Evaluating the efficacy of 8Spheres microsphere embolization combined with iodine-125 seed implantation in advanced refractory lung cancer: A retrospective study

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Abstract. Patients with advanced non-small cell lung cancer (NSCLC) have seen improvements in care; however, outcomes remain poor for certain individuals despite treatment with radiation, chemotherapy, targeted therapies and immunotherapy. The present study aimed to assess the safety and efficacy of combining 8Spheres microsphere embolization with iodine-125 seed implantation for treating advanced refractory NSCLC. The retrospective analysis included 45 patients with advanced refractory NSCLC. Using the surv_cutpoint function in R, the optimal maximum tumor diameter threshold was determined as 53 mm, dividing patients into two groups: ≤53 mm and >53 mm. The study evaluated the association between treatment regimen, tumor diameter, and progression-free survival (PFS) and overall survival (OS). The findings demonstrated that the experimental group achieved a significantly longer median PFS (12 vs. 10 months; P=0.006) and OS (19 vs. 12 months; P=0.032) compared with the control group. Both the treatment approach and tumor size were identified as independent factors influencing survival. The risk of death was 2.291-fold higher for patients on the control regimen than for those in the experimental group. Similarly, patients with a tumor diameter of >53 mm had a 2.723-fold higher risk of death than those with a tumor diameter of ≤53 mm. Adverse events were mild and resolved in both groups. In summary, the combination of 8Spheres microsphere embolization and iodine-125 seed implantation demonstrate promising clinical outcomes and it may be a viable treatment for advanced refractory NSCLC. Additionally, maximum tumor diameter was strongly associated with patient survival and therefore it may serve as a valuable prognostic indicator to guide treatment decisions.

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Abbreviations: CR, complete remission; DCR, disease control rate; DSA, digital subtraction angiography; ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial remission; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease

Key words: 8Spheres microspheres, iodine-125 seeds, NSCLC, bronchial artery infusion chemotherapy embolization

Introduction

Lung cancer remains the leading cause of cancer-related morbidity and mortality globally; it accounts for ~2 million new cases and 1.76 million deaths per year, with rates continuing to increase (1). Non-small-cell lung cancer (NSCLC) accounts for >85% of all lung cancer cases (2). A notable proportion of patients are diagnosed at advanced stages of the disease, and the treatment for these patients typically involves radiation therapy, chemotherapy, targeted therapy and immunotherapy (3,4). However, despite these comprehensive approaches, outcomes for patients with advanced lung cancer are often poor, with such cases classified as advanced refractory lung cancer (5). Currently, there is no established optimal clinical treatment for advanced refractory NSCLC, with most patients receiving primarily palliative and symptomatic supportive care (6). This highlights the urgent need for developing more effective and targeted therapeutic strategies to improve the prognosis of these patients.

Advancements in precision medicine have highlighted the clinical potential of localized therapies, such as bronchial artery chemoembolization (BACE) and iodine-125 seed implantation, which are increasingly recognized as important therapeutic options. Iodine-125 seed implantation, a type of brachytherapy, involves placing iodine-125 seeds

directly into tumor tissues. These seeds emit low-dose γ-rays continuously, selectively targeting and destroying cancer cells whilst minimizing radiation exposure to surrounding healthy tissues and reducing collateral damage (7). BACE delivers chemotherapeutic agents and embolic materials directly into tumor-feeding arteries using a catheter, ensuring high localized drug concentrations. This approach not only enhances the effects of the drugs but also decreases the blood supply to the tumor, inducing ischemia, which ultimately result in necrosis (8). Compared with systemic chemotherapy, BACE markedly improves the local efficacy of chemotherapeutic drugs whilst reducing systemic side effects (9). However, conventional embolization materials, such as gelatin sponge and polyvinyl alcohol particles, have notable limitations, including incomplete embolization and a higher risk of complications (10).

8Spheres microspheres, a novel embolic material comprising a polyvinyl alcohol skeleton with covalent bonding and cross-linking agents, exhibit excellent elasticity and compliance. These characteristics enable more uniform embolization of tumor-feeding arteries, thereby improving therapeutic outcomes, and their potential as a localized therapy has attracted considerable attention (11).

