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ORIGINAL RESEARCH

The Clinical Value of Computed Tomography (CT)-Guided ^{125}I Brachytherapy for Locally Advanced Non-Small Cell Lung Cancer After Progression of Concurrent Radiochemotherapy

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Purpose: To further evaluate the efficacy and safety of computed tomography (CT)-guided iodine 125 (^{125}I) brachytherapy to treat locally advanced non-small cell lung cancer (NSCLC) after progression of concurrent radiochemotherapy (CCRT).

Methods: This study obtained written consent from all patients and was approved by our institution. From January 2006 to June 2018, 210 NSCLC patients (progression of first-line CCRT) were retrospectively recruited and then divided into two groups. A total of 116 patients were given CT-guided ^{125}I brachytherapy and second-line chemotherapy (group A), and 94 were treated with second-line chemotherapy alone (group B).

Results: In group A, local response rate (LRR) within 3 years was significantly better ($P<0.05$). Mean survival time [progression-free survival time (PFST) and overall survival (OS)] was 15.1±1.4 months and 21.2±1.6 months in group A compared with 10.0±1.4 months and 16.2±1.7 months in group B (PFST: $P<0.01$, HR=1.472, 95% CI 1.097–1.975; OS: $P = 0.036$, HR=1.342, 95% CI 1.005–1.791). Tumor size and No. of first cycle chemotherapy were independent factors that affected survival, ≤3cm largest tumor diameter and more than 4 first cycles of chemotherapy showed longer PFST and OS ($P<0.05$). Tumor-related clinical symptoms were relieved in group A ($P<0.01$). No serious complications occurred in the two groups.

Conclusion: ^{125}I brachytherapy is effective and safe in locally advanced NSCLC after progression of CCRT.

Keywords: ^{125}I, brachytherapy, NSCLC, concurrent radiochemotherapy, efficacy, safety

Introduction

Clinically, more than 75% of lung cancers is non-small cell lung cancer (NSCLC), and the main causes of death are tumor recurrence, cancer progression, and metastasis.[1] In fact, only a few patients are suitable for surgery, the percentage is less for advanced stage III–IV NSCLC.[2] As we all know, the first-line treatments for advanced NSCLC with sensitive mutations are epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors and anaplastic lymphoma kinase (ALK) inhibitors.[3,4] Similarly, for high expression of program death-ligand 1 (PD-L1), the first-line treatment is programmed death-1 (PD-1) inhibitors.[5]

For patients not suitable for surgery or without sensitive mutations or less than 50% PD-L1 expressions, concurrent radiochemotherapy (CCRT) is seen as the standard

treatment.[6,7] Many studies have also reported that about 20% of patients could be cured by CCRT alone.[8] In addition, the latest research confirmed that CCRT combined with immunotherapy had significantly improved survival rate for advanced NSCLC patients and was a standard treatment.[9] However, 80% of patients had recurrence within 1–2 years after CCRT treatment, the long-term survival was disappointing.[10] Moreover, due to severe toxicity after radiotherapy and chemotherapy, poor general condition and tumor staging, many patients could also not tolerate the next available treatment, these were considered to be important factors in tumor recurrence.[11,12]

As a minimally invasive therapy, ^{125}I brachytherapy has been considered a meaningful therapy and a method to achieve remission for many tumors (eg, pancreatic cancer, hepatocellular carcinoma, gynecologic malignancies, and glioma).[13–15] Similarly, we also reviewed some reports about ^{125}I brachytherapy in lung cancer, the results showed that CT-guided ^{125}I seed implantation was feasible and safe.[16] In 2015, we enrolled 78 locally advanced NSCLC patients from a single center, the local response rate (LRR) was 63.6% in ^{125}I brachytherapy versus 41.5% in second-line chemotherapy (P=0.033), the overall survival (OS, 1-, 2-, 3-year) rates were 56.8%, 16.2%, 2.7% versus 36.6%, 9.8%, 2.4%, respectively (P= 0.059).[17] However, this study had a relatively short follow up and small sample; there were no further analyses of prognostic factors affecting survival, which would affect our thinking regarding suitable patients for ^{125}I brachytherapy. Furthermore, in the past 5 years, there have been few reports on ^{125}I brachytherapy in locally advanced NSCLC after progression of CCRT.

Thus, this study aimed to further confirm the efficacy and safety of CT-guided ^{125}I implantation in advanced NSCLC after progression of CCRT.

Materials and Methods

210 patients with stage III–IV NSCLC participated in this study from January 2006 to June 2018. This retrospective study was approved by the institutional review board at our hospital. All patients were previously treated by first cycle of CCRT after the confirmation of NSCLC but had progression of disease, the interval time from the end of first cycle CCRT was 7.6±1.2 months versus 7.3±0.8 months between two groups. After signed consent form regarding CT-guided ^{125}I brachytherapy-related risks, 116 patients underwent ^{125}I seed implantation and second-line chemotherapy for lung lesions (group A), and 94 were only given second-line chemotherapy (group B). The characteristics of patients in the two groups can be found in Table 1.

