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Evaluate Efficacy and Safety of Patients with Oligometastatic NSCLC Harboring EGFR-Unmutated Treated with Stereotactic Body Radiation Therapy

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Abstract

Objectives: To investigate the efficacy and adverse effects of high-dose radiotherapy to the chest primary site and all metastases sites in EGFR-unmutated Oligometastatic NSCLC patients.

Methods: Retrospective analysis of 40 cases of EGFR-unmutated Oligometastatic NSCLC patients. (Metastatic lesions ≤ 5) who were initial treated by our department from 2009 to 2016. All patients underwent SBRT to the primary site and all metastases sites. Median BED10: 102.7 Gy (range: 94.5-113.5), median chemotherapy period: 4 cycle. Kaplan-Meier survival analysis, Cox model multi-factor prognosis analysis.

Results: The Overall Survival (OS) of 1, 2, and 3 years is 100%, 75%, and 65.63%, respectively. The median OS was 42 months (range: 34.27-49.73M). The Progress Free Survival (PFS) of 1, 2, and 3 years are 65.00%, 10.00%, and 0%, respectively. The median PFS: was 13 months (range: 10.687-15.313 M). Multivariate analysis suggested that ECOG<2 and ECOG ≥ 2 (P=0.002) were associated with OS, BED10<100 Gy and ≥ 100 Gy (P=0.015) were associated with OS; BED10<100 Gy and ≥ 100 Gy (P=0.047) were associated with PFS. 90% of patients experienced grade 1-2 adverse reactions, no grade 3 or more side effects and treatment-related deaths.

Conclusion: The EGFR-unmutated Oligometastatic NSCLC patients receiving systemic chemotherapy, combined with high-dose radiotherapy to primary site and all metastases sites can significantly improve OS and PFS. The patient has a slight adverse reaction.

Keywords: EGFR-unmutated; Oligometastatic NSCLC; SBRT; BED10; High-dose radiotherapy

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Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide, of which 85% is NSCLC [1-3]. More than half of the patients at the time of preliminary diagnosis have had distant metastases [4]. But IV NSCLC is a relatively broad category. Some studies have reported that some patients only have isolated metastases sites and can be in this relatively stable state for a long time [5,6]. In 1995, Hellman and Weichsel proposed the concept of "oligometastasis", which was initially described as metastasis sites, occurs in 1 or a limited number of organs [7]. Recently, "oligometastasis" was defined as the number of total metastases sites in single or multiple organs ≤ 5 [8-10]. The state occurs before extensive metastasis, when the tumor biological aggressiveness milder. Platinum-based doublets chemotherapy is considered the standard of care for patients presenting with stage IV non-small cell lung cancer, for which survival is usually less than 1 year the treatment needs to be improved [11,12]. A number of studies have reported that IV NSCLC patients can benefit from systemic therapy combined with local radiotherapy and can prolong OS and PFS [13-16]. The aim of the current study was to investigate the efficacy and adverse effects of high-dose radiotherapy to the chest primary site and all metastases sites in EGFR-unmutated Oligometastatic NSCLC patients.

Materials and Methods

General clinical data

From February 2009 to October 2016, among the 1238 lung cancer patients who were initial treated by the Radiation Therapy Department of The Air Force General Hospital. A total of 40 patients with Oligometastatic NSCLC harboring EGFR-unmutated who were treated with SBRT to

the primary site and all metastases sites. The patient characteristics are presented in Table 1.

Inclusion and exclusion conditions

Inclusion conditions: 1. Pathologically confirmed of EGFR-unmutated Oligometastatic NSCLC patients. (Including NSCLC with unclear pathological classification, all patients underwent genetic testing); 2. After comprehensive imaging diagnosis, the number of metastases is ≤ 5 (inspective methods include head MR + body PET-CT or head MR + chest, abdomen, pelvic CT). 3. After systemic therapy, the primary tumor and all metastases did not progress, also did not occur new metastases for at least 1 month. 4. Age >18 years old; 5. Before treatment, there must be sufficient bone marrow hematopoietic function, lung function, heart function, and liver function reserve; 6. All lesions are suitable for high-dose radiation therapy; 7. Pre-systemic therapy, if chemotherapy is used, local radiotherapy is started after the end of the course of chemotherapy (if there is central nervous system symptoms, local radical radiotherapy for intracranial lesions can be performed first).

