



Salvage lymphadenectomy for isolated cervical lymph node recurrence after curative resection of thoracic esophageal squamous cell carcinoma

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Background: Patients with thoracic esophageal squamous cell carcinoma (ESCC) often display recurrence in the cervical lymph nodes after surgery. The optimal treatment strategy for these patients has not been established. We retrospectively reviewed patients who underwent salvage lymphadenectomy plus adjuvant radiotherapy/chemotherapy for recurrence limited to the cervical lymph nodes to explore whether salvage treatment could provide an opportunity for curing these patients and to observe the prognostic factors for the patients after salvage treatment.

Methods: All patients with ESCC who underwent esophagectomy with lymphadenectomy and who were diagnosed with a relapse in the cervical nodes between 2007 to 2014. All cases received salvage lymphadenectomy plus adjuvant radiotherapy/chemotherapy. Their clinical characteristics and outcomes were analysed.

Results: A total of 66 patients were diagnosed with recurrence in the cervical nodes after esophagectomy. Among these patients, 21 (31.8%) relapsed 6 months after esophagectomy and 45 (68.2%) recurrences were found 6 months later. Solitary cervical node recurrence was found in 31 (47.0%) patients while 35 (53.0%) cases showed multiple node relapse. Fifty-four (81.8%) patients underwent radical resection while 12 (18.2%) received reduction surgery. The univariate survival analysis showed that patients with solitary cervical node relapse had a better prognosis than patients with multiple node relapse ($P=0.001$). Patients who were diagnosed with a recurrence in 6 months after esophagectomy had worse outcomes than patients who relapsed 6 months later ($P=0.007$). Patients who underwent radical salvage lymphadenectomy had better survival than patients who underwent reduction dissection ($P=0.004$). The number of positive nodes at esophagectomy (3 or more/2 or less) and surgical treatment for recurrence (reduction/radical surgery) were found to have independent prognostic values by multivariate analysis, whereas the other two factors were not statistically significant.

Conclusions: Salvage cervical lymphadenectomy plus adjuvant radiotherapy/chemotherapy is an effective and safe treatment for ESCC patients who develop cervical lymph node recurrence after curative esophagectomy. A lower primary N stage and radical resection of recurrent nodes were found to have independent prognostic values for these patients.

Keywords: Esophageal neoplasms; salvage lymphadenectomy; lymph node recurrence

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Introduction

Esophageal cancer is the fifth most common cancers in China, accounting for about 20,000 cancer related deaths annually. More than 90% of esophageal cancer cases have been classified as ESCC in China while esophageal adenocarcinoma is the predominant type in western countries (1,2). Advances in multimodal treatment in recent years, including neoadjuvant chemoradiotherapy and minimally invasive esophagectomy have improved the prognosis and quality of life of patients with ESCC (3,4). However, more than half of these patients develops locoregional or distant recurrence within 3 years after esophagectomy (5-7).

Distant recurrences, commonly found in the lungs, liver, and bones, are usually considered to have a small chance of a complete cure as no effective treatment for such advanced diseases is currently available (8-10). Locoregional recurrences including recurrences at the site of the primary tumor or locoregional lymph nodes are the most frequent patterns of recurrence after esophagectomy. Lymph node recurrences in the cervical or at the celiac trunk region were also considered to be locoregional (11). Lymph node recurrence limited to the cervical nodes is observed sometimes, especially in cases without preventive cervical lymphadenectomy (12-16). Compared with recurrence in the mediastinum or the abdominal cavity, salvage lymphadenectomy for cervical node recurrence seems to be the optimal choice for treatment. However, the optimal therapy strategy for isolated recurrence in the cervical lymph nodes after curative resection of ESCC has not been established at present.

In this study, we retrospectively reviewed 66 patients who received salvage lymphadenectomy plus adjuvant radiotherapy/chemotherapy for recurrence isolated in the cervical lymph nodes in our center. The aim of this study is to explore whether salvage lymphadenectomy could provide an opportunity for curing patients with isolated cervical node recurrence, and what are the prognostic factors for the patients after salvage treatment.

