RESEARCH ARTICLE

Relationship Between the SER Treatment Period and Prognosis of Patients with Small Cell Lung Cancer

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Abstract

Purpose: To explore the relationship between SER (time between the start of any treatment and the end of radiation therapy) and the survival of patients with limited-stage small cell lung cancer. Materials and Methods: Between 2008 and 2013, 135 cases of limited-stage small cell lung cancer (LS-SCLC) treated with consecutively curative chemoradiotherapy were included in this retrospective analysis. In terms of SER, patients were divided into early radiotherapy group (SER<30 days, n=76) and late radiotherapy group (SER≥30 days, n=59) with a cut-off of SER 30 days. Outcomes of the two groups were compared for overall survival. Results: For all analyzable patients, median follow-up time was 23.8 months and median overall survival time was 16.8 months. Although there was no significant differences in distant metastasis free survival between the two groups, patients in early radiotherapy group had a significantly better PFS (*p*=0.003) and OS (*p*=0.000). Conclusions: A short SER may be a good prognostic factor for LD-SCLC patients treated with concurrent chemoradiotherapy.

Keywords: Small cell lung cancer - retrospective study - prognosis - treatment period

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Introduction

Small cell lung cancer (SCLC) accounts for about 13% of lung cancer, the prognosis is poor (Govindan et al., 2006). Compared with non small cell lung cancer (NSCLC), SCLC generally has a more rapid doubling time, a higher growth fraction, and earlier development of widespread metastases. Although SCLC has a relatively good initial response to chemotherapy as well as radiotherapy, relapse or disease progression may occur quickly after the initial treatment (Chen et al., 2012). Although 30%-40% patients present with limited disease confined to the chest, but most patients will develop distant metastases. 2 important meta analysis had confirmed that chest radiotherapy can not only reduce the local recurrence rate, but also can improve the survival rate of the patients. Therefore, systemic chemotherapy and local accelerated hyperfractionated thoracic radiotherapy had became the standard treatment for small cell lung cancer for it could significantly improve local control rate, prolong the survival time of patients, and patients could well tolerate the treatment side effects (Stinchcombe et al., 2010; Kalemkerian et al., 2011; Amini et al., 2014). Prophylactic cranial irradiation (PCI) is recommended for patients achieving a complete response (CR) due to the improvement of survival (Le-Pechoux et al., 2009; Viani et al., 2012).

Nowadays, the golden treatment for LD-SCLC is concurrent chemoradiotherapy, but the precise intervention time of radiotherapy is still inconclusive (Manapov et al., 2013). In this study, we retrospectively analyzed 135 clinical data of patients with SCLC treated in our hospital from 2008 to 2013, to discuss the effect of interventional radiotherapy time on treatment effect and prognosis.

Materials and Methods

Patients characteristics

From Aug. 2008 to Jan. 2013, 135 patients' follow-up data with SCLC treated in oncology department of Tongji Hospital affiliated to Tongji Medical College of Huazhong University of Science and Technology were analyzed. With fiberoptic bronchoscopy, CT guided percutaneous lung biopsy or cervical lymph node biopsy method to obtain the histopathologic specimens, and the pathological diagnosis confirmed for small cell lung cancer. Using the VALG (veterans administration lung study group) staging system to determine the limited stage small cell lung cancer. The patients were treated with concurrent radical radiotherapy and chemotherapy. Staging routine inspection generally include: a comprehensive physical examination, blood cell count, liver and kidney function, electrolyte, enhanced chest CT scan, ultrasound B or CT

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scan of abdomen, whole body bone scan of ECT and brain MRI scan. After the inspection, such as clinical doubted for patients with extensive stage, further confirmed PET-CT could be considered. The selected patients'clinical characteristics

Principles of treatment

According to the ECOG scores of patients, accompany diseases, also refer to the NCCN guidelines for the treatment of small cell lung cancer. In general, patients were treated with "sandwich treatment", namely "induction chemother apy+radiotherapy+consolidate chemotherapy" (Tsujino et al., 2014). Standard combination chemotherapy regimens were "VP-16+DDP" recommended by the NCCN guidelines, according to the tolerance to chemotherapy in patients with 4-6 cycles (Ha et al., 2013; Zhang et al., 2014). In view of the important significance of PCI on the prognosis of patients with small cell lung cancer, patients who reach CR by the treatment of radiotherapy and chemotherapy should accepted PCI (25Gy/10F/2W) (Simon et al., 2007).