Building on these advancements, the present study aimed to evaluate the safety and efficacy of combining 8Spheres microsphere embolization with iodine-125 seed implantation for treating advanced refractory NSCLC. Using retrospective clinical data, the study compared outcomes between the combined treatment group and the iodine-125 seed implantation group. Furthermore, the analysis assessed the potential of the combined regimen to enhance therapeutic effectiveness, extend patient survival, minimize treatment-related side effects and provide a scientific foundation for the broader adoption of this innovative therapeutic approach.

Materials and methods

Patient population. The present study retrospectively reviewed 45 patients with advanced refractory NSCLC who were treated at The First Affiliated Hospital of Chongqing Medical University (Chongqing, China) between January 2020 and December 2022. The study received approval from the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University. As a retrospective analysis, the need for patient consent was waived, and all data were anonymized. The inclusion criteria were as follows: i) Histopathologically-confirmed diagnosis of NSCLC; ii) tumor-node-metastasis (TNM) stage (12) IIIB or IVA with manageable distant metastatic tumors; iii) prior treatment failure, including radiotherapy, chemotherapy, targeted therapy and immunotherapy; iv) at least one measurable tumor focus as defined by Response Evaluation Criteria in Solid Tumors (RECIST) (13); v) expected survival of >6 months based on clinical assessment at the start of treatment; and vi) an Eastern Cooperative Oncology Group (ECOG) performance status score (14) of 0-2. The exclusion criteria included the following: i) History of iodine allergy or allergy to the chemotherapeutic drugs used; ii) comorbid severe cardiovascular disease (New York Heart Association class III-IV) (15), severe psychiatric disorder or other severe physical illness; iii) immune dysfunction or coagulation dysfunction; and iv) cognitive dysfunction.

The patients were categorized into a test group and a control group (Table I). The test group comprised 23 patients who received 8Spheres microsphere embolization combined with bronchial artery perfusion chemotherapy and iodine-125 seed implantation. This group included 13 men and 10 women, with 8 patients aged ≤60 years and 15 aged >60 years. A total of 14 patients had adenocarcinoma, and nine had squamous carcinoma. Tumor diameters were ≤53 mm in 12 cases and >53 mm in 11 cases. TNM staging indicated stage IIIB in 13 patients and stage IVA in 10 patients. The control group consisted of 22 patients treated with iodine-125 seed implantation alone. This group included 12 men and 10 women, with 4 patients aged ≤60 years and 18 aged >60 years. Adenocarcinoma was observed in 13 cases, and squamous carcinoma in 9 cases. Tumor diameters were ≤53 mm in 13 cases and >53 mm in 9 cases (Fig. 1). TNM staging indicated stage IIIB in 10 patients and stage IVA in 12 patients. All patients were last followed up in June 2024.

Treatment methods. Standard preoperative evaluations were performed on all patients, which included screenings for infectious disorders (human immunodeficiency virus/acquired immunodeficiency syndrome, syphilis and hepatitis), coagulation function evaluations, liver and kidney function testing and comprehensive blood and urine tests. Additional evaluations included electrocardiograms, cardiac enzyme tests and contrast-enhanced chest CT scans. Informed consent was obtained from all patients for iodine-125 seed implantation, bronchial artery chemoembolization and other related procedures.

Patients in the control group received only iodine-125 seed implantation. Treatment plans were created using the Therapy Planning System (Beijing Astro Technology Co., Ltd.), which outlined the needle insertion route and angle, the number of needles to be implanted and the arrangement of the particles. The iodine-125 seeds, purchased from Beijing Atom High-Tech Co., Ltd., had a diameter of 0.8 mm and a length of 4.5 mm, with a titanium shell, an activity of 0.6-0.8 mCi, a half-life of 59.6 days, and a prescribed dose of 120-140 Gy. The procedure was performed under local anesthesia using a Revolution™ HD CT scanner (GE Healthcare). CT-guided implantation was performed using a layer thickness of 5 mm, following the planned protocol.

