Is neoadjuvant chemotherapy mandatory for limited-disease small-cell lung cancer?

Yong-jie Xu,†, Hui Zheng,‡, Wen Gao,§, Ge-ning Jiang,¶, Hui-kang Xie,‖, Chang Chen,* and Ke Fei,‡

*,‡ Department of Pathology, Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai, China
§ Department of General Thoracic Surgery, Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai, China
¶ Department of Pathology, Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai, China
† Corresponding author. Zhengmin RD. 507, Shanghai 200433, China. Tel: +86-21-65115006; fax: +86-21-65111298; e-mail: changchenc@hotmail.com (C. Chen), ffeik126@126.com (K. Fei).

Received 1 December 2013; received in revised form 16 April 2014; accepted 2 May 2014

Abstract

OBJECTIVES: The present study attempted to evaluate the role of neoadjuvant chemotherapy combined with surgery in limited-disease small-cell lung cancer (LD-SCLC).

METHODS: A retrospective analysis was performed on 106 LD-SCLC patients who underwent complete resections from February 2000 to February 2012 in Shanghai Pulmonary Hospital. Among these cases, two cycles of neoadjuvant chemotherapies were administered to all pathologically confirmed patients [Group Neoadjuvant (Group N)]. For those without pathology, operations followed by adjuvant chemotherapies were performed [Group Adjuvant (Group A)]. Prognostic features and overall survival (OS) were compared using the log-rank test and calculated using the Kaplan–Meier method.

RESULTS: Group N included 47 cases and Group A included 59 cases. A total of 57 patients were male and 49 were female, with a mean age of 56.1 ± 10.2 years. A total of 41 patients were at pathological stage (p-Stage) I-II, and 65 patients were at I or II. The overall 5-year survival rate (5-YS) was 28%. The 5-YS for p-Stage I-II (n = 65) was significantly better than that of p-Stage III (n = 41) (35 vs 20%, P = 0.034). For p-Stage I-II (pN2 positive), the 5-YS of Group N was significantly better than that of Group A (34 vs 12%, P = 0.020). The median overall survival for Group N and Group A in I-IIa (pN2 positive) LD-SCLC patients were 46 and 15 months (P = 0.009), respectively. Multivariate analysis for survival showed mediastinal lymph node involvement; surgery and histopathology of SCLC were both significant independent predictors of long-term survival.

CONCLUSIONS: Neoadjuvant chemotherapy combined with surgery provided reasonable options for pIIa-N2 LD-SCLC patients, which can give them a better chance of survival.

Keywords: Small cell lung cancer • Neoadjuvant chemotherapy • Surgery

INTRODUCTION

Small-cell lung cancer (SCLC) accounts for about 14% of all lung cancers [1] and is particularly well known for its highly malignant nature and frequently occurring metastasis at an early stage [2]. Although chemotherapy has been the mainstay of treatment [3, 4] because of the extreme high sensitivity of these tumours, multi-modality treatment combined with surgery provides additional survival benefits for surgically indicated SCLC cases. Eberhardt et al. [5] reported that the 5-year survival rate (5-YS) was 63% and the local control rate was 100% for 23 completely resected SCLC cases. Using chemotherapy alone, the local recurrence rate reached 50% [6, 7]. Therefore, an effective combination of chemotherapy and surgery is the key treatment for indicated SCLC candidates.

A usual management of a newly diagnosed limited-disease SCLC (LD-SCLC) case is to treat the patient with immediate chemotherapy; however, operations are commonly performed after two or more cycles of chemotherapy. Fujimori et al. [8] reported experiences of induction chemotherapy with subsequent operations for LD-SCLC patients; the 3-year survival rate (3-YS) was 73%. However, few data exist regarding a contemporary survival comparison between LD-SCLC surgery patients who undertook neoadjuvant and adjuvant chemotherapy. In Hara’s case series [9], for LD-SCLC patients, the 3-YS of induction chemotherapy with subsequent operations was 42%, whereas that of initial surgery combined with adjuvant chemotherapy was 33%; there was no significant difference between these groups (P > 0.05).

The report by the Japan Clinical Oncology Lung Cancer Study Group [10] showed that patients with LD-SCLC who were receiving adjuvant chemotherapy, four cycles of cisplatin and etoposide, followed by initial surgery yielded a 57% 5-YS. Brock et al. [11] reported a similar result that patients with LD-SCLC receiving surgery combined with adjuvant platinum chemotherapy yielded a 5-YS of 68%. However, according to the guideline [12], this result that initial surgery combined with adjuvant chemotherapy was performed for LD-SCLC surgery patients can be further discussed.
In this statement, for LD-SCLC cases, operations may be performed before chemotherapy. Therefore, a potentially conflicting circumstance may arise in managing a new LD-SCLC case: which should be the initial option, chemo or surgery? The present study attempted to evaluate whether the neochemotherapy option for patients with LD-SCLC yield long-term survival.