The inclusion criteria were: a) treatment for locally advanced NSCLC was CCRT but the disease progressed; b) pathologically confirmed NSCLC, clinical stage: III–IV; c) patient refused external beam re-irradiation; d) no mutation (EGFR or ALK fusion genes) or patient refused targeted therapy; e) ≤3 lesions (unilateral lung), the largest diameter ≤5 cm (single lesion); f) ECOG score was 2 or less.

Exclusion criteria: history of other malignancies; intolerance to percutaneous ^{125}I brachytherapy; cachexia; and severe cardiopulmonary insufficiency.

^{125}I Seed and Radiation Dosimetry

The ^{125}I seed (Zhibo Gaoke Biotechnology Company, Beijing, China) was made into cylindrical nickel-titanium tubes (wall thickness: 0.05 mm, diameter: 0.8 mm, length: 4.5 mm). The center of the tube was a silver rod (3.0 mm length, adsorption of ^{125}I). Parameters of ^{125}I: initial activity, 1.85–2.22×1010 Bq; half life, 59.6 days; average energy, 27–35 keV; and antitumor activity, 1.7 cm. After these seeds were implanted, 95% of low-dose γ-ray and X-ray was released within 8–10 months.

5- mm thickness CT images were obtained and entered into a treatment planning system (TPS, Qilin Company, Beijing, China) to target areas of interest before ^{125}I implantation. Two radiologists (Z.W.X or M.S.H, with 7 and 23 years experience performing ^{125}I brachytherapy) and one physicist (Z.H.Z, with 6 years experience) performed preoperative plan together for each patient. According to recommendations of American Brachytherapy Society (ABS) and previous ^{125}I brachytherapy studies in malignant tumors,[18–20] we defined that the prescribed dose was 100–140Gy (average: 120Gy) for lung cancer. Puncture path, number of seeds, dose-volume histogram (Figure 1A and B) were calculated and generated by TPS. The dose prescription of surrounding vital organs or tissues should also be decreased (such as: large vessels, heart, spinal cord, and trachea).

^{125}I Implantation

Based on the established treatment plan (TPS), the applicator's position was marked, then CT scan with 5 mm thickness was performed to confirm the border of the lung lesion (Figure 2A). After 2% lidocaine local infiltration anesthesia (Yichang, China), and avoiding puncture of vital organs, 18-G spinal needles were inserted to reach lung lesion and kept its deepest margin, the distance between every needle was about

Table 1 Summary of Patient and Tumor Characteristics

Characteristics	Value		Statistical Analysis (*P*)
	Group A (n=116%)	Group B (n=94%)	
Age			0.305
Mean age (years)*	58.5±12.4	55.4±11.5	
≤60 y	73 (62.9)	55 (58.5)	
>60y	43 (37.1)	39 (41.5)	
Sex			0.223
Male	81 (69.8)	71 (75.5)	
Female	35 (30.2)	23 (24.5)	
ECOG performance status			0.759
0	74 (63.8)	57 (60.6)	
1	39 (33.6)	33 (35.1)	
2	3 (2.6)	4 (4.3)	
Smoking			0.355
Yes	46 (39.7)	34 (36.2)	
No	70 (60.3)	60 (63.4)	
UICC TNM classification			0.106
Stage IIIA	27 (23.3)	23 (24.5)	
Stage IIIB	31 (26.7)	14 (14.9)	
Stage IV	58 (50.0)	57 (60.6)	
Histology			0.338
Squamous	38 (32.6)	34 (36.2)	
Adenocarcinoma	62 (53.4)	53 (56.4)	
Others	16 (13.8)	7 (7.4)	
No. of tumors			0.138
1	90 (77.6)	62 (65.6)	
2	14 (12.1)	20 (21.3)	
3	12 (10.3)	12 (12.8)	
Tumor size			0.451
Largest tumor diameter (cm)*	3.6±0.6	3.8±0.5	
≤1 cm	15 (12.9)	9 (10.6)	
>1 to 3cm	20 (35.3)	21 (37.2)	
>3 to ≤5cm	81 (51.7)	64 (52.1)	
Classification of tumor			0.852
Center type	56 (30.2)	45 (31.9)	
Peripheral type	60 (69.8)	49 (68.1)	
Tumor marker			0.320
Within normal	48 (41.4)	35 (37.2)	
Elevated	68 (58.6)	59 (62.8)	
No. of first cycle chemotherapy			0.286
≤4	45 (38.8)	32 (34.0)	
>4	71 (61.2)	62 (64.0)	
Radiotherapy*			0.966
Radiation dose	61.2±6.3	60.6±5.8	
Frequency	30.6±2.5	29.8±3.3	
Treatment time	44.3±6.2	46.2±8.3	

(*Continued*)

Table 1 (Continued).

Characteristics	Value		Statistical Analysis (*P*)
	Group A (n=116%)	Group B (n=94%)	
Disease-free Interval (months)*			0.211
Mean no. of months	7.6±1.2	7.3±0.8	
≤ 6m	48 (41.4)	45 (47.9)	
>6m	68 (58.6)	49 (52.1)	
Distant metastasis			0.403
Yes	30 (25.9)	22 (23.4)	
No	86 (74.1)	72 (96.6)	

Note: *Data are mean±standard deviation.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; UICC TNM, Union for International Cancer Control Tumor Node Metastasis.

