Original paper

Computed tomography-guided iodine-125 radioactive seed implantation in small-cell lung cancer: A retrospective study

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Abstract

Purpose: To explore the efficacy of computed tomography (CT)-guided iodine-125 (^{125}I) radioactive seed implantation for the treatment of small-cell lung cancer (SCLC).

Material and methods: A total of 12 SCLC patients were retrospectively enrolled. All patients underwent CT-guided ^{125}I seed implantation therapy, and were followed up until death, the last visit time, or study end time. Primary endpoint was the overall response rate (ORR). Secondary endpoints were local control rate (LCR), progression-free survival (PFS), overall survival (OS), and safety.

Results: All patients were successfully implanted with ^{125}I radioactive seeds. The ORR at 2, 6, 12, and 24 months after implantation was 83.3%, 63.6%, 50%, and 40%, respectively; the LCR at 1 and 2 years were 75% (6/8) and 60% (3/5), respectively; the median PFS and OS were 8 and 12 months, respectively; and the OS rate at 6, 12, and 24 months after implantation was 91.67%, 66.67%, and 41.67%, respectively. No surgery-related deaths occurred. During the follow-up period, mild complications were observed in patients, including worsening cough, hemoptysis, and pneumothorax.

Conclusions: CT-guided ^{125}I seed implantation therapy is a safe and effective supplementary treatment for SCLC patients, who cannot tolerate radiotherapy.

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Key words: small-cell lung cancer, iodine-125 radioactive seed implantation, computed tomography-guided, brachytherapy.

Purpose

Lung cancer is the second most common cancer worldwide [1], and is generally categorized into small-cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC), according to the morphology of the cancer cells [2]. SCLC is an aggressive epithelial tumor characterized by a high propensity for early development, which accounts for about 15% of all lung cancers [3, 4]. Approximately, two-thirds of SCLC patients develop metastatic diseases with limited treatment options, suggesting that SCLC remains one of the most lethal malignancies [2]. Radiotherapy and chemotherapy are the cornerstones of SCLC treatment, and a combination of immune checkpoint inhibitors can also be employed to treat extensive SCLC [3, 5]. Etoposide and platinum-doublet chemotherapy is recommended as the standard first-line therapy, and combination chemotherapy with other agents, including carboplatin (paraplatin) and irinotecan (camptosar), is considered the standard second-line treatment [4, 6]. In patients with limited-stage SCLC (LS-SCLC), the combination of chemotherapy and radiotherapy may improve local control as well as overall survival (OS). However, for patients with extensive-stage SCLC (ES-SCLC), who make up the majority of SCLC patients in clinical practice, the most common initial chemotherapy regimen remains etoposide plus cisplatin (EP regimen), and no novel chemotherapy combinations have shown superior efficacy [3, 6]. Therefore, there is an urgent need for a safe and effective treatment to improve the clinical prognosis of SCLC patients.

Iodine-125 (^{125}I) radioactive seed implantation therapy is a local treatment that has been widely used in treatment of various malignancies [7-9]. With the advantages of low doses, small adverse reactions, and minimal invasiveness, it has been increasingly applied in treating NSCLC, achieving certain efficacy [10-12]. However, this method is rarely used in SCLC treatment. Therefore,

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this study retrospectively analyzed data of SCLC patients treated with ^{125}I seed implantation, and evaluated its' efficacy and the corresponding complications.

Material and methods

Patient data

A total of 12 SCLC patients, who were admitted to the respiratory and critical care medicine department of our hospital from September 2014 to September 2018 were enrolled into this study. Inclusion criteria: (1) Patients aged ≥ 18 years; (2) Diagnosed with SCLC by fiberoptic bronchoscopy or percutaneous lung biopsy; (3) Those who received ^{125}I radioactive seed implantation. Patients with respiratory failure, heart failure, severe arrhythmia, severe emphysema, high-risk of bulla puncture, and severe coagulation dysfunction as well as patients with incomplete data or follow-up information were not considered for this retrospective analysis. Clinical characteristics of the patients at baseline are shown in Table 1. Characteristics of each patient are presented in Tables 2 and 3, which included TNM stage, tumor location and size, prescription dose, previous treatment, and reasons for omitting standard treatment.