PATIENTS AND METHODS

Approval for the study was obtained from the Ethics Committee of the Hospital.

Patients

A total of 112 LD-SCLC patients underwent radical surgical resections in Shanghai Pulmonary Hospital, from February 2000 to February 2012. LD-SCLC was characterized by tumors confined to one hemithorax, with local involvement of ipsilateral and contralateral supraclavicular nodes, and ipsilateral and contralateral hilar or mediastinal nodes could be present [13].

Preoperative workup included chest CT, ultrasound scan of abdomen, brain MRI, whole-body bone scan and bronchoscopy, which aimed to exclude remote metastasis. Positron emission tomography was not commonly used. All 112 patients underwent exfoliative cell examination of sputum, bronchoscopic brush biopsy and traditional bronchoscopic biopsy. In addition, 13 patients received transthoracic needle pneumocentesis and 2 patients underwent mediastinoscopy. According to the SCLC management guideline in our department [14], in patients with a definite SCLC diagnosis obtained before surgery, neoadjuvant chemotherapy was performed, including an etoposide and cisplatin (EP) regimen (etoposide 25 mg/m² on Days 1–3; cisplatin 100 mg/m² on Day 1). The regimen was administered in 2 courses at an interval of 3 weeks. After neoadjuvant therapy, the tumour stage was re-evaluated by chest CT, ultrasound scan of abdomen, brain MRI, whole-body bone scan and bronchoscopy. Given that endobronchial ultrasonography (E-BUS) was introduced to our hospital in 2004, it had been the standard procedure to perform tumour staging for patients between 2004 and 2012. However, before 2004, invasive mediastinal staging after neoadjuvant chemotherapy was not carried out and, so far, mediastinoscopy has not become universal. Patients underwent surgery when they were diagnosed as being partially in remission or when their tumour was stable after preoperative chemotherapy. However, patients who had indefinite pathological diagnosis of SCLC before surgery received initial surgery followed by postoperative adjuvant therapy.

After neoadjuvant chemotherapy, patients in complete remission or those whose conditions had progressed were excluded from the study because surgery was not performed for these patients. In this study, cases were excluded because the results yielded incomplete follow-up data for 1 case and 5 patients did not receive postoperative chemotherapy; 2 of the patients underwent surgery alone because they refused postoperative adjuvant therapy and 3 patients only received postoperative radiotherapy for distant metastasis of tumour. R0 resections with either neoadjuvant or adjuvant chemotherapy were administered to the remaining 106 patients, who were included in this study.

Pathological diagnosis was based on the 2004 WHO classification of tumours. The pathological stage (p-Stage) was determined according to the 6th edition of Tumor, Node, Metastasis classification of lung cancer [15].

Grouping

Two groups were assigned for further statistical analysis: Group Adjuvant (Group A), in which only postoperative chemotherapies were administered, and Group Neoadjuvant (Group N), in which surgery was combined with both 2 cycles of pre- and postoperative chemotherapy, respectively. Patients were assigned to Group A if they had an indefinite pathological diagnosis before surgery. Those with a definite SCLC diagnosis obtained before surgery were assigned to Group N.

Adjuvant treatment and follow-up

All 106 patients received postoperative adjuvant EP (cisplatin 80 mg/m² on Day 1, etoposide 100 mg/m² on Days 1–3)-based chemotherapy for at least 2 cycles. When relapse was apparent or lymph node fusion occurred during operation, postoperative radiotherapy was performed. All patients were followed up by telephone, letters or an out-clinic visit. Every follow-up assessment included a chest CT, ultrasound scan of abdomen, brain MRI and whole-body bone scan. Follow-up intervals were 1 month, 3 months, 6 months, within 2 years postoperatively and then every 1 year thereafter.

Statistical analysis

The survival rate and evaluation of the difference was calculated using the Kaplan–Meier method and the log-rank test. Multivariate analysis of the prognostic factors was performed using Cox’s regression model [16]. Categorical variables were compared using a χ² test. The differences between continuous variables were assessed using the Mann–Whitney U-test. A P ≤ 0.05 was considered statistically significant. All statistical analyses were performed with SPSS 20.0.