Methods

Patients

We screened the records of all 2,688 patients diagnosed with ESCC who underwent esophagectomy with lymph node dissection between January 2007 and December 2014 at Fujian Cancer Hospital. Among all these patients, 66 were diagnosed with lymph node recurrence limited to the cervical lymph nodes and underwent salvage cervical lymphadenectomy. We excluded patients with cervical node recurrence plus other sites of recurrence from the analysis. Patients with cervical node involvement extending into the mediastinum and patients who did not receive salvage cervical lymphadenectomy were also excluded from this study. This study was approved by the Human Ethics Review Committee of Fujian Cancer Hospital.

Diagnosis of recurrence

Diagnosis of recurrence was based on physical examinations and imaging studies including cervical ultrasonography and cervical computed tomography (CT). Chest and abdominal CT, abdominal ultrasonography, bone emission computed tomography (ECT) or ¹⁸F-fluorodeoxy glucose positron emission tomography (PET-CT) were used to exclude distant recurrences or locoregional recurrence at other sites.

Salvage lymphadenectomy

All 66 patients underwent salvage cervical lymphadenectomy. The range of the lymphadenectomy included the lymphatic stations containing the suspicious metastatic nodes and the other homolateral supraclavicular nodes. After the salvage surgery, patients who underwent radical resection of the recurrent nodes. were treated with 2–4 courses of adjuvant chemotherapy using platinum based, two-drug regimen. Postoperative chemoradiotherapy was delivered to the supraclavicular, and up mediastinal lymphatics, with a total dose of 45–60 Gy for patients who underwent reduction surgery.

Table 1 Patient characteristics at the time of initial esophagectomy of the 66 patients who showed recurrence at cervical nodes

| Characteristic | n=66 |
|--------------------------------|-----------|
| Gender (%) | |
| Male | 54 (81.8) |
| Female | 12 (18.2) |
| Median age (years) | 57 |
| Tumor location (%) | |
| Upper thoracic | 12 (18.2) |
| Middle thoracic | 41 (62.1) |
| Lower thoracic | 13 (19.7) |
| Esophagectomy procedure (%) | |
| McKeown esophagectomy with 3FL | 9 (13.6) |
| Mckeown esophagectomy with 2FL | 44 (66.7) |
| Ivor-Lewis esophagectomy | 7 (10.6) |
| Sweet esophagectomy | 6 (9.1) |
| pTNM (%) | |
| I | 2 (3.0) |
| II | 29 (43.9) |
| III | 35 (53.0) |
| Number of positive nodes (%) | |
| 0 | 19 (28.8) |
| 1–2 | 27 (40.9) |
| 3–6 | 13 (19.7) |
| 7 or more | 7 (10.6) |

3FL, three-field lymphadenectomy; 2FL, two-field lymphadenectomy.

Follow-up

After salvage treatment, most patients were followed up in the outpatient clinic every three months for the first 2 years, and every 6 months thereafter. For patients who could not afford regular follow-up visits, we performed telephone follow-up instead. The median follow-up period was 27 (range, 4–98) months.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) program version

22.0 for Windows. Overall survival was defined from the date of salvage lymphadenectomy to the date of death or final follow-up. Survival time was derived using the Kaplan-Meier method, and the differences between curves were assessed by the log-rank test. Factors with statistical significance ($P < 0.05$) in univariate analyses were introduced into multivariate analysis. Multivariate analysis was performed with the Cox proportional hazard regression model.

Results

Patient characteristics at prior esophagectomy

The characteristics of the 66 patients at the time of prior esophagectomy are described in *Table 1*. The majority of the patients (81.8%) were male, and their median age was 57 years. Nine (13.6%) of the patients underwent McKeown esophagectomy with three-field lymphadenectomy, 44 (66.7%) underwent McKeown esophagectomy with two-field lymphadenectomy, 7 (10.6%) underwent Ivor-Lewis esophagectomy and 6 (9.1%) patients received Sweet esophagectomy. The fields of lymphadenectomy were dictated mainly by the location of tumor, the clinical lymph nodes status, as well as the surgeon's experience and preference. For lymph nodes positive patients, the average number of positive nodes was 3.0 and 5.4 for two- and three-field lymphadenectomy respectively ($P = 0.068$). The primary tumor locations included the upper (12/66, 18.2%), middle (41/66, 62.1%), and lower (13/66, 19.7%) esophagus. The pathological stages were stage I in 2 (3.0%), stage II in 29 (43.9%), and stage III in 35 (53.0%) patients. There were 19 (28.8%) pathologically node-negative patients, 27 (40.9%) with 1–2 positive nodes, 13 (19.7%) with 3–6 positive nodes and 7 (10.6%) with more than 7 positive nodes.