Patients in the test group underwent BACE 4-6 days after iodine-125 seed implantation (using the same protocol as in the control group). The procedure involved the following steps: The right femoral artery was punctured and a 5F RLG catheter (Terumo Corporation) was selectively inserted into the bronchial artery for angiography. Other arteries, such as the phrenic and internal thoracic arteries, were also assessed to identify the blood supply of the tumor if needed. A 2.7F microcatheter (APT Medical Inc.) was then super-selectively inserted into the target tumor vessel. Chemotherapy drugs were administered first, following oncological guidelines (National Comprehensive Cancer Network Guidelines for Non-Small-Cell Lung Cancer) (16). For patients with adenocarcinoma, 500 mg/m^2 pemetrexed disodium + 75 mg/m^{2}cisplatin was administered, whilst for patients with

Table I. Clinical characteristics of the patients in each treatment group.

Characteristic	Test group (n=23)	Control group (n=22)	χ^2	P-value
Age			1.585	0.208
≤60 years	8 (34.8)	4 (18.2)		
>60 years	15 (65.2)	18 (81.8)		
Sex			0.018	0.894
Male	13 (56.5)	12 (54.5)		
Female	10 (43.5)	10 (45.5)		
ECOG PS[a]			N/A	0.999
0	1 (4.4)	1 (4.6)		
1	15 (65.2)	14 (63.6)		
2	7 (30.4)	7 (31.8)		
Pathological type			0.015	0.903
Adenocarcinoma	14 (60.9)	13 (59.1)		
Squamous cell carcinoma	9 (39.1)	9 (40.9)		
TNM stage			0.551	0.458
IIIB	13 (56.5)	10 (45.5)		
IVA	10 (43.5)	12 (54.5)		
Maximum tumor diameter			0.218	0.641
≤53 mm	12 (52.2)	13 (59.1)		
>53 mm	11 (47.8)	9 (40.9)		
PFS	12 (10-19)	10 (6-12)	2.769	0.006
OS	19 (13-24)	12 (10-21)	2.140	0.032

Data are presented as n (%) or median (interquartile range). [a]Analyzed using Fisher's exact test. ECOG PS, Eastern Cooperative Oncology Group Performance Status; TNM, tumor-node-metastasis; PFS, progression-free survival; OS, overall survival.