RESULTS

General information

The current study included 57 males (54%) and 49 females. The mean age was 56.1 ± 10.2 years. A total of 25 cases were confirmed at p-Stage Ia, 13 at pIb, 13 at pIIa, 14 at pIIb and 41 at pIIIA. Pure SCLC was confirmed in 88 cases and 18 cases were of mixed SCLC type containing small-cell carcinoma and squamous-cell carcinoma (Table 1). In addition to radical resection, 47 patients received neoadjuvant treatment as well as followed adjuvant chemotherapy (Group N); of these, 24 were proved to be SCLC before surgery by exfoliative cell examination of sputum and bronchoscopic brush biopsy, 12 patients by transthoracic needle pneumocentesis, 9 patients by E-BUS and 2 patients by mediastinoscopy. The remaining 59 patients only received adjuvant chemotherapy (Group A) because there was no pathological evidence of SCLC before surgery, although all of them underwent exfoliative cell examination (59), 5 of them E-BUS and 1 received transthoracic needle pneumocentesis. During the study period, a total of 7
patients experienced progression of disease after receiving neoadjuvant therapy and 3 of them died. Given that no surgery was performed, these 7 patients were not enrolled in our study.

During our follow-up, prophylactic cranial irradiation (PCI) was performed in 36 patients with brain metastases. Thirteen patients received thoracic radiotherapy because of local recurrence and lung metastasis. Thoracic radiotherapy also was performed in 6 patients in whom lymph node fusion occurred during operation. In this study, recurrence was noted 59 patients. Local failure was noted in 4 patients in Group N and 9 in Group A. Distant failure was found in 46 (43%) patients, including 19 in Group N and 27 in Group A. Furthermore, the study showed that distant failure was most frequently found in the brain (Group N: 14 patients; Group A: 22 patients) and the overall incidence rate of brain metastasis was 34% (36 patients). PCI was performed in all patients with brain metastases. Thirteen patients received thoracic radiotherapy because of local recurrence and lung metastasis (Group N: 4 patients; Group A: 9 patients). Ten patients did not complete radiotherapy, including 4 patients in Group N and 6 in Group A, because of progressive disease in 3 patients, adverse effects in 4 and refusal of radiotherapy in 3. Thoracic irradiation was performed at 2 Gy per day up to 45 Gy, whereas PCI was performed at 2.5 Gy per day up to 25 Gy.

Table 2 gives the clinical and pathological staging. For the 106 (Group N: 47, Group A: 59) patients with both clinical and pathological staging, the number whose stage was considered better at pathological staging (down-staging) was 14 (30%) in Group N. The number of patients whose pathological staging was reported as worse than the clinical staging (up-staging) was 11 (19%) in Group A and 2 (4%) in Group N. In terms of Tumor and Node stage, 24 and 2% in Group N were regarded as having a lower N stage and the respective proportions for T stage after surgery.

**Table 2:** Comparison of the clinical and pathological stage for the 2 groups

<table>
<thead>
<tr>
<th>Clinical stage (preoperative)</th>
<th>Pathological stage (postoperative)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>Group N</td>
</tr>
<tr>
<td>IA</td>
<td>59</td>
</tr>
<tr>
<td>IB</td>
<td>22 (37%)</td>
</tr>
<tr>
<td>II</td>
<td>12 (20%)</td>
</tr>
<tr>
<td>IIIa</td>
<td>7 (12%)</td>
</tr>
<tr>
<td>IIIb</td>
<td>5 (9%)</td>
</tr>
<tr>
<td>IIIA</td>
<td>13 (22%)</td>
</tr>
</tbody>
</table>

Group N: Group Neoadjuvant; Group A: Group Adjuvant.

**Operations and postoperative complications**

As expected during chemotherapy, the severity of several symptoms among Group N diminished; there were no clear differences between the 2 groups. Both groups were occasionally reported as having continued cough, breathlessness, lethargy and chest pain.

All 106 patients underwent radical resections and systematic sampling. Ninety-three patients underwent thoracotomy: 42 in Group N and 51 in Group A. Thirteen patients received Video Assisted Thoracic Surgery: 5 in Group N and 8 in Group A. The intraoperative mediastinal lymph node strategy was performed by the systematic sampling of L4, L5, L6, L7, L8, L9, L10 on the left side, and R2, R4, R7, R8, R9, R10 on the right side, if present. In addition, sleeve resections were performed in 12 patients.

Lobectomy was performed in 54 patients, including right upper lobectomy (n = 17), right middle lobectomy (n = 3), right lower lobectomy (n = 11), left upper lobectomy (n = 17) and left lower lobectomy (n = 6). Bilobectomies were performed in 14 patients, included right middle and upper lobectomy (n = 1), and right middle and lower lobectomy (n = 13). Pneumonectomy was performed in 38 patients, including left side (n = 22) and right side (n = 16).