Clinical features of recurrent nodes

The clinical features of the recurrent nodes in the 66 patients are summarized in *Table 2*. The median interval from the date of prior surgery to the date of recurrence was 10 (range, 1–69) months. Among all these patients, 21 (31.8%) patients relapsed within 6 months after esophagectomy and 45 (68.2%) recurrences were found 6 months later. Solitary cervical node relapses were found in 31 (47.0%) patients while 35 (53.0%) cases showed multiple nodes relapses. Fifty-four (81.8%) patients underwent

radical resection, and 12 (18.2%) received reduction surgery. In addition, 22 (33.3%) patients were found to have supraclavicular nodes recurrence, 39 (59.1%) patients were found to have cervical paratracheal nodes recurrence and 5 (7.6%) patients showed both supraclavicular and cervical paratracheal nodes recurrence. Four minor postoperative complications were observed including lymphorrhea and hoarseness, which were managed conservatively. There was no perioperative mortality.

Table 2 Clinical characteristics of cervical nodes recurrence

| Characteristic | n=66 |
|---|-----------|
| Time to recurrence (%) | |
| ≤6 months | 21 (31.8) |
| >6 months | 45 (68.2) |
| Number of recurrence node (%) | |
| Solitary | 31 (47.0) |
| Multiple | 35 (53.0) |
| Surgical treatment for recurrence | |
| Radical surgery | 54 (81.8) |
| Reduction surgery | 12 (18.2) |
| Site of recurrence (%) | |
| Supraclavicular LNs | 22 (33.3) |
| Cervical paratracheal LNs | 39 (59.1) |
| Supraclavicular and cervical paratracheal LNs | 5 (7.6) |

Table 3 Univariate analysis of prognostic factors for patients with cervical node recurrence that underwent salvage lymphadenectomy

| Factor | P value |
|--|---------|
| Age (more than 58/58 or younger) | 0.58 |
| Gender (male/female) | 0.23 |
| Tumor location (Ut/Mt + Lt) | 0.18 |
| Depth of tumor invasion at esophagectomy (T3-4/T1-2) | 0.21 |
| Number of positive nodes at esophagectomy (3 or more/2 or less) | <0.001 |
| Time to recurrence (>6/≤6 months) | 0.007 |
| Number of recurrence nodes (multiple/solitary) | 0.001 |
| Surgical treatment for recurrence (reduction/radical surgery) | 0.004 |
| Site of recurrence (supraclavicular/cervical paratracheal nodes) | 0.49 |

Ut, upper thoracic; Mt, middle thoracic; Lt, lower thoracic.

Prognostic factors for patients with isolated cervical node recurrence who underwent salvage lymphadenectomy

Univariate analysis was performed for clinico-pathological factors related to prior surgery and recurrent nodes to explore factors affecting the prognosis of patients who had recurrence limited to the cervical nodes. Among the factors analysed, the number of positive nodes at esophagectomy (3 or more/2 or less), time to recurrence (>6/≤6 months), number of recurrence nodes (multiple/solitary) and surgical treatment for recurrence (reduction/radical surgery) were found to be significant prognostic factors (*Table 3* and *Figure 1*). Other factors such as age, gender, tumor location, depth of tumor invasion and site of recurrence, did not affect the prognosis. Afterwards, we subjected the above four factors detected by univariate analysis to multivariate analysis to identify independent prognostic factors. As shown in *Table 4*, the number of positive nodes at esophagectomy (3 or more/2 or less) and surgical treatment for recurrence (reduction/radical surgery) were found to have significant prognostic values, whereas the other two factors were not statistically significant.

