RESEARCH ARTICLE

Optimal Timing of Radiotherapy with Alternating/Sequential Radio-Chemotherapy for Limited-stage Small Cell Lung Cancer

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Abstract

Objective: To investigate the optimal timing of radiotherapy with alternating/sequential radio-chemotherapy for limited-stage small cell lung cancer (LS-SCLC). Methods: 91 patients with LS-SCLC were retrospectively analyzed and divided into two groups according to the number of chemotherapy cycles before radiotherapy. If the patient received radiotherapy after 3 cycles or fewer cycles of chemotherapy, classification was into the early group, if not, into the late group. All patients received 6 cycles of standard chemotherapy (EP/EC) and conventional radiotherapy (56 gy~ 60 gy/28 f ~30 f). Results: The response rate (RR) of the early and late groups were 85.7% and 81.6%, respectively, with no significant difference ($p>0.05$). In contrast, the progression-free survival (PFS) in the early group was better than that in the late group (11.8 months vs 9.86 months), and the difference was significant ($p<0.05$). There was no significant difference between two groups in adverse reactions, which gastrointestinal irritation and bone marrow suppression being the most common ($p>0.05$). Conclusions: Radiotherapy after 3 cycles or fewer cycles of chemotherapy does not bring significant benefits for RR of patients with LS-SCLC, but it could significantly prolong their PFS without increase in adverse reactions.

Keywords: Carcinoma - small cell lung cancer - chemotherapy - radiotherapy - timing

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Introduction

Lung cancer is one of the most common malignant tumors worldwide and its incidence and mortality has ranked first among all cancers. Small cell lung cancer (SCLC) accounts for nearly 15% of human lung cancers and is one of the most aggressive solid tumors (Chen et al., 2012). Only less than one third of SCLC patients present with limited-stage disease, while remaining two thirds have extensive-stage disease. The combination of chemotherapy and radiotherapy has been considered as the standard treatment for patients with limited stage small cell lung cancer (LS-SCLC). It was found in the previous studies that the effect of concurrent radio-chemotherapy was better than that of sequential radio-chemotherapy in patients with LS-SCLC (Tsukada et al., 2001;Takada et al., 2002;El Sharouni et al., 2009). But some patients in the concurrent group cannot complete the treatment due to serious side effects. Therefore alternating/sequential radio-chemotherapy is usually used to treat the patients with LS-SCLC who are not able to tolerate concurrent therapy. But the optional timing of radiotherapy in alternating/sequential radio-chemotherapy has been controversial. In order to solve this problem, a number of studies (Pijls-Johannesma et al., 2005;Zhao et al., 2010) have been made. But because the definitions of the early radiotherapy and the late radiotherapy were very varied, the conclusions were inconsistent. Therefore to explore the optimal timing of radiotherapy in alternating/sequential radio-chemotherapy, we performed the retrospective analysis.

Materials and Methods

Patient selection

We retrospectively analyzed 91 patients with LS-SCLC at Shandong Cancer Hospital from January 2008 to January 2013. All patients required cytologic or histopathologic confirmation of SCLC. Patients were staged with computer tomography (CT) and bone scans, positron emission tomography (PET) scanning. All of the patients received 6 cycles of EP (VP-16 0.1 d1-5, DDP 40mg d1-3, 21days a cycle) or EC (VP-16 0.1 d1-5, CBP 500mg d1, 21days a cycle) and alternating/sequential radiotherapy (56gy~60gy/28f~30f).

General information

A total of 91 patients with LS-SCLC were enrolled our study, male 60, female 31; aged 28-77 years old, mean age 56 years old. Of the patients, 13 cases received

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Table 1. Comparison of the Basic Clinical Features between the Early Group and the Late Group

Feature		Early group (N=42)	Late group (N=49)
Gender	Female	14	17
	Male	28	32
Age/year	≤45	9	7
	46~60	26	32
	>60	7	10
Smoking history	Yes	23	26
	No	19	23
KPS	≥80	40	44
	<80	2	5
PCI	Yes	7	8
	No	35	41

*p>0.05; **KPS: Karnofsky performance status score; PCI: Prophylactic cranial irradiation

Table 2. Comparison of the Short-Term Responses between the Early Group and the Late Group

	CR	PR	SD	PD	RR
Early group (N=42)	10	26	4	2	85.71%
Late group (N=49)	13	27	5	4	81.63%

*CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease; RR: Response rate

Table 3. Comparison of the Common Adverse Reactions between the Early Group and the Late Group

Adverse reactions	Early group (N=42)	Late group (N=49)	p
Gastrointestinal reaction			p>0.05
I~II	39	44	
III~IV	3	5	
Bone marrow suppression			p>0.05
I~II	34	36	
III~IV	8	13	

radiotherapy after 2 cycles of chemotherapy. 29 cases received radiotherapy after 3 cycles of chemotherapy. 23 cases received radiotherapy after 4 cycles.10 cases received radiotherapy after 5 cycles.16 cases received radiotherapy after 6 cycles.

Case group

91 patients with LS-SCLC were divided into the early and late radiotherapy groups according to the number of chemotherapy cycles before radiotherapy. If the patient received 3 cycles or fewer cycles of chemotherapy before radiotherapy, he was classified into the early group, if not, he was in the late group. There was no significant difference between clinical data of the two groups. Details are shown in Table 1

Evaluation criteria

Evaluation of efficacy according to the standard of WHO, is complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD), the response rate (RR)= (CR+PR)/total number of cases *100%. Progression-free survival (PFS) was calculated from the beginning of the treatment to the onset of disease progression or death. All adverse reactions were evaluated according to the WHO classification.

