Determination of Risk Factors Related to Supraclavicular Recurrence for Limited-Stage Small Cell Lung Cancer (SCLC) Patients

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Background: This research aimed to determine high-risk factors of supraclavicular recurrence for limited-stage small cell lung cancer (LS-SCLC) patients to discover a potential subpopulation that can benefit from prophylactic supraclavicular irradiation (PSCI).

Material/Methods: Between July 2006 and July 2011, LS-SCLC patients without supraclavicular lymph node (SCLN) involvement consecutively treated with concurrent chemo-radiation but without PSCI in the Radiotherapy Department of the Cancer Institute and Hospital of Tianjin Medical University, were retrospectively analyzed. SCLN recurrence rate, overall survival (OS), and distant metastasis-free survival (DMFS) were assessed. Binary logistic regression analysis was conducted to discover the high-risk factors related to the SCLN recurrence. The receiver operating characteristic (ROC) curves were drawn to evaluate logistic regression model prediction performance.

Results: Eighty-eight LS-SCLC patients were analyzed in this study. During 99 months (ranging from 72 months to 124 months) for survivors, 28 (31.8%) had SCLN recurrence. There were significant differences for median DMFS and OS between LS-SCLC patients with and without SCLN recurrence. The logistic regression model revealed that lymphadenopathy at mediastinal level 2 and level 3 prior to chemotherapy were significantly associated with SCLN recurrence, which was validated by ROC.

Conclusions: Lymphadenopathy at mediastinal level 2 and level 3 prior to chemotherapy were the high-risk factors associated with SCLN recurrence for patients with LS-SCLC. Further work is needed to determine whether patients with these factors can benefit from PSCI.

MeSH Keywords: Local Lymph Node Assay • Lymph Nodes • Radiotherapy • Risk Factors • Small Cell Lung Carcinoma

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Background

It was estimated that more than 30% of small cell lung cancer (SCLC) cases could be classified as limited-stage (LS-SCLC) according to descriptions of the Veterans Administration Lung Cancer Study Group [1]. Early concurrent chemo-radiotherapy followed by prophylactic cranial irradiation has been considered the standard treatment for LS-SCLC patients [2–8]. However, delivery of prophylactic supraclavicular irradiation (PSCI), which requires radiotherapy for the supraclavicular lymph node (SCLN) area when no sign of supraclavicular involvement exists, is still controversial.

Although some researchers found that SCLN area was one of the most frequently observed recurrent sites when supraclavicular fossa was not included in the radiotherapy field [9–13], and PSCI could achieve dramatically low incidence of SCLN recurrence [14], many radiation oncologists do not use PSCI, given the limited improvement in survival outcomes for the whole cohort of LS-SCLC patients [12]. However, based on our clinical experience, we hypothesized that for LS-SCLC patients with high-risk factors, PSCI could bring significant benefits.

In our previous research [15], we found that the SCLN area was especially vulnerable to tumor metastasis for LS-SCLC patients with mediastinal level 2 and/or level 3 lymphadenopathy, but in that research, the phenomenon was detected in patients with tumor involvement of SCLN at onset of diagnosis. In the long-term follow-up, we could not be sure whether the high-risk factors would still be associated with SCLN recurrence for patients without initial SCLN involvement.

Therefore, we performed the present observational study with long-term follow-up to determine the risk factors associated with SCLN recurrence. Identifying the high-risk factors for SCLN recurrence might help determine the subpopulation that could benefit from PSCI, paving the way for further research on PSCI for LS-SCLC patients.

Material and Methods

Patients

From July 2006 to July 2011, we retrospectively analyzed data from all LS-SCLC patients without SCLN involvement consecutively treated with concurrent chemo-radiation but no PSCI in the Radiotherapy Department of the Cancer Institute and Hospital of Tianjin Medical University. Disease had to be proven by histology through bronchoscopy, percutaneous core needle biopsy, or lymph node excision. The staging processes were mainly contrast-enhanced CT scans of neck, thorax, upper abdomen, and brain, as well as bone scans. Some patients also received cervical and abdominal ultrasound examinations to complement the corresponding CT scans. Enhanced brain magnetic resonance imaging was used if the brain CT was ambiguous. Staging of LS-SCLC was performed according to the AJCC staging manual (sixth edition). The Ethics Committee of Tianjin Medical University Cancer Institute and Hospital approved the research (approval no. 02901510, dated 9 March 2006).

Treatment

Chemotherapy regimens contained etoposide (dosage 100 mg/m^2/day on day 1 to day 3) and cisplatin (dosage 70 mg/m^2/day on day 1). These chemotherapy regimens were also intravenously administered every 3 weeks with 4–6 cycles.

