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ORIGINAL ARTICLE

Efficacy of surgery combined with chemoradiotherapy in treating limited-stage small cell lung cancer and prognosis analysis

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Summary

Purpose: *The aim of this study was to compare the efficacy of surgery combined with conventional chemoradiotherapy in the treatment of limited-stage small cell lung cancer (LS-SCLC), and analyze the factors affecting prognosis.*

Methods: *A total of 122 LS-SCLC patients were diagnosed via histopathology, of which 61 were operated combined with chemoradiotherapy (comprehensive treatment group), and 61 underwent conventional chemoradiotherapy (chemoradiotherapy group). The Kaplan-Meier method wand log-rank test were used to analyze the overall survival of the patients. Cox proportional hazard regression model was utilized for multivariate analysis of prognosis.*

Results: *The median survival time of the patients was 27 months in the comprehensive treatment group and 22 months in chemoradiotherapy group. The 1-, 3- and 5-year survival rates were 91.8% (56/61), 49.2% (30/61) and 31.1% (19/61), respectively, in the comprehensive treatment group, and 80.3% (49/61), 32.8% (20/61) and 23.0% (14/61), respectively, in the chemoradiotherapy group. The results of log-rank test on the overall survival rate of the two groups of patients revealed that the overall survival rate was overtly higher in the comprehensive treatment group than that in the chemoradiotherapy group. According to stratification analysis of the TNM stage, the 1-, 3- and 5-year survival rates of the patients with stage I + II LS-SCLC were evidently higher in the comprehensive treatment group than those in the chemoradiotherapy group. Multivariate analysis results uncovered that the clinical TNM stage was an independent factor affecting the survival time of the patients.*

Conclusions: *Surgery combined with chemoradiotherapy may benefit the patients with stage I and II LS-SCLC, while radiotherapy combined with chemotherapy is more suitable for the patients at stage III. TNM stage is an independent factor affecting the prognosis of LS-SCLC.*

Key words: *small cell lung cancer, limited-stage, surgery, chemoradiotherapy, efficacy, prognosis*

Introduction

Small cell lung cancer (SCLC), one of the basic types of lung cancer, accounts for 15-20% of lung cancers, which is clinically featured by short tumor cell doubling time, fast progression, distant metastasis in the early stage, sensitivity to radiotherapy and chemotherapy, fast local recurrence and poor long-term efficacy, with a mean survival time of 8-10 months and a 2-year survival rate of 10-15% [1, 2]. According to the Veterans Administration Lung Study Group staging, SCLC is divided into limited-

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stage and extensive-stage [3]. At first visit to a doctor, about 1/3 patients are diagnosed with limited-stage SCLC (LS-SCLC), and the standard treatment adopted is radiotherapy combined with chemotherapy [4]. Radiotherapy combined with chemotherapy greatly improves the survival rate and local control rate of LS-SCLC in comparison with previous monotherapy [5,6]. After TNM staging system is introduced in SCLC, the role of surgery in LS-SCLC is reassessed, but comparative studies of the prognosis of surgery combined with chemotherapy and radiotherapy combined with chemotherapy in treating LS-SCLC remain absent [7].

This study, therefore, retrospectively analyzed the clinical data of 122 LS-SCLC patients receiving surgery-based combined therapy and conventional chemotherapy and radiotherapy, evaluated the curative effect of the combined therapy in LS-SCLC, and investigated the prognosis and survival and relevant influencing factors, hoping to provide a reasonable reference for decision-making in clinical practice.

Methods

Subjects

A total of 122 LS-SCLC patients receiving radical treatment in our hospital from March 2014 to March 2016 were selected, including 79 males and 43 females, aged 21-70 years old with a median of 53.1 years old. All patients were definitely diagnosed with SCLC by histopathology or cytopathology. Besides, they had good general condition, and had not surgery or radiotherapy previously. These patients were divided into comprehensive treatment group (n=61, surgery combined with chemoradiotherapy was adopted) and chemoradiotherapy group (n=61, conventional radiotherapy combined

Table 1. Baseline demographic and clinical characteristics of the studied patients