Postoperative complications were noted in 21 cases, which included prolonging air leaks in 10 cases with prolonged chest tube drainage under negative pressure (>2 weeks); pulmonary infections in 6 cases, which was cured after an additional 2 weeks of antibiotic therapy; respiratory failure in 1 case; arrhythmias in 3 cases; and chylothorax in 1 case. All patients were cured after symptomatic treatment.

**Follow-up information**

The follow-up ended on 1 June 2012. The follow-up rate was 89% and the mean follow-up time was 28.9 months. At the end of follow-up, 51 patients were alive, including 24 in Group N and 27 in Group A, whereas 55 patients had died (23 patients in Group N and 32 in Group A). Local–regional recurrence was found in 6 patients who were alive; 2 in the bronchial stump and 4 in the mediastinal lymph nodes. Twenty-one patients died of distant metastasis. Remote metastasis was most frequently noted, which accounted for 38% overall.
Survival analysis

The overall 5-YS was 28%. There was no statistical difference in 5-YS of Group N and Group A (32 and 25%, $P = 0.63$), respectively. However, the 5-YS of the 65 patients with p-Stage I–II was significantly better than that of the 41 patients with p-Stage III (35 vs 20%, $P = 0.034$) (Fig. 1A). It was also revealed that the 5-YS of patients with lobectomy was better than that of those who underwent pneumonectomy, 33 vs 18% ($P = 0.023$, Fig. 1B).

In p-Stage I–II (pN0–1), the 5-YS of 33 patients in Group A was 37% and that of the 32 patients in Group N was 33%; there was no statistical difference between the two groups ($P = 0.19$) (Fig. 2A). However, for patients with p-Stage III, especially pN2 positive, neoadjuvant chemotherapy combined with surgery provided a better long-term survival than adjuvant chemotherapy combined with surgery. Interestingly, there was a significant difference in survival between the 2 groups for patients with p-Stage III (pN2 positive). The median overall survival (OS) for Group N and Group A in IIIa (pN2 positive) LD-SCLC patients were 46 and 15 months ($P = 0.009$), respectively. The 5-YS of Group N was 34%, which was much higher than the 12% of Group A ($P = 0.020$) (Fig. 2B).

Univariate survival analysis

A univariate analysis for prognostic factors of survival was performed first by a log-rank test. Results showed that the survival of patients with p-Stage III (pN2 positive) was worse than that of those with p-Stage I–II (pN0–1) ($P = 0.039$). In addition, different histological types of SCLC ($P = 0.022$) and surgical types ($P = 0.027$) were statistically significant risk factors for survival (Table 3).
patients with LD-SCLC [17]. Unfortunately, local–regional relapse is still frequent (26–63%) [18–20]. Some reports [5, 21, 22] have suggested that, in the multimodality approach of LD-SCLC, surgical resection reduces local relapse and improves the survival outcome of patients with LD-SCLC. Therefore, surgery combined with chemoradiotherapy has become a candidate treatment modality for patients with LD-SCLC. A survival benefit has also been shown in advanced and non-metastatic diseases [23]. A significant survival advantage can be obtained in patients with initially resectable NSCLC with neoadjuvant chemotherapy as well as after surgery as an adjuvant treatment. However, neoadjuvant chemotherapy is mandatory for patients with LD-SCLC, which has yet been indefinable.

The results clearly showed that neoadjuvant chemotherapy is feasible; 47 of the patients in Group N who received 2 cycles of chemotherapy showed acceptable improvement of several symptoms. Furthermore, a comparison of prechemotherapy clinical staging and surgical–pathological staging showed that, although 19% of Group A and 2% of Group N patients had their staging revised, a greater proportion, 30% in Group N, were reported as having a better pathological than clinical stage; this is presumably as a result of neoadjuvant chemotherapy. Surgery seemed unaffected by the delay of about 9 weeks taken to deliver the neoadjuvant chemotherapy, with similar proportions of patients proceeding to surgery. It is suggested that a small proportion of patients (~5%) were able to have lobectomy rather than a pneumonectomy as a result of neoadjuvant chemotherapy, which is in line with surgical expectations and dependent on the position of the tumour and nodes. Similar proportions of patients were considered to have had a complete resection, and postoperative complications and time in hospital post-surgery were also similar in the 2 treatment arms. In addition, we did not observe any increase in treatment-related deaths after neoadjuvant chemotherapy and pneumonectomy.