Table 1. Patients' characteristics

Characteristics	Value (*n*)
Gender	
Male	5
Female	7
Age (years), mean (range)	64.4 (55-80)
VALSG stage	
Limited	1
Extensive	11
Treatment history	
Chemotherapy	9
Radiotherapy	1
None	2
Tumor size (cm), mean (range)	4.5 (3-7)
Clinical presentation	
Cough	10
Hemoptysis	2
Difficulty in feeding	2
Weakness	3
Chest tightness and dyspnea	6
Chest pain	2
Infection	3
Complications	
Atelectasis	3
Superior vena cava syndrome	2
Mediastinal lymph node enlargement and compression	7

Table 2. Characteristics of patients with 125I seed implantation

Patient number	Gender	Age (years)	KPS score	Stage	TNM stage	Tumor location	Tumor size (cm)	Prescription dose, PD (Gy)	Surgical lesion number	Seed number	OS (months)
1	Female	55	90	Extensive	T3N3M1a IVa	Right lower lobe of the lung; No. 10 lymph nodes metastasis; No. 7 lymph nodes metastasis	4.3 × 5.4, 4.3 × 5.2, 3.2 × 3.5	110	3	15, 39, 16	24
2	Male	56	70	Limited	T3N3M0 IIIc	Right lower lobe of the lung	5.2 × 5.5	110	1	40	26
3	Male	68	80	Limited	T3N2M0 IIIb	Left upper lobe of the lung	6.2 × 5.5	120	1	60	29
4	Male	61	70	Extensive	T2aN2M1c IVb	Left lower lobe of the lung	3.8 × 4.3	100	1	26	5
5	Female	68	90	Limited	T3aN0M0 IIb	Left lower lobe of the lung; No. 10 lymph nodes metastasis	5.2 × 6.3, 3.7 × 4.2	110	2	54, 35	71
6	Female	63	70	Limited	T3N3M0 IIIc	Right upper lobe of the lung	6.5 × 5.1	110	1	60	18
7	Female	80	80	Limited	T2aN0M0 Ib	Left upper lobe of the lung	3.0 × 3.6	100	1	20	> 69
8	Female	67	80	Extensive	T3N3M1a IVa	Right upper lobe of the lung	5.7 × 6.4	110	1	50	7
9	Female	66	40	Extensive	T2bN2M1a IVa	Right lower lobe of the lung; No. 1 lymph nodes metastasis	4.5 × 3.6, 2.8 × 2.3	100	3	30, 26, 13	9
10	Female	73	50	Extensive	T2aN3M1c IVb	Left upper lobe of the lung; No. 7 lymph nodes metastasis	3.6 × 3.7, 5.7 × 6.8	120	2	28, 40	12
11	Male	60	90	Limited	T4N3M0 IIIc	Right upper lobe of the lung	7.0 × 6.3	100	1	58	12
12	Male	56	60	Extensive	T2bN2M1c IVb	Left upper lobe of the lung; Right upper lobe of the lung	3.5 × 3.7, 4.3 × 3.1	100	2	24, 28	7

OS – overall survival

Table 3. Previous treatments of patients with 125I seed implantation and reason for omitting a standard treatment