Exclusion conditions: 1. Patients with other second primary tumor; 2. A patient who has undergone radiation therapy for a primary or metastatic lesion; 3. Pregnant or lactating women.

Radiation dose mode

A total of 40 patients enrolled in the study treated a total of 210 lesions; Median BED10 102.7 Gy (range: 94.5-113.5). Its contents are presented in Table 2.

Evaluation of adverse reactions

Acute reactions: Adverse reactions occurring from the start of radical radiotherapy from all lesions to 3 months after the end of radiotherapy were evaluated using the CTC 3.0 standard.

Late response: All lesions received adverse reactions after 6 months of radical radiotherapy were evaluated using the CTC 3.0 standard.

Statistical methods

Statistical analysis was performed on the data using the SPSS 24.0 software package. Use Kplan-Meier to perform survival analysis and plot survival curves. Using the COX proportional hazard model, Analyze the influencing factors of single factor and multi-factor on OS and PFS. All tests were bilaterally tested and the results were statistically significant at P<0.05.

Efficacy evaluation and follow-up

The lesions were evaluated by CT or MR at 1 to 3 months after radiotherapy using the RECIST criteria. Overall Survival (OS) is defined as the date from the start of treatment to the date of death or the date of follow-up. Progress Free Surviral (PFS) was defined as the patient's progress from the start of treatment to the observation of disease progression. All follow-up information was obtained from patient outpatient review information and telephone follow-up. The follow-up time was calculated from 1 month after the end of treatment, and ended in September 9, 2018.

Results

Survival situation

As of September 9, 2018, 33 of 40 patients died, 25 died of multiple organ failure due to tumor progression, 1 died of pulmonary embolism, 2 died of severe pneumonia and 5 died of unknown causes;

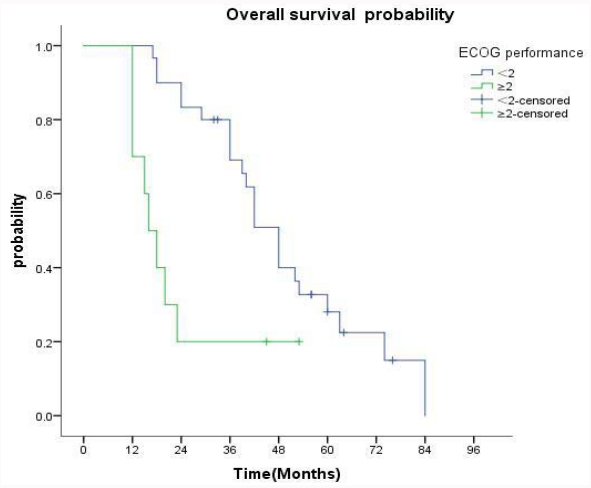

Figure 1: Overall survival according to the EOCG.

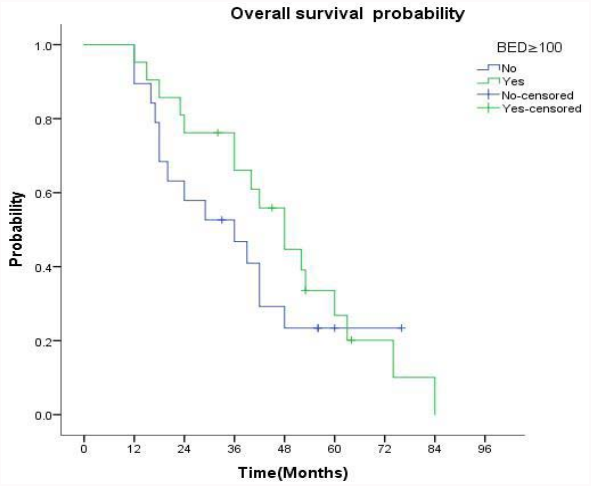

Figure 2: Overall survival according to the BED_{10}.

