Journal of
Cancer Science & Therapy

Li et al., J Cancer Sci Ther 2020, 12:1

Research Article Open Access

Effects of Radiotherapy Technique and Doses on Lung Cancer Patients with Brain Metastases

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Abstract

The aim of this study was to investigate the effects of FSRT and conventional radiotherapy with or without WBRT on OS and short-term outcome of lung cancer patients with brain metastases. 92 patients were involved the study. All the brain MR images were fusioned under the Pinnacle system, then they received local conventional radiotherapy (1.8-2.0 Gy/F) or FSRT (2.5-4 Gy/F), with or without WBRT, according to the size and number of brain lesions. The OS of all patients was 2 to 33 months with the median survival 15 months. GPA (P=0.050), pathological type (P=0.012), oral targeted drugs (P=0.016), number of BM (P=0.002), radiotherapy technique (P=0.001), radiotherapy dose (P=0.031) and short-term outcome (P=0.002) were the influencing factors of OS. And local radiotherapy was better than local + WBRT than WBRT (P=0.001), FSRT significantly better than conventional radiotherapy (P=0.001). Hierarchical analysis displayed that local radiotherapy was better than local + WBRT than WBRT for those who hadn't received targeted therapy (P=0.001). For SCLC, local + WBRT was better than WBRT (P=0.003) and for NSCLC FSRT was better than conventional radiotherapy (P=0.024. For patients with lower GPA (≤ 1.5), local radiotherapy was better than local + WBRT than WBRT (P=0.033). The CR rate of the whole group was 6.5%, with PR rate 78.3%. Logistic regression showed that FSRT was more likely to have CR and PR probability (P=0.009). For lung cancer patients with brain metastases, FSRT was superior to conventional radiotherapy, which could improve short-term outcome and extend OS. Local radiotherapy was better than local + WBRT than WBRT.

Keywords: Lung cancer with brain metastasis; Radiotherapy; Hypofractionated stereotactic radiotherapy (FSRT); Overall survival; Short-term outcome

Abbreviations: BM: Brain Metastases; CT: Computed Tomography; CTV: Clinical Target Volume; EGFR: Epidermal Growth Factor Receptor; FSRT: Hypofractionated Stereotactic Radiotherapy; GTV: Gross Tumour Volume; MR: Magnetic Resonance; NSCLC: Non-Small-Cell Lung Cancer; OS: Overall Survival Time; PGTV: Primary Tumor Planning Target Volume; PTV: Planning Target Volume; SCLC: Small Cell Lung Cancer; WBRT: Whole Brain Radiotherapy

Introduction

In China, the incidence and mortality of lung cancer rank first in all malignancies [1]. Although the survival period has been extended because of comprehensive treatment such as surgery, radiotherapy and chemotherapy, patients with advanced lung cancer have a predilection to develop BM. In the lung cancer autopsy of more than 1000 cases, the incidence of lung cancer BM is 23%-36%. Lung cancer is the most common malignant tumor to lead to BM [2,3]. Moreover, once patients with lung cancer deteriorate to BM, the survival period will decline rapidly. BM remain lethal in lung cancer patients. In 2008, Sperduto PW proposed a graded prognosis evaluation (GPA) for patients with BM, which included clinical information such as age, KPS score, number of metastases. According to the GPA score and the prognosis, four prognostic scores of 0-1, 1.5-2, 2.5-3 and 3.5-4 were calculated. The corresponding median survival time was only 3 months, 5.5 months, 9.4 months, and 14.8 months [4-6].

The National Comprehensive Cancer Network (NCCN) guidelines recommend WBRT as an important treatment of BM. Although WBRT has a certain effect on lung cancer patients with BM, the prognosis is not ideal [4]. As a standard-of-care treatment for BM, WBRT can kill micrometastases effectively, but the control rate is not satisfactory due to insufficient dose in the tumor area, with survival period shortened. However, intensity-modulated radiotherapy can make the dose distribution of BM more accurate, enhance the effect of tumor treatment, and reduce the occurrence of neurological dysfunction by protecting important organs [5]. Intensity-modulated radiotherapy is divided into hypofractionated stereotactic radiotherapy (FSRT) and conventional radiotherapy. We therefore carried out a retrospective study to compare the efficacy of FSRT and conventional radiotherapy with or without WBRT in patients with lung carcinoma with BM.