Radiation beam mainly used selection is 6-10MV photonic wires. According to the patient's enhanced chest CT delineation after chemotherapy to design the radiotherapy planning. The imaging showed pulmonary primary tumor and lymph node involvement is defined as gross tumor volume (Gross tumor volume, GTV). In patients who start chemotherapy before radiotherapy, GTV can be limited to the post–induction chemotherapy volume to avoid excessive toxicity (Socinski et al., 2007). GTV extended to 5-8mm is defined as the clinical target volume (Clinical tumor volume, CTV). According to the hilar and mediastinal and other regional lymph nodes groups to sketch node lymph, and in accordance with the actual location scanning CT image are modified, avoid the normal tissues and organs of the edge extension to CTV (Cai et al., 2014). CTV margin extend 10mm to form the planning target volume (planning target volume, PTV). Radiotherapy generally includes primary tumor and lymph node involvement area. According to the Intergroup trial 0096 in the study field: the tumor edge external 1.5cm, ipsilateral hilar, mediastinal from thoracic entrance to the subcarinal region. Contralateral hilar and bilateral supraclavicular region generally do not receive prophylactic irradiation. For chemotherapy of CR patients, the clinical target volume should include regional lymph node metastasis or chemotherapy may have involved lymph nodes (Han et al., 2012). Bilateral supraclavicular region don't usually accept preventive irradiation, but for supraclavicular metastasis in patients with small cell lung cancer, radiotherapy should include supraclavicular area. Consensus on ENI (elective nodal irradiation) is evolving. Several retrospective and prospective study suggest that omission of ENI results in low rates of isolated nodal recurrence, particularly when incorporating PET staging definition (Feng et al., 2013). Radiation therapy techniques include conventional three-dimensional conformal or intensity-modulated radiotherapy. The main risk organ by limiting the amount of the following: double lung V20<25%, maximum tolerated dose of<45Gy for spinal cord (Jassem et al., 2012). Radiotherapy modes included conventional fractionation and accelerated hyperfractionation.

Adverse events

The grade of adverse events of patients were evaluated by NCI-CTC-AE (NCI-common toxicity criteria-adverse events) version 3.0.

Follow-up visit

A helical chest CT scan with or without contrast and ultrasound B or CT scan of whole abdomen are recommended every 3 months after chemoradiotherapy. Information about smoking cessation should be provided to aid the treatment of lung cancer and to improve the life quality of patients. Follow up modes included outpatient follow-up, inpatient follow-up, telephone or e-mail follow-up.

The end of the study and the statistical method

The primary endpoint of this study was OS (overall survival), OS is defined as the time from randomization of patients to death due to any cause. PFS (progression free survival) is defined as the time from randomization of patients to the first occurrence of tumor progression. The types of therapy failure are classified to LRF (local regional failure) and DM (distant metastasis). DMFS (distant metastasis free survival) refers to the time from

Table 1. Clinical Characteristics of Patients

item	early RT group	Late RT group	*p*
number	76	59	
gender			0.274
male	52(68.4%)	46(77.9%)	
female	24(31.6%)	13(22.1%)	
age			
median value	57	58	0.689
range	38-74	35-72	
ECOG score			
median value	1	1	0.791
range	0-2	0-2	
smoking			
yes	40(52.6%)	32(54.2%)	0.523
no	36(47.4%)	27(45.8%)	
LDH			
≤225IU/L	29(38.2%)	22(37.3%)	0.688
>225IU/L	47(61.8%)	37(62.7%)	
bodyweight loss>5%			
yes	27(28.1%)	19(32.2%)	0.519
no	49(71.9%)	40(67.8%)	
supraclavicular lymph node metastasis			
yes	12(15.2%)	8(13.6%)	0.467
no	64(84.8%)	51(76.4%)	
SIADH			
yes	45(59.2%)	35(59.3%)	0.845
no	31(40.8%)	24(40.7%)	
chemotherapy cycle			
median value	5	5	0.784
range	4.0-6.0	3.0-6.0	
BED(Gy)			
median value	56.5	58.9	0.715
range	48.6-62.1	51.1-63.3	
fractionation pattern			
conventional	45(59.2%)	35(59.3)	0.487
hyperfractionated	31(41.8%)	24(40.7%)	
PCI			
yes	30(39.5%)	18(30.6%)	0.131
no	46(60.5%)	41(69.4%)	