Thoracic radiotherapy began within 3 cycles of chemotherapy. Radiotherapy simulation CT images were obtained with intravenous contrast in supine position with arms above the head during full inspiratory breath-hold. The cervical and thoracic CT images, extending from the cricoid to the second lumbar vertebra, with a 5-mm-thick slices, were acquired when patients were immobilized on a special board for radiotherapy simulation.

Gross tumor volumes (GTV), including primary tumors (GTV primary) and positive lymph nodes (GTV node), were contoured according to radiological images before induction chemotherapy and simulation CT. The primary tumors were delineated on the lung window (level 800 HU; width 1600 HU), while the mediastinal nodes were delineated on mediastinal setting (level 40 HU; width 400 HU). Lymph nodes were considered positive if the short-axis diameter exceeded 1 cm. Mediastinal lymph nodes were classified into different levels according to the 2009 IASLC lymph node map for lung cancer [16].

Clinical target volumes (CTV) consisted of subclinical foci and motion scopes of primary tumors, as well as lymph drainage areas. Subclinical foci were formed by extending 8 mm from GTV primary in every direction. X-ray fluoroscopy was carried out to assess motion of primary tumors. Lymph drainage areas included ipsilateral hilum, the level of GTVnode, and its adjacent mediastinal levels.

Planning target volumes (PTV) were formed by unanimous extension of CTV by setup error, which was approximately 5 mm in our institute. Total dosage of 60 Gy was administered to the PTV (once daily, 5 days a week, with a fraction size of 2 Gy), given concurrently with chemotherapy. If feasible, three-dimensional conformal radiotherapy (3D-CRT) plans were delivered, which were performed using the Electa Precise treatment planning system (Electa AB, Stockholm, Sweden). However, for patients whose tumor coverage or avoidance of normal organs were not satisfactory, intensity-modulated radiotherapy (IMRT)
plans made using the Eclipse treating planning system (purchasing from the Varian Medical Systems, Inc., Palo Alto, CA, USA) were implemented.

The prophylactic cranial irradiations (25 Gy in 10 fractions) were administered to patients who completely or partially achieved response, within 1 month after completion of thoracic radiation and chemotherapy.

Follow-up

The patients underwent chest CT, laboratory tests, physical examination, and the cervical/abdominal ultrasonography once every 2–3 months in 1st year and then once every 3–6 months after 1 year. The metastasis was observed any time by using bone scans or brain MRIs.

We observed SCLN recurrence rate, overall survival (OS), and the distant metastasis-free survival (DMFS) in the cohort. DMFS was defined as the period from when definitive treatment was initiated until the date that distant metastasis occurred. OS was defined as the interval from commencement of definitive treatment to the time of death.

Statistical analysis

Statistical analysis was conducted using Statistical Package for Social Sciences software (version: 19.0, SPSS, Inc., Chicago, Illinois, USA). The actual survival rate and SCLN recurrence rate were calculated with Kaplan-Meier analysis. Differences in survival were analyzed using the log-rank test. We used binary logistic regression analysis to discover the high-risk factors related to SCLN recurrence. The candidate factors involved patient- and tumor-related parameters, including sex, age, primary tumor location, SCLC pathology, stage, radiotherapy technique, and lymphadenopathy in different mediastinal levels prior to chemotherapy. A statistically significant difference was defined as \( p < 0.05 \). We established a model to predict the possibility of SCLN recurrence using the statistically significant features. The receiver operating characteristic (ROC) curve was drawn to evaluate the logistic regression model's prediction performance.

Results

Patient characteristics

From July 2006 to July 2011, 88 patients (median age 57 years, range 18–78 years) were enrolled into the cohort, which had a preponderance of males (65 out of 88, 73.9%). All the patients responded well, with performance scores more than or equal to 80 at the beginning of chemo-radiation. Most patients (75 out of 88, 85.2%) were diagnosed by pathological examination as having pure SCLC. None of the patients had detectable distant metastasis at onset of diagnosis. Three-quarters of patients were classified as stage III, with patient and tumor data shown in Table 1. The patients underwent 4–6 cycles (median 5 cycles) of etoposide-cisplatin triggered chemotherapy. The majority of

### Table 1. Characteristics of the patients and tumors.

| Characteristics             | Cases (n) | Percentage (%) |
|-----------------------------|-----------|----------------|
| Gender                      |           |                |
| Male                        | 65        | 73.9           |
| Female                      | 23        | 26.1           |
| Age                         |           |                |
| ≤60 years                   | 62        | 70.5           |
| >60 years                   | 26        | 29.5           |
| Tumor location              |           |                |
| Upper lobe                  | 45        | 51.1           |
| Middle or lower lobe        | 43        | 48.9           |
| Pathology                   |           |                |
| Pure SCLC                   | 75        | 85.2           |
| Combined SCLC               | 13        | 14.8           |
| N stage                     |           |                |
| N0 stage                    | 2         | 2.3            |
| N1 stage                    | 26        | 29.5           |
| N2 stage                    | 35        | 39.8           |
| N3 stage                    | 25        | 28.4           |
| Staging                     |           |                |
| IIA stage                   | 11        | 12.5           |
| IIB stage                   | 11        | 12.5           |
| IIIB stage                  | 28        | 31.8           |
| Radiotherapy technique      |           |                |
| 3D-CRT                      | 70        | 79.5           |
| IMRT                        | 18        | 20.5           |