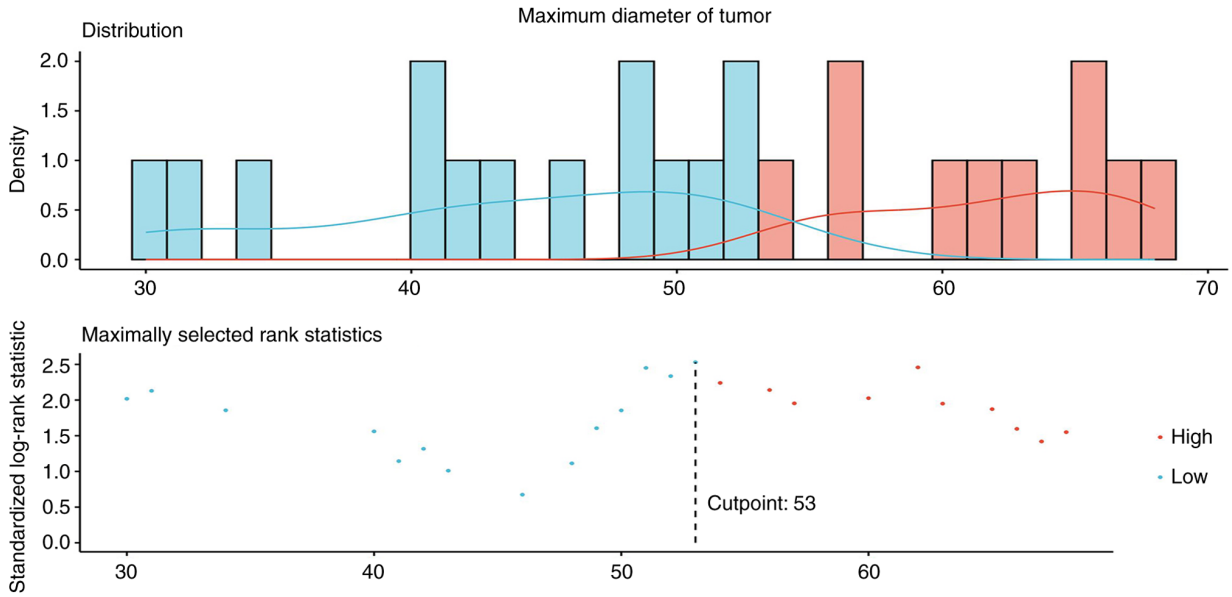

Figure 1. Optimal Cut-off value for the maximum tumor diameter of treatment-related continuous variables was calculated using the surv_cutpoint function in the R package 'survminer'. The original continuous variable type of tumor diameter was converted to a binary index, resulting in a Cut-off value of 53 mm, and the association between tumor diameter and the progression-free survival and overall survival of patients was analyzed comparatively.

squamous carcinoma, 135 mg/m^2 paclitaxel + area under the curve 5 carboplatin was administered. After chemotherapy, embolization was performed using 8Spheres microspheres (Suzhou Hengrui Medical Devices Co., Ltd.) with a diameter of 300-500 μm. The microspheres were injected into the target vessel at a rate of 1 ml/min. The embolization effect

was evaluated using digital subtraction angiography (DSA). If needed, additional embolization was performed based on DSA findings.

Efficacy evaluation. Efficacy was evaluated using the RECIST 1.1 guidelines (13). Efficacy categories included complete remission (CR), defined as the total disappearance of all target lesions; partial remission (PR), defined as a ≥30% reduction in the maximum diameter of target lesions; stable disease (SD), defined as insufficient change in lesion size to meet the criteria for PR or progressive disease (PD); and PD, defined as a ≥20% increase in the maximum diameter of target lesions. The efficacy metrics were calculated using the following formulae: Objective response rate (ORR)=CR + PR; and disease control rate (DCR)=CR + PR + SD. Patients were evaluated for efficacy at 2, 4, and 6 months after treatment.

Adverse reactions and complications. All adverse reactions and complications occurring during and after treatment were recorded, including pneumothorax, chest pain, fever, gastrointestinal symptoms and hemoptysis. The Common Terminology Criteria for Adverse Events was used to categorize adverse reactions (17) and promptly addressed to ensure patient safety.

Follow-up. All patients were regularly followed up after treatment until June 2024, death or loss to follow-up. Follow-up visits were scheduled every 2 months during the first 6 months and every 3 months thereafter. These visits included physical examinations, assessments of lesion progression, blood tests, evaluations of liver and kidney function, and chest imaging. Follow-ups focused on evaluating progression-free survival (PFS) and overall survival (OS).

Statistical analysis. Data were analyzed using SPSS 29.0 (IBM Corp.) and R (version 4.3.1; The R Foundation). The normality of continuous variables was assessed using the Shapiro-Wilk test. Based on the distribution, continuous data are presented as mean ± standard deviation if normally distributed, or as median (interquartile range) if not. Baseline characteristics between the groups were compared using either a two-sample t-test or a Wilcoxon rank-sum test, depending on the data distribution. For categorical data analysis, the χ^2 test was applied for variables with expected frequencies ≥5 in all cells, whereas the Fisher's exact test was used to analyze variables with small sample sizes or expected frequencies <5. Survival analyses included all patients and were performed using the Kaplan-Meier method, with group comparisons made using the log-rank test. The optimal cutoff value for the maximum tumor diameter, as a treatment-related continuous variable, was calculated using the surv_cutpoint function in the R package 'survminer' (version 0.5.0) (18). The effect sizes of several factors were assessed using Cox proportional hazards analysis. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Analysis of treatment response. At 2 months, the ORR for patients in the test and control groups was 82.6 and 40.9%, respectively ($\chi^2=8.318$; $P<0.05$), whilst the DCR was 100% for both groups. At 4 months, the ORR was 87.0 and 59.1%, respectively ($\chi^2=4.465$; $P<0.05$), and the DCR was 95.7 and 86.4%, respectively ($\chi^2=0.325$; $P>0.05$). At 6 months, the ORR was 82.6 and 50.0%, respectively ($\chi^2=5.380$; $P<0.05$), whilst the DCR was 91.3 and 77.3%, respectively ($\chi^2=0.786$; $P>0.05$). These findings are summarized in Table II. A comparison between the imaging results for patients in the experimental group before and after treatment is presented in Fig. 2.

