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ORIGINAL ARTICLE

Clinical analysis of ^{125}I seed implantation combined with epidermal growth factor receptor-tyrosine kinase inhibitors in advanced non-small cell lung cancer

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Summary

Purpose: *To explore the efficacy and safety of ^{125}I radioactive seed implantation combined with epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) in the treatment of advanced non-small cell lung cancer (NSCLC).*

Methods: *108 patients with EGFR mutation-positive unresectable advanced NSCLC (stage IIIB-IV) were randomly divided into ^{125}I group (treated with ^{125}I radioactive seed implantation combined with EGFR-TKIs, n=54) and EGFR-TKIs group (treated with EGFR-TKIs alone, n=54). The short-term efficacy and adverse reactions were analyzed and evaluated, the changes in the levels of peripheral blood T lymphocyte subsets, natural killer (NK) cells and related immune-inflammatory factors were analyzed, and the long-term survival and progression of disease were recorded.*

Results: *The objective response rate was 61.1% (33/54) and 51.9% (28/54), and the disease control rate was 88.9% (48/54) and 68.5% (37/54), respectively, in ^{125}I group and EGFR-TKIs group. At 6 months after treatment, the levels of peripheral blood cluster of differentiation 3^+ ($CD3^+$), $CD4^+$, $CD4^+/CD8^+$ and NK cells significantly rose in both groups compared with those before treatment ($p<0.05$), while the levels of $CD8^+$, serum tumor necrosis factor-a (TNF-a), interferon-γ (IFN-γ), interleukin-6 (IL-6) and IL-10 significantly declined compared with those before treatment. The 2-year overall survival (OS) rate was 53.7% (29/54) and 40.7% (22/54), and the median progression-free survival (PFS) was 14.5 months and 9.8 months, respectively, in ^{125}I group and EGFR-TKIs group.*

Conclusions: *^{125}I radioactive seed implantation combined with EGFR-TKIs is safe and effective in the treatment of advanced NSCLC, and its short-term efficacy and long-term survival rate of patients are significantly superior to those of EGFR-TKIs alone. At the same time, it can regulate the expressions of T lymphocyte subsets, NK cells and immune-inflammatory factors in patients, and improve their immune function.*

Key words: *^{125}I seed implantation, epidermal growth factor receptor-tyrosine kinase inhibitors, non-small cell lung cancer*

Introduction

In China, the morbidity and mortality rates of lung cancer rank 1st among all tumors [1]. Studies have shown that the incidence rate of lung cancer increases at an annual rate of 1.63%, seriously threatening the physical health and affecting the patient quality of life [2,3]. Non-small cell lung cancer (NSCLC) accounts for 80% of lung cancers, most patients have been in the intermediate and late stage when diagnosed, and the effect of surgery or simple radiochemotherapy is unsatisfactory [4]. Epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) have been widely used in the treatment of NSCLC, their efficacy is superior to that of platinum-based chemotherapy drugs, and

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the incidence rate of adverse reactions is also low. Therefore, EGFR-TKIs are expected to become the first-line therapy drugs for NSCLC [5,6]. For example, gefitinib as an EGFR-TKI can be applied to treat NSCLC.

Radioactive seed interstitial implantation has been extensively applied in the treatment of solid tumors, such as head-neck tumors, pancreatic cancer and prostate cancer, and its efficacy has been widely recognized [7-9]. It is reported in the literature that ^{125}I radioactive seed implantation has definite efficacy on patients with advanced NSCLC, and molecular targeted drugs combined with minimally invasive therapy can exert a dual-targeted effect [10]. In the present study, the efficacy and safety of ^{125}I radioactive seed implantation combined with EGFR-TKIs and EGFR-TKIs alone were compared in the treatment of advanced NSCLC, so as to provide a strong basis for the treatment of such patients.