Patient number	Previous treatment and reason for omitting a standard treatment
1	The patient progressed after 6 cycles of EP regimen chemotherapy. Grade 4 myelosuppression occurred and radiotherapy was refused. Iodine-125 seeds were implanted and then metastasized into the lung.
2	Two cycles of EP regimen chemotherapy were ineffective. Due to the occurrence of IV degree myelosuppression, the patient was unable to continue chemotherapy and refused radiotherapy. Iodine-125 seeds were implanted and then metastasized into the liver.
3	Two cycles of EP regimen chemotherapy were ineffective. Grade 3 myelosuppression occurred in chemotherapy, and radiotherapy was refused. Iodine-125 seeds were implanted, followed by pleural metastasis and peritoneal metastasis.
4	The patient progressed after 5 cycles of EP regimen chemotherapy and atelectasis occurred. Due to the occurrence of grade 4 myelosuppression, the patient refused radiotherapy. Iodine-125 seeds were implanted and then the primary lesions progressed.
5	Oral Chinese medicine was ineffective, the patient refused radiotherapy and chemotherapy; the primary lesion increased. Iodine-125 seeds were implanted, regular re-examination found a dose cold area, and then the EP regimen for a total of 8 cycles of chemotherapy was applied, followed by liver metastasis.
6	One cycle of EP regimen chemotherapy; the patient refused radiotherapy. Iodine-125 seeds were implanted and post-operative 6 cycles of EP regimen chemotherapy were given. Then, intra-pulmonary metastasis and supra-clavicular lymph node metastasis occurred.
7	Progressed after 4 cycles of EP regimen chemotherapy, the patient refused radiotherapy because of grade 4 myelosuppression, and ^{125}I seeds were implanted.
8	Progressed after 7 cycles of IP regimen chemotherapy, and the patient refused radiotherapy due to grade 4 myelosuppression. Iodine-125 seeds were implanted, and posterior pleural metastasis and liver metastasis occurred.
9	Two cycles of EP regimen chemotherapy were ineffective; the patient refused radiotherapy. KPS score during seed implantation was 40, which indicated intolerant to radiotherapy and chemotherapy, and then intra-pulmonary metastasis occurred.
10	KPS score 50, intolerant to radiotherapy and chemotherapy. Iodine-125 seeds were implanted and then, posterior head skin metastasis, rib metastasis, and abdominal metastasis occurred.
11	Progressed after 6 cycles of EP regimen chemotherapy and radiotherapy. Iodine-125 seeds were implanted and then, posterior pleural metastasis and liver metastasis occurred.
12	Grade 4 myelosuppression occurred after the first cycle of EP regimen chemotherapy; the patient refused radiotherapy. KPS score before seed implantation was 60, which indicated intolerant to radiotherapy and chemotherapy. Iodine-125 seeds were implanted and then, hindbrain metastasis, liver metastasis, and bone metastasis occurred.

Instruments and equipment

For ^{125}I radioactive seed implantation, 18 G implantation needles and a turntable implantation gun were obtained from HAKKO Medical Co., Ltd. (Nagano, Japan) and Zhuhai Hejia Medical Equipment Co., Ltd. (Zhuhai, China), respectively. ^{125}I seeds were produced by Beijing ZHIBO Bio-Medical Technology Co., Ltd. (Beijing, China), and were fully enclosed in a titanium shell, with a length of 4.5 mm, a diameter of 0.8 mm, a half-life of 60.1 d, and an activity of 0.7 mCi. Seed implantation was guided by a Siemens 32-row helical computed tomography (CT) scanner (Siemens, Erlangen, Germany), with a slice thickness of 5 mm.

Pre-operative preparation

Before ^{125}I seed implantation, patients underwent a blood routine examination, accompanied by withdrawal of antiplatelet and anticoagulant drugs. An enhanced chest CT examination was performed to clarify the lesion scope and its' relationship with blood vessels as well as the route of needle insertion. Then, treatment planning system (TPS; Beijing Tianhang Kelin Technology Development Co., Ltd., Beijing, China) was applied to determine the number and distribution of ^{125}I seeds. Prescribed dose was 100-120 Gy. Prior to implantation, codeine was given to relieve cough, and diazepam was applied for sedation according to a patient's condition. Those with a high-risk of bleeding were administered hemostatic drugs, such as intra-muscular injection of hemagglutinin, and intravenous access was established.