Table II. Comparison of outcomes in patients with different treatments.

A, 2 months

Outcome	Test group (n=23)	Control group (n=22)
CR	2	0
PR	17	9
SD	4	13
PD	0	0
ORR, %	82.6	40.9
DCR, %	100.0	100.0

B, 4 months

Outcome	Test group (n=23)	Control group (n=22)
CR	5	3
PR	15	10
SD	2	6
PD	1	3
ORR, %	87.0	59.1
DCR, %	95.7	86.4

C, 6 months

Outcome	Test group (n=23)	Control group (n=22)
CR	7	3
PR	12	8
SD	2	6
PD	2	5
ORR, %	82.6	50.0
DCR, %	91.3	77.3

CR, complete response; PR, partial response; SD, stable disease; PD, progression disease; ORR, objective response rate; DCR, disease control rate.

Analysis of survival probability. The baseline characteristics of patients selecting different treatment regimens were comparable between the two groups ($P>0.05$); however, statistically significant differences were demonstrated for the median PFS

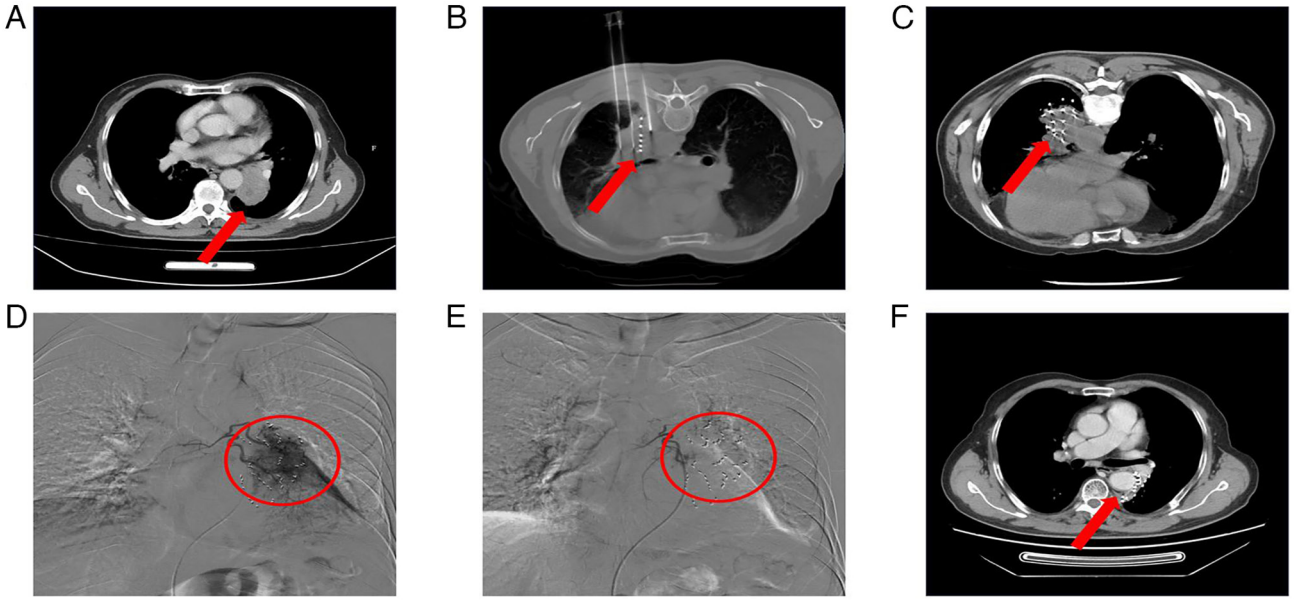

Figure 2. Imaging assessment and follow-up of 8Spheres microsphere embolization combined with iodine-125 seed implantation in the treatment of non-small cell lung cancer. (A) Enhanced CT imaging revealed an irregular mass in the lower lobe of the left lung, which was in close proximity to the adjacent blood vessels and bronchial tubes. The red arrow indicates the tumor lesion. (B) Intraoperative CT guidance was used in real-time, with the iodine-125 seed puncture needle inserted parallel to the tumor tissue. The red arrow highlights the puncture needle and the released iodine-125 seeds. (C) Iodine-125 seed implantation was reviewed in real-time to assess the distribution of the particles post-operation. The red arrow points to the iodine-125 seeds. (D) Bronchial arteriography, performed 4 days post-surgery, revealed tortuous thickening of the left bronchial artery with prominent tumor staining, as indicated by the red circle. (E) Following embolization with 8Spheres microspheres, the left bronchial artery displayed a characteristic pestle-like shape, and the tumor staining in the was no longer visible (red circle). (F) A follow-up examination 4 months after surgery demonstrated complete tumor resolution, with residual iodine-125 seeds observed, as indicated by the red arrows.