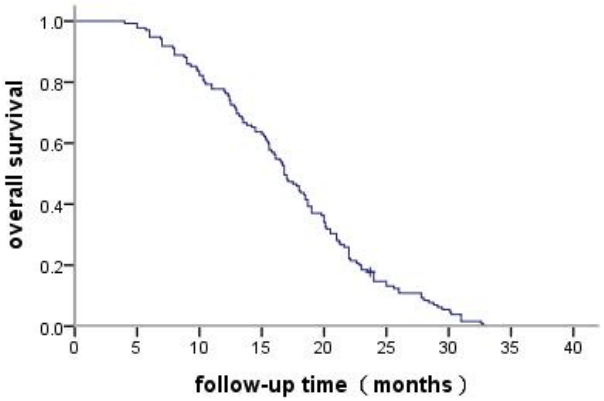

Figure 1. The Overall Survival of Total Patients

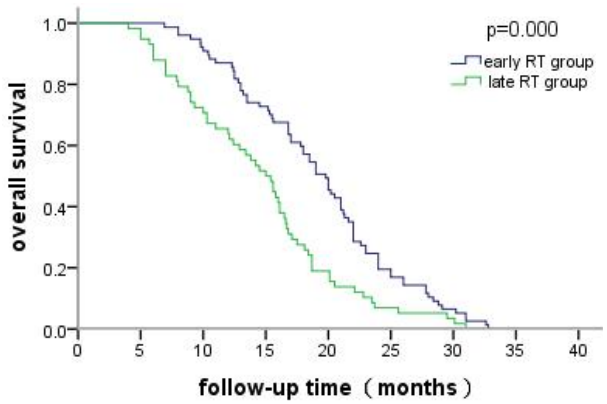

Figure 2. The OS Compare between 2 Groups Note: RT=Radiotherapy

randomization to the first distant metastasis. The research indexes are calculated by Kaplan-Meier survival analysis.

A meta analysis involved 7 randomized controlled trial of LD-SCLC conducted by De-Ruysscher reports showed early radiotherapy may improve 5 year survival rate compared to late radiotherapy. Early radiotherapy was defined as 30 days after the start of chemotherapy in the meta analysis (De-Ruysscher et al., 2006). Therefore, in this study, we choose SER=30 as the value of the day to divide into early radiotherapy group (SER≤30 days, n=76) and late radiotherapy group (SER>30, n=59). Using Log-rank test, OS, PFS, and DMFS treatment failure types of the two groups were compared. The value of $p<0.05$ that results are statistically significant difference.

Results

The overall survival analysis

The study demonstrated that the median follow-up time was 23.8 months and overall median survival time was 16.8 months (95%Confidence interval, 15.4 months-18.2months, Figure 1). Among 135 patients, the median survival time of the early radiotherapy group was 21.8 months (95% Confidence interval [CI], 17.9 months-23.7 months); however, that of late radiotherapy group was 15.1 months (95% Confidence interval [CI], 12.8 months-17.2 months). Significant difference was observed between two groups, and survival time of the early radiotherapy group was obviously better than that of late radiotherapy group (Figure 2). Moreover, we found that survival time exhibited decreased trend