Parameters	*Comprehensive group (n=61)* *n (%)*	*Chemoradiotherapy group (n=61)* *n (%)*	*p value*
Age, years			0.453
<60	41 (67.2)	36 (59.0)	
≥60	20 (32.8)	25 (41.0)	
Gender			0.449
Male	37 (60.7)	42 (68.9)	
Female	24 (39.3)	19 (31.1)	
Tumor location			0.717
Left lobe	33 (54.1)	30 (49.2)	
Right lobe	28 (45.9)	31 (50.8)	
Tumor site			0.129
Central	35 (57.4)	44 (72.1)	
Peripheral	26 (42.6)	17 (27.9)	
T staging			0.415
T_1+T_2	47 (77.0)	42 (68.9)	
T_3+T_4	14 (23.0)	19 (31.1)	
N staging			0.273
N_0-N_1	38 (62.3)	31 (50.8)	
N_2-N_3	23 (37.7)	30 (49.2)	
TNM staging			0.602
I+ II	36 (59.0)	31 (50.8)	
III_A	24 (39.4)	28 (45.9)	
III_B	1 (1.6)	2 (3.3)	
ECOG score			0.309
0	43 (70.5)	36 (59.0)	
1	16 (26.2)	20 (32.8)	
2	2 (3.3)	5 (8.2)	
Chemotherapy cycles			0.462
<4	23 (37.7)	27 (44.3)	
≥4	38 (62.3)	34 (55.7)	

TNM: tumor, lymph node, metastasis; ECOG: Eastern Cooperative Oncology Group.

with chemotherapy was performed) based on different local treatment methods. In accordance with the 2010 American Joint Committee on Cancer (AJCC) staging criteria for lung cancer applied, there were 67 cases of stage I + II LS-SCLC, 52 cases of stage III_A LS-SCLC and 3 cases of stage III_B LS-SCLC. The clinical baseline data of the patients in two groups (Table 1) showed no statistically significant differences (p>0.05). All patients enrolled were informed and signed the informed consent in accordance with Declaration of Helsinki. This study was approved by the Ethics Committee of Shanghai Pudong New Area People's Hospital.

Therapeutic methods

In the comprehensive treatment group (n=61), 41 patients underwent radical lobectomy, including 23 patients undergoing left lung lobectomy and 18 patients undergoing right lung lobectomy, and 20 patients had total pneumonectomy plus non-pulmonary hilar and mediastinal lymph node dissection, including 10 cases of left total pneumonectomy and 10 cases of right total pneumonectomy. The chemotherapy regimen: EP (etoposide at 100 mg/d from day 1 to day 5 + cisplatin at 20 mg/d from day 1 to day 5) or EC (etoposide at 100 mg/d from day 1 to day 5 + carboplatin at 0.1 g/d from day 1 to day 5) for 1-10 cycle(s), with 21-28 days as one cycle, and the median cycle was 4 cycles.

In chemoradiotherapy group (n=61), 13 patients received induction chemotherapy + concurrent chemoradiotherapy, 17 patients underwent concurrent chemoradiotherapy + consolidation chemotherapy, and 31 patients had induction chemotherapy + concurrent chemoradiotherapy + consolidation chemotherapy, and the chemotherapy regimen was the same as that in the comprehensive treatment group. The radiotherapy dose: the dose at the tumor isocenter was used as prescribed dose, 30.0-73.0 Gy/15-36 times, once a day, with a single dose of 1.8-2.0 Gy and a median dose of 56 Gy. The ray energy: 6 MV X-ray was selected to irradiate lesions and metastatic lymph nodes, and three-dimensional conformal or intensity-modulated radiotherapy was performed throughout the whole process. The principle of radiation therapy was to concentrate the high-dose area into the lesion area, and to minimize the volume and dose to normal lung tissues and the heart. The length of the spinal cord irradiated was <10 cm, and the highest dose was <45 Gy.

Observation indexes

The response evaluation was carried out as per the World Health Organization (WHO) early response evaluation grading standards in solid tumors. Chest CT or MRI was performed at 2-3 months after the end of treatment, and the results were compared with those before treatment. The response was classified into complete response (CR): complete regression of tumors for at least 4 weeks, without new lesions, partial response (PR): tumor regression >50% for at least 4 weeks, without new lesions, stable disease (SD): tumor regression <50% or tumor enlargement <25%, without new lesions, and progressive disease (PD): tumor enlargement ≥25% or with new lesions (including metastasis).

Acute adverse reactions were evaluated in accordance with the commonly used drug toxicity standard (version 3.0), and hematologic changes and acute radiation induced pneumonia and esophagitis were mainly recorded. Advanced adverse reactions were assessed according to the American Radiation Therapy Oncology Group classification criteria for advanced radiation injury.

All patients were followed up to record their survival. Total survival time referred to the time from the first day of treatment to the day of death or last follow-up. Progression-free survival time was defined as the time from the first day of treatment to the day of first event (recurrence, metastasis or tumor progression). The last follow-up was on May 31, 2019.

