To evaluate the efficacy and safety of $^{125}$I seed implantation in SCLC as second line therapy

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Abstract
This study aimed to evaluate the efficacy and safety of iodine 125 ($^{125}$I) radioactive seed implantation for small cell lung cancer at the limited stage of relapse as second line therapy. We collected 6 patients with recurred limited stage small cell lung cancer, who got pathological diagnosis after a bronchoscopic biopsy and then received standard first line treatment, combined chemotherapy and radiotherapy, including prophylactic cranial irradiation. These recurred small cell lung cancer patients got $^{125}$I seed implantation treatment as second line therapy, if the treatment not good responsive or the disease got rapid progress, we used the second line chemotherapy as salvage treatment. Clinical data of these patients were collected and short-term effects were observed. The follow-up period lasted for 42 months. All the patients tolerated the procedure of $^{125}$I radioactive seed implantation very well. We followed up the patients to 42 months. Five patients got complete remission and 1 patient got partial remission at 1 month after implantation. The objective response rate was 100%. The median survival time was 26 months. And median progression-free survival was 12 months after $^{125}$I treatment. And about the complications, 1 patient suffered from the light aerothorax, 1 patient had a little hemoptysis. Our study showed that $^{125}$I seed implantation as second line regimen in small cell lung cancer that recurred locally after first line treatment was effective and safe. That could improve the overall survival and progression-free survival only comparing to the second line chemotherapy. Therefore $^{125}$I seed implantation as brachytherapy protocol is a promising method and can be applied as second line treatment to control the locally recurred small cell lung cancer.

Abbreviations: $^{125}$I = Iodine-125, CR = complete remission, CT = computed tomography, OS = overall survival, PFS = progression-free survival, PR = partial remission, SCLC = small cell lung cancer.

Keywords: $^{125}$I seed implantation, branchytherapy, overall survival, progression-free survival, small cell lung cancer

1. Introduction
Small cell lung cancer is a highly malignant cancer, fast to grow, easy and early to disseminate, easy to relapse, sensitive to both chemotherapy and radiotherapy, but has bad prognosis. The 5 years survival rate is only <7%.[1] Small cell lung cancer (SCLC) is usually classified into a 2-stage system, limited disease (LD), and extensive disease (ED) according to the Veterans Administration Lung Study Group (VALG) of America that was widely used now.[2] Most patients are found in extensive stage and lose chance to get radical surgery. And even in limited stage many people could not accept operation or have a very high recurrence rate after radical surgery because of its potential transfer characteristics.[3] So for patients with limited stage SCLC the standard treatment regimen is chemotherapy combining external radiotherapy.[4] Prophylactic cranial irradiation can improve the 3-year survival. Despite high initial response rate, most patients eventually relapse. Except for topotecan, few treatment options then remain. Signaling pathways have been identified that might yield new drug targets.[5] But, SCLC still has a bad prognosis. Hence, we still need to explore new methods. $^{125}$I radioactive seed implantation has been studied for many years and is widely used in many solid tumors like non-small cell lung cancer, prostate cancer, pancreatic cancer, liver cancer or brain cancer as supplementary therapy or palliative therapy,[6] that has become a very important method. But for small cell lung cancer, not so much data to prove the efficacy

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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and safety. Here we retrospectively analyzed 6 patients to prove that.

2. Patients and Methods

2.1. Patients

A total of 6 patients who received 125I seed implantation from January 2014 to July 2019 in traditional Chinese medicine hospital of Rizhao city. This study was approved by the ethical committee of the hospital. All the patients were diagnosed with pathological results (Fig. 1) by bronchoscopic biopsy and with immunohistochemical support like Syn, CgA, and CD56 positive results. All these 6 patients, 52 to 67 years old (median age 59 years), 4 men, 2 women, were diagnosed in limited stage in initial diagnosis and got complete remission (CR) after the first line therapy, when they suffered from recurrence, the recurred lesion was only solitarily located in lung and the size of the solitary lesion was <3 cm. All the characteristics of these patients were listed in Table 1.