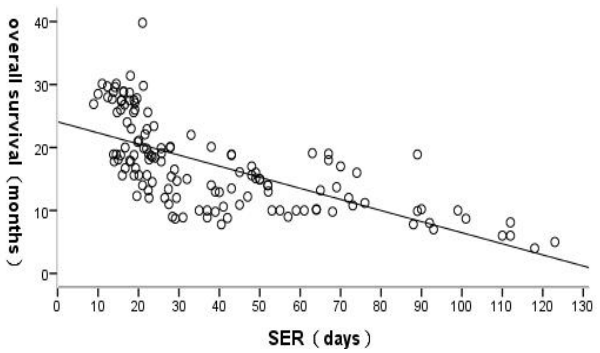

Figure 3. The Scatter Diagram of SER and OS

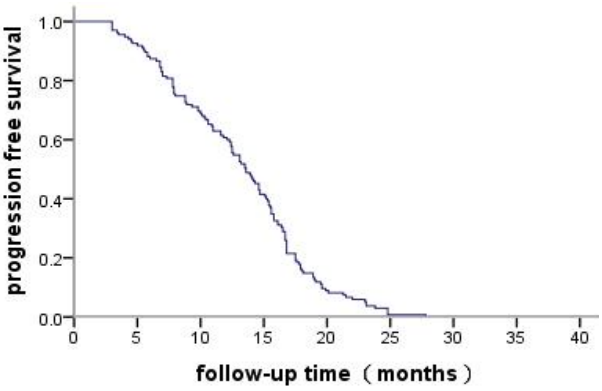

Figure 4. The Overall PFS of Total Patients

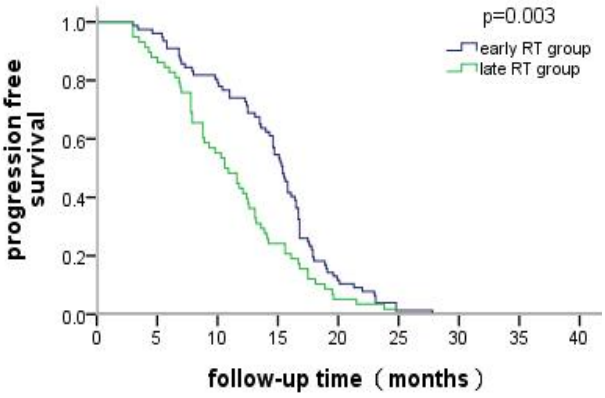

Figure 5. The PFS Compare between 2 Groups Note: RT=Radiotherapy

with prolonged SER from the scatter diagram (Figure 3). The overall median progression-free survival time was 11.4 months (95% Confidence interval [CI], 9.0 months-14.8 months) (Figure 4). Median progression-free survival time of early radiotherapy group and late radiotherapy group was 15.4 months (95% Confidence interval [CI], 14.5 months-16.3 months) and 10.6 months (95% Confidence interval [CI], 8.4 months-12.8 months) respectively. Significant difference was also observed between two groups. progression-free survival time of early radiotherapy group was obviously longer than that of late radiotherapy group (p=0.003, Figure 5).

Initial treatment failure analysis

The reasons for initial treatment failure were presented. Local recurrence failure (LRF) in the radiation field was the main factor of initial treatment failure, accounting for 23.6% and 22%, respectively in early and late radiotherapy

Table 2. Reason for Initial Treatment Failure

Group	Number of patients	LRF	DM	LRF DM	*p*
Early radiotherapy group	76	18 (23.6%)	48 (63.2%)	10 (13.2%)	0.367
Advanced radiotherapy group	59	13 (22.0%)	38 (64.4%)	8 (13.6%)	

groups. Additionally, the most common metastases sites are located in the brain, liver, bone and adrenal. There was no significant difference in DMFS of these two groups.

Adverse events

Since multiple factors may affect chemotherapy, severe adverse events that resulted in treatment interruption were regarded as alternative indicators in the study to evaluate adverse events during treatment. Haematological toxicity criteria include IV neutropenia and thrombocytopenia; severe non-hematologic toxicity was mainly radiation-induced esophagitis, such as eating pain, burning sensation, severe difficulty eating; or radiation-reduced pneumonitis, such as severe cough, wheezing, difficulty breathing. we should highlight these adverse reactions and distinguish the difference with complications caused by tumor itself. Throughout the treatment period, 14 patients developed severe hematological or non-hematological toxicity and failed to subsequent treatment, including 8 cases (10.5%) in the early radiotherapy group and 6 patients (10.2%) in patients with late radiotherapy group, and occurrence of adverse events between the two groups had no significant difference (p=0.739). The main cause of patient treatment interruption included esophagitis, neutropenia, radiation pneumonitis, nausea and vomiting, and serious adverse reaction was common found in the patients that BED>60Gy during radiotherapy.

Discussion

It is well known that the prognosis for SCLC is very poor. Typical survival is still measured by months, and the 5-year survival is less than 5% (Wu et al., 2014). Current standard treatment of LD-SCLC is chemoradiotherapy. However, The time of when to start radiation therapy for SCLC remains unclear (De-Ruysscher et al., 2006). Although many scholars had explored the influence of the early or late radiation on the prognosis of LD-SCLC, the conclusion remains contradictory (Perry et al., 2006).