3D-CRT – three-dimensional conformal radiotherapy; IMRT – intensity modulated radiotherapy.
the patients underwent 3D-CRT (70 out of 88, 79.5%), while others underwent IMRT. No patient received PSCI. Median follow-up duration was 27 months (range, 10–124 months) for all patients and 99 months (range, 72–124 months) for survivors. One patient was lost to follow-up immediately after treatment.

SCLN recurrence of patients

After the follow-up, 68 of 88 patients died, and none of the 19 patients remaining alive had evidence of metastatic disease. One patient was lost to follow-up and could not be assessed for survival outcome. Twenty-eight patients (31.8%) had SCLN recurrence by the last follow-up (Figure 1).

Survival outcomes

For the whole cohort, the median DMFS and OS were 18 months and 27 months, respectively. We analyzed DMFS and OS in terms of whether patients had SCLN recurrence. The median DMFS was 21 months and 16 months for patients without and with SCLN recurrence, respectively (p=0.012) (Figure 2A). The median OS were 31 months and 23 months for patients without and with SCLN recurrence, respectively, (p=0.009) (Figure 2B).

Logistic regression and ROC

In the logistic regression model, level 2 denoted the status of mediastinal level 2 lymph nodes, with lymphadenopathy as 1 and no lymphadenopathy as 0. Similarly, level 3 denoted the status of mediastinal level 3 lymph nodes. From the model, we could calculate that lymphadenopathy at either level 2 or level 3 made the possibility of SCLN recurrence close to 100%.

ROC analysis was used to assess the prediction power of logistic regression (Figure 3). The area under the ROC curve (AUC) for using this model to predict SCLN recurrence probability was 0.905.

Discussion

Thoracic irradiation has been demonstrated to be an indispensable part of concurrent chemo-radiotherapy for LS-SCLC
According to the survival analysis and logistic regression model, our research confirmed the previous findings by our team and also confirmed our hypothesis. Lymphadenopathy in mediastinal level 2 and/or level 3 before chemotherapy dramatically increases the possibility of SCLN recurrence for patients with LS-SCLC, and this was validated by an AUC of more than 0.90. Thus, these patients might potentially benefit from PSCI.

When long-term survival outcomes (DMFS and OS) were taken into consideration, SCLN recurrences were found to be significantly correlated with poor prognosis or progression, consistent with findings of Urban et al. and Han et al. [9,11]. The close association of SCLN recurrence with distant metastasis might be explained by the closeness of the SCLN with the thoracic duct and right lymphatic duct, which are also the drainage destinations of supraclavicular lymph vessels. These 2 lymphatic ducts eventually drain into the systemic blood circulation. Our findings emphasize the need to prevent SCLN recurrence, with PSCI as a direct and potentially effective approach to prevent migration of tumor cells into blood, thus cutting off one path of systematic metastasis.

We found a formidable SCLN recurrence rate of as high as 31.8%. The reason for more frequent SCLN recurrence could be the much longer follow-up duration (a median of 99 months for survivors in our study) than in any other study mentioned above. When follow-up duration was extended, more recurrence could be observed. The other reason might be the larger proportion of high-risk patients in our cohort. More than one-third (30 out of 88) of the cohort were defined as high-risk patients according to our regression model.

However, the shortcomings of this research are obvious and should be addressed in future trials. The most notable weakness was the retrospective nature of this study. Some bias must exist in retrospective analysis, so our future work will include a prospective randomized controlled clinical trial to reach firm conclusions. The other problem of this study was use of radiation delivered once daily (QD) instead of the standard practice of twice daily (BID). However, some previous studies found there were no differences in overall survival with QD (more than or equal to 60 Gy) versus BID (45 Gy) radiotherapy [24,25], which could justify our method. Even the BID cornerstone study – the Intergroup 0096 trial – allowed the radiation field to incorporate the supraclavicular region if there was bulky superior mediastinal adenopathy [18], which was similar with our definition of the SCLN recurrence high-risk group.

**Conclusions**

LS-SCLC patients with lymphadenopathy in mediastinal level 2 and/or level 3 before chemotherapy experienced extraordinarily
high SCLN recurrence if no PSCI was used. SCLN recurrence was significantly related to poor prognosis and/or progression. It may be necessary to perform PSCI for LS-SCLC patients with high-risk factors. However, further prospective clinical trials are needed.

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Conflict of interest

None.