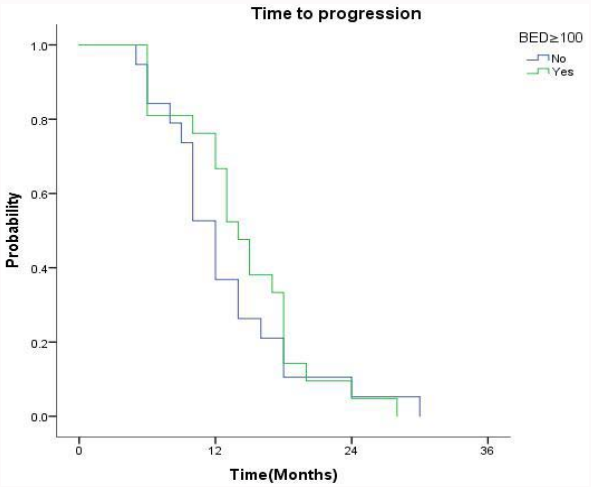

Figure 3: Progress free survival according to the BED_{10}.

the 1, 2, and 3 year survival rates and progress free survival rates were 100%, 75%, 65.63%, and 65.00%, 10.00%, and 0%, respectively. The median OS and median FPS were 42 months (95% CI 34.27 to 49.73) and 13 months (95% CI 11.75 to 18.25), respectively.

Table 1: Baseline Patient Characteristics.

Characteristics	N	No. of patients
Gender		
Female	23	57.50%
Male	17	42.50%
Age (Years)		
<65	27	67.50%
≥ 65	13	32.50%
Histology		
Non-adenocarcinoma	9	22.50%
adenocarcinoma	29	72.50%
NSCLC	2	5%
Smoking status		
No	28	70%
Yes	12	30%
Smoking Index[a]		
<800	24	60%
≥ 800	16	40%
ECOG performance[b]		
<2	30	75%
≥ 2	10	25%
N stage		
N0-N1	14	35%
N2	17	42.50%
N3	9	22.50%
CNS metastases		
No	27	67.50%
Yes	13	32.50%
No. of metastases organs		
1	32	80%
≥ 2	8	20%
No. of metastases		
1	20	50%
2	12	30%
5-Mar	8	20%
BED ≥ 100 Gy[c]		
No	21	52.50%
Yes	19	47.50%
PET-CT[d]		
No	1	2.50%
Yes	39	97.50%

a: Smoking Index: Number of cigarettes smoked per day x years of smoking
b: ECOG: Eastern Cooperative Oncology Group
c: BED: Biological Effective Dose
d: PET-CT: Positron Emission Tomography - Computed Tomography

Prognosis analysis

First, univariate analysis of gender, age, histology, smoking status, Smoking Index, ECOG performance, N stage, CNS metastases, No. of metastases organs, No. of metastases, and whether BED10 is ≥ 100 Gy. Then, after collinear diagnosis, factors such as $p \leq 0.2$ and important factors such as BED10 were included in the multivariate analysis (Table 3 & 4).

Discussion

Currently, the preferred targeted therapy for EGFR mutations in patients with IV NSCLC was EGFR-Tyrosine Kinase Inhibitor Therapy (TKI) platinum-based doublets chemotherapy is considered the standard treatment for patients with EGFR-unmutated NSCLC. However, the efficacy of first-line chemotherapy is not ideal. It is prone to disease progression during chemotherapy performing or chemotherapy ending, and its toxic side effects are large. Patients are poorly tolerated, and the median OS is only 8 to 10 months [17]. And Oligometastatic NSCLC patients are in the tumor biological aggressiveness milder state. Between the local primary lesion and the excessive phase of extensive metastasis. At this time, the tumor burden is small and there is a potential possibility for cure. But there is no ideal standard for the treatment of Oligometastatic NSCLC. Previous studies have shown that definitive local treatment can make Oligometastatic NSCLC patients have significant survival benefits has a potential role in the management of pulmonary metastases patients while increasing the quality of life and survival [18-20]. Linda et al. reported that 22 patients were treated by SABR [21]. CR 21%, PR 69% and SD 10%. 91% patients had complete metabolic response and 9% patients had a partial metabolic response. At median follow up of 18 months, the 1-, 2-year OS and PFS were 86%, 49% and 79%, 40%, respectively; Median time to progression and median OS were 18 months and 24 months, respectively. Local control was 93% at 1 year and 64% at 2 years. Janssen retrospectively analyzed [22]. The 46 patients receiving SABR for 1 to 3 lung metastases. Local control of SABR at 1, 2 and 3 years were 93%, 93% and 78%, and overall survival rates were 66%, 56% and 36%. Only 1 (2%) patient experienced radiation-induced pneumonitis. Hasselle et al. [23] retrospective analysis of 25 Oligometastatic NSCLC patients, primary tumor and metastases were given local radiotherapy, the results showed a median OS of 22.7 months, a median PFS of 7.6 months. Landmark clinical trials have shown that advanced NSCLC patients with activating EGFR mutations have higher response rates and better PFS when treated with EGFR tyrosine kinase inhibitors compared with classical platinum-based chemotherapy [24,25]. Whether consolidative therapy can improve the survival outcomes of patients with Oligometastatic EGFR-mutant NSCLC treated with first-line EGFR-Tyrosine Kinase Inhibitor (TKI) Xu Q et al. [26] reported that 145 patients with stage IV EGFR-mutant NSCLC and no more than five metastases within 2 months of diagnosis were enrolled. All patients were treated with first-line EGFR-TKIs, including 51 (35.2%) who received consolidative Local Ablative Therapy (LAT) to all Oligometastatic sites all-LAT group, 55 (37.9%) who received consolidative LAT to either tumor or Oligometastatic sites part-LAT group and 39 (26.9%) who did not receive any consolidative LAT non-LAT group. The median OS in all-LAT, part-LAT, and non-LAT groups were 40.9, 34.1 and 30.8 months, respectively. In my research, 40 patients with oligometastasis NSCLC were treated by SABR combined comprehensive therapy, the 1-, 2- and 3-year OS were 100%, 75% and 65.6%; the median OS was 42 months. Although all of my enrolled patients don't have EGFR mutation, which was the poor predict factor for NSCLC, in my study SABR provided better OS and PFS. Are they comparable between SABR and Metastasectomy? Widder et al. [26] reported that from 2007 until 2010, 110 patients were treated and analyzed (Metastasectomy =68; SABR=42). Median follow-up time was 43 months. Estimated overall survival rates at one, three, and five years were 87%, 62%, and 41% for Metastasectomy, and 98%,