10–15 mm (Figure 2B). Then these seeds were released while withdrawing the needles (a distance of 0.5–1.0 cm apart) (Figure 2C) from deep to shallow. Postoperative complications (pneumothorax or bleeding) were assessed by the last CT scan, more than 30% pulmonary compression of lung volume should be drained by using a pigtail catheter (Cook Medical, Bloomington, Ind). The position and intensity of ^{125}I seeds was also verified by using the last CT images on TPS (Figure 1C).

Second-Line Chemotherapy

As second-line chemotherapy, the following medications were administered: single-agent docetaxel was given for squamous cell carcinomas (75 mg/m^2/3 weeks); single-agent pemetrexed was given for others (500 mg/m^2/3 weeks). Chemotherapy should be delayed or reduced in patients with major complications. All patients had received at least 4–6 cycles of second-line chemotherapy successfully. In group A, the time interval of ^{125}I brachytherapy and first second-line chemotherapy was no more than 2 weeks.

Follow-Up

All postoperative symptoms were recorded. The effectiveness of ^{125}I brachytherapy was recorded by follow-up imaging (Figure 2D and E). 1 and 3 months after treatment, enhanced chest CT images were taken, and then every 3 months. Local response rate (LRR), survival, complications, and relief of clinical symptoms were recorded.

The response of tumor was evaluated according to the Tumor Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, which defines complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD). LRR was the proportion of patients who achieved CR+PR. Survival time was also defined and calculated (PFST: time from initial ^{125}I brachytherapy or second-line chemotherapy to initial radiological progression or death from any cause; OS: the time from initial ^{125}I brachytherapy or second-line chemotherapy to death from any cause). Chemotherapy-related adverse events were evaluated by Common Terminology Criteria Adverse Events Version 4.0 (CTCAE v4.0).

Statistical Analyses

The characteristics of the patients, complications and relief of clinical symptoms were compared with Pearson's χ^2 test between the two groups. Kaplan-Meier curve (Log rank test) was applied for the analyses of PFST and OS. A stratified Cox proportional hazards regression model was applied for evaluating the relationship between variables (eg, histology, UICC TNM classification, No. of lesions, lesion diameter, etc.) and survival (PFST and OS). SPSS version 20.0 was applied for the statistical analyses, and a p value less than 0.05 was considered as significant.

Results

Local Response Rate

The median follow-up time was 21 months (3–65 months). As shown in Table 2, the rate of local control was better in Group A. Although there were no statistically significant differences at 48 and 60 months, the LRR at 1, 2, 4, 6, 12, 18, 24 and 36 months in group A was 58.6%, 53.4%, 50.0%, 41.4%, 22.4%, 18.1%, 16.4%, 11.2% respectively, and was 42.6%, 37.2%, 31.9%, 27.7%, 20.2%, 15.9%, 12.8% and 7.4% in group B (P <0.05).