CT-guided ^{125}I radioactive seed implantation

Patients were placed in a supine, prone, or lateral position, depending on the lesion location. Oxygen inhalation and ECG monitoring were given during the operation, and CT scans were conducted to determine the tumor site and the needle insertion point of ^{125}I seeds, with a line spacing of 1-1.5 cm and particle spacing of 0.5-1 cm. After routine skin disinfection with iodophor, a sterile hole towel was laid, and the puncture point area was anesthetized with local infiltration of 2% lidocaine. The syringe needles were indwelled after local anesthesia at all puncture points. Next, a CT scan was performed to examine whether the puncture point and puncture angle were correct. Then, the syringe needle was pulled out,

and the implant needle was punctured at a suitable point and angle. After confirming the correct puncture location by a CT scan, ^{125}I seeds were implanted and post-operative verification was conducted. Subsequently, the needle was removed, and the puncture point was covered and fixed with sterile gauze and tape. If there was a bleeding from the puncture point, compression was carried out.

Outcomes and assessments

Post-operative complications were closely monitored, and all patients were reviewed every 2 months. Patients were followed up until death, last visiting time, or the end of study. The efficacy was evaluated using response evaluation criteria in solid tumors (RECIST) guideline, version 1.1 [13]: (1) Complete response (CR): All target lesions disappeared and short-axis of any pathological lymph node (whether target or non-target) must be less than 10 mm; (2) Partial response (PR): A reduction of at least 30% in the sum of target lesion diameters compared with that of baseline sum diameters; (3) Progressive disease (PD): At least 20% of an increase in the sum of target lesion diameters compared with the smallest sum in the study (including the baseline sum if that was the smallest in the study). In addition to the relative increase of 20%, the absolute increase in the sum of diameters must be greater than 5 mm. The appearance of one or more new lesions was also considered progression; (4) Stable disease (SD): Neither sufficient shrinkage to qualify for PR nor enough increase to qualify for PD, the smallest sum diameters were used as a reference for the study. Overall response rate (ORR) = (CR + PR)/total number of cases × 100%. Local control rate (LCR) = (CR + PR + SD)/total number of cases × 100%. OS was defined as the time from the start of treatment to the death of a patient due to any cause. Progression-free survival (PFS) was considered the period between implantation and the date of recurrence, loco-regional progression, metastasis, or death.

Statistical analysis

Data were analyzed by SPSS version 20.0 (SPSS, Chicago, IL, USA). Continuous data were presented as mean (minimum-maximum) and categoric data were shown as absolute numbers (percentages). Median OS and PFS were estimated using Kaplan-Meier method.

Results

Characteristics of iodine-125 seed implantation

All patients were successfully implanted with ^{125}I radioactive seeds. As depicted in Table 2, a total of 662 ^{125}I seeds were implanted into 19 tumor lesions among the 12 patients, with a range of 20-89 seeds implanted in each patient. One of the cases 9 was found to have a dose cold zone, localized, with a supplemental implantation of 13 seeds.

Efficacy

The ORR was 83.3%, 63.6%, 50%, and 40% at 2, 6, 12, and 24 months after implantation, respectively (Table 4). The LCR at 1 and 2 years was 75% (6/8) and 60% (3/5), respectively. The patient's treatment results are shown in Figure 1. Of the 12 patients, 2 patients with superior vena cava syndrome had complete remission, and 2 of the 3 patients with atelectasis had lung recruitment.

Survival analysis

As shown in Figure 2, the patients who received ^{125}I seed implantation had a median OS of 12 months (range, 5-71 months). Moreover, the OS rate at 6, 12, and 24 months after implantation was 91.67%, 66.67%, and 41.67%, respectively (Table 2). The median PFS was 8 months (range, 3-69 months).

Surgical complications

No surgery-related death occurred. During the follow-up period, mild complications were observed, including 2 (16.67%) cases of cough aggravation, 1 (8.33%) case of hemoptysis, and 2 (16.67%) cases of pneumothorax.