Inclusion criteria were: patients with limited stage small cell lung cancer without chance to get resection and get complete remission after chemotherapy and radiotherapy as first line treatment. And they suffered from recurrence, the recurred lesion was only solitarily located in lung and the size of the solitary lesion was <3 cm. And the ECOG score was <2. The case records were complete. Patients who could not tolerate puncture because of severe basic disease were excluded. According to the inclusion criteria we collected 6 patients for the study. And every patient was informed consent. Some patients were excluded because case records were incomplete or following up was not timely or standard. Those included 3 cases.

2.2. Treatment process and complications

Contrast computed tomography (CT) scan before 125I seed implantation was prepared to recognize the relationship between tumor and vessels, according to the CT image, the total volume of each tumor was calculated using a treatment planning system (TPS). Radioactive particles were purchased from Tianjin Said Biological Pharmaceutical Co, LTD (Tianjin, China). Iodine-125 seed source was a sealed source for radionuclide. The parameters of 125I seed were as follows: half-life 59.6 days; tissue penetration 1.7 cm; half value layer 0.025 mm lead; activity 0.6 × 0.8 mCi. Selected particle activity (individual particle surface activity of 0.6 mCi) and a prescription dose (120 Gy) were fed into the TPS system, the implant channel was designed, and the number of particles was calculated. Before treatment the patients got blood examination including CBC, blood coagulation, and electrolytes etc. Besides, we gave the patient codeine phosphate tablet in case of severe cough that would result in increasing the incidence rate of aerothorax and other complications.

When everything was prepared, the therapeutic intervention was performed in the CT room. All patients underwent local disinfection anesthesia before 125I seed implantation. And then used 18G needle to puncture at the predetermined point and angle according to the preoperative plan under CT-guidance. When the needle reached the edge of the tumor lesion and determined the position and angle of needle by CT scan. Using a seed implant machine to perform seed implantation retrogradely and keep the interval distance 0.5 to 1.5 cm. During the procedure, neural structures and large vascular structures were carefully avoided. Giving CT scan again after operation and compared with the TPS planning to check the prescription dose and the real distribute dose. If necessary, complement the needed seeds again. When completing the procedure, performed CT scan again to make

| Table 1 |
|-----------------------------|
| **Patient characteristics (n = 6).** |
| Characteristic | Value |
| Median age (range) | 59 (52–67) |
| Sex | 4 males/2 females |
| Primary tumor stage (n) | limited stage (6) |
| Tumor size (preoperation, before implantation) | =3 cm |
| Other metastatic sites | No |
| ECOG | 0–2 |
| Previous regimen | EP (chemotherapy)+RT (radiotherapy) |
| Tumor marker (before implantation) |   |
| Syn | normal |
| Pro-GRP | normal |
| Tumor marker (1 month after implantation) |   |
| Syn | normal |
| Pro-GRP | normal |
| hyponatremia | none |
and median overall survival time (mOS2) was 12 months. The overall survival time (mOS) of the 6 patients was 26 months and none of them was lost during the follow-up. The median (Table 2). All of the 6 patients were followed up to 42 months, among which 4 patients were still alive, 2 patients died of disease. The median progression-free survival time (mPFS) was 7 months. Up to September 2021, 2 out of the 6 patients had survived for the whole 42-month follow-up. The survive curves by Kaplan–Meier method were showed below (Figs. 2 and 3).

3. Results

3.1. Tumor control

After 1 month of $^{125}$I seed implantation, the outcomes of CT examination showed that 5 patients had complete disappearance of the tumor lesion (CR), 1 patient had PR. The percentage of tumor control in 6 patients (CR or PR) was 100% (Table 2). All of the 6 patients were followed up to 42 months, and none of them was lost during the follow-up. The median overall survival time (mOS) of the 6 patients was 26 months and median overall survival time (mOS2) was 12 months. The median progression-free survival time (mPFS) was 7 months. Up to September 2021, 2 out of the 6 patients had survived for the whole 42-month follow-up. The survive curves by Kaplan–Meier method were showed below (Figs. 2 and 3).

3.2. Complications

One patient had a little pneumothorax and 1 patient had spu
tum blood, they both recovered without treatment. None of the patients had any severe complications such as bleeding or heavy aerothorax. Long-term complications such as particle-migra
tion or radioactive radiation pneumonitis were not presented. And also no other complicates were found during the follow-up period.