Discussion

More than 50% of patients with ESCC developed a recurrence even after curative esophagectomy with extended lymphadenectomy. Locoregional recurrences including lymph node relapse are frequently observed after esophagectomy. More than 11% of patients have been

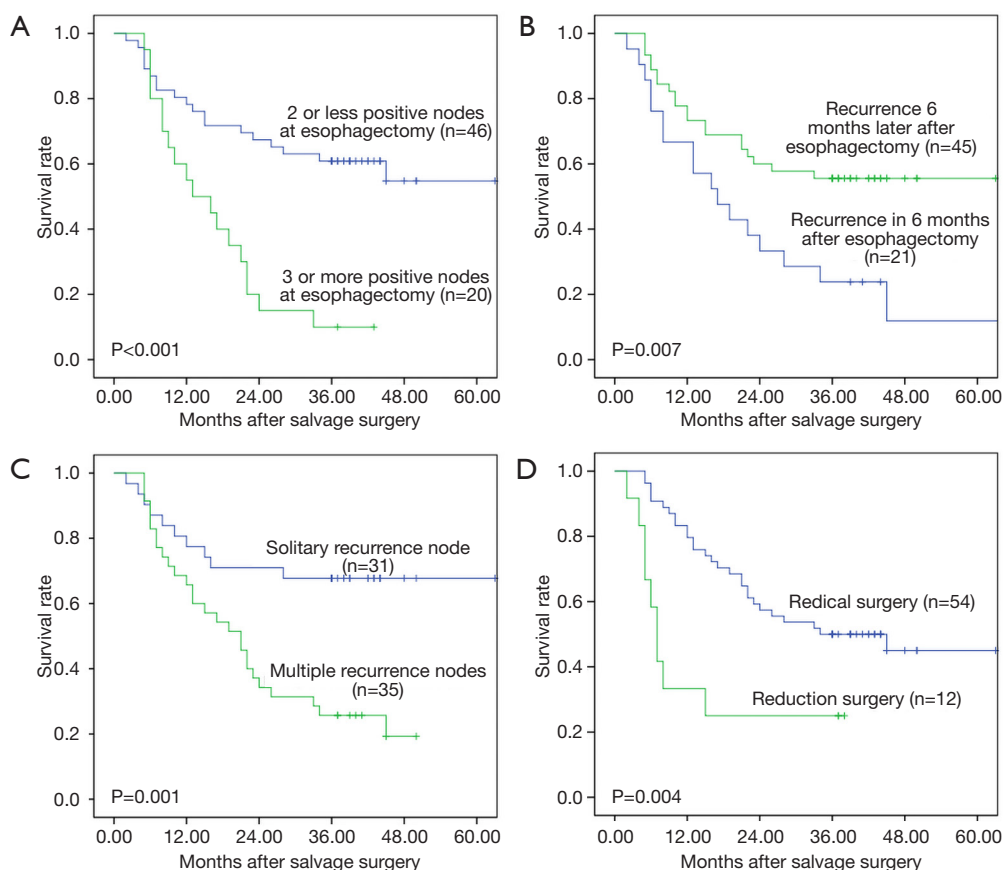


Figure 1 Univariate analysis of prognostic factors for patients with recurrence in the cervical nodes. (A) Patients with 2 or less positive nodes at esophagectomy had a better prognosis than those with 3 or more positive nodes at esophagectomy ($P<0.001$); (B) patients who were diagnosed with recurrences within 6 months after esophagectomy had worse outcomes than patients who relapsed 6 months later ($P=0.007$); (C) patients with a solitary cervical node relapse had a better prognosis than patients with a multiple node relapse ($P=0.001$); (D) patients who underwent radical lymphadenectomy had better survival than patients who underwent reduction surgery ($P=0.004$). The statistical analysis was conducted using a log-rank test.