Materials and Methods

Inclusion criteria

Patients with stage IV lung carcinoma, were confirmed by pathological analysis, such as detailed postoperative pathology, CT-guided lung puncture or bronchoscopy bited pathology, and the diagnosis of BM must be verified by intracranial enhanced MR imaging. All the patients should complete the radiotherapy successfully, and if the treatment was interrupted, the time could not be longer than 3 days. One month after the end of radiotherapy, a brain-enhanced MR imaging was performed to evaluate the effect. No history of other malignancy. No serious respiratory, circulatory, digestive, urinary diseases.

General clinical data

A total of 92 patients meeting the inclusion criteria in our department from January 2016 to June 2018 and were enrolled in our

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Received December 17, 2019; **Accepted** January 07, 2020; **Published** January 14, 2020

Citation: Li L, Lanhui Y, Jingyun L, Xuefeng W, Xi Z, et al. (2020) Effects of Radiotherapy Technique and Doses on Lung Cancer Patients with Brain Metastases. J Cancer Sci Ther 12: 005-009.

study. There were 57 males (62.0%) and 35 females (38.0%), aged 28-82 years (median age 60 years). 28 patients (30.4%) with a GPA score of 0-1, 54 (58.7%) with a score of 1.5-2.5, and 10 (10.9%) with a score of 3-4. There were 36 cases (39.1%) with small cell carcinoma, 42 cases (45.7%) with adenocarcinoma, and 14 cases (15.2%) with other types. The lung tumor originated from the left side in 36 cases (12 cases in the lower lobe, 17 cases in the upper lobe, 7 cases in the hilar), and 53 cases in the right side (19 in the upper lobe, 5 in the middle lobe, 24 in the lower lobe, 5 cases in the hilar) and 3 cases of mediastinal or double primary. There were 466 countable brain metastatic lesions, 370 in the brain (frontal 124, parietal 88, occipital lobe 89, temporal lobe 65, other 4), 85 cerebellum, 11 brain stem, and 3 cases of meningeal metastasis. The lesions were limited on the left side in 19 patients, 21 on the right side, and 52 patients on the bilateral side. Twenty-two patients underwent EGFR gene testing, and 18 were mutations. Among all the patients, 20 cases (30.4%) received local intensity-modulated radiotherapy with mean BM of 1.5, 36 cases (39.1%) received WBRT with mean BM of 6.5, 36 cases (39.1%) received local and WBRT with average BM of 3.92 (except for meningeal metastasis). 20 cases (21.7%) received conventional radiotherapy and 72 cases (78.3%) received hypofractionated stereotactic radiotherapy.

Radiotherapy

Target delineation: Firstly, localized CT images and brain-enhancedMR images were fused in the Pinnacle [3] system, then the gross tumor target and adjacent normal tissues and organs such as brain stem, optic nerve, optic chiasm, crystal, temporal lobe, etc. were delineated. Non-small cell lung cancer with less BM (1-3) were given local intensity-modulated radiotherapy: GTV included imaging-visible tumor, which expanded 0.3 cm to form PGTV, modified on the basis of anatomical barrier. Patients with more BM (>3) were given local and WBRT or WBRT: CTV was the whole brain, expanding 0.3 cm to form the PTV. Small cell lung cancer patients received WBRT or whole brain and local intensity-modulated radiotherapy regardless of the number of BM.

Prescription dose: Conventional radiotherapy 1.8-2.0 Gy/F, FSRT 2.5-4 Gy/F, WBRT: 40 Gy/2 Gy/20F or 30 Gy/3 Gy/10F, 5 fractions/week. Normal tissue dose limitation: brain stem maximum ≤ 54 Gy, chiasma opticum maximum ≤ 54 Gy, optic nerve maximum ≤ 54 Gy, lens maximum ≤ 9 Gy, temporal lobe maximum ≤ 54-60 Gy. Mannitol and/or dexamethasone were intravenously to control intracranial pressure during radiotherapy treatment.

Evaluation standard

GPA score is the graded prognostic index recommended by the US Radiation Therapy Oncology Group (RTOG) [6]. (Age, KPS, number of BM, extracranial metastasis condition) [7]. The short-term outcome evaluation standard is 2009 RECIST revision 1.1 [8].