Methods

Objects of study

The clinical data of 108 patients with advanced NSCLC treated in our hospital from October 2016 to January 2018 were retrospectively analyzed. The patients were randomly divided into ^{125}I group (treated with ^{125}I radioactive seed implantation combined with EGFR-TKIs, n=54) and EGFR-TKIs group (treated with EGFR-TKIs alone, n=54). Inclusion criteria involved 1) patients diagnosed with inoperable stage IIIB-IV NSCLC *via* cytological or pathological examination, 2) those with EGFR mutation-positive NSCLC, 3) those with observable and measurable intrapulmonary lesions [lesions on computed tomography (CT) images ≥1 cm], 4) those who did not undergo radiochemotherapy within 1 month before treatment, 5) those with good physical conditions, 6) those with a Karnofsky performance scale score ≥70 points, and 7) those with an expected survival time >3 months. Exclusion criteria were set as follows: 1) patients complicated with other tumors, 2) those with severe dysfunction of heart, liver, kidney or other vital organs, 3) those with uncontrolled severe medical diseases or acute infections, 4) those with severe disturbance of blood coagulation or bleeding tendency, or 5) those with a history of definite neurological or mental disorders. Among the 108 patients, there were 66 males and 42 females aged 39-79 years old (mean 57.64±9.59). The baseline data such as gender, age, pathological type, tumor stage, tumor size and EGFR mutation status had no statistically significant differences between the two groups, and they were comparable (p>0.05) (Table 1). This study was approved by the Ethics Committee of Affiliated Hospital of Inner Mongolia University for Nationalities. Signed written informed consents were obtained from all participants before the study entry.

Treatment methods

After definite diagnosis, all patients took orally gefitinib once a day (250 mg/time). Two weeks later, the patients in ^{125}I group underwent ^{125}I radioactive seeding

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

Parameters	*^{125}I group (n=54)* *n (%)*	*EGFR-TKIS group (n=54)* *n (%)*	*p value*
Age	56.84±9.02	58.05±9.81	0.506
Gender (Male/ Female)	31/23	35/19	0.554
Pathologic type			0.423
Adenocarcinoma	37 (44.0)	32 (48.8)	
Squamous cell carcinoma	17 (56.0)	22 (51.2)	
TNM staging			0.677
IIIB	36 (86.9)	39 (81.0)	
IV	18 (86.9)	15 (81.0)	
Tumor type			0.557
Central	34 (52.4)	30 (58.3)	
Peripheral	20 (47.6)	24 (41.7)	
Largest tumor diameter (cm)	4.2±1.7	4.4±1.5	0.518
Initial EGFR status			0.560
19 del	29 (8.3)	33 (10.7)	
21 L858R	25 (0)	21 (1.2)	
KPS score			0.699
80-90	31 (63.1)	28 (57.1)	
70-80	23 (36.9)	26 (42.9)	

EGFR-TKIS: epidermal growth factor receptor tyrosine kinase inhibitors; TNM: tumor, node, metastasis; KPS: Karnofsky performance status.

[Seeds Biological Pharmacy (Tianjin) Co., Ltd., source activity: 0.7-0.9 mCi, half-life: 59.6 d, average photon energy: 28 KeV, tissue penetration distance: 1.7 cm] implantation in intrapulmonary lesions. The HGGR-3000 radioactive seed treatment plan system (TPS) (HOKAI) was used, and the total radiation dose and the number of seeds required were determined according to the volume of tumor and the activity of a single seed. Before operation, blood routine examination, coagulation function examination and electrocardiography were performed. Before and during operation, the position, direction and depth of needle insertion were determined *via* CT scan. After routine disinfection, draping and local anesthesia, ^{125}I radioactive seeds were implanted at an interval of 0.5-1.0 cm at each slice. The seed implantation spacing was preferably greater than 1 cm at the site near or invading important organs such as heart, great vessels and esophagus, so as to avoid esophageal fistula and other adverse events. During operation, electrocardiograph monitoring was adopted, venous access was constructed, and oxygen was inhaled. After operation, CT scan was performed to confirm the seed implantation status and whether complications such as pneumothorax, hemothorax and hydropneumothorax occurred. At the same time, whether there was seed loss and missing was checked in the operation environment, and the use of seeds was recorded.