Statistics

SPSS 22.0 statistical software (IBM, Armonk, NY, USA) was utilized for statistical analyses. Measurement data were expressed as mean ± standard deviation, and t-test was employed for comparison between two groups. Enumeration data were expressed as ratio (%), and x^2 test was used for comparison among groups. Survival curves were plotted according to Kaplan-Meier method. Log-rank test was utilized to compare the effects of single factors such as age, gender, tumor site, surgical procedure, tumor (T) stage, node (N) stage, chemotherapy cycle and treatment method on the prognosis of patients. With Cox proportional hazard regression model, the variables with statistical significance in univariate analysis were included in multivariate analysis to find out the independent risk factors affecting prognosis. P<0.05 suggested that the difference was statistically significant.

Results

Comparison of preoperative stage with postoperative pathological stage in the comprehensive treatment group

The postoperative staging was also carried out based on the TNM staging criteria. Stage change was detected in 13 patients at preoperative clinical stage I, II and III, and the conformity of clinical

Table 2. Comparison of pre-surgery and post-surgery TNM staging of the studied patients in the comprehensive group

Pre-surgery TNM staging	*Post-surgery TNM staging*					
(Cases)	I_A	I_B	II_A	II_B	III_A	III_B
I_A (3)	2	1	0	0	0	0
I_B (10)	1	8	1	0	0	0
II_A (7)	0	0	6	1	0	0
II_B (16)	0	0	2	13	1	0
III_A (24)	0	0	1	2	19	2
III_B (1)	0	0	0	0	0	1

TNM: tumor, lymph node, metastasis.

stage was 78.7% (Table 2). The conformity of stage I_A, I_B, II_A, II_B, III_A and III_B was 66.7, 80, 85.7, 81.3, 79.2 and 100%, respectively.

Short-term response in the chemoradiotherapy group

There were 21 cases of CR, 32 cases of PR, 5 cases of SD, and 3 cases of PD among the 61 patients in the chemoradiotherapy group, and the response rate was 86.9%.

Adverse reactions in the patients of the two groups

The main toxic reactions of the patients in the chemoradiotherapy group included myelosuppression, gastrointestinal reactions, and radiation-induced pneumonia and esophagitis. The incidence rates of ≥3 grade myelosuppression and ≥3 gastrointestinal reactions in the patients were 32.8% and 18.0% in the comprehensive treatment group and 39.3% and 11.5% in the chemoradiotherapy group, respectively. The incidence rates of symptomatic radiation-induced pneumonitis and ≥2 grade radiation-induced esophagitis were 9.8% and 31.3% in the chemoradiotherapy group, respectively. No statistically significant differences were found in

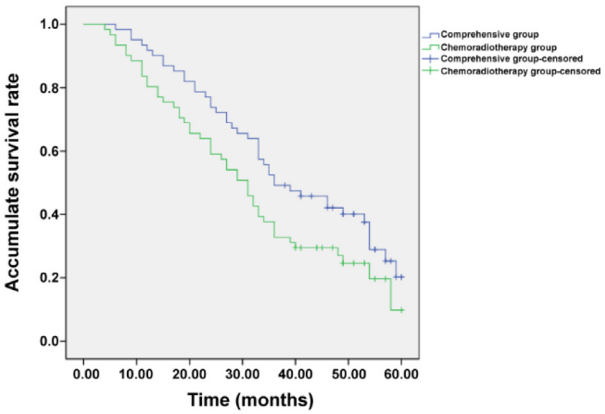

Figure 1. Kaplan-Meier survival curves of the studied patients. The overall survival rate of patients in the comprehensive group was significantly higher than that of the chemoradiotherapy group (p=0.043).

Table 3. Univariate analysis of predictors for survival in the studied patients

Predictors	*Cases n (%)*	*Median survival time (months)*	x^2	*p value*
Age, years			2.166	0.189
<60	77 (28.3)	25		
≥60	45 (71.7)	28		
Gender			0.913	0.336
Male	79 (19.6)	24		
Female	43 (80.4)	21		
Tumor location			0.453	0.675
Left lobe	63 (58.7)	26		
Right lobe	59 (41.3)	23		
Tumor site			4.612	0.013
Central	79 (89.1)	24		
Peripheral	43 (10.9)	35		
T staging			11.830	0.001
T_1+T_2	89 (30.4)	33		
T_3+T_4	33 (69.6)	19		
N staging			13.644	0.001
N_0+N_1	69 (34.8)	38		
N_2+N_3	53 (65.2)	21		
TNM staging			19.582	0.001
I+ II	67 (30.4)	41		
III_A	52 (69.6)	25		
III_B	3 (69.6)	20		
Chemotherapy cycle			5.494	0.018
<4	50 (32.6)	18		
≥4	72 (32.6)	28		
Treatment			10.721	0.031
Comprehensive	61 (34.8)	27		
Chemoradiotherapy	61 (15.2)	22		

TNM: tumor, lymph node, metastasis.

the toxic reactions between the comprehensive treatment group and the chemoradiotherapy group (p>0.05), and the adverse reactions related to chemoradiotherapy were tolerated by the patients and mitigated after symptomatic treatment. No severe surgical-related complications were detected in the patients in the comprehensive treatment group.

