

CXCL10 Expression Status is Prognostic in Patients with Advanced Thoracic Esophageal Squamous Cell Carcinoma

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ABSTRACT

Background. CXCL10, a member of the CXC chemokine family, is known to mediate chemotaxis, apoptosis, angiogenesis, and cell growth. It is also reportedly involved in tumor development and can affect prognosis in several cancers. However, the precise relationship between CXCL10 and the prognosis of patients with esophageal squamous cell carcinoma (ESCC) is not fully understood.

Methods. We used ESCC tissue microarrays containing samples from 177 patients to test whether the CXCL10 expression status, determined using immunohistochemical analysis, is predictive of prognosis. We also tested whether CXCL10 expression status could serve as a clinically useful marker for evaluating the need for adjuvant chemotherapy after surgery.

Results. We found that high CXCL10 expression in clinical samples was an independent prognostic factor and was predictive of a favorable 5-year overall survival and disease-specific survival ($p = 0.0102$ and 0.0332 , respectively). Additionally, no significant difference was detected between patients in the CXCL10-high group treated with surgery alone and those treated with surgery followed by adjuvant chemotherapy. In the CXCL10-low group, on the other hand, patients treated with surgery followed by adjuvant chemotherapy had better 5-year overall survival than those treated with surgery alone.

Conclusions. High CXCL10 expression is an independent prognostic factor and has the potential to serve as a

clinically useful marker of the need for adjuvant chemotherapy after surgery in patients with advanced thoracic ESCC.

Esophageal cancers rank as the sixth leading cause of cancer death worldwide.¹ Indeed, thoracic esophageal squamous cell carcinoma (ESCC) is the most common pathologic condition in many regions of the world; it is characterized by an extremely poor prognosis and rapid clinical progression.^{2,3} Thanks to recent advances in surgical technique, perioperative management, chemotherapy, and radiotherapy, however, the outcomes of these patients have improved somewhat, though the 5-year survival rate remains unsatisfactory, and the treatment strategy for these patients—surgery, chemotherapy, and/or radiotherapy—is still controversial.^{4–7}

CXCL10 (or interferon gamma–induced protein 10, IP-10) is a member of the CXC chemokine family and is known to mediate chemotaxis, apoptosis, angiogenesis, and cell growth.⁸ CXCL10 is also reportedly involved in tumor development in several cancers, including brain cancer, breast cancer, colorectal cancer, head and neck cancer, lung cancer, and lymphoma.^{9–14} According to those reports, CXCL10 has dual effects on tumorigenesis, exhibiting both antitumor and tumor-promoting properties. In ESCC, CXCL10 expression inhibits cancer cell invasion and promotes migration of immune cells to the cancer microenvironment, suggesting that CXCL10 exerts antitumor effects on ESCC progression.^{15,16} Whether CXCL10 expression correlates with prognosis in patients with ESCC remains unclear, however.

In the present study, therefore, we examined whether CXCL10 expression status correlates with prognosis in patients with advanced ESCC. We also evaluated whether CXCL10 expression status can serve as a clinically useful marker of the need for adjuvant chemotherapy after surgery in these patients.

MATERIALS AND METHODS

Thoracic ESCC Patients

This study was approved by the ethics committee of the Akita University School of Medicine. All of the participants provided informed consent and signed human subject institutional review board consent forms. Between January 2000 and December 2011, 507 esophageal cancer patients received esophagectomy at Akita University Hospital. Of those, 177 pT2–4 thoracic ESCC patients who had received curative surgery with no preoperative treatment were enrolled onto this study. For all patients, the esophageal cancer stage and the treatment strategy were decided by the esophageal cancer board, which includes radiologists, oncologists, physicians, and surgeons. In addition, the disease was classified according to the World Health Organization 7th tumor, node, metastasis classification system.¹⁷ The clinicopathologic features of these patients are summarized in Table 1.