and OS between the groups (Table I). Among the patients in the test group, 12/23 (52.2%) had previously received chemotherapy with the aforementioned regimens, whilst 11/23 (47.8%) had not. In the control group, 10/22 (45.5%) had previously received chemotherapy with the aforementioned regimens, and 12/22 (54.5%) had not. The results revealed no significant difference in ORR (P=0.213) or DCR (P=0.456) between subgroups, suggesting that prior chemotherapeutic agents use did not significantly influence the observed treatment efficacy (Table SI). The median PFS for the experimental group was 12 months, whilst for the control group, it was 10 months (P<0.05; Fig. 3). The median OS for the experimental group was 19 months, compared with 12 months for the control group (P<0.05; Fig. 4). The cutoff value for the maximum tumor diameter was determined to be 53 mm using the surv_cutpoint function in R. Univariate analysis of OS and PFS demonstrated that both the treatment regimen and maximum tumor diameter had a significant impact on patient outcomes. According to the results of the univariate Cox regression analysis, the factors influencing OS included the treatment regimen and the maximum tumor diameter (Table III). Furthermore, multivariable Cox regression analysis with forward stepwise selection (Forward LR) indicated that, after controlling for tumor size, patients receiving the control regimen had a 2.291-fold higher risk of death than those in the test group [95% confidence interval (CI), 1.194-4.396]. Similarly, patients with tumors of >53 mm had a 2.723-fold higher risk of death than those with tumors of ≤53 mm (95% CI, 1.416-5.238) (Table IV). Moreover, univariate Cox regression analysis revealed that both the treatment regimen and tumor size were significant factors influencing PFS (Table V). Multivariable analysis confirmed these findings, demonstrating that after adjusting for tumor size, patients in the control group had a 2.567-fold higher recurrence risk compared with those in the test group (95% CI, 1.332-4.949). Additionally, patients with tumors of >53 mm had a 2.440-fold higher recurrence risk than those with smaller tumors (95% CI, 1.276-4.665) (Table VI). In summary, the combined univariate and multivariable analyses indicate that the experimental therapy achieved superior PFS and OS outcomes compared with the control regimen, and it was more effective in delaying disease recurrence [HR (PFS)=2.567 and HR (OS)=2.291].

Adverse events. No severe adverse events, such as treatment-related death, unintended embolism or grade ≥3 hematologic toxicity, occurred in either group. Common adverse events, including pneumothorax, hemoptysis, fever, chest pain and nausea, all resolved with symptomatic treatment. Furthermore, the incidence of adverse events did not significantly differ between the two groups (Table VII).