Results of patient survival follow-up

Up to May, 2019, the patients were followed up for 4-60 months with a median follow-up of 34 months. Among the 122 patients, there were 86 cases of tumor progression, 31 cases of local recurrence, 77 cases of distant metastasis (with brain metastasis in 35/77), and 20 cases of concurrent local recurrence and distant metastasis. In the 122 patients, the 1-, 3- and 5-year survival rates were 86.1% (105/122), 41.0% (52/122) and 27.0% (33/122), respectively, and the median survival time was 25 months.

In the comprehensive treatment group, the median survival time of the patients was 27 months, and the 1-, 3- and 5-year survival rates were 91.8% (56/61), 49.2% (30/61) and 31.1% (19/61), respectively. In the chemoradiotherapy group, the median survival time of the patients was 22 months, and the 1-, 3- and 5-year survival rates were 80.3% (49/61), 32.8% (20/61) and 23.0% (14/61), respectively. The overall survival curves of two groups of patients plotted by Kaplan-Meier method are shown in Figure 1. The Log-rank test on the overall survival of patients in two groups revealed that the difference was statistically significant (p=0.043). According to the stratification analysis of the TNM staging, the 1-, 3- and 5-year survival rates of the patients at stage I + II were 93.4, 65.6 and 44.3%, in the comprehensive treatment group, and 82.0, 45.9 and 29.5% in the chemoradiotherapy group, respectively, and the differences had statistical significance (p<0.05), while the 1-, 3- and 5-year survival rates of the patients at stage III_A had no statistical differences between two groups (p>0.05).

Analysis of prognostic factors

The correlations of survival time with gender, age, tumor site, lesion location, T stage, N stage, clinical TNM stage, chemotherapy cycle and treatment method were analyzed via univariate analysis which showed that tumor site, T stage, N stage, clinical TNM stage, chemotherapy cycle and treatment method were of significant statistical significance for the survival of the patients (p<0.05) (Table 3). The median survival time of the patients with peripheral tumors was notably longer than that of the patients with central tumors (35 months vs. 24 months, p=0.013). The median survival time of the patients in stage T_1 and T_2 was significantly longer than that of the patients in stage T_3 and T_4 (33 months vs. 19 months, p<0.001). The median survival time of the patients in stage N_0 and N_1 was clearly better than that in the patients in stage N_2 and N_3 (38 months vs. 21 months, p<0.001). In terms of the TNM stage, the median survival time of the patients in stage I and II was obviously better than that of the patients in stage III_A and III_B (41 months vs. 25, and 41 months vs. 20 months, p<0.001). As to the chemotherapy cycle, the median survival time of the patients with ≥4 cycles was remarkably longer than that of the patients with <4 cycles (28 months vs. 18 months, p=0.018). The median survival time of the patients was evidently better in the comprehensive treatment group than that in the chemoradiotherapy group (27 months vs. 22 months, p=0.031). The factors with p<0.05 in the results of univariate analysis were subjected to Cox multivariate analysis which showed that clinical TNM stage was an independent factor affecting the survival time of the patients [odds ratio (OR) = 1.610, 95% confidence interval (CI): 1.441-2.921, p=0.012, Table 4].

Table 4. Multivariable Cox regression analysis of predictors for survival in the studied patients

Parameters	*OR*	*95% CI*	*p value*
Tumor site	1.132	0.749-1.633	0.466
T staging	0.980	0.895-1.076	0.489
N staging	0.845	0.599-1.264	0.373
TNM staging	1.610	1.441-2.921	0.012
Chemotherapy cycle	1.203	0.820-1.106	0.418
Treatment	1.088	0.912-1.307	0.191

RR: relative risk; CI: confidence interval; TNM: tumor, lymph node, metastasis, OR: odds ratio.