Surgery and Adjuvant Chemotherapy

Our standard operative procedure is right transthoracic esophagectomy with resection of the cardiac portion of the stomach and dissection. Three-field lymph node dissections of the mediastinal (involving the periesophageal region and areas around the trachea and bilateral main bronchus), abdominal (involving the perigastric region and areas around the celiac axis), and cervical (involving the bilateral periesophageal region and supraclavicular region) lymph nodes were performed. Reconstruction commonly involved inserting a gastric tube through the posterior mediastinal route.¹⁸

On the basis of the pathologic results, administration of adjuvant chemotherapy was initiated within 2 months after esophagectomy. Some patients declined adjuvant chemotherapy or did not receive it because of their clinical condition. The chemotherapy consisted of protracted infusion of 5-fluorouracil (800 mg/m² per day) on days 1–5 and 8–12, combined with cisplatin (80 mg/m² per day) on days 1 and 8. This protocol was repeated twice with 3-week intervals in between.¹⁹

ESCC Tissue Microarray (TMA)

An ESCC TMA was constructed at the Pathology Institute, Toyama, Japan, using 177 paraffin-embedded blocks of primary tumor samples from the study participants, as described elsewhere.^{19,20} Triplicate cores measuring 0.6 mm in diameter were collected randomly from cancer areas to account for cancer tissue heterogeneity and transferred to the TMA. As a result, the TMA block contained 531 cores (three cores each from 177 paraffin blocks).

TABLE 1 Clinicopathologic features of 177 ESCC patients

| Characteristic | CXCL10 high (n = 96) | CXCL10 low (n = 81) | p |
|----------------------------|-------------------------|------------------------|-------|
| Gender | | | 0.509 |
| Female | 15 | 9 | |
| Male | 81 | 72 | |
| Age at surgery (years) | 65.1 ± 8.1 | 64.9 ± 8.4 | 0.840 |
| Tumor location | | | 0.266 |
| Upper | 3 | 3 | |
| Middle | 68 | 48 | |
| Lower | 25 | 30 | |
| Depth of invasion (pT) | | | 0.735 |
| T2 | 17 | 14 | |
| T3 | 73 | 64 | |
| T4a | 6 | 3 | |
| Lymph node metastasis (pN) | | | 0.211 |
| N0 | 28 | 21 | |
| N1 | 34 | 21 | |
| N2 | 22 | 20 | |
| N3 | 12 | 19 | |
| Pathologic stage | | | 0.872 |
| IB | 7 | 3 | |
| IIA | 20 | 17 | |
| IIB | 4 | 3 | |
| IIIA | 32 | 25 | |
| IIIB | 16 | 14 | |
| IIIC | 17 | 19 | |
| Tumor differentiation | | | 0.749 |
| Not poor | 64 | 56 | |
| Poor | 32 | 25 | |
| Adjuvant chemotherapy | | | 0.549 |
| Yes | 55 | 50 | |
| No | 41 | 31 | |
| Recurrence of ESCC | | | 0.484 |
| Yes | 40 | 38 | |
| No | 56 | 43 | |
| Prognosis | | | 0.135 |
| Alive | 56 | 33 | |
| Dead with ESCC | 27 | 34 | |
| Dead with other cancer | 2 | 2 | |
| Dead with other diseases | 11 | 12 | |

ESCC esophageal squamous cell carcinoma

Immunohistochemical (IHC) Staining

Four-micron-thick sections from the TMA were deparaffinized in xylene and rehydrated through a graded ethanol series. For antigen retrieval, the slides were first incubated for 10 min in pH 6.0 citrate buffer at 121 °C in an autoclave. Endogenous peroxidase activity was inactivated

by incubation for 30 min in 3.0 % H₂O₂, and protein blocking was accomplished by incubation for 30 min in 10 % normal rabbit serum/Tris (Vector Laboratories, Burlingame, CA). The tissue sections were then incubated overnight at 4 °C with goat anti-human CXCL10/IP-10 polyclonal antibody (R&D Systems, Minneapolis, MN), after which the antigen was visualized using a Histofine simple stain kit (Nichirei, Tokyo, Japan) with DAB peroxidase substrate according to the manufacturer's instructions.