Table 2: Radiation dose segmentation mode.

(TOMO Therapy Hi·Art)	
Primary lung and lymph nodes	Dt 60-75Gy, 10-20f
Bone and adrenal metastases	Dt 60-70Gy, 10-20f
Thoracic and lumbar spine metastasis	Dt 30-60Gy, 10-20f
Spinal cord metastases	Dt 40Gy, 20f
Head metastases	Dt 60-70Gy, 10-20f
(Gamma-knife Radio surgery)	
Primary lung pulmonary lesions metastases, bone and adrenal metastases 70% Isodoseline (GTV)	Dt 70-78.4Gy, 10-14f
Liver metastases 70% Isodoseline (GTV)	Dt 84-98Gy, 10-12f

Table 3: Factors associated with overall survival in univariate and multivariate analyses.

	Univariate			Multivariable		
Characteristics	**HR**	**HR 的 95% CI**	**P**	**HR**	**HR 的 95% CI**	**P**
Gender			0.414			0.983
Female	Reference			Reference		
Male	0.715	0.32-1.598		0.98	0.157-6.137	
Age (Years)			0.689			0.624
<65	Reference			Reference		
≥ 65	1.16	0.561-2.396		1.265	0.495-3.233	
Histology			0.51			0.291
NSCLC	Reference			Reference		
adenocarcinoma	1.078	0.457-2.544	0.864	2.209	0.689-7.077	0.182
Non-adenocarcinoma	2.482	0.506-12.174	0.262	5.847	0.375-91.136	0.208
Smoking status			0.727			0.702
No	Reference			Reference		
Yes	1.15	0.525-2.519		0.693	0.106-4.542	
Smoking Index			0.961			0.571