Discussion

SCLC accounts for 15-20% of the total number of lung cancers and has an extremely high invasiveness compared with other types of lung cancer, and the median survival time is only 2-4 months if no treatment is conducted [8]. Currently, the combined therapy of radiotherapy and chemotherapy remains the standard treatment method for LS-SCLC, and concurrent chemoradiotherapy is the recommended comprehensive treatment mode [9]. At present, among the results of known large-sample studies in foreign countries, the effect of the randomized controlled study on the efficacy of concurrent chemoradiotherapy and sequential chemoradiotherapy in the treatment of LS-SCLC reported by Takada et al [10] is the best: The median survival time of patients

in the concurrent chemoradiotherapy group is 27.2 months, and the 5-year survival rate is 23.7%, significantly better than those in the sequential chemoradiotherapy group. Moreover, in several randomized controlled studies on radiotherapy intervention time and segmentation scheme in which concurrent chemoradiotherapy is adopted, the median survival time of patients is 13.7-23 months, and the 5-year survival rate is 15-27% [11-13].

Surgery is generally recommended for early stage non-SCLC and only $T_{1-2}N_0M_0$ SCLC, the main reason being that distant metastasis can occur in the early stage [14]. Given this, simple local treatment methods including surgery or radiotherapy cannot realize long-term survival, and the local treatment combined with systemic chemotherapy is able to achieve local control and long-term survival of SCLC [15]. There are rare reports on whether there is a difference in the efficacy of local treatment such as surgery or radiotherapy, especially after staging SCLC as per 2010 AJCC TNM staging criteria, and the effects of surgery [16-18]. In this study, the prognosis of LS-SCLC was compared between the comprehensive treatment group and chemoradiotherapy group. The results displayed that the effect was relatively good in the comprehensive treatment group. The overall survival rate of the patients in the two groups was subjected to log-rank test, and it was discovered that the overall survival rate was statistically significant (p=0.043). The stratified analysis uncovered that the 1-, 3- and 5-year survival rates of the patients with stage I + II LS-SCLC were significantly higher in the comprehensive treatment group than those in the chemoradiotherapy group, while such rates of the patients with stage III_A LS-SCLC in the comprehensive treatment group were not statistically significant from those in the chemoradiotherapy group, suggesting that surgical treatment benefits the survival of the patients with stage I + II LS-SCLC, but it should not be applied for the advanced patients in stage III, and the combination of radiotherapy and chemotherapy should be the major method in treating the patients with stage III LS-SCLC, which is in line with the findings reported in the literature [18,19]. The comparison of preoperative clinical stage with postoperative pathological stage of the patients in the comprehensive treatment group showed that there were 13 cases of stage change, and the conformity of clinical stage was 78.7%. The clinical efficacy of the patients in the chemoradiotherapy group was evaluated as per WHO early response evaluation criteria in solid tumor, and it was found that the response rate was 86.9%. There were no statistically significant differences in the toxic reactions related to chemoradiotherapy between the comprehensive treatment group and the chemoradiotherapy group (p>0.05). No severe surgical-related complications were detected in the patients in the comprehensive treatment group. These results imply that the treatment method adopted is reliable and tolerable.

The results of univariate analysis showed that tumor site, T stage, N stage, clinical TNM stage, chemotherapy cycle and treatment method were of significant statistical significance for the survival time of the patients (p<0.05). To eliminate the interplay of various factors, the Cox proportional hazard regression model was further employed in this study for multivariate analysis, and it was confirmed that clinical TNM stage was an independent factor affecting the survival time of patients, which conforms to the findings of previous research [20]. The incidence rate of brain metastases in SCLC is increased. The data of this research have shown that the incidence rate of brain metastasis is 45.5%, and brain metastasis is a leading cause of treatment failure, so it is recommended to apply prophylactic cranial irradiation after local treatment and systemic chemotherapy so as to reduce the incidence rate of brain metastasis [21].

There are some shortcomings in this study. First, it was a retrospective study, the number of patients enrolled was limited, and the prognostic factors in the medical records were unevenly distributed. In addition, the pathology was postoperative in the comprehensive treatment group, with a relatively obvious pathological type, and in the chemoradiotherapy group, the pathological type was detected via fiberoptic bronchoscopy or puncture cytological examination that may affect the pathological type. Hence, multicenter large-sample prospective randomized studies are needed in the future to verify the findings of this study.

Conclusions

Surgery combined with chemotherapy may benefit the survival of patients with stage I and II LS-SCLC, while the combined therapy of radiotherapy combined with chemotherapy is more suitable for patients with stage III LS-SCLC. TNM stage is an independent factor affecting the prognosis of LS-SCLC.

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Conflict of interests

The authors declare no conflict of interests.

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