Photomicrographs of the IHC staining were taken for analysis with a NanoZoomer Digital Pathology C9600 (Hamamatsu Photonics, Hamamatsu, Japan) and were viewed with a NanoZoomer Digital Pathology Virtual Slide Viewer (version 1.2.33; Hamamatsu Photonics). For each sample, a staining score was assigned on the basis of the HER2 IHC scoring system (American Society of Clinical Oncology and CAP guidelines) by an investigator masked to the clinical data.²¹ Positivity for protein expression was given an IHC score of 3+ if more than 30 % of the cell cytoplasm or nuclei stained intensely, 2+ if there was moderate cytoplasmic or nuclear staining in >10 % of cells, and 1+ if there was weak staining. Samples with IHC scores of 3+ or 2+ were judged as high expression and 1+ or – as low expression.

Biostatistical Analysis

Mean, standard deviation, and frequency were used to summarize characteristics of subjects in the CXCL10 high and CXCL10 low groups. The Wilcoxon test (for continuous variables) or χ^2 and Fisher's exact tests (for categorical variables) were used to evaluate the differences between these groups. Survival length was determined from the date of surgery to the patient's death or date of last clinical follow-up. Survival curves were constructed by the Kaplan–Meier method, and the differences between curves were analyzed by the log rank test. The Cox proportional hazard regression model was used for univariate and multivariate analyses. Age, gender, lymph node metastasis, pathologic stage, tumor differentiation, and CXCL10 expression status were included in the multivariate model. Statistical analyses were performed using JMP11 (SAS Institute, Cary, NC). Values of $p \leq 0.05$ (two-sided) were considered significant.

RESULTS

CXCL10 Expression and 5-Year Overall and Disease-Specific Survival Among Patients with ESCC

We used IHC analysis of a TMA to evaluate the relationship between CXCL10 expression status and 5-year

overall and disease-specific survival (OS and DSS, respectively) among patients with ESCC. Representative photomicrographs of three cores from individual specimens with 3+, 2+, 1+, and – IHC scores are shown in Fig. 1. CXCL10 expression was mainly observed in the cytoplasm of ESCC cells. The Kaplan–Meier curves revealed that patients expressing high levels of CXCL10 had significantly better 5-year OS and DSS than those expressing lower levels of CXCL10 ($p = 0.0102$ and 0.0332 , respectively) (Fig. 2). Consistent with this finding, univariate analysis of age (70 years and older vs. younger), gender, depth of invasion (T2–3 vs. T4), lymph node metastasis (N0–1 vs. N2–3), pathologic disease stage (stage IIIB–IIIC vs. stage IB–IIIA), tumor differentiation (poorly differentiated vs. not poorly differentiated), CXCL10 expression (low vs. high), and treatment (surgery alone vs. surgery followed by adjuvant chemotherapy) showed that lymph node metastatic status, pathologic stage, tumor differentiation, and CXCL10 expression status were all significant prognostic factors affecting 5-year OS (Table 2). In addition, multivariate analysis revealed CXCL10 expression status to be a significant prognostic factor in every combination with age, gender, lymph node metastasis, pathologic stage, and tumor differentiation (Table 3).

Low CXCL10 Expression and Adjuvant Chemotherapy

We also evaluated whether CXCL10 expression status could serve as a clinically useful marker of the need for adjuvant chemotherapy after surgery. In the CXCL10 high expression group, 41 patients were treated with surgery alone and 55 were treated with surgery followed by adjuvant chemotherapy. The Kaplan–Meier curves showed that there was no significant difference in 5-year OS between patients treated with surgery alone and those treated with surgery followed by adjuvant chemotherapy (Fig. 3). On the other hand, in the CXCL10 low expression group, the 50 patients treated with surgery followed by adjuvant chemotherapy had better 5-year OS than the 31 patients treated with surgery alone ($p = 0.07$). However, the difference did not reach statistical significance.