Table 4 Multivariate analysis of prognostic factors for patients with cervical node recurrence that underwent salvage lymphadenectomy

| Factor | P value | Exp value | 95% CI |
|--|---------|-----------|-------------|
| Number of positive nodes at esophagectomy (3 or more /2 or less) | 0.004 | 3.020 | 1.415–6.444 |
| Time to recurrence (>6/≤6 months) | 0.133 | 0.580 | 0.285–1.181 |
| Number of recurrence nodes (multiple/solitary) | 0.113 | 1.895 | 0.859–4.183 |
| Surgical treatment for recurrence (reduction/radical surgery) | 0.001 | 3.928 | 1.743–8.852 |

reported to develop cervical lymph node recurrence after curative resection for thoracic ESCC (17,18). Although isolated node recurrence in the cervical is not frequent, it is a clinically important problem. Only a few previous studies have reported a salvage treatment for these patients and the

efficacy of salvage cervical node dissection has not yet been established (19). In this study, we have demonstrated that salvage lymphadenectomy can provide a chance for a cure among patients with isolated cervical node recurrence, and we analysed the prognostic factors affecting their survival

after recurrence.

Salvage cervical lymphadenectomy or salvage chemoradiotherapy has been reported to offer some benefit to patients with isolated cervical node recurrence after esophagectomy (12-16,20-22). It was reported that compared with salvage chemoradiotherapy, salvage cervical lymphadenectomy might be the optimal treatment strategy for patients who have developed cervical lymph node recurrence after radical esophagectomy (16). Nevertheless, there was no randomized, controlled trial to establish the optimal treatment for such patients. In our center, salvage lymphadenectomy and subsequent chemotherapy were performed when recurrence was limited to the cervical lymph nodes, which are usually evaluated for removal by R0 resection. Supplementary chemoradiotherapy was delivered to patients who underwent reduction surgery. Salvage radiotherapy or chemoradiotherapy was only performed for patients with cervical lymph nodes that were fixed to main vessels or vital organs such as the trachea and gastric conduit. Thus, it is difficult to compare outcomes in patients who underwent salvage lymphadenectomy and those who underwent salvage radiotherapy/chemoradiotherapy for recurrence in cervical lymph nodes.

A higher primary N stage and a shorter disease-free interval from esophagectomy and multiple cervical lymph nodes recurrence have been reported to be associated with a poor prognosis after salvage treatment (13,21,22). In our present retrospective study, the number of positive nodes at esophagectomy (3 or more/2 or less), time to recurrence (>6/≤6 months), the number of recurrent nodes (multiple/solitary) and surgical treatment for recurrence (reduction/radical surgery) were found to be significant prognostic factors by univariate analysis, which are consistent with previous studies. A lower primary N stage and R0 resection of recurrent nodes were found to have better independent prognostic values for patients with cervical node recurrence that underwent salvage lymphadenectomy. Therefore, salvage lymphadenectomy should be prudent for patients with higher primary N stage and recurrent nodes that can not be radically dissected.

Conclusions

Salvage cervical lymphadenectomy plus adjuvant radiotherapy/chemotherapy is an effective and safe treatment for thoracic ESCC patients who develop isolated cervical lymph node recurrence after curative esophagectomy. A lower primary N stage and radical

resection of recurrent nodes were found to have independent prognostic values for these patients.

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Footnote

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

Ethical Statement: This study was approved by the Research Ethics Committee of Fujian Medical University Cancer Hospital (ID: 2017-048-1). Due to its retrospective design, individual patient consent was waived by the Review Board of Fujian Medical University Cancer Hospital.

References

1. Chen W, Zheng R, Baade PD, et al. Cancer statistics in China, 2015. *CA Cancer J Clin* 2016;66:115-32.
2. Chen W, Zheng R, Zeng H, et al. The incidence and mortality of major cancers in China, 2012. *Chin J Cancer* 2016;35:73.
3. Biere SS, van Berge Henegouwen MI, Maas KW, et al. Minimally invasive versus open oesophagectomy for patients with oesophageal cancer: a multicentre, open-label, randomised controlled trial. *Lancet* 2012;379:1887-92.
4. van Hagen P, Hulshof MC, van Lanschoot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med* 2012;366:2074-84.
5. Ninomiya I, Okamoto K, Tsukada T, et al. Recurrence patterns and risk factors following thoracoscopic esophagectomy with radical lymph node dissection for thoracic esophageal squamous cell carcinoma. *Mol Clin Oncol* 2016;4:278-84.
6. Liu Q, Cai XW, Wu B, et al. 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.
7. Jang NY, Kim IA, Byun SS, et al. Patterns of failure and prognostic factors for locoregional recurrence after radical surgery in upper urinary tract transitional cell