60%, and 49% for SABR, respectively (log rank-test, p=0.43). Local control at two years was 94% for SABR and 90% for Metastasectomy. Although SABR was second choice after Metastasectomy, survival after Metastasectomy was not better than after SABR. In addition, Chang JY et al. [27] reported that 58 operable stage I NSCLC patients were randomly assigned to the SABR group (N=31) and the surgical group (N=27). The median follow-up time was 40.2 and 35.4 months, respectively. The results showed that the 3 year survival rates were 95% and 79%, respectively. The 3 year progress free survival rate is 86% and 80%.In the surgical treatment group, 12 (44%) patients had 3-4 treatment-related adverse reactions. One (1) patient (4%) died of surgical complications, while only 3 patients (10%) in the SABR group developed grade 3 adverse reactions, and no grade 4 adverse reactions occurred. Therefore, SABR radiotherapy is well tolerated, local control rate is high, OS may be better than surgery, and can be used as an option to refuse surgery or intolerable surgery patients. At present, it is recognized that BED110 is optimally controlled at 100~150Gy. In this study, 19 patients (47.5%) had primary lesions and all metastases treated with BED10>100 Gy; Multivariate analysis showed that BED10 ≥ 100 Gy was an independent prognostic factor. Previous studies have also shown that increasing the dose of radiotherapy can extend the OS in oligometastatic NSCLC patients, indicating that high-dose radiotherapy to the primary tumor and all metastases is beneficial to improve survival and significantly improve local control rate [28]. The single factor and multiple factors analysis of prognosis showed that good ECOG is a good prognostic factor. Previous studies have also reported on these independent prognostic factors [29]. A good performance status indicates that the quality of life is high, nutrition intake is sufficient, systemic treatment is well tolerated, treatment continuity is guaranteed. Re-treatment of new lesions and their own immune function can still play a part. In this study, ECOG<2 patients received a continuous treatment rate of 90%, and ECOG ≥ 2 patients received a continuous treatment rate of 46%. The importance of good performance status in the overall treatment of cancer patients can be seen. The results of this study showed that the N stage, CNS metastases, No. of metastases organs, No. of metastases and other factors had no significant effect on the difference in survival prognosis. This may be related to the definitive radiotherapy or SBRT in the mild phase of Oligometastatic metastasis, which greatly reduces the tumor burden and reduces the mortality rate of important organ metastases, while actively systemic treatment. Anderson Cancer Center, Gomez et al. [30] a multicenter randomized phase II clinical trial, 49 Oligometastatic NSCLC patients were systematically treated with standard first-line chemotherapy and were randomized to a local consolidative therapy group (definitive local consolidative therapy to all lesions) and a maintenance treatment group (chemotherapy or close observation). The results showed that the PFS was 11.93 months and 3.9 months, respectively. This is currently the first randomized

controlled study of clinical treatment of Oligometastatic NSCLC. The results show that standard systemic chemotherapy combined with definitive local treatment can prolong the appearance of new lesions, significantly improved PFS. In the above report, 20% of patients with EGFR-mutated and treated with TKI in the local consolidative therapy group. The results of our study showed that 40 EGFR-unmutated Oligometastatic NSCLC patients had a 1 year progress free survival rate of 65.00%, a 2 year progress free survival rate of 10.00%, and a median progress free survival time of 13 months. Another randomized controlled study 29 EGFR-unmutated Oligometastatic NSCLC patients were randomly assigned to the local SABR group (systemic chemotherapy + local radiotherapy) and the maintenance treatment group (chemotherapy alone) [31]. The results showed that the PFS in the local SABR group increased nearly three-fold compared with the maintenance treatment group (9.7 *vs.* 3.5 months).

Conclusion

Definitive radiotherapy on the primary tumor and all metastases on the basis of systemic chemotherapy can prolong the appearance of new lesions in Oligometastatic NSCLC patients, improve patients' quality of life, reduce systemic tumor burden, and significantly increase PFS. Univariate analysis of PFS showed that a good EOCG score was a favorable prognostic factor. This indicates that good physical condition is highly tolerant to systemic chemotherapy and definitive local treatment, the patient accept a doctor's treatment plan (medical compliance). At the same time, the autoimmune mechanism can also partially inhibit tumors. In the case of multivariate analysis, BED10 ≥ 100 Gy (independent prognostic factor). This also shows that increasing the local radiotherapy dose can increase the local control rate, reduce the tumor burden, prolong the time of new lesions, and improve PFS. There are also some shortcomings in this research 1. Less sample size; 2. This study is a retrospective study, cannot replace prospective randomized controlled trials, because there are many factors influencing the radical treatment of Oligometastatic NSCLC patients with primary tumor and all metastases. This is related to the patient's general physical condition, medical compliance, economic status, tolerance to systemic treatment, and doctor's treatment model; 3. Thirdly, no studies have been conducted on definitive radiotherapy for non-Oligometastatic NSCLC patients. It is not further certain that Oligometastatic metastasis patients can benefit from radical radiotherapy. In short, EGFR-unmutated Oligometastatic NSCLC patients receiving systemic chemotherapy, combined with high-dose radiotherapy to primary tumor and all metastases, may improve OS and PFS.

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