4. Discussion

Small cell lung cancer is a highly aggressive malignant tumor of neuroendocrine origin, strongly associated with smoking tobacco and accounting for 15% of all lung cancers.[7] Small-cell lung cancer is considered limited-stage if it is still within the chest or extensive-stage if it has spread outside the chest.[8] Currently, chemotherapy and radiation therapy are recommended for treatment of limited-stage small-cell lung cancer if it is localized and has not spread outside of one side of the chest. Current treatment guidelines recommend platinum-based chemotherapy plus thoracic radiotherapy for the treatment of limited stage SCLC, and chemotherapy alone for extensive disease, with prophylactic cranial irradiation.[9] These recommendations are based on the premise that SCLC disseminates early and is very chemosensitive. The high throughput sequencing has deepened our understanding of its biology. The arrival of immune checkpoint inhibitors revolutionizes the management of extensive disease. Atezolizumab in combination with chemotherapy as a first-line treatment also demonstrated improved efficacy in the IMpower133 study.[10] This is the first phase III study to achieve an improvement OS in >30 years for extensive stage SCLC. But the treatment of localized disease has changed little.[11]

For limited stage SCLC, combined chemotherapy and concurrent or sequential radiotherapy are the standard treat
tment as we said before. Even the patients have chance to get radical resection, they still need to accept chemotherapy and radiotherapy. Therefore, when the limited stage SCLC patients suffer from recurrence after first line therapy that treatment got complete remission, they also need to accept chemotherapy that will be chosen according to the interval time from the first line regimen. But for the patients with localized recurrence, maybe we can use local methods to control the disease to prolong the survival time and avoid the patient from adverse effect that will be brought by the second chemotherapy. Of course, if the patients get extensive metastasis we plan to give them chemotherapy as rescue regi
den. As we know, iodine $^{125}$ seed implantation has been used in many solid tumors widely in the world in recent years and become more mature.[12] Iodine $^{125}$ particle implantation

| Time                  | CR    | PR    | SD    | PD    | ORR (CR+PR, %) |
|-----------------------|-------|-------|-------|-------|----------------|
| 1 month after operation | 5     | 1     | 0     | 0     | 100            |
| 3 months after operation | 4     | 1     | 1     | 0     | 83.3           |
| 6 months after operation | 3     |       | 3     | 1     | 50             |

CR = complete remission, ORR = objective response rate, PD = progressive disease, PR = partial remission, SD = stable disease.
therapy is an effective method and is available to achieve truly synchronous chemo-radiotherapy, which belongs to internal radiotherapy, its local dose is much higher than external radiation, and therefore iodine 125 can improve the local control rate. To interfere with DNA synthesis of tumor cells by emitting continuous low energy gamma rays, iodine seed produces killing effect at the late mitotic stage. Its effective irradiation distance is only 1.7 cm, so it can produce high dose in the local tumor and low dose in the normal tissue.

So in our study, we tried to retrospectively analyzed 6 patients to determine the efficacy and safety of 125I seed implantation. From our results we can see that: after 1 month of 125I seed implantation, 5 cases had complete remission and 1 case had PR. The percentage of tumor control was 100% (Fig. 1). All of the 6 patients were followed up to 42 months, the median overall survival time (mOS) of the 6 patients was 26 months and media overall survival time (mOS2) was 12 months. The media progression-free survival time (mPFS) was 7 months. Up to September 2021, 2 out of the 6 patients had
survived for the whole 42-month and still had very good quality of life. Besides, to the last followed time, all the patients did not present severe complications. Compared with the date of 4 to 5 months median survive time,[8] iodine 125 seed implantation in our study can improve the survive time very well. So for the patients with locally recurred SCLC, especially for those who refuse to receive chemotherapy or could not tolerate chemotherapy because of severe complications like neutropenia or leukopenia, iodine 125 seed implantation can be a choice. But, the patients we choose were only locally recurred cases and the size of lesion was smaller than 3 cm, that was optimal choice. So the results just can represent a part of patients with SCLC and further study with more cases should be explored again.

5. Conclusions
In summary, our study showed that 125I seed implantation as second line therapy in small cell lung cancer that recurred locally after first line treatment was effective and high safe. That could improve the overall survival and progression-free survival. Therefore 125I seed implantation as brachytherapy protocol is a promising method and can be applied as second line treatment to control the locally recurred small cell lung cancer. That may be a suitable and optional method.

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