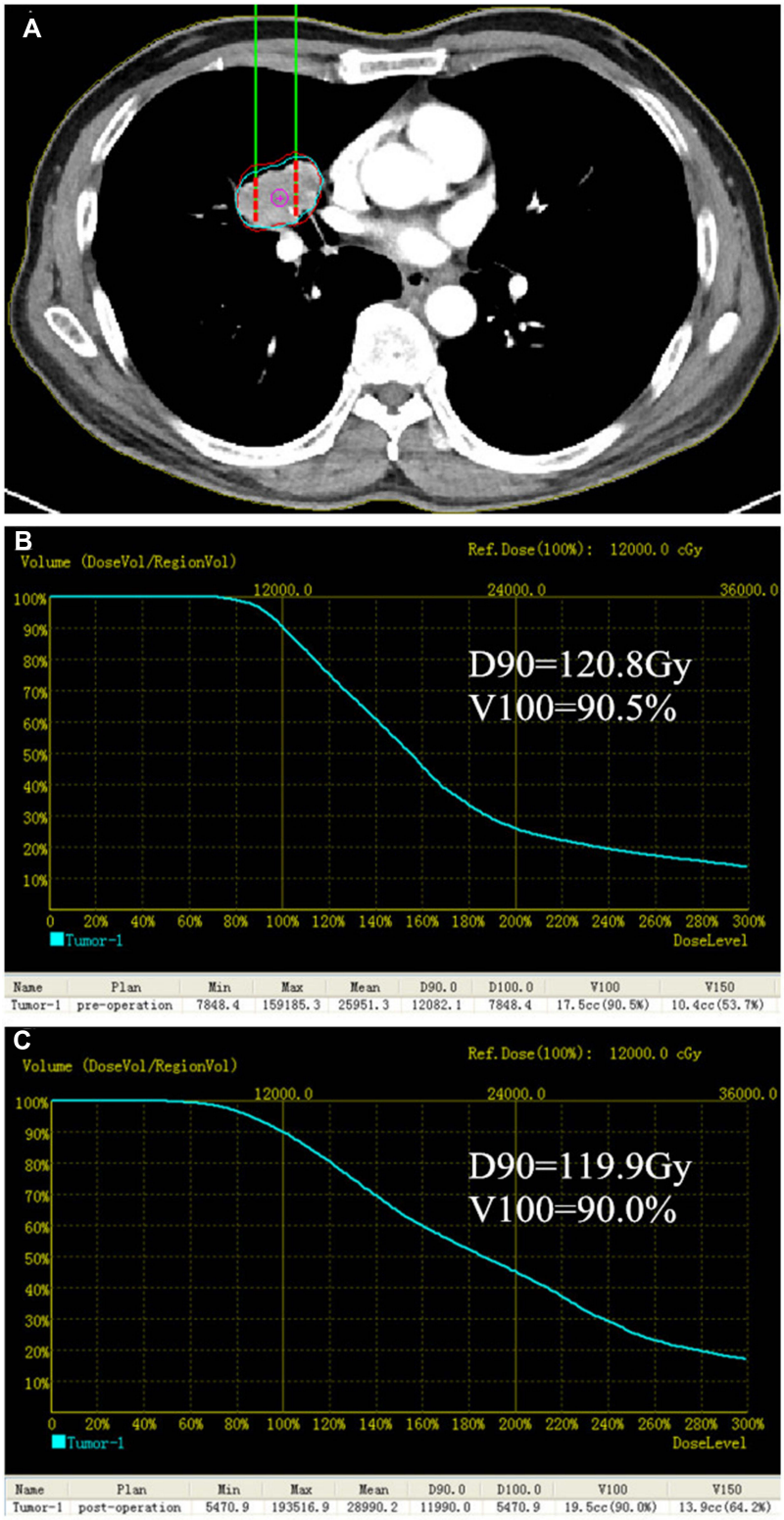

Figure 1 Preoperative treatment planning system (TPS). (**A**) Red line represented the tumor's contour, the planning target volume edge was covered by the isodose curve from 70 to 90%. (**B**) Preoperative dose-volume histograms (DVH). The prescription dose (PD) was 120Gy, a total of 90% of the tumor target (D_{90}) received 120.8Gy and 90.5% of the tumor received 100% of the prescribed dose (V_{100}). (**C**) Postoperative DVH. After ^{125}I brachytherapy, the dose intensity was verified, D_{90} = 119.9Gy and V_{100} = 90.0%.

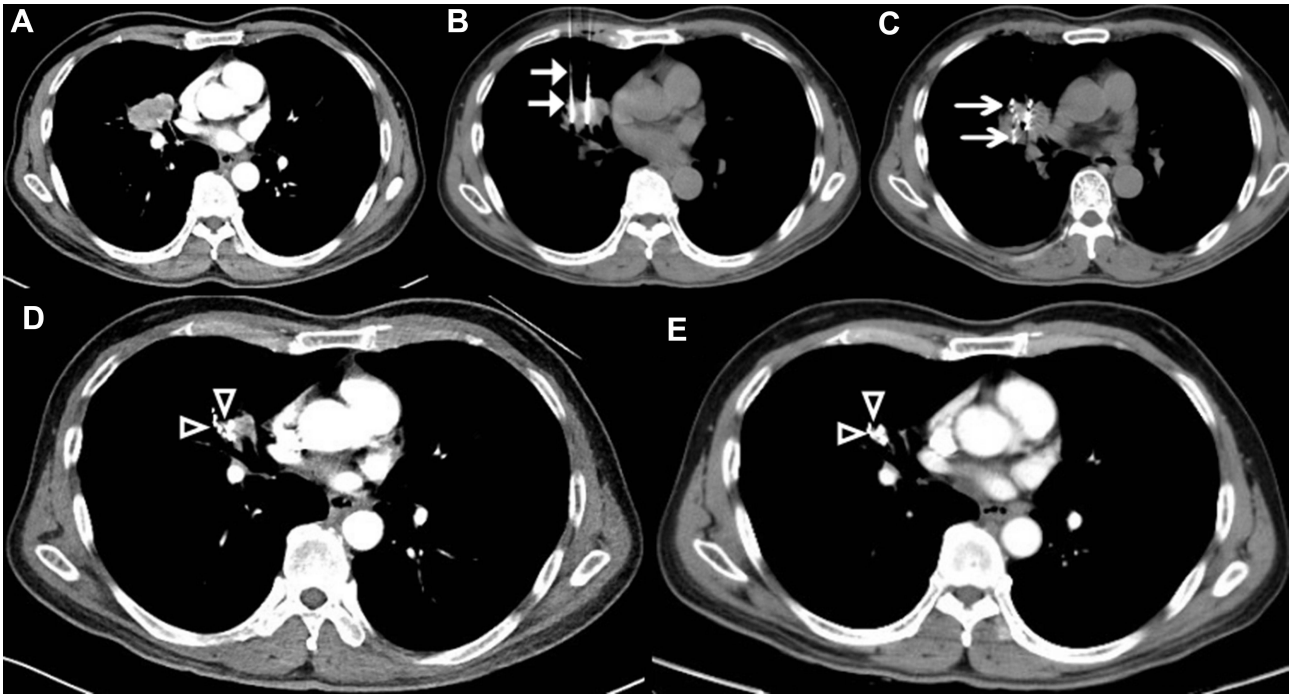

Figure 2 Computed tomography (CT)-guided percutaneous ^{125}I seed implantation was performed. (**A**) CT scan before brachytherapy. (**B** and **C**) The procedure of CT-guided ^{125}I brachytherapy was performed according to preoperative TPS, 18 G spinal needles were inserted to reach the tumor (arrows), seeds were released from deep to shallow (arrows). (**D**) One month after treatment, the lesion apparently shrunk (arrows). (**E**) Six months after treatment, the tumors disappeared, with only seeds remaining (arrows).