Statistical analysis

Univariate analysis of total survival using the Kaplan–Meier method and analysis of influencing factors of short-term efficacy by logistic regression. All statistical analyses were carried out using spss software (version 22.0) and the correlation was significant at the 0.05 level (two-tailed).

Results

Treatment effect of the whole group

Data cut-off for this retrospective analysis was September 15, 2018, and the median survival time of the whole group was 15 months, and the overall survival rate was 13.0% and 30.3% of 1 and 2 years (Figure 1A). The median survival time of patients with small cell lung cancer was 10 months, and the 1- and 2-year overall survival rates were 36.9% and 9.1% (Figure 1B). The median survival time of patients with adenocarcinoma was 23 months, and the 1- and 2-year overall survival rates were 71.9% and 44.0% (Figure 1C). Patients received local intensity-modulated radiotherapy (mean BM of 1.5), with a total survival of 4-31 months, while median survival cannot be calculated (more than half still survived). Patients received WBRT (mean BM of 6.5), with a total survival of 2-32 months and a median survival of 9 months. Patients received local and WBRT (mean BM of 3.92), with a total survival of 3-33 months and a median survival of 19 months. There were 18 patients who had mutations after genetic testing and also took targeted drugs orally. Among them, 9 patients in the early radiotherapy group (brain radiotherapy was interposed within 1 month when brain metastasis was found), the median survival time could not be calculated (more than half of the patients still survived), and 9 patients in the late radiotherapy group (brain radiotherapy was interposed longer than 1

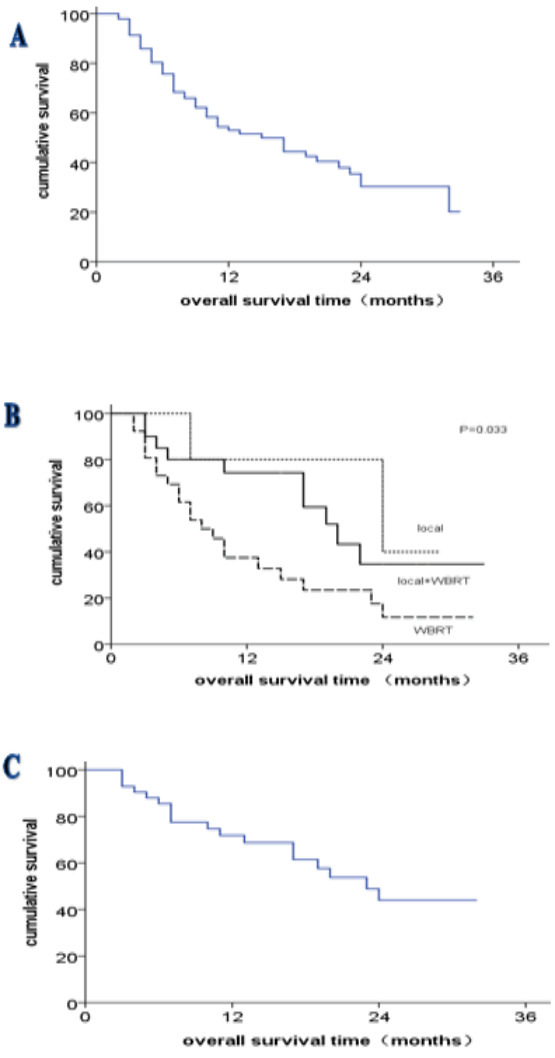

Figure 1: Overall survival curves (1A) Patients in the whole group, (1B) Patients of small cell lung cancer, (1C) Patients of adenocarcinoma.

month when brain metastasis was discovered), with a median survival of 23 months.

Univariate analysis results

Pathological type (P=0.012), number of BM (P=0.002), GPA score (P=0.050), whether to receive targeted therapy (P=0.016), radiotherapy techniques (P=0.001), radiotherapy dose (P=0.031) and short-term outcome (P=0.002) were the factors affecting overall survival according to KaPlan-Meier method (Table 1). And local radiotherapy was better than local + WBRT than WBRT (P=0.001, FSRT significantly better than conventional radiotherapy (P=0.001).

Hierarchical analysis

Radiotherapy technique and radiotherapy dose were analyzed hierarchically on the basis of the univariate analysis results.