When surgery was combined with chemotherapy-treated LD-SCLC, the survival of Stage I–II was better than that of Stage III. Ju et al. [24] reported that the 3-YS of p-Stage I–II was 84%, which was obviously better than the 13% 3-YS of p-Stage III. In our study, the 5-YS of p-Stage I–II was 35% and that of p-Stage III was 20%, which was significantly different (P = 0.034). In the multimodality treatment of patients with p-Stage I–II, initial surgery followed by adjuvant chemotherapy resulted in more favourable survival and prognosis, which was similar to that seen in neoadjuvant chemotherapy with surgery. Hara et al. [9] reported that the 5-YS of 14 patients with Stage I–II who received surgery and postoperative chemotherapy was 54%, and that of 10 patients with Stage I–II who received surgery combined with pre- and postoperative chemotherapy was 51%. In our study, during the treatment of p-Stage I–II, 5-YS of 33 patients in Group A was 37%, which was not significantly different from that of 32 patients in Group N (33%, P = 0.19). Similar benefits will be obtained by initial neoadjuvant chemotherapy combined with surgery as well as radical resection followed by postoperative chemotherapy for patients with Stage I and, probably, Stage II disease.

There was an improvement of the OS for patients who received neoadjuvant chemotherapy before surgery for LD-SCLC. For resectable Stage III, particularly in patients with N2 disease, neoadjuvant chemotherapy after resection may be a favourable choice in the management of LD-SCLC because neoadjuvant chemotherapy provided a better survival than did surgery followed by adjuvant chemotherapy. Hara et al. [9] revealed that the median survival time of patients with Stage III who received initial chemotherapy was 29 months, which was significantly higher than the 17 months for those received initial surgical resection. When

**DISCUSSION**

In general, systemic chemotherapy using cisplatin/etoposide with concurrent thoracic irradiation is rational in the treatment of
comparing our results, the 5-YS of 34% for 15 patients with p-Stage III who received neoadjuvant chemotherapy combined with surgery was apparently higher than the 12% of 26 patients with p-Stage III who did not receive preoperative chemotherapy; this difference was statistically significant (P = 0.020). It was revealed that neoadjuvant chemotherapy was not an independent prognostic factor, rather a strong tendency in the multivariate analysis for survival in all cohorts (P = 0.052; HR: 1.85; 95% CI: 1.00–3.43). The probable reason for this finding might be that there was a large proportion of p-Stage I–II patients in our study, ~61%. It is interesting that, in our further multivariate analysis of prognostic factors based on LD-SCLC patients with p-Stage III (pN2 positive) disease, the result showed that neoadjuvant chemotherapy was an independent factor that strongly affected survival and prognosis (P = 0.001; HR: 5.77; 95% CI: 2.15–15.47). The present study supports the result that neoadjuvant chemotherapy combined with surgery is a reasonable option for LD-SCLC patients with p-Stage III, especially pN2 positive disease because of the improved survival of these patients.

We also considered the methods of surgery as another important predictive factor for long-term survival. Weksler et al. [16] reported that the median survival of patients who received lobectomy or pneumonectomy resection was significantly longer than that of patients who received wedge resection. This study revealed that the 5-YS of patients with lobectomy was better than that of those who underwent pneumonectomy: 33 vs 13% (P = 0.023, Fig. 1B). This result may be attributed to the effect of Stage T or N down-staging by neoadjuvant chemotherapy, which helps patients obtain more survival benefit from radical resection.

Despite these positive results, several limitations of our study must be noted. First, this was a retrospective single-institution study. A retrospective analysis is susceptible to various sources of bias, which may not have been identified and controlled. Second, information of local recurrence and disease-free survival is limited because of the long time period of data collection (from 2000 to 2012). Third, because our study used a small series, additional prospective randomized, controlled trials with the same background are needed using a larger series.

We concluded that neoadjuvant chemotherapy combined with surgery is a reasonable option for LD-SCLC patients with Stage III, especially pN2 positive disease because of the significant improvement in survival. In addition, down-staging induced by neoadjuvant chemotherapy helps diminish several symptoms, although there is no significant difference in the 5-YS for LD-SCLC patients with Stage I–II disease. Finally, neoadjuvant chemotherapy combined with surgery might be recommended, especially for Stage III patients with LD-SCLC.

ACKNOWLEDGEMENT

The authors thank Li-ling Zou (Department of Statistics, Tongji University School of Medicine) for her assistance with statistical analysis.

Funding

This work was supported by Shanghai Municipal Committee of Science and Technology research projects (Nos. 11411951300 and 11DZ1973202).

Conflict of interest: none declared.

REFERENCES