Progression-Free Survival Time

The median PFST was 15.1±1.4 months (95% CI 12.4–17.8) in group A, while 10.0±1.4 months (95% CI 7.3–12.8) in group B [P<0.01, HR=1.472, (95% CI 1.097–1.975), Figure 3]. Better PFST was observed in the combined group. Tumor size and No. of first cycle chemotherapy were independent factors, better PFST was found in patients with ≤3cm largest tumor diameter [≤3cm vs >3 to≤5cm: P=0.026, HR=0.843, (95% CI 0.626–1.135), Figure 4A] and more than 4 number of first cycle chemotherapy [P=0.035, HR=1.321, (95% CI 0.971–1.797), Figure 4B]. Other factors (eg, age, sex, ECOG score, smoking, TNM classification, histology, No. of tumors, classification of tumor, tumor marker, disease-free interval and distant metastasis) were not related to PFST.

Table 2 The Clinical Efficacy of Treatment in Two Groups

Months	Local Control Efficacy									
	Group A					Group B				
	CR	PR	SD	PD	LRR (%)	CR	PR	SD	PD	LRR (%)	*P*
1m	21	47	41	7	68/116 (58.6)	9	31	38	16	40/94 (42.6)	0.023
2m	17	45	39	15	62/116 (53.4)	9	26	36	25	35/94 (37.2)	0.039
4m	22	36	26	32	58/116 (50.0)	8	22	33	33	30/94 (31.9)	0.030
6m	26	22	14	54	48/116 (41.4)	6	20	25	43	26/94 (27.7)	<0.01
12m	15	11	4	86	26/116 (22.4)	4	15	19	56	19/94 (20.2)	<0.01
18m	11	10	3	92	21/116 (18.1)	2	13	13	66	15/94 (15.9)	<0.01
24m	10	9	2	95	19/116 (16.4)	2	10	9	73	12/94 (12.8)	0.015
36m	8	5	2	101	13/116 (11.2)	2	5	6	81	7/94 (7.4)	0.035
48m	4	3	1	108	7/116 (6.0)	1	3	2	88	4/94 (4.3)	0.596
60m	1	1	1	113	2/116 (1.7)	1	2	1	90	3/94 (3.2)	0.887

Notes: CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease, based on the Response Evaluation Criteria in Solid Tumors (RECIST); local response rate (LRR) defined as the proportion of patients with complete response and partial response.

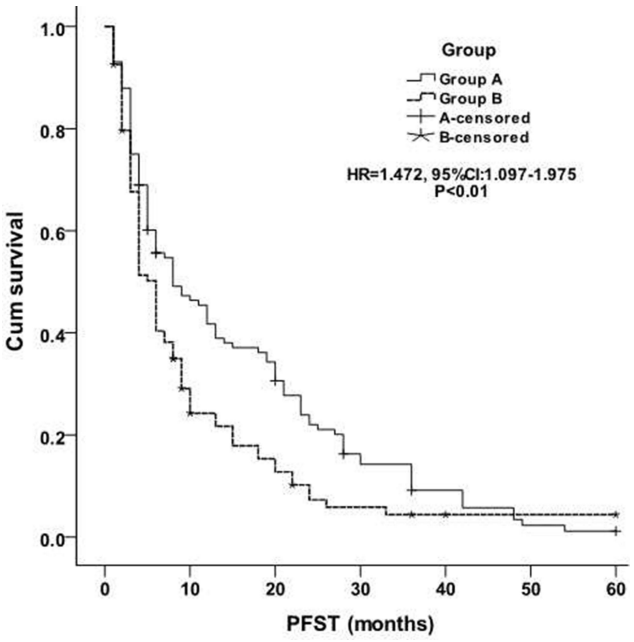

Figure 3 Comparison of progression-free survival time (PFST) in group A and group B.
Abbreviation: HR, hazard ratio.

Overall Survival

The median OS in group A was significantly better than that in group B [21.2±1.6 months vs 16.2±1.7 months, P = 0.036, HR=1.342, (95% CI 1.005–1.791), Figure 5]. The 1-, 2-, 3-, 4- and 5-year OS in group A was 62.1%, 31.9%, 19.8%, 10.3%, 4.3% respectively, and 45.7%, 20.2.4%, 10.6%, 6.4%, 4.3% in group B respectively. Tumor size and No. of first cycle chemotherapy were independent factors, better OS was found in patients with ≤3cm largest tumor diameter [≤3cm vs >3 to≤5cm: P=0.046, HR=1.289, (95% CI 0.950–1.749), Figure 6A] and more than 4 number of first cycle chemotherapy [P=0.031, HR=0.848, (95% CI 0.633–1.138), Figure 6B]. Other factors (eg, age, sex, ECOG score, smoking, TNM classification, histology, No. of tumors, classification of tumor, tumor marker, disease-free interval and distant metastasis) were not related to OS.