Observation indexes

The clinical efficacy was evaluated at 2 months after treatment based on the imaging examination results and Response Evaluation Criteria in Solid Tumors (RECIST) of World Health Organization (WHO). Complete response (CR): The lesions completely disappear, and there are only cord-like images or no lesions in the imaging examination. Partial response (PR): The lesions shrink, and the volume of lesions is reduced by ≥50% compared with that before treatment or new lesion(s) appear. Stable disease (SD): The volume of lesions is reduced by <50%, or increased by <25%. Progressive disease (PD): The volume of lesions is increased by >25% compared with that before treatment or new lesion(s) appears. Objective response rate (ORR) = (CR + PR)/total cases × 100%, and disease control rate (DCR) = (CR + PR + SD)/total cases × 100%. The treatment-related adverse reactions were recorded, including seed missing or migration, myelosuppression, hemoptysis, pneumothorax and gastrointestinal reactions, and they were classified into grades 0-IV according to the WHO Common Toxicity Criteria.

Before treatment and at 6 months after treatment, the levels of peripheral blood immune cells were detected using flow cytometry, including T lymphocyte subsets [cluster of differentiation 3$^+$ (CD3$^+$), CD4$^+$, CD8$^+$ and CD4$^+$/CD8$^+$] and natural killer (NK) cells. The levels of serum immune-inflammatory factors [tumor necrosis factor-α (TNF-α), interferon-γ (IFN-γ), interleukin-6 (IL-6) and IL-10] were determined using enzyme-linked immunosorbent assay kits before treatment and at 1, 3 and 6 months after treatment.

After treatment, the patients were reexamined in the clinic once every 1-2 months in the 1st year, once every 3 months in the 2nd year, and once every 3-6 months in and after the 3rd year. The survival status of patients and progression of disease were recorded *via* follow-up till January 2020.

Statistics

SPSS 22.0 software package (IBM, Armonk, NY, USA) was used for statistical analyses. Measurement data were expressed as mean ± standard deviation, and t-test was performed for intergroup comparison. Enumeration data were expressed as rate (%), and x^2 or Fisher exact probability test was performed for comparison. T-test was used for the intragroup comparison of paired data, and two-way analysis of variance (ANOVA) for the intergroup comparison. The survival curves were plotted using the Kaplan-Meier method and log-rank test were performed to check survival differences. P<0.05 suggested statistically significant difference.

Results

Treatment efficacy

The short-term efficacy was evaluated at 2 months after treatment. In ^{125}I group, there were 12 (17.6%) cases of CR, 31 (45.6%) cases of PR, 19 (27.9%) cases of SD, and 6 (8.8%) cases of PD. The ORR and DCR were 61.1% (33/54) and 88.9% (48/54), respectively. In EGFR-TKIs group, there were 6 (8.8%) cases of CR, 24 (35.3%) cases of PR, 22 (32.4%) cases of SD, and 16 (23.5%) cases

Table 2. Comparison of tumor response of patients in the two studied groups

Parameters	*^{125}I group (n=54)* *n (%)*	*EGFR-TKIS group (n=54)* *n (%)*	*p value*
Complete response (CR)	12 (17.6)	6 (8.8)	
Partial response (PR)	31 (45.6)	24 (35.3)	
Stable disease (SD)	19 (27.9)	22 (32.4)	
Progressive disease (PD)	6 (8.8)	16 (23.5)	
ORR (CR + PR)	33 (61.1)	28 (51.9)	0.438
DCR (CR + PR+SD)	48 (88.9)	37 (68.5)	0.018

EGFR-TKIS: epidermal growth factor receptor tyrosine kinase inhibitors; ORR: objective response rate; DCR: disease control rate.

of PD. The ORR and DCR were 51.9% (28/54) and 68.5% (37/54), respectively. It can be seen that there was no statistically significant difference in the short-term ORR between the two groups (p=0.438), and the DCR was significantly superior in ^{125}I group to that in EGFR-TKIs group (p=0.018) (Table 2).

