Clinical study on postoperative recurrence in patients with pN1 esophageal squamous cell carcinoma

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Abstract

Background: The 7th edition Union for International Cancer Control esophageal cancer staging system has changed the pathological N stage from N0, N1 (the existence state of regional lymph node metastasis) to N0, N1, N2, and N3 (number of regional lymph node metastasis). This study was designed to analyze the influencing factors of early recurrence in patients with pathological N1 stage (pN1 stage) esophageal squamous cell carcinoma (ESCC) after radical esophagectomy.

Method: A retrospective study of 95 consecutive pN1 stage ESCC patients was conducted. The Cox proportional hazards model was used to determine the independent risk factors for recurrence.

Results: Recurrence was recognized in 52 patients (54.7%) within three years after surgery. The median time to tumor recurrence was 14.2 months. Locoregional recurrence was found in 42 patients (44.2%) and hematogenous metastasis in 10 patients (10.5%). Recurrence closely correlated with pT stage, positive lymph node metastasis (LNM) in 2-station and/or 2-field, pathologic stage, intramural metastasis, lymph-vascular invasion, and postoperative adjuvant chemotherapy ($\chi^2 = 8.853 \sim 65.695, P < 0.05$). Cox multivariate analysis showed that pT3-4a stage (odds ratio [OR] = 3.604, $P = 0.027$), positive LNM in 2-station (OR = 4.834, $P = 0.009$) or 2-field (OR = 5.689, $P = 0.003$) and no adjuvant chemotherapy (OR = 1.594, $p = 0.048$) were independent risk factors for postoperative recurrence.

Conclusion: Adjuvant chemotherapy might be helpful to reduce the recurrence rate of pN1 patients with thoracic ESCC. Induction therapy could further improve the therapeutic effect of pN1 ESCC with suspected multi-station and/or multi-field LNM.

Introduction

Lymph node metastasis after radical resection of esophageal cancer is the leading cause of treatment failure. Previous studies have shown that patients with pathological N2-3 stage esophageal squamous cell carcinoma (ESCC) (more than three regional lymph nodes metastasized) still receive a poor prognosis, despite radical esophagectomy with 3-field lymph node dissection and postoperative treatment. For patients with suspected preoperative lymph node metastasis (LNM) (clinical N1-3 stage), the National Comprehensive Cancer Network esophageal cancer treatment guidelines (NCCN, 2013 version) recommend preoperative induction concurrent chemoradiation. However, these guidelines are mainly based on studies of esophageal adenocarcinoma, and the suggestions for ESCC still lack adequate evidence from phase III clinical trials. According to our previous study, the five-year survival rate is similar between pN0 (32%) and pN1 (48%), compared to pN2 (12%) and pN3 patients (0%). In this study, we attempt to find the risk factors of recurrence for pN1 ESCC after surgery in accordance with the 7th edition of the Union for International Cancer Control (UICC) esophageal cancer staging system and to explore new methods to improve survival.

Patients and methods

Patients

A retrospective study of total of 95 consecutive pN1 stage ESCC patients who underwent esophagectomy with lymphadenectomy by the same surgical team from January 2004 to
December 2010 was conducted. Cases who had undergone preoperative induction chemotherapy or chemoradiation and those who underwent R1 or R2 resection confirmed by pathology were excluded from this study. Among the 95 patients, 79 were men and 16 were women, with an average age of 60.4 ± 3.8 years old. Tumor location included: nine in the upper thoracic; 63 in the middle thoracic; and 23 in the lower thoracic. The differentiation of tumor cells was as follows: nine well; 38 moderate; and 48 poor. Pathologic T stages were: nine pT1b; 17 pT2; 60 pT3; and 12 pT4a. We selected 112 patients with pN0 stage ESCC in the same period as the control group.5

**Surgical procedure**

Thoraco-abdominal 2-field lymphadenectomy was performed. Some patients were treated with cervico-thoraco-abdominal 3-field lymphadenectomy based on the positive results of preoperative cervical ultrasonography.

Sixty-nine patients received postoperative adjuvant chemotherapy for two cycles with a combination of fluorouracil and cisplatin (FP) or paclitaxel and cisplatin (TP).