Relief of Clinical Symptoms

The clinical symptoms of tumors were significantly better in group A (Table 3, P < 0.01). The remission rates of chest pain, cough, hoarseness, bloody sputum, and chest tightness (significant remission + partial response) were 88.7%, 84.9%, 78.9%, 77.8%, 79.4% and 21.4%, 24.7%, 28.6%, 30.4%, 25.7% between two groups, respectively.

Complications

The major complications were summarized in group A, no severe complications occurred during follow-up (Table 4). Pneumothorax was found in 44 patients (≤30% unilateral lung volume: 23 patients; ≥30% unilateral lung volume: 11 patients), these patients with more than 30% pulmonary compression volume recovered after drainage. There were no clinical symptoms in three patients with minor displacement of ^{125}I seeds. There was no statistical difference in complications (Table 4, P > 0.05).

Discussion

According to our study, ^{125}I implantation might be an alternative treatment for advanced NSCLC after progression of

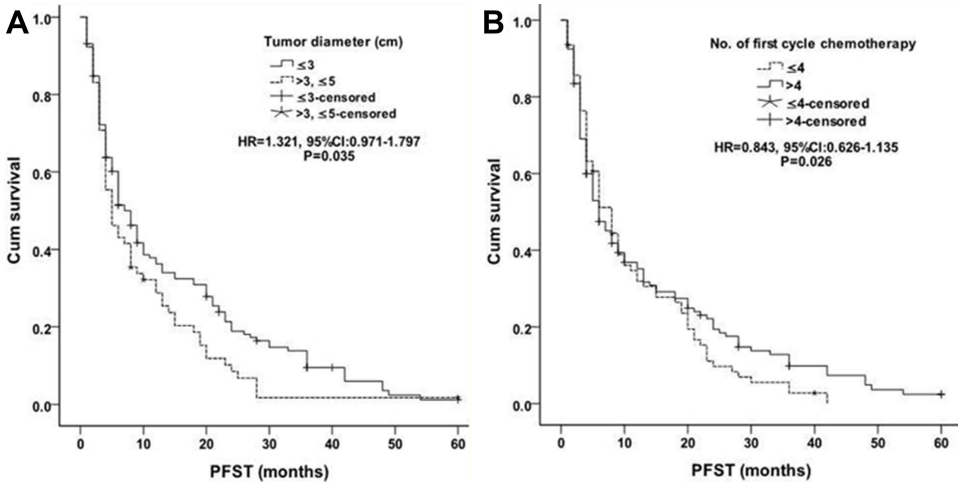

Figure 4 Cox proportional hazards regression model explored the factors related to progression-free survival time (PFST). (**A**) Tumor diameter (cm), (**B**) No. of first cycle chemotherapy.
Abbreviation: HR, hazard ratio.

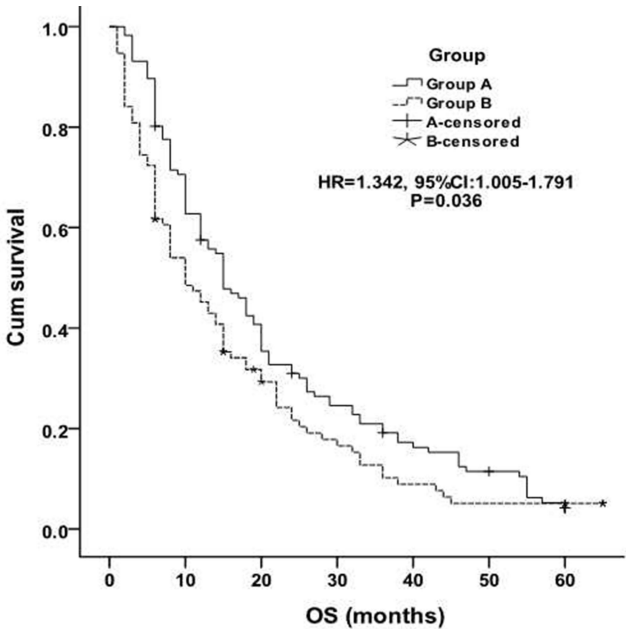

Figure 5 Overall survival (OS) in group A and group B.
Abbreviation: HR, hazard ratio.

CCRT. Our finding is important because ^{125}I brachytherapy had to overcome some difficulties of disease progression on CCRT (eg, poor general condition, severe toxicity). In fact, these patients (more than 50%) were not candidates for re-irradiation and it had a lower success rate than the standard treatment modality and subsequent treatments.[21] So, ^{125}I brachytherapy provided an opportunity for remission in advanced NSCLC after progression of CCRT. As we all know, the goal of treatment for these patients was to control local tumor and prolong survival time.[22] Brachytherapy ^{125}I seed could inhibit the proliferation and promote the apoptosis by effecting the mitosis of cell cycle.[23–25] Similarly, due to the biological effect of ^{125}I seed and full preoperative TPS, many studies have confirmed that it could guarantee a sufficiently high local dose without damaging the surrounding tissue.[26] So, ^{125}I brachytherapy could be an alternative therapy for locally advanced NSCLC even if diseased progressed on CCRT.