DISCUSSION

In this study, we found that high CXCL10 expression is an independent prognostic factor affecting 5-year OS in patients with advanced ESCC. We also found that CXCL10 expression status has the potential to serve as a clinically useful marker for evaluating the need for adjuvant chemotherapy after surgery in these patients. To our knowledge, this is the first report showing an association

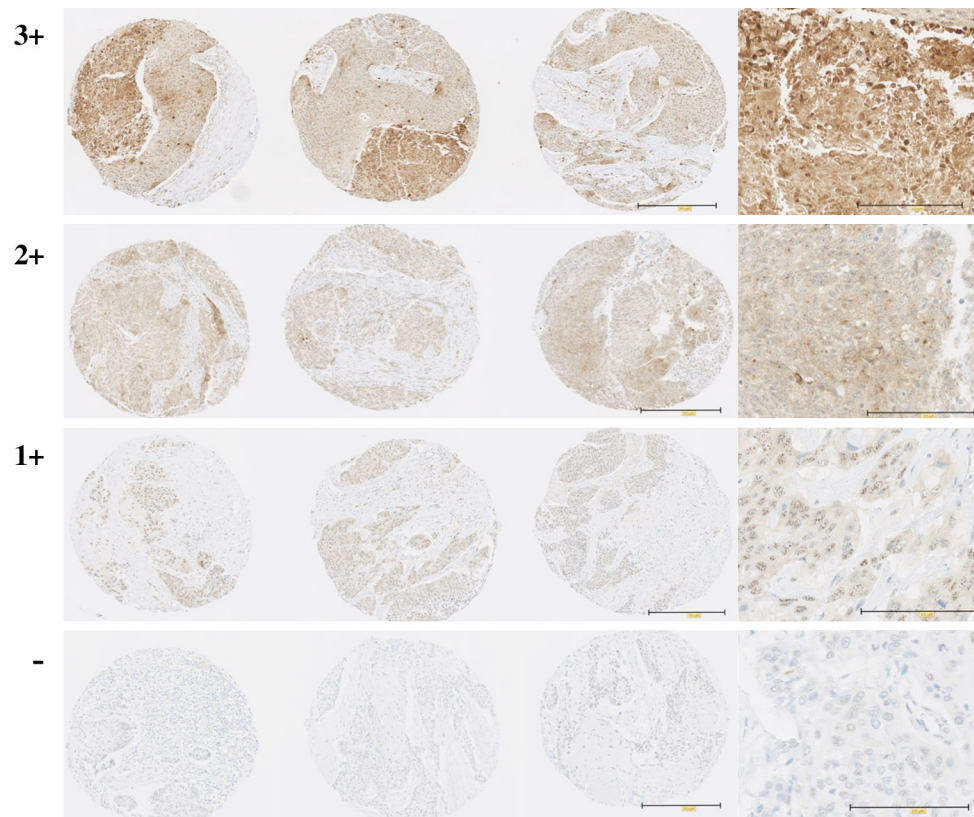


FIG. 1 IHC staining of CXCL10 in ESCC TMA. Representative photomicrographs showing 3 cores from individual specimens with 3+, 2+, 1+, and – IHC scores for expression of CXCL10. For each

condition, 3 whole cores from ESCC TMA are shown at $\times 100$ magnification (scale bar 300 μm), along with corresponding $\times 400$ magnification images (scale bar 100 μm)