**Follow-up examination**

Patients routinely received their first post-operative examination three to four weeks after surgery, then were examined at three-month intervals for one year, and at six-month intervals thereafter. During each follow-up visit, the patient underwent a clinical evaluation and a blood biochemistry examination including tumor markers and chest radiography. Endoscopy, ultrasonography (US) of the neck and abdomen, and computed tomography (CT) of the neck, thorax, and abdomen were performed at least once a year. More selective investigations, such as positron emission tomography (PET), bone scintigraphy, and head-enhanced magnetic resonance imaging (MRI) were carried out based on specific symptomatology, clinical examination, and biochemical profile. Detection of a suspected recurrence at any one site was followed by a thoroughly detailed investigation to confirm or refute the occurrence and to examine every other site.

**Definition of locoregional and hematogenous recurrence**

The first recurrence was noted, and any additional recurrence found within one month was considered to have occurred simultaneously. These lesions were classified as locoregional (at the remaining esophagus, the anastomotic site, or the mediastinum, cervical, supraclavicular and celiac axis lymph nodes) and hematogenous (in the distant organs such as liver, lung, bone and pleura, peritoneum) recurrences. Simultaneous locoregional and hematogenous recurrences were classified as hematogenous recurrences.6

**Statistical methods**

The SPSS 16.0 software package was used for data analysis. Data were expressed as median with ranges (minimum-maximum) or as percentages. The chi-square test was used to evaluate differences in clinicopathologic features. The Cox proportional hazards model was used to determine the independent risk factors for recurrence within three years after surgery. A p value of <0.05 was considered statistically significant for all procedures.

**Results**

**Pattern of recurrence**

The three-year survival rate of the 95 pN1 ESCC patients was 52.3%, which was significantly lower than the pN0 patients (79.5%) during the same period. Of the 95 patients, recurrence was recognized in 52 patients (54.7%) within three years after surgery, which was higher than pN0 patients (40.2%, 45/112, P = 0.041).5 The median disease-free interval until recurrence was 14.2 months. Of the 52 patients experiencing recurrence, 43 were men and nine were women.

Among the 52 patients experiencing recurrence, 42 cases developed locoregional recurrence, all in the form of regional lymph node metastasis; the other 10 cases developed hematogenous metastasis. Locoregional was the main form of recurrence in both pN0 and pN1 stage ESCC patients. However, the main site of pN1 stage recurrence was in the mediastinal lymph nodes, which accounted for 66.7% (especially in the middle mediastinum) in cases of locoregional recurrence, and was much higher than that of pN0 ESCC (34.2%, P = 0.027).6 Meanwhile, the proportion of cervical and supraclavicular lymph node metastasis of pN1 (33.3%) was much lower than that of pN0 (55.3%, P = 0.004)5 (Table 1).

**Univariate analysis for recurrence**

Univariate analysis showed that the recurrence of pN1 stage ESCC closely correlated with the pathologic T stage, positive lymph nodes metastasis (number, stations, and fields), pathologic stage, intramural metastasis, lymph-vascular invasion, and postoperative adjuvant chemotherapy (Table 2).

**Multivariate analysis for recurrence**

Multivariate analysis by the Cox proportional hazards model demonstrated that pathologic T stage, multi-station and/or
Discussion

Our study showed that the most common recurrence pattern of pN1 stage ESCC was regional LNM, and hematogenous metastasis appeared much later than regional LNM, which was a distinctive feature of ESCC. In our study, 54.7% of pN1 patients experienced recurrence within three years after surgery, which was significantly higher than the pN0 patients (40.2%, \( P = 0.041 \)) during the same period.\(^5\) These results suggest that pN1 patients were more likely to develop recurrence than pN0 patients; therefore, multidisciplinary treatment was necessary for pN1 patients.

Though regional LNM was the main form of recurrence in both the pN1 and pN0 patients, the recurrence of pN1 patients mostly occurred in the mediastinal lymph nodes, which accounted for 66.7% of locoregional recurrence cases, and particularly middle mediastinal lymph node metastasis, which accounted for 42.9%. This result was remarkably different with pN0 patients, whose commonly recurrent site was cervical and supraclavicular lymph nodes (55.3%); the mediastinal lymph nodes only accounted for 7.9%.\(^5\) Such a phenomenon closely correlates to the special anatomical structure of the esophagus. There were plenty of submucosal longitudinal lymphatic vessels in the submucosa of the tho-