Radiotherapy technique: For patients with small cell lung cancer with BM, local intensity-modulated radiotherapy and WBRT was superior to WBRT (P=0.003). In the lower GPA score group (GPA≤ 1.5), local intensity-modulated radiotherapy was better than local and WBRT than WBRT (P=0.033). Although the P value was 0.079 in the higher GPA score group (GPA>1.5), the three curves also had separate trends (Figure 2 and Table 2).

Radiotherapy dose: For patients with non-small cell lung cancer, FSRT was apparently better than conventional segmentation radiotherapy (P=0.024) (Table 3).

Short-term efficacy

The CR rate was 6.5% (6 cases), PR rate was 78.3% (72 cases), SD rate was 8.7% (8 cases), and the PD rate was 6.5% (6 cases). Logistic regression analysis was used to analyze the factors affecting the short-term efficacy. The results showed that patients whose brain metastasis lesions ≤ 3 and those received FSRT were more likely to achieve CR and PR rates (Table 4).

Discussion

We reported that FSRT was significantly better than conventional radiotherapy, which not only made patients obtain better short-term results but also improved overall survival rate. In this study, the average number of BM in local radiotherapy (20 cases) was 1.2, and the number of local BM in local + WBRT (36 cases) was 3.3. In our study, there were 35 cases with BM above 2.0 cm in diameter, and the largest volume was $6.3 \times 5.7 \times 5$ cm^3. We found that local intensity-modulated radiotherapy was better than local and WBRT than WBRT, while the size of BM had no statistical value on prognosis.

There is no consensus on the impact of the number and volume of BM on prognosis. Sperduto PW [6] performed a prognostic analysis of 1960 patients with BM, suggesting that patients with single BM have a longer survival than patients with multiple BM. However, in the study reported by Kaul [9], the importance of the number of BM was not found. Instead, the total volume of BM had important prognostic value by univariate analysis. Likhacheva [10] performed a prognostic analysis of 251 patients with BM received SRS. The prognosis of volume >2 cm^3 was worse. It was thought that the volume of brain metastasis rather than the number of BM affected prognosis, and the relationship between the size of maximal metastases and prognosis also had been confirmed in this study [11]. However, Kim [12] believed that the size of BM had no effect on prognosis. Consequently, a trial with bigger sample of the number versus the size of BM on prognosis is needed.

Characteristics	cases	Overall survival (%)		χ^2-value	*P*-value
		1-year	2-year		
Gender					
Male	57	52.9	31.5	0.344	0.558
Female	35	56.7	52.3		
Age (Years)					
<60	46	62.1	37.4	2.195	0.138
≥60	46	44.3	23.4		
Pathology					
Small cell carcinoma	36	36.9	9.1	8.842	0.012
Adenocarcinoma	42	85.5	44.0		
Other	14	40.0	40.0		
Number of BM					
1~3	44	63.9	47.7	9.394	0.002
≥4	48	44.1	17.2		
GPA score					
0~1	28	47.9	8.2	5.984	0.050
1.5~2.5	54	52.8	36.4		
3~4	10	71.4	71.4		
Oral targeted drug					
Yes	24	74.8	55.2	5.828	0.016
No	68	45.0	19.4		
Radiotherapy technique					
Local	20	73.7	61.4	13.303	0.001
WBRT	36	31.1	10.4		
Local+WBRT	36	64.4	35.2		
Radiotherapy dose (Gy)					
≤ 2.0	20	42.4	0.0	4.655	0.031
>2.0	72	56.1	34.8		
Short-term outcome					
SD+PD	14	28.6	28.6	9.904	0.002
PR+CR	78	57.5	32.8		

Table 1: Univariate analysis results of 92 patients with brain metastases of lung carcinoma.

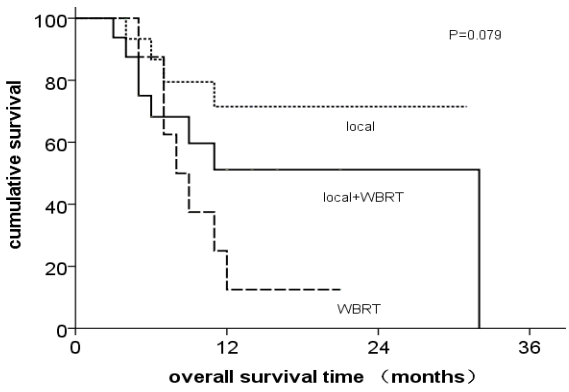

Figure 2: Overall survival curves of hierarchical analysis (Patients of the lower GPA score group (GPA ≤ 1.5), patients of the higher GPA score group (GPA>1.5).