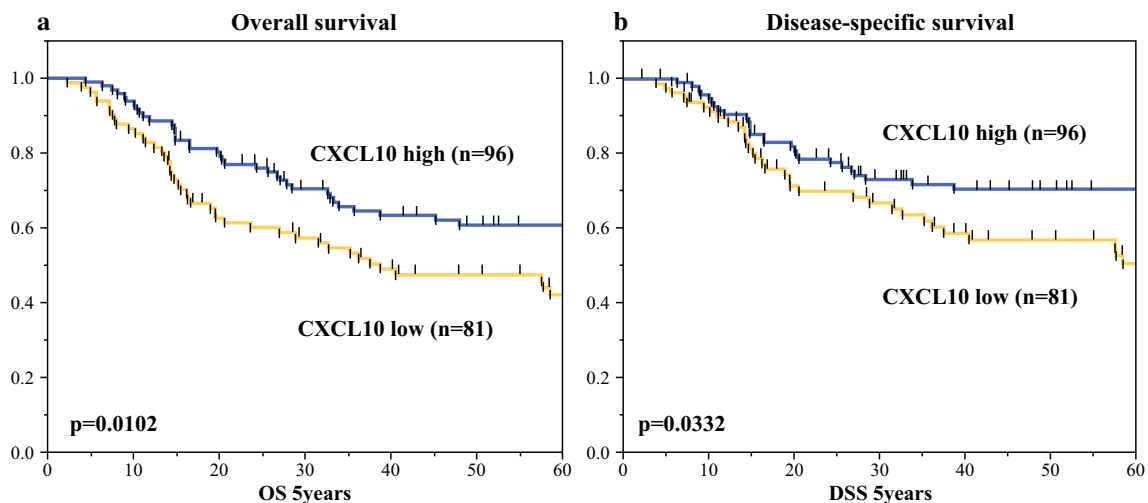


FIG. 2 Five-year OS, DSS, and CXCL10 expression status. Kaplan-Meier analysis of association between CXCL10 expression status (high or low), determined on basis of IHC staining, and 5-year OS (a)

and DSS (b) among ESCC patients. Patients expressing high levels of CXCL10 showed significantly better 5-year OS and DSS than those expressing lower levels ($p = 0.0102$ and 0.0332 , respectively)

between CXCL10 expression status and prognosis in patients with ESCC.

Consistent with the results of this study, low CXCL10 expression was previously found to be an independent

adverse prognosticator in stage II and III colorectal cancer patients.²² This may reflect the inhibitory effects of CXCL10 on angiogenesis and its promotion of immune cell migration to the cancer microenvironment. For

TABLE 2 Analysis by univariate Cox proportional hazard model of 5-year OS

| Variable | <i>p</i> | HR | 95 % CI |
|--|----------|-------|-------------|
| CXCL10 expression: low (<i>n</i> = 81) versus high (<i>n</i> = 96) | 0.0110* | 1.763 | 1.139–2.749 |
| Age: 70 years and older (<i>n</i> = 68) versus younger (<i>n</i> = 109) | 0.0325* | 1.626 | 1.042–2.520 |
| Gender: male (<i>n</i> = 153) versus female (<i>n</i> = 24) | 0.1786 | 1.601 | 0.821–3.606 |
| Depth of invasion: T4 (<i>n</i> = 9) versus T2–3 (<i>n</i> = 168) | 0.3815 | 1.537 | 0.540–3.432 |
| Lymph node metastasis: N2–3 (<i>n</i> = 73) versus N0–1 (<i>n</i> = 104) | <0.0001* | 4.213 | 2.674–6.781 |
| Pathologic stage: IIIB–IIIC (<i>n</i> = 66) versus IB–IIIA (<i>n</i> = 111) | <0.0001* | 3.811 | 2.443–6.017 |
| Tumor differentiation: poor (<i>n</i> = 57) versus not poor (<i>n</i> = 120) | 0.0170* | 1.757 | 1.109–2.742 |
| Treatment: surgery alone (<i>n</i> = 72) versus surgery followed by adjuvant chemotherapy (<i>n</i> = 105) | 0.2205 | 1.318 | 0.845–2.040 |

OS overall survival, HR hazard ratio, CI confidence interval

* Statistically significant

TABLE 3 Multivariable Cox proportional hazard model analysis showing HRs of CXCL10 expression status for 5-year OS

| Variable | <i>p</i> | HR | 95 % CI |
|---|----------|-------|-------------|
| Crude (CXCL10 expression) | 0.0110* | 1.763 | 1.139–2.749 |
| Adjusted for age and gender | 0.0107* | 1.769 | 1.142–2.761 |
| Adjusted for age, gender, lymph node metastasis, pathologic stage and tumor differentiation | 0.0306* | 1.642 | 1.048–2.590 |

OS overall survival, HR hazard ratio, CI confidence interval

* Statistically significant

example, CXCL10 production reportedly correlates inversely with tumor growth in lymphoma, adenocarcinoma of lung, and breast cancer as a result of a marked reduction in tumor-associated angiogenesis.^{23,24} Several investigators

have also shown that CXCL10 exerts significant synergistic antitumor effects through its ability to recruit immature antigen-presenting dendritic cells and activated T cells into the cancer microenvironment in glioma and melanoma.^{25,26}