Discussion

Iodine-125 seed implantation therapy was first used in the treatment of prostate cancer, and with the continuous innovation and improvement of medical technology, it is now widely used in treating various malignancies. Its' efficacy has been fully verified in the treatment of NSCLC [10-12]. A meta-study on NSCLC showed significant differences in ORR, disease control rate (DCR), and OS between ^{125}I brachytherapy in combination with chemotherapy and chemotherapy alone, confirming the clinical benefit of ^{125}I seed implantation for NSCLC treatment [14]. Additionally, lung squamous cell carcinoma is sensitive to ^{125}I seed irradiation, which exhibits significant therapeutic effects. However, there is little information on other pathologic lung tumor types irradiated by ^{125}I seed irradiation in addition to NSCLC [15]. In the current study, 12 SCLC patients received ^{125}I seed implantation, and it was found that tumor growth was inhibited and the quality of life improved. The ^{125}I radioactive particles can continuously release low-dose

Table 4. Efficacy evaluation of ^{125}I radioactive seed implantation

Time after surgery (months)	*n*	CR	PR	SD	PD	ORR (%)	LCR (%)
2	12	4	6	2	0	83.3	100.0
6	11	3	4	3	1	63.6	90.9
12	8	2	2	2	2	50.0	75.0
24	5	1	1	1	2	40.0	60.0

CR – complete response; PR – partial response; SD – stable disease; PD – progressive disease; ORR – overall response rate; LCR – local control rate

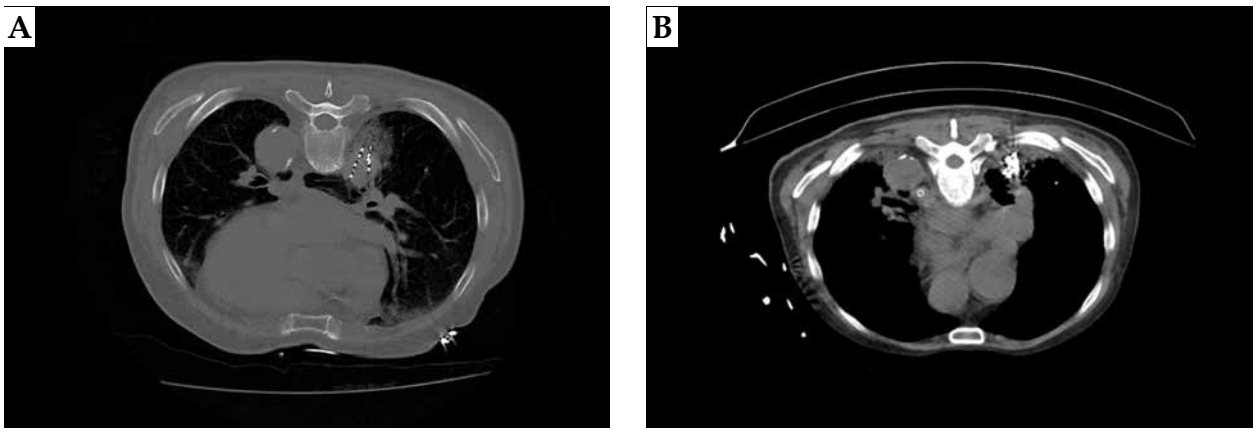

Fig. 1. CT images showing particle distribution after ^{125}I radioactive seed implantation in small-cell lung cancer (SCLC) patients and treatment after 3 months. **A**) After ^{125}I radioactive seed implantation, a few bleeding complications appeared in the dorsal lung of the tumor. **B**) Three months after ^{125}I radioactive seed implantation, the tumor gradually shrunk, and the gathered particles could be seen at the original tumor site: mild radiation pneumonia in the lung tissue around the tumor

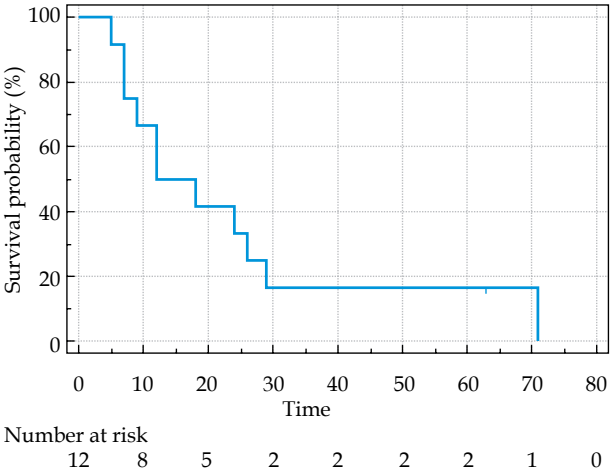

Fig. 2. Kaplan-Meier curve showing overall survival of 12 small-cell lung cancer (SCLC) patients treated with ^{125}I seed implantation