Levels of peripheral blood immune cells before and after treatment

Before treatment, the levels of $CD3^+$, $CD4^+$, $CD8^+$, $CD4^+/CD8^+$ and NK cells had no statistically significant differences between the two groups (p>0.05). At 6 months after treatment, the levels of peripheral blood $CD3^+$, $CD4^+$, $CD4^+/CD8^+$ and NK

Table 3. Comparison of immunological indicators of patients in the two studied groups

	^{125}I group (n=54)	*EGFR-TKIS group (n=54)*	*p value*
$CD3^+$ T cell (%)			
Pretreatment	65.09±10.48	65.79±9.88	0.721
Posttreatment	71.31±11.53	69.62±10.54	0.428
$CD3^+CD4^+$ T cell (%)			
Pretreatment	25.24±5.17	24.65±5.03	0.629
Posttreatment	37.71±7.48	39.78±7.07	0.142
$CD3^+CD8^+$ T cell (%)			
Pretreatment	38.22±6.65	39.97±7.68	0.205
Posttreatment	25.52±9.59	27.89±9.74	0.206
$CD4^+/CD8^+$ ratio			
Pretreatment	0.76±0.45	0.65±0.39	0.115
Posttreatment	1.42±0.48	1.27±0.37	0.051
NK cell (%)			
Pretreatment	15.51±8.24	14.86±8.74	0.794
Posttreatment	22.62±9.08	20.90±8.44	0.181

EGFR-TKIS: epidermal growth factor receptor tyrosine kinase inhibitors; NK: natural killer.