In ESCC, Lu et al. reported that interleukin 17 could induce ESCC tumor cells to produce inflammatory chemokines, including CXCL10, which were associated with the recruitment of T cells, NK cells, and dendritic cells.¹⁵ On the other hand, high CXCL10 expression was predictive of a significantly poorer prognosis in patients with ovarian cancer.^{27,28} Further, CXCL10 overexpression reportedly promotes tumor growth in breast cancer, colon cancer, basal cell carcinoma, and glioma.^{29–32} These seemingly contradictory effects of CXCL10 in cancer may reflect the expression status of the two splice variants of its receptor, CXCR3.⁸ Whereas overexpression of CXCR3-A appears to

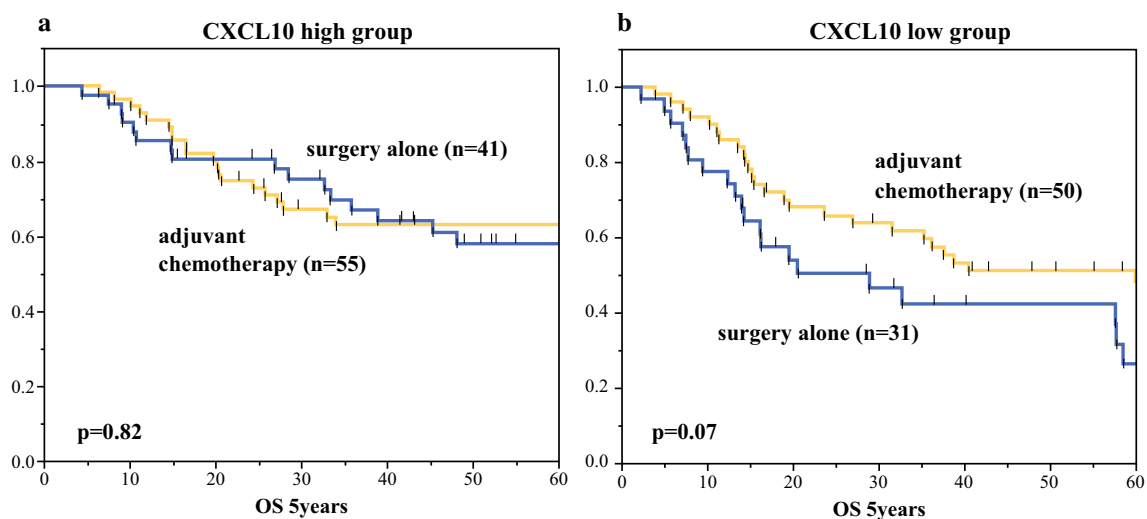


FIG. 3 Adjuvant chemotherapy and 5-year OS among CXCL10 high and low groups. OS among patients in CXCL10 high and low groups treated with surgery alone or with surgery followed by adjuvant chemotherapy. No significant difference between patients treated with

surgery alone or surgery followed by adjuvant chemotherapy was found in CXCL10 high group (a). In CXCL10 low group, patients treated with surgery followed by adjuvant chemotherapy had better 5-year OS than those treated with surgery alone (b)

be involved in promoting breast cancer, CXCR3-B appears to limit tumor growth through angiostatic and/or immunomodulatory actions in several types of cancer.²⁹ However, further study will be needed to clarify the relationship between the CXCR3 splice variants and CXCL10 in ESCC.

In the present study, there was no significant difference in 5-year OS between patients in the CXCL10 high expression group treated with surgery alone and those treated with surgery followed by adjuvant chemotherapy. Among patients in the CXCL10 low expression group, however, those treated with surgery followed by adjuvant chemotherapy had better 5-year OS than those treated with surgery alone. This was despite the fact that the patients treated with surgery followed by adjuvant chemotherapy had more advanced disease than those treated with surgery alone.¹⁹ These results suggest that adjuvant chemotherapy after surgery has the potential to improve the 5-year OS of CXCL10 low patients and might serve as one option for personalized treatment of patients with advanced thoracic ESCC. That said, the beneficial effect of postsurgical adjuvant chemotherapy did not reach statistical significance. Further study with a larger patient population and/or with other populations is needed before clinical application.

In conclusion, our findings indicate that high CXCL10 expression is an independent prognostic factor affecting 5-year OS among patients with advanced ESCC. Moreover, CXCL10 expression status has the potential to serve as a clinically useful marker for evaluating the need for adjuvant chemotherapy after surgery.

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