Another finding was that the combined group achieved better LRR and survival, these results were consistent with previous studies. Zhang et al reported that ^{125}I brachytherapy had good local control and could relieve symptoms of locally advanced NSCLC, the 1-, 2-, and 3-year OS rates were 68.7%, 37.5%, 20.8%, the 3-, 6-,12- and 24-months of LRR and local PFS for ^{125}I brachytherapy was 85%, 77.6%, 64.3%, 39.9% and 100%, 97%, 86.6%, 79.1%, respectively.[27] Zhang et al also showed that the RR was higher in ^{125}I implantation (79.2%), the survival rates of 1-, 2-year were 62.5% and 16.7%.[28] Wu et al reported 50 patients with stage III or IV NSCLC were treated with ^{125}I brachytherapy and chemotherapy, the symptoms of patients were significantly relieved in ^{125}I brachytherapy group, the OS and PFS were also prolonged (20 months and 13 months).[29] The median PFST and OS in group A were 15.1±1.4 months and 21.2±1.6 months in our study, suggesting that ^{125}I brachytherapy with second-line chemotherapy was valuable because the lung lesion was well controlled and survival time was prolonged. For these patients, ^{125}I brachytherapy could be a radical treatment.

Our results also showed that patients with more than 4 number of first cycle chemotherapy and tumor size

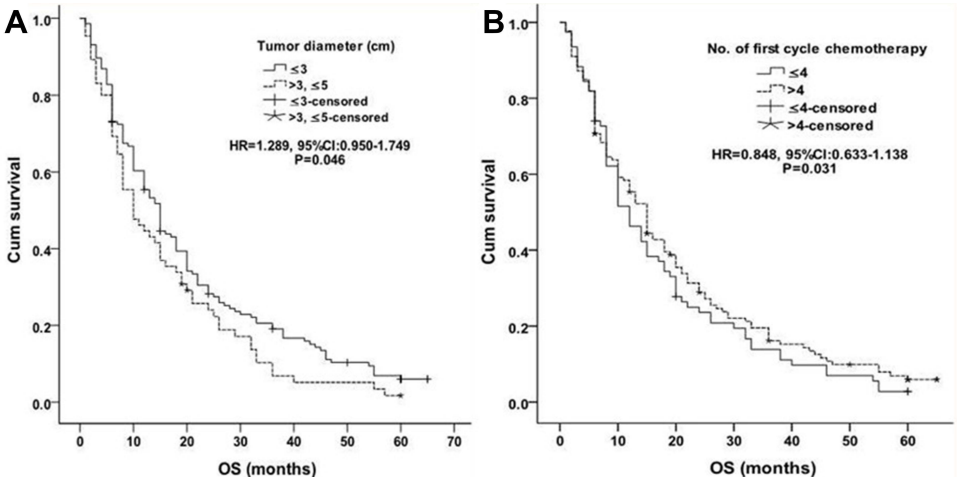

Figure 6 Cox proportional hazards regression model explored the factors related to overall survival (OS). (**A**) Tumor diameter (cm), (**B**) No. of first cycle chemotherapy.
Abbreviation: HR, hazard ratio.

Table 3 Relief of Clinical Symptoms Associated with the Tumor in Two Groups

Symptoms	Group A(%)				Group B(%)				*P*
	SR	PR	NR	AG	SR	PR	NR	AG	
Cough	62/106 (58.5)	28/106 (26.4)	9/106 (8.5)	7/106 (6.6)	12/85 (14.1)	9/85 (10.6)	43/85 (50.6)	21/85 (24.7)	<0.01
Chest pain	53/87 (64.6)	21/87 (24.1)	9/87 (10.3)	4/87 (4.6)	5/75 (6.7)	11/75 (14.7)	41/75 (54.7)	18/75 (24.0)	<0.01
Bloody sputum	28/50 (53.8)	12/50 (24.0)	6/50 (12.0)	4/50 (8.0)	7/46 (15.2)	7/46 (15.2)	27/46 (58.7)	5/46 (10.9)	<0.01
Hoarseness	12/19 (63.1)	3/19 (15.8)	3/19 (15.8)	1/19 (5.3)	1/21 (4.8)	5/21 (23.8)	5/21 (23.8)	10/21 (47.6)	<0.01
Chest tightness	18/34 (52.9)	9/34 (26.5)	6/34 (17.6)	1/34 (2.9)	7/35 (20.0)	2/35 (5.7)	21/35 (60.0)	5/35 (14.3)	<0.01

Abbreviations: AG, aggravation; NR, no remission; PR, partial response; SR, significant remission.