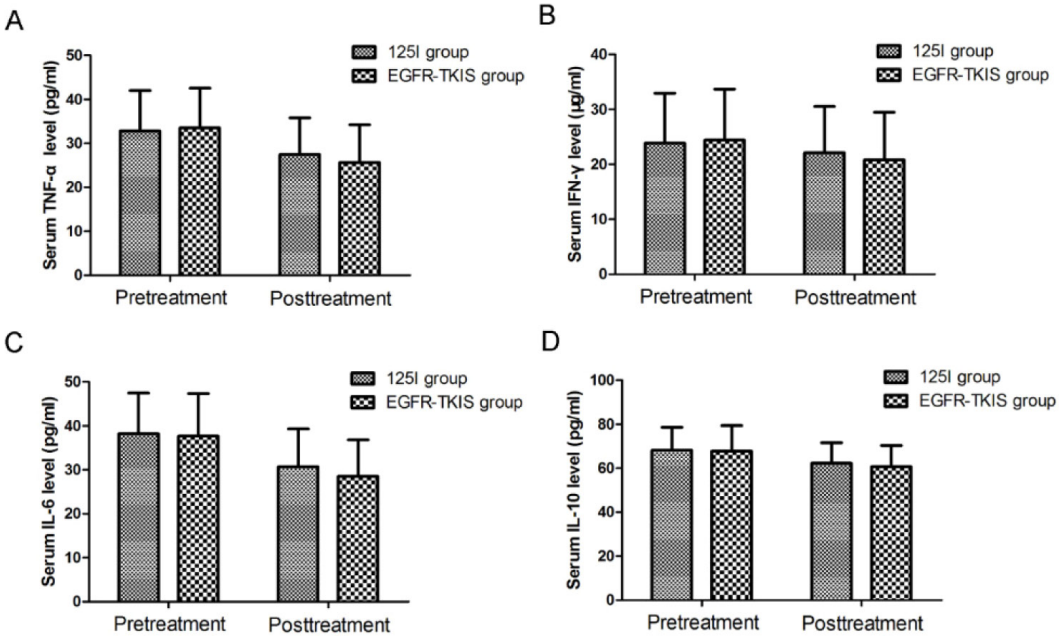

Figure 1. Comparison of pretreatment and posttreatment serum TNF-α **(A)**, IFN-γ **(B)**, IL-6 **(C)**, IL-10 **(D)** levels of the studied patients. The difference between pretreatment serum TNF-α **(A)**, IFN-γ **(B)**, IL-6 **(C)**, IL-10 **(D)** levels of patients in ^{125}I group and EGFR-TKIS group had no statistical significance (p>0.05). Serum TNF-α **(A)**, IFN-γ **(B)**, IL-6 **(C)**, IL-10 **(D)** levels of patients were significantly decreased after treatment (p<0.05). The difference between posttreatment serum TNF-α **(A)**, IFN-γ **(B)**, IL-6 **(C)**, IL-10 **(D)** levels of patients in ^{125}I group and EGFR-TKIS group had no statistical significance (p>0.05).

cells significantly rose in both groups compared with those before treatment (p<0.05), while the level of $CD8^+$ significantly declined compared with that before treatment (p<0.05). After treatment, the levels of the above indexes had no statistically significant differences between the two groups (p>0.05) (Table 3).

Levels of serum inflammatory factors before and after treatment

Before treatment, there were no statistically significant differences in the levels of serum TNF-α, IFN-γ, IL-6 and IL-10 between the two groups (p>0.05). At 6 months after treatment, the level of serum TNF-α declined from 32.82±9.16 pg/mL and 33.49±9.03 pg/mL to 27.45±8.32 pg/mL and 25.62±8.58 pg/mL, the level of IFN-γ declined from 23.83±9.09 μg/mL and 24.41±9.26 μg/mL to 22.10±8.39 μg/mL and 20.78±8.67 μg/mL, the level of IL-6 dropped from 38.18±9.27 pg/mL and 37.66±9.65 pg/mL to 30.70±8.59 pg/mL and 28.48±8.29 pg/mL, and the level of IL-10 dropped from 68.16±10.51 pg/mL and 67.76±11.63 pg/mL to 62.26±9.30 pg/mL and 60.72±9.69 pg/mL, respectively, in ^{125}I group and EGFR-TKIs group. The differences in the above indexes were statistically significant after treatment compared with those before treatment (p<0.05). After treatment, the levels of the above indexes had no statistically significant differences between the two groups (p>0.05) (Figure 1).

Incidence of adverse reactions

After seed implantation, a little pneumothorax and hemoptysis occurred in 5 (9.3%) cases and 3 (5.6%) cases, respectively, in ^{125}I group, more than those in EGFR-TKIs group (0 and 1 case), which were all relieved after oxygen inhalation and hemostasis. In ^{125}I group, 1 (1.9%) case had seed loss and dislocation, and no radiation pneumonitis occurred. All patients underwent CT examinations at 1 month after operation, and no severe complications such as radiation pneumonitis and esophagitis were found. In ^{125}I group and EGFR-TKIs group, the incidence rates of myelosuppression, cutaneous adverse reaction, nausea and vomiting and diarrhea were 11 (20.4%) *vs.* 5 (9.3%), 22 (40.7%) *vs.* 25 (46.3%), 13 (24.1%) *vs.* 8 (14.8%), and 13 (24.1%) *vs.* 10 (18.5%). These adverse reactions were mostly of grade I-II, and they were remarkably relieved after symptomatic treatment. The incidence of adverse reactions had no statistically significant difference between the two groups (p>0.05) (Table 4).

Recurrence and survival

The patients were followed up till January 2020, with a median follow-up period of 28.7 months. The 1-year overall survival (OS) rate was 81.5% (44/54) and 63.0% (34/54), the 2-year OS rate was 53.7% (29/54) and 40.7% (22/54), and the median progression-free survival (PFS) was 14.5 months and 9.8 months, respectively, in ^{125}I group and EGFR-TKIs group. The OS curves of patients were

