni L, Birronzo P, Sapino A, Gasparri G, Ciaffreda L, Ricardi U. Neoadjuvant chemo-radiotherapy for locally advanced esophageal cancer: a monocentric study. *Tumori* 2012; **98**: 451-457 [PMID: 23502516 DOI: 10.1700/1146.12639]

29 Makino T, Miyata H, Masamaki M, Fujiiwara Y, Takiguchi S, Nakajima K, Higuichi I, Hatazawa J, Mori M, Doki Y. Utility of response evaluation to neo-adjuvant chemotherapy by (18)F-fluorodeoxyglucose-positron emission tomography in locally advanced esophageal squamous cell carcinoma. *Surgery 2010*; **148**: 908-916 [PMID: 20738140 DOI: 10.1016/j.surg.2010.02.016]

30 Greer SE, Goodney PP, Sutton JE, Birkmeyer JD. Neoadjuvant chemoradiotherapy for esophageal carcinoma: a meta-analysis. *Surgery 2005*; **137**: 172-177 [PMID: 15674197 DOI: 10.1016/j.surg.2004.06.033]

31 Groth SS, Vimga BA, Whitson BA, DeFor TE, Li ZZ, Tuttle TM, Maddaus MA. Determination of the minimum number of lymph nodes sampled for definitive treatment outcomes of resected esophageal cancer: data from the Surveillance Epidemiology and End Results database. *J Thorac Cardiovasc Surg* 2010; **139**: 612-620 [PMID: 1970965 DOI: 10.1016/j.jtcvs.2009.07.017]

32 Kawahara K, Maekawa T, Okabayashi K, Shiraishi T, Yoshinaga Y, Yoneda S, Hideshima T, Shirakusa T. The number of lymph node metastases influences survival in esophageal cancer. *J Surg Oncol* 1998; **67**: 160-163 [PMID: 9530885 DOI: 10.1002/(SICI)1096-909X(19980306)67:2<160::AID-SUA9>3.0.CO;2-9]

33 Chao YK, Liu HP, Hsieh MJ, Wu YC, Liu YH, Yeh CH, Chang HK, Tseng CK. Impact of the number of lymph node metastases on outcome in ypT0N0 esophageal squamous cell carcinoma patients. *J Surg Oncol 2012*; **106**: 436-440 [PMID: 22566367 DOI: 10.1002/jso.23103]

34 Zhang HL, Chen LQ, Liu RL, Shi YT, He M, Meng XL, Bai SX, Ping YM. The number of lymph node metastases influences survival and International Union Against Cancer tumor-node-metastasis classification for esophageal squamous cell carcinoma. *Dis Esophagus* 2010; **23**: 53-58 [PMID: 19392846 DOI: 10.1111/j.1442-2050.2009.00971.x]

P- Reviewer: Kuehn F  S- Editor: Qi Y  L- Editor: AmEditor  E- Editor: Zhang DN