Table 4 The Complications of ^{125}I Brachytherapy and Chemotherapy in Two Groups

Complications	Group A (n=116,%)					Group B (n=94,%)					*P*
	0	1	2	3	4	0	1	2	3	4	
Myelosuppression	80 (69.0)	12 (10.3)	12 (10.3)	7 (6.0)	5 (4.3)	73 (77.7)	5 (5.3)	9 (9.6)	4 (4.3)	3 (3.2)	0.614
Gastrointestinal response	77 (66.4)	25 (21.6)	9 (7.8)	5 (4.3)	0 (0)	65 (69.1)	25 (26.6)	3 (3.2)	1 (1.1)	0 (0)	0.219
Fever	82 (70.7)	34 (29.3)	0 (0)	0 (0)	0 (0)	55 (58.5)	39 (41.5)	0 (0)	0 (0)	0 (0)	0.065
Allergy	114 (98.3)	2 (1.7)	0 (0)	0 (0)	0 (0)	94 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0.201
Alopecia	106 (91.4)	8 (6.9)	2 (1.7)	0 (0)	0 (0)	88 (93.6)	5 (5.3)	1 (1.1)	0 (0)	0 (0)	0.821
Pneumothorax	82 (70.7)	23 (19.8)	8 (6.9)	3 (2.6)	0 (0)	94 (100)	0 (0)	0 (0)	0 (0)	0 (0)	–
Local pulmonary hemorrhage	90 (77.6)	21 (18.1)	5 (4.3)	0 (0)	0 (0)	94 (100)	0 (0)	0 (0)	0 (0)	0 (0)	–
Bloody sputum	95 (81.9)	18 (15.5)	3 (2.6)	0 (0)	0 (0)	94 (100)	0 (0)	0 (0)	0 (0)	0 (0)	–
Displacement of seeds	113 (97.4)	3 (2.6)	0 (0)	0 (0)	0 (0)	94 (100)	0 (0)	0 (0)	0 (0)	0 (0)	–
Radiation pneumonitis	116 (100)	0 (0)	0 (0)	0 (0)	0 (0)	94 (100)	0 (0)	0 (0)	0 (0)	0 (0)	–
Radiation esophagitis	116 (100)	0 (0)	0 (0)	0 (0)	0 (0)	94 (100)	0 (0)	0 (0)	0 (0)	0 (0)	–
Massive bleeding	116 (100)	0 (0)	0 (0)	0 (0)	0 (0)	94 (100)	0 (0)	0 (0)	0 (0)	0 (0)	–

(≤3 cm) had better OS and PFST, No. of first cycle chemotherapy and tumor size were closely related to survival. Many studies reported that the more chemotherapy cycles received, the better survival in NSCLC patients, number of chemotherapy cycles was one of predictors of metastasis or recurrence.[30] Similarly, the tumor size could reflect the invasiveness and metastatic ability of cancer, and it was also the most sensitive marker related to survival.[31] However, proportional hazard regression found no association between tumor number and PFST/

OS, which could be explained by enrolled indication criteria (more than 65% was a single lesion in this study).[32]

Clinical symptoms associated with tumors were the most common and severely affected quality of life of NSCLC patients.[33] Chest pain could be observed in more than 70% of patients with advanced NSLCLC.[34] During follow-up, the clinical symptoms were significantly relieved in group A ($P < 0.01$), cough and chest pain remission rates (significant remission + partial response) were higher in group A (84.9%, 88.7% versus 24.7%, 21.4%) ($P < 0.01$). However, we also found that pain and cough were worse in two patients with large lesions after postoperative follow up, while the CT images showed that the tumor had shrunk significantly. We considered that nerve damage caused by repeated puncture or large lesions near the pleura could explain this, this might require further clinical and statistical exploration.

The effectiveness of ^{125}I brachytherapy and rate of related complications were dependent on position of seeds and complete TPS. The American Brachytherapy Society's "dual 90" guideline showed that 90% of the tumor volume acquired 90% prescription dose for achieving cancer cure.[35] According to preoperative TPS plan and 3D images within CT scan, our study could make more than 95% of the tumor get 100% of the prescription dose. Therefore, all patients were successfully treated using CT guidance. The location and boundary of tumor, important blood vessels and organs were well confirmed, no massive bleeding or related deaths occurred due to ^{125}I brachytherapy.

Our study had limitations. First, although more than 200 patients were recruited in our hospital, this was just a retrospective study, more hospitals and prospective clinical studies are needed. Second, it was a little difficult to find accurate position for larger lesion (>5cm) because of the described TPS and applicators. So, we recommend that ^{125}I brachytherapy combined with ablation (eg, radiofrequency) might be a suitable method. Finally, we did not compare ^{125}I brachytherapy with external beam re-irradiation, which would be meaningful for our further study.

In conclusion, as a minimally invasive method, ^{125}I brachytherapy combined with second-line chemotherapy in selected patients with progressive NSCLC following CCRT might improve treatment results without serious treatment-related toxicity.

Abbreviations

CT, computed tomography; NSCLC, non-small cell lung cancer; CCRT, concurrent radiochemotherapy; LRR, local response rate; PFST, progression-free survival time; OS, overall survival; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Ethics and Consent Statement

This study protocol was approved by the institutional review board of the Third affiliated hospital of Sun Yat-sen University. The study was conducted in accordance with the ethical principles laid down in the Declaration of Helsinki. Written informed consent was obtained from all patients before treatment.

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Disclosure

The authors declare that there are no conflicts of interest.

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