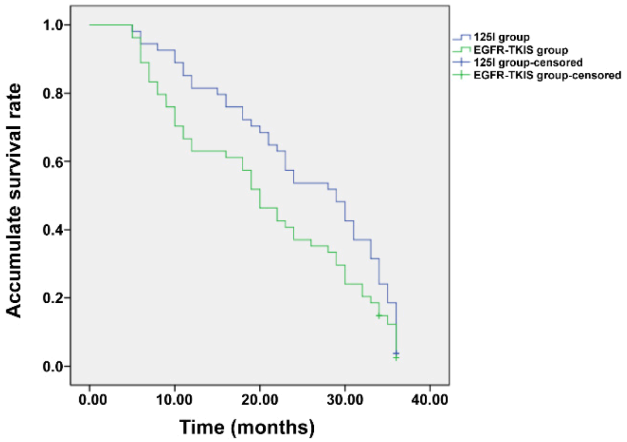

Figure 2. Kaplan-Meier survival curves of patients in ^{125}I group and EGFR-TKIS group. The overall survival rate of patients in ^{125}I group was significantly higher than that of EGFR-TKIS group (p=0.036).

Table 4. Comparison of adverse reactions of patients in the two studied groups

Parameters	*^{125}I group (n=54)* *n (%)*	*EGFR-TKIS group (n=54)* *n (%)*	*p value*
Myelosuppression	11 (20.4)	5 (9.3)	0.174
Cutaneous adverse reaction	22 (40.7)	25 (46.3)	0.698
Nausea and vomiting	13 (24.1)	8 (14.8)	0.331
Diarrhea	13 (24.1)	10 (18.5)	0.639
Pneumothorax	5 (9.3)	0 (0)	0.057
Hemoptysis	3 (5.6)	1 (1.9)	0.618
Particle dislocation	1 (1.9)	0 (0)	0.826

EGFR-TKIS: epidermal growth factor receptor tyrosine kinase inhibitors.

plotted using the Kaplan-Meier method (Figure 2). The results of log-rank test revealed that the OS had a statistically significant difference between the two groups, and it was significantly better in ^{125}I group than that in EGFR-TKIs group (p=0.036).

Discussion

The diagnosis and treatment of advanced NSCLC has always been difficult in the clinic. Chemotherapy and radiotherapy are the first-line treatment methods for patients with inoperable advanced lung cancer. The effect of simple chemotherapy is often unsatisfactory due to adverse drug reactions and drug resistance of cancer cells [11]. Traditional external beam radiotherapy requires a dose of about 100 Gy to kill lung cancer cells, but it will endanger various organs such as lung, esophagus, heart, spinal cord, bronchus and great vessels in clinical treatment. In particular, it will cause severe radiation pneumonitis. It is reported that the increase of radiation dose does not improve greatly the survival time, but will have the opposite effect due to its serious adverse reactions instead [12].

^{125}I radioactive seed interstitial implantation is a type of internal radiotherapy. ^{125}I seed implantation can be conformal with the tumor to the greatest extent, and low-dose irradiation can enhance the sensitivity of hypoxic tumor cells, kill tumor cells at close range, and effectively improve the distribution ratio of radiation dose in local tumor tissues and normal tissues. As a result, it not only achieves a relatively high rate of treatment, but also reduces the damage to normal tissues [13]. The half-value thickness of radiation in tissues and lead is 20.0 mm and 0.025 mm, respectively, that is, 0.025 mm of lead or 20.0 mm of human tissues can offset more than 99% of the radiation, so it is easy to protect the human body. Studies have found that close-range and continuous interstitial irradiation can significantly raise the local dose in tumors and reduce the damage to normal tissues. At the same time, chemotherapy drugs can inhibit the mitosis of tumor cells in M phase, and greatly kill tumor cells in G/S phase. Therefore, ^{125}I seed implantation combined with chemotherapy can obviously control the local recurrence rate and metastasis rate, and prolong the survival time [14].