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**Table 1** Site of locoregional and hematogenous recurrence in pN1 and pN0 ESCC

| Site of recurrence                  | pN1[n(%)] | pN0[n(%)] |
|------------------------------------|-----------|-----------|
| Locoregional recurrence†           | 42 (33.3) | 38 (55.3) |
| Cervical/supraclavicular node      | 14 (21.4) | 9 (23.7)  |
| Mediastinal node                   | 28 (66.7) | 13 (34.2) |
| Upper                              | 9 (42.9)  | 3 (7.9)   |
| Middle                             | 1 (2.4)   | 1 (2.6)   |
| Lower                              | 1 (11.9)  | 6 (15.8)  |
| Abdominal node                     | 0 (0.0)   | 2 (57.1)  |
| Anastomotic                        | 1 (10.0)  | 0 (0.0)   |
| Hematogenous recurrence‡           | 10 (70.0) | 7 (85.7)  |
| Liver                              | 2 (20.0)  | 2 (28.6)  |
| Lung                               | 2 (20.0)  | 1 (14.3)  |
| Others (brain/pleura/omentum)      | 1 (10.0)  | 0 (0.0)   |

†Five and three patients experienced locoregional recurrence at more than one site in pN1 and pN0 ESCC, respectively. ‡Two pN1 and pN0 ESCC patients experienced hematogenous recurrence at more than one site. ESCC, esophageal squamous cell carcinoma.

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**Table 2** Univariate analysis for recurrence of 95 pN1 ESCC patients undergoing radical esophagectomy with lymphadenectomy

| Variables                      | n. | Recurrence [n. (%)] | P-value |
|-------------------------------|----|---------------------|---------|
| Gender (M/F)                  | 79/16 | 43/35(54.4)/9(59.2) | 0.168   |
| Age (years)≥60/<60             | 62/33 | 35/35(56.5)/17(51.5) | 0.134   |
| Tumor location                |     |                     | 0.182   |
| Upper                         | 9   | 5/5(55.6)           |         |
| Middle                        | 63  | 37/4(58.7)          |         |
| Lower                         | 23  | 10/10(43.5)         |         |
| Grade of differentiation      |     |                     | 0.138   |
| Well (G1)                     | 9   | 4(44.4)             |         |
| Moderately (G2)               | 38  | 22/22(57.9)         |         |
| Poorly (G3)                   | 48  | 26/26(54.2)         |         |
| T status                      |     |                     | 0.003   |
| T1b                            | 6   | 1/6(16.7)           |         |
| T2                             | 17  | 5/17(29.4)          |         |
| T3                             | 60  | 39/60(65.0)         |         |
| T4a                            | 12  | 7/12(58.3)          |         |
| Positive lymph nodes number (1/2) | 73/23 | 34/18(78.3)       | 0.041   |
| Positive lymph nodes stations (1/2) | 76/19 | 34/18(94.7)       | 0.001   |
| Positive lymph nodes fields (1/2) | 87/8  | 44/8(100.0)       | 0.000   |
| Pathologic stage               |     |                     | 0.012   |
| IIb                            | 23  | 6/23(26.1)          |         |
| IIa                            | 60  | 39/60(65.0)         |         |
| IIIc                           | 12  | 7/12(58.3)          |         |
| Lymphadenectomy (2-field/3-field) | 76/19 | 43/9(47.4)       | 0.174   |
| Intramural metastasis (yes/no) | 5/90 | 5/10(50.0)/47(52.2) | 0.000   |
| Lymph-vascular invasion (yes/no)| 7/88 | 6/47(85.7)/46(52.3) | 0.019   |
| Postoperative adjuvant chemotherapy (yes/no) | 69/26 | 33/19(73.1) | 0.036   |

ESCC, esophageal squamous cell carcinoma.
racic esophagus. Therefore, early stage ESCC (pT1b-T2) was more likely to develop leaping metastasis to the lymph nodes of the juncture of the thorax and cervix, such as recurrent laryngeal nerve lymph nodes, which were distant to the primary tumor location. When the tumor invaded or penetrated the adventitia of the esophagus (pT3-T4a), the probability of peri-tumor LNM then increased because of the lateral mediastinal lymphatic vessels originating from the muscle layer.