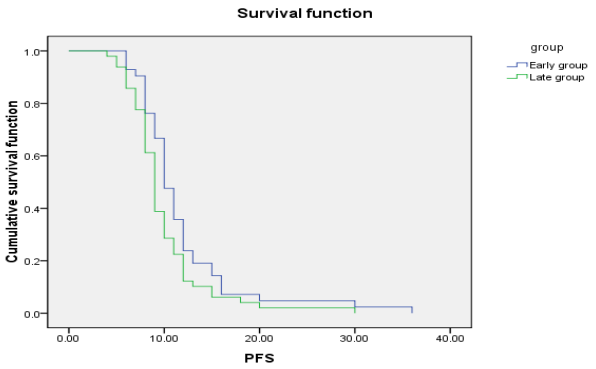

Figure 1. Survival Function Diagram of PFS of Patients with LS-SCLC Between the Early Group and the Late Group

Statistical analysis

Data analysis was performed by SPSS17.0 package. The rates of survival were calculated using Kaplan-Meier product limit method. The chi-square test was used to analyze count data. Significance level was defined as p=0.05 (two-sided).

Results

Short-term effects

For the early and late groups, the response rates (RRs) were 85.71% and 81.63%, respectively. While the efficacy of early group was better than that of the late group, but there was no significant difference in the two groups (p>0.05). The results are as Table 2:

PFS results

The progression-free survival (PFS) in the early group and the late group were 11.76 months and 9.86 months, with the significant difference (p<0.05). Survival function diagram is as (Figure 1)

Adverse reaction

Adverse reactions of all patients were evaluated according to the WHO classification. The common adverse reactions were gastrointestinal reaction and bone marrow suppression in the two groups, and the difference was not significant (p>0.05). No patient did not complete the treatment due to side reactions. The results are as Table 3:

Failure reasons

Most of the patients failed to cure the disease due to distant metastases. And the brain, bone, liver, adrenal metastases were the most common. A few patients failed because of the local recurrence, such as the increase of pulmonary primary tumors and mediastinal lymph node metastasis.

Discussion

Small cell lung cancer (SCLC) is a rapid progress of malignant tumor with a poor prognosis. About two-thirds of newly diagnosed patients have had extrapulmonary metastases. In recent years, with the progress of the comprehensive treatment, the treatment of SCLC has

achieved encouraging results. A number of Meta-analyses (Pignon et al., 1992;Arriagada et al., 1994;Pignon et al., 1996) have showed that: the combination chemotherapy and radiotherapy could bring better response rate and longer survival time than chemotherapy alone or radiotherapy alone. The radio- chemotherapy has been considered as the standard treatment for patients with LS-SCLC.

The combination modes of chemotherapy and radiotherapy have concurrent, alternating and sequential. Previous studies (Tsukada et al., 2001; Takada et al., 2002; El Sharouni et al., 2009)have suggested that the effect of concurrent radio- chemotherapy was better than that of alternating or sequential radio-chemotherapy in patients with LS-SCLC. But some patients in the concurrent group cannot complete the treatment due to serious side effects. Therefore alternating/sequential radio-chemotherapy is usually used for the patients with LS-SCLC who are not able to tolerate concurrent therapy. And the issue about the timing of radiotherapy in alternating/sequential radio-chemotherapy has been controversial. In order to solve this problem, a number of studies (Pijls-Johannesma et al., 2005; Zhao et al., 2010)have been made. But because the definitions of early radiotherapy and late radiotherapy were very varied, the conclusions were inconsistent. Therefore to explore the optimal radiotherapy timing in alternating/sequential radio-chemotherapy, we performed the retrospective analysis.

In our study, 91 patients with LS-SCLC were divided into the early radiotherapy group and the late radiotherapy group according to the number of chemotherapy cycles before radiotherapy. If the patient received radiotherapy after 3 cycles or fewer cycles of chemotherapy, he was classified into the early group, if not, he was in the late group. For the early and late groups, the RRs were 85.71% and 81.63%. While RR of the early group was better than that of the late group, but there was no significant difference in the two groups ($p>0.05$). The PFS in the early group was longer than that in the late group (11.76months versus 9.86months) , with the significant difference ($p<0.05$). The common adverse reactions were gastrointestinal reaction and bone marrow suppression in the two groups, and the difference was not significant ($p>0.05$). Therefore early radiotherapy did not increase the adverse reactions of patients with LS-SCLC.

According to our current understanding of tumor diseases, the reason may be that tumors are heterogeneous. Human primary tumors show extensive variation in all properties ranging from growth to metastasis. The cells of a tumor in a patient have different drug sensitivity. Long-term chemotherapy before radiotherapy may increase the number of drug-resistant tumor cells. They could form some small distance metastases which the local radiotherapy can't kill. If the patient receives 3 cycles or fewer cycles of chemotherapy before radiotherapy, drug-resistant tumor cells will be able to be killed by radiotherapy before forming extrapulmonary metastases. The early radiotherapy in alternating/sequential radio-chemotherapy can avoid the early local recurrence and distant metastasis. And the progression-free survival (PFS) is prolonged.

In the conclusion, the radiotherapy after 3 cycles or fewer cycles of chemotherapy could not bring significant benefits for RRs of the patients with LS-SCLC. But it could significantly prolong their PFSs and did not increase the adverse reactions. Further prospective studies are required to better explore the issue of optimal timing of thoracic radiotherapy.

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