Sperduto PW analyzed 1960 patients with a GPA score of 0-1 (143 cases), 1.5-2.5 (666 cases), 3 (168 cases) and 3.5-4.0 (102 cases), and their median survival time were 2.6 months, 3.8 months, 6.9 months and 11 months (P < 0.001) respectively [6]. In view of the differences in biological characteristics of BM from different histological sources, the researcher further analyzed 4259 cases of BM from 11 treatment centers from 1985 to 2007, and proposed pathology-specific GPA,

Characteristics	Radiotherapy technique	cases	Overall survival (%)		χ^2-value	*P*-value
			1-year	2-year		
Pathology						
Small cell	WBRT	19	12.9	0.0	9.055	0.003
	local+WBRT	17	62.4	25.0		
Non-small cell	local	20	73.7	61.4	3.976	0.137
	WBRT	17	50.7	24.1		
	Local+WBRT	19	68.4	39.1		
GPA score						
≤ 1.5	local	5	80.0	40.0	6.821	0.033
	WBRT	26	37.5	11.7		
	Local+WBRT	20	74.3	34.7		
>1.5	local	4	71.5	71.5	5.084	0.079
	WBRT	7	12.5	0.0		
	Local+WBRT	8	51.1	51.1		
Oral targeted drug						
Yes	local	11	81.8	81.8	2.647	0.266
	WBRT	9	66.7	35.6		
	Local+WBRT	4	75.0	37.5		
No	local	9	75.0	31.7	13.027	0.001
	WBRT	27	17.9	0.0		
	Local+WBRT	32	63.4	34.8		

Table 2: Hierarchical analysis results of radiotherapy technique.

Characteristics	Radiotherapy dose	cases	Overall survival (%)		χ^2-value	*P*-value
			1-year	2-year		
Pathology						
Small cell	≤ 2.0	4	0.0	0.0	0.057	0.811
	>2.0	32	38.4	9.5		
Non-small cell	≤ 2.0	4	25.0	0.0	5.063	0.024
	>2.0	52	64.8	47.2		

Table 3: Hierarchical analysis results of radiotherapy dose.

Characteristics	Group	β-value	χ^2-value	*P*-value	OR-value
Number of BM	>3/≤ 3	-3.403	7.493	0.006	0.033
Radiotherapy dose	> 2.0 / ≤ 2.0 Conventional segmentation	4.376	6.792	0.009	79.496

Table 4: Logistic regression analysis results of short-term outcome.

including 1888 cases of non-small cell lung cancer and 299 cases of small cell lung cancer. The median survival time for patients with non-small cell lung cancer and small cell lung cancer were 3.02 and 2.79 months, 6.53 and 5.3 months, 11.33 and 9.63 months, 14.78 and 17.05 months, with GPA score of 0-1, 1.5-2.5, 3 and 3.5-4.0 respectively [7]. In our study, the median survival time of all the cases was 15 months, the median survival time of small cell lung cancer patients was 10 months, and adenocarcinoma patients was 23 months, which was higher than the study of Sperduto PW markedly [13]. Genetic testing has been included on the basis of the latest GPA scoring standard [14]. In our study, because of the high proportion of small cell cancer patients with low positive rate of genetic testing, we did not bring into the latest GPA score. In later analyses, we will conduct a more detailed study of small cell lung cancer and adenocarcinoma patients.

The advantage of FSRT is that proper dose segmentation mode plays an important role in the prognosis of patients. 3-4 Gy/fraction, 13-18 fractiions, which was the main dose and segmentation mode adopted by our department and it turned out that this dose split mode was appropriate. A multi-institutional analysis demonstrated that the use of upfront EGFR-TKI, and deferral of radiotherapy, was associated with inferior OS in patients with EGFR-mutant NSCLC who developed brain metastases [15].

Conclusion

In our study, there were 18 EGFR-mutant patients with oral EGFR-TKI, 9 cases in the early radiotherapy group and 9 in the late group. Although there was no statistical diversity between the two groups, the median survival time of the early radiotherapy group could not be calculated (more than half of the patients still survived), while the late group was 23 months. We will continue to expand the database and extend the follow-up time to further study.

Disclosure Statement

The authors have no conflict of interest.

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