Two Phase III clinical studies conducted by Murray and Jeremic have suggested that the early radiotherapy can achieve better survival benefit than late radiotherapy. Survival benefit that radiotherapy intervention was carried out on the first day or 22 days of chemotherapy (early radiotherapy) in patients was superior to that of radiotherapy intervention was implemented on the first 36 days or 106 days of chemotherapy (late radiotherapy): median survival time was respectively 21.2 months vs.16 months (p=0.008) and 34 months *vs* 26 months (p=0.052) (Murray et al., 2003; Jeremic et al., 2007). However, unfortunately, the other Phase III clinical studies did not obtain the consistent results (Stinchcombe et al., 2010). Currently, the results of phase III clinical studies are not all transformed to operational guidelines, then whether the Meta-analysis based on above data can provide some valuable information? The meta-analysis performed by De-Ruysseher involved seven studies, and the results shown that the 2-year and 5-year overall survival rates between early radiotherapy (≤30 days) and late radiotherapy (>30days) had no significant difference (p=0.42) when no selectivity for chemotherapy regimen. However, the 2-year and 5-year overall survival rates between early radiotherapy and late radiotherapy displayed significant difference if patients received platinum-based chemoradiotherapy: risk ratio (HR) of death was respectively 0.73 for 2 years and 0.64 for 5 years, and overall survival rate was respectively 20.2% for 2 years and 13.8 for 5 years. But local control rate had no statistic difference between early and late radiotherapy. In addition, there was a marked difference in 5-year survival for patients receiving time of radiotherapy between within 30 days and more than 30 days. Therefore, the researchers recommended that radiotherapy for LD-SCLC should start after chemotherapy begin within 30 days and total radiotherapy should completed in 30 days, which would exhibit better benefit for 5-year survival rate of patients (De-Ruysscher et al., 2004). Moreover, another meta-analysis included four phase III clinical study of LD-SCLC and analyzed SER. The results shown that 5-year survival rate was higher with shorter SER treatment options: when SER less than 30 days, 5-year survival rate was 20%; while SER extend one week each, 5-year survival rate corresponding decreased by 1.8% (De-Ruysscher et al., 2007). It has been reported that tumor cell accelerated proliferation for many solid tumors when 30 days after receiving chemotherapy. Hence, accelerated proliferation of tumor cells can be overcome by earliest possible radiotherapy for improving survival (Davis et al., 2002; Brade et al., 2006). According to reported literature, Huncharek et al summarized that LD-SCLC would obtain optional efficacy when chemotherapy and radiotherapy were completed within 6 weeks (Huncharek et al., 2004).

However, the tolerance that radiotherapy started in the first 30 days of chemotherapy was the concerns of the clinicians and patients (Spiro et al., 2006; Paumier et al., 2010). Previous report found that the risk of severe radiation-induced pneumonia and radiation-induced esophagitis in early radiotherapy group significant increased compared with that in late radiotherapy group, and the HR was 1.95 (p=0.006) and 1.50 (p=0.04), respectively; the HR of hematologic toxicity, especially neutropenia for early radiotherapy group was 2.45 (p=0.0004) (De-Ruysscher et al.,2004). Moreover, medical imaging of most patients with small cell lung cancer frequently presents as central occupation near hilar and large tumor oppressing vena cava with multiple lymph node metastasis. If radiotherapy begins with initial treatment, radiotherapy target might involve larger scale to sufficiently cover the tumor tissue and subclinical lesions. Consequently, this would be a tremendous challenge to oncologists since they need to consider including GTV in radiation field, the amount of each risk organ and ensure the implementation of subsequent chemotherapy.

In the present study, we investigated that early

radiotherapy group significantly improve OS and PFS compared with late radiotherapy group, which was consistent with previous study. In addition, we found that OS decreased when SER prolonged, but there was no marked difference in distant metastasis free survival for two groups. However, this study used a retrospective analysis that would inevitably produced some selective bias, and the proportion of patients undergoing PCI in subsequent treatment was relatively lower, which may also impact the results of distant recurrence and survival analysis. Additionally, the retrospective study exist certain heterogeneity in many aspects. Although significant difference was not observed in clinical characteristics and treatment regimens for two groups, many interacting factors should be paid more attention. Firstly, the total dose and segmentation methods of radiotherapy are not uniform: fractionation patterns included conventional and hyperfractionated fractionation radiotherapy, while the total dose of radiotherapy fluctuated between 48Gy-70Gy. Secondly, there were no unified treatment regimens, including standard platinum-containing EP and IP regimens and non-platinum-containing CAV programs. Finally, the time to radiotherapy intervention spans, and the time definition of early and late radiotherapy remains lacking uniform standards.

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