With the constant development of molecular biology, EGFR-TKIs have been used in the clinical treatment of advanced NSCLC and achieved good efficacy. The EGFR signaling pathway is closely related to tumor proliferation, metastasis and angiogenesis. EGFR-TKIs block the EGFR signaling pathway *via* specifically preventing phosphorylation of tyrosine residues, thereby exerting an anti-tumor effect. Currently, the representative drugs of small-molecule EGFR-TKIs are gefitinib and erlotinib [15]. In a large number of clinical studies, such as the TRUST, OPTIMAL and INFORM studies, the efficacy and superior survival of EGFR-TKIs have been proved in advanced NSCLC, in which the median PFS in Erlotinib group in the OPTIMAL study is up to 13.7 months [16-19]. Similarly, the IPASS, First-SIGNAL (South Korea) and NEJGS002 and WJOG3405 (Japan) studies all showed that the PFS, ORR and quality of life of EGFR-mutated patients treated with gefitinib are all better than those of patients treated with standard chemotherapy. In each study, PFS has obvious improvement, but OS is not improved more significantly than that in chemotherapy group [20-22].

Clinical practice proved that it is difficult for any single treatment to achieve the best efficacy on advanced NSCLC. It has been found that EGFR-TKIs are also an ideal kind of radiotherapy sensitizer, and their combination with radiotherapy can delay tumor growth. According to research results, the median PFS and median survival are 10.2 months and 21.8 months, respectively, in the treatment of stage III/IV NSCLC with EGFR-TKIs combined with radiotherapy, indicating that the combination therapy is safe and effective [23,24]. In this study, it was found that in the treatment of NSCLC with ^{125}I radioactive seed interstitial implantation combined with EGFR-TKIs, the ORR and DCR were 61.1% (33/54) and 88.9% (48/54), the 2-year OS rate and median PFS were 53.7% and 14.5 months, respectively, and its efficacy was superior to that of EGFR-TKIs alone.

Radioactive seed implantation and chemotherapy have a significant impact on the body's immune function in the treatment of NSCLC, so the efficacy is less satisfactory. In the regulation of cellular immunity and anti-tumor immunity, T lymphocyte subsets play a dominant role. When the levels of relevant immune cells such as T lymphocyte subsets ($CD3^+$, $CD4^+$, $CD8^+$, $CD4^+/CD8^+$), NK cells and cytokine-induced killer cells decline, the body's immunoregulatory function will be weakened, leading to the occurrence and development of tumors [25]. The expression and secretion of immunoregulatory factors not only have a close correlation with the function of immune cells, but also play an important role in regulating the occurrence and development of tumors, and anti-tumor immunoregulation. In this study, at 6 months after treatment, the levels of peripheral blood $CD3^+$, $CD4^+$, $CD4^+/CD8^+$ and NK cells significantly rose in both groups compared with those before treatment ($p<0.05$), while the level of $CD8^+$ significantly declined compared

with that before treatment ($p<0.05$). The levels of TNF-α, IFN-γ, IL-6 and IL-10 were also lower than those before treatment ($p<0.05$). It can be seen that the therapeutic regimen in this study can regulate the expressions of T lymphocyte subsets, NK cells and immunoregulatory factors in patients, thereby improving the patient's immune function. In terms of adverse reactions, no radiation pneumonia and radiation esophagitis occurred, the main adverse reactions were pneumothorax, hemoptysis and skin reactions, and no serious hepatic-renal damage was found. The incidence of adverse reactions had no statistically significant difference between the two groups ($p>0.05$).

This was a retrospective study, so the sample size was small, the follow-up period was short, and the follow-up content was not comprehensive enough. Therefore, the conclusion made in this study remains to be verified by more rigorous prospective large-sample multicenter randomized studies.

Conclusion

^{125}I radioactive seed implantation combined with EGFR-TKIs is safe and effective in the treatment of advanced NSCLC, and its short-term efficacy and long-term survival rate of patients are significantly superior to those of EGFR-TKIs alone. At the same time, it can regulate the expressions of T lymphocyte subsets, NK cells and immune-inflammatory factors in patients, and improve the patient immune function.

Conflict of interests

The authors declare no conflict of interests.

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