γ-rays to break molecular chains and chemical bonds of biological macro-molecules, thereby destructing DNA, RNA, proteins, and various catalytic enzymes, with no or only slight damage to normal tissues. In addition, in the tumor micro-environment, ^{125}I irradiation inhibits cell proliferation by reducing the level of Ki-67, and induces apoptosis by increasing the P21 level and reducing the surviving level *in vivo* [15]. Therefore, inhibition of cell proliferation and induction of apoptosis by ^{125}I irradiation is the key mechanism for the therapeutic effect of ^{125}I seed implantation [16].

Unlike other types of lung cancer, SCLC is initially sensitive to chemotherapy and radiotherapy. However, despite the sensitivity to radiotherapy and chemotherapy, patients with newly diagnosed extensive-stage SCLC generally have a poor prognosis, with a median PFS of 5.5 months and a median OS of 10 months [17]. According to a previous study, the low OS rate in highly chemotherapy-sensitive SCLC populations is due to the rapid development of drug resistance and the failure of second-line and follow-up treatments to affect or slow tumor growth and metastasis [18]. For decades, both ESMO [6] and NCCN [4] clinical treatment guidelines have recommended chemotherapy containing EP as the standard treatment for ES-SCLC. An earlier paper reported that the average response rate of patients treated with the EP regimen ranged from 60% to 80%, with a median OS of 8-10 months [19]. In this research, patients receiving ^{125}I seed implantation had an ORR of 83.3%, 63.6%, 50%, and 40% at 2, 6, 12, and 24 months, respectively. Furthermore, the median PFS was 8 months, the median OS was 12 months, and the mean OS was 23.6 months, which was superior to the efficacy of standard treatment. In addition, a randomized phase 3 CREST trial published in 2015 [20] evaluating thoracic radiotherapy for ES-SCLC, revealed that 247 patients who received thoracic radiotherapy (30 Gy in ten fractions) had a 1-year OS rate of 33% and 2-year OS rate of 13% as well as a 6-month PFS rate of 24%. In this study, the incidence of OS at 12 and 24 months after the surgery was 66.67% and 41.67%, respectively, which was higher than that of ES-SCLC patients, who received general systemic treatment or chest radiotherapy after chemotherapy [20]. Nevertheless, more studies are still needed to compare thoracic radiotherapy and high-dose-rate brachytherapy (HDR-BT) with ^{125}I seeds brachytherapy for the treatment of SCLC. However, HDR-BT lacks experience and data from large phase III clinical trials in lung cancer, since most studies have focused on NSCLC, with few data on SCLC. In addition, the quality control of HDR-BT technology is difficult to be guaranteed due to the characteristics of personal proficiency and individualized operation techniques.

Although ^{125}I seed implantation has the advantages of minimal invasiveness, quick recovery, and few adverse reactions, there are various complications, such as worsening cough, pneumothorax, and hemoptysis. Generally, patients who cannot tolerate radiotherapy or chemotherapy and refuse radiotherapy and chemotherapy, present with tumor emergencies, and whose disease has progressed after radiotherapy and chemotherapy, could benefit from ^{125}I seed implantation therapy. However, for

SCLC, ^{125}I seed implantation is the only local treatment, and systemic treatment is still required.

Conclusions

Iodine-125 seed implantation is a safe and effective supplementary treatment for patients with small-cell lung cancer, who cannot tolerate radiotherapy.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Cangzhou Fifth Hospital (People's Hospital of Qingxian) (No. 201407141), and all patients have signed written informed consent.

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Disclosure

The authors report no conflict of interest.

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