We studied the relationship between the different status of LNM (number, stations, and fields) and recurrence of pN1 ESCC. According to the stratification analysis, 2-node (78.3%), 2-station (94.7%) and 2-field (100%) LNM had significantly higher risks of recurrence after surgery than 1-node (47.2%, \( P = 0.041 \)), 1-station (44.7%, \( P = 0.001 \)) and 1-field (50.6%, \( P = 0.000 \)), although they were all staged pN1. Cox multivariate analysis showed that multi-stations and/or multi-fields of positive lymph node metastasis were independent risk factors for postoperative recurrence. The N stage was based on the number of positive lymph nodes in the UICC staging system. However, the metastatic lymph nodes were always swollen and fused, making it difficult to determine an accurate number or separate these during surgery. Furthermore, one lymph node was easily torn apart into several segments. Therefore, it was difficult to get a precise N stage according to the number of metastatic lymph nodes. Studies have shown that the stations and fields of metastatic lymph nodes are more exact and objective in revealing the extent of LNM. It might be more reasonable to assess prognosis and select postoperative adjuvant treatment according to the metastatic stations and fields of lymph nodes, rather than the number. In consideration of patients with 2-station or 2-field LNM that had a high risk of recurrence after surgery, we suggested induction treatment for those patients who were suspected to have more than two stations of LNM by preoperative evaluation.

Some cases in our study had pathologically confirmed intramural metastasis and/or lymph-vascular invasion. However, there were few of these cases and they subsequently did not have statistical significance in Cox multivariate analysis; most of these patients developed lymph node recurrence within a short time after surgery. This result implied that intramural metastasis and lymph-vascular invasion were high-risk factors for postoperative recurrence of pN1 ESCC. In the 7th UICC TNM staging system, intramural metastasis

Table 3 Multivariate analysis for recurrence of pN1 ESCC

| Variable                                      | B    | SE   | Wald  | pValue | OR    | 95% CI      |
|-----------------------------------------------|------|------|-------|--------|-------|-------------|
| Depth of invasion (pT3-4a versus pT1b-2)      | 2.405| 1.084| 4.921 | 0.027  | 3.604 | 1.401–9.276 |
| Positive lymph nodes stations (2/1)           | 2.232| 0.853| 6.846 | 0.009  | 4.834 | 2.612–11.301 |
| Positive lymph nodes fields (2/1)             | 2.446| 0.832| 8.640 | 0.003  | 5.689 | 2.459–13.179 |
| Postoperative adjuvant chemotherapy (no/yes)  | 2.517| 1.396| 2.915 | 0.048  | 1.594 | 1.228–8.027  |

B, regression coefficient; CI, confidence interval; ESCC, esophageal squamous cell carcinoma; OR, odds ratio; SE, standard error; Wald, wald value.

Figure 1 Recurrence-free survival according to depth of invasion (\( P = 0.027 \)). •, t1b-2; •, t3a-4; •, t1b-2-censored; •, t3a-4-censored.

Figure 2 Recurrence-free survival according to adjuvant chemotherapy (\( P = 0.046 \)). •, Adjuvant chemo; •, No adjuvant chemo; •, Adjuvant chemo-censored; •, No adjuvant chemo-censored.
and lymph-vascular invasion were listed as risk factors for poor prognosis, but they were not included in the staging system. In our opinion, intramural metastasis and lymph-vascular invasion closely correlated with regional LNM and including these two factors into the TNM staging system might be helpful for diagnosis and treatment in clinical work. Moreover, our study showed that patients with pT3-pT4a (63.8%) had a significantly high risk of recurrence compared with pT1b-pT2 (26.1%, \( P = 0.003 \)). Because of the correlation between pathologic T stage and N stage of ESCC, we found that the invasion of adventitia was an indication of poor prognosis.

In the present study, there was no significant difference in recurrence rate after surgery between patients treated with thoraco-abdominal 2-field lymphadenectomy and those who underwent cervico-thoraco-abdominal 3-field lymphadenectomy. We could not decrease the postoperative recurrence rate only by extended lymph node dissection. Once metastasis occurred in the regional lymph nodes, it was difficult to achieve a satisfactory therapeutic effect simply relying on surgery, which represented a local and physical therapy. The result of this study shows that postoperative adjuvant chemotherapy was an independent predictor of recurrence. Our previous study had shown that the combination of radical esophagectomy with systemic lymph node dissection following postoperative adjuvant chemotherapy could improve the overall survival of thoracic ESCC patients, compared with surgery alone. The result of multi-center phase III clinical trial in Japan also showed that postoperative adjuvant chemotherapy can effectively reduce the probability of postoperative recurrence for ESCC.

**Conclusion**

In conclusion, we suggest that postoperative adjuvant chemotherapy is essential for pN1 ESCC patients who have undergone radical esophagectomy. Preoperative induction therapy might be helpful to reduce the recurrence rate of ESCC patients with suspected multi-station or even multi-field lymph node metastasis by preoperative evaluation.

**Disclosure**

No authors report any conflict of interest.

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