- carcinoma: implications for adjuvant radiotherapy. *Urol Int* 2013;90:202-6.
8. Sugiyama M, Morita M, Yoshida R, et al. Patterns and time of recurrence after complete resection of esophageal cancer. *Surg Today* 2012;42:752-8.
 9. Kunisaki C, Makino H, Takagawa R, et al. Surgical outcomes in esophageal cancer patients with tumor recurrence after curative esophagectomy. *J Gastrointest Surg* 2008;12:802-10.
 10. Nakagawa S, Kanda T, Kosugi S, et al. Recurrence pattern of squamous cell carcinoma of the thoracic esophagus after extended radical esophagectomy with three-field lymphadenectomy. *J Am Coll Surg* 2004;198:205-11.
 11. Oppedijk V, van der Gaast A, van Lanschot JJ, et al. Patterns of recurrence after surgery alone versus preoperative chemoradiotherapy and surgery in the CROSS trials. *J Clin Oncol* 2014;32:385-91.
 12. Watanabe M, Nishida K, Kimura Y, et al. Salvage lymphadenectomy for cervical lymph node recurrence after esophagectomy for squamous cell carcinoma of the thoracic esophagus. *Dis Esophagus* 2012;25:62-6.
 13. Yano M, Takachi K, Doki Y, et al. Prognosis of patients who develop cervical lymph node recurrence following curative resection for thoracic esophageal cancer. *Dis Esophagus* 2006;19:73-7.
 14. Motoyama S, Kitamura M, Saito R, et al. Outcome and treatment strategy for mid- and lower-thoracic esophageal cancer recurring locally in the lymph nodes of the neck. *World J Surg* 2006;30:191-8.
 15. Lee DH, Kim HR, Kim DK, et al. Outcomes of cervical lymph node recurrence in patients with esophageal squamous cell carcinoma after esophagectomy with 2-field lymph node dissection. *J Thorac Cardiovasc Surg* 2013;146:365-71.
 16. Ma X, Zhao K, Guo W, et al. Salvage lymphadenectomy versus salvage radiotherapy/chemoradiotherapy for recurrence in cervical lymph node after curative resection of esophageal squamous cell carcinoma. *Ann Surg Oncol* 2015;22:624-9.
 17. Law SY, Fok M, Wong J. Pattern of recurrence after oesophageal resection for cancer: clinical implications. *Br J Surg* 1996;83:107-11.
 18. Katayama A, Mafune K, Tanaka Y, et al. Autopsy findings in patients after curative esophagectomy for esophageal carcinoma. *J Am Coll Surg* 2003;196:866-73.
 19. Yuan X, Lv J, Dong H, et al. Does cervical lymph node recurrence after oesophagectomy or definitive chemoradiotherapy for thoracic oesophageal squamous cell carcinoma benefit from salvage treatment? *Interact Cardiovasc Thorac Surg* 2017;24:792-5.
 20. Watanabe M, Mine S, Yamada K, et al. Outcomes of lymphadenectomy for lymph node recurrence after esophagectomy or definitive chemoradiotherapy for squamous cell carcinoma of the esophagus. *Gen Thorac Cardiovasc Surg* 2014;62:685-92.
 21. Takemura M, Kaibe N, Takii M, et al. Treatment outcomes of patients with cervical lymph node recurrence after esophagectomy for esophageal cancer. *Gan To Kagaku Ryoho* 2014;41:2010-2.
 22. Komatsu S, Shioaki Y, Ichikawa D, et al. Survival and clinical evaluation of salvage operation for cervical lymph node recurrence in esophageal cancer. *Hepatogastroenterology* 2005;52:796-9.

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