Discussion

Treating advanced refractory NSCLC is challenging. Local therapies such as BACE and iodine-125 seed implantation have received considerable attention and are increasingly applied in clinical practice and research (19). Therefore, the present study aimed to evaluate the efficacy and safety of 8Spheres microsphere embolization combined with iodine-125 seed implantation for advanced refractory lung cancer, and compare it with iodine-125 seed implantation alone. The results indicate that the combination therapy outperformed iodine-125

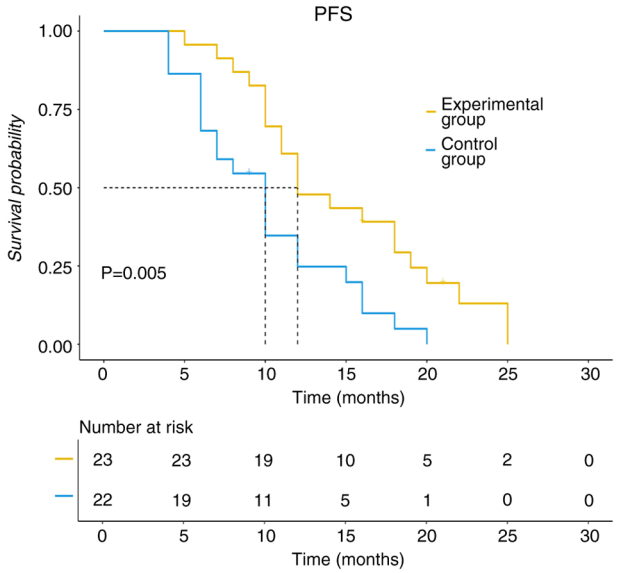

Figure 3. Median progression-free survival for the experimental group was 12 months, compared with 10 months for the control group (P<0.05).

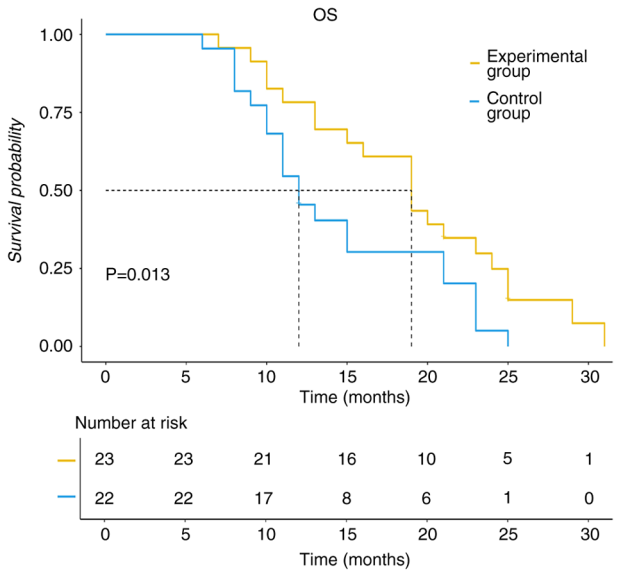

Figure 4. Median overall survival for the experimental group was 19 months, compared with 12 months for the control group (P<0.05).

seed implantation alone in terms of local tumor control, OS and PFS, suggesting the potential benefits of this combined approach for patients with advanced refractory lung cancer.

In the present study, the ORR, DCR, median PFS and median OS were significantly higher in the test group compared with that in the control group (P<0.05). Furthermore, the test group demonstrated improved efficacy in delaying disease recurrence [HR (PFS)=2.567 and HR (OS)=2.291].

Whilst certain patients experienced mild adverse effects, such as chest pain and fever, these were managed effectively with symptomatic treatment, and no serious complications occurred. This highlights the therapeutic advantage of 8Spheres microspheres, which are considered to be effective due to their role as a vascular embolic agent. The optimal cutoff value for the maximum tumor diameter, determined using the surv_cutpoint function in R, was revealed to be 53 mm. Patients with tumors exceeding this size had a worse survival prognosis than those with tumors less than this size. Therefore, this cutoff value may aid in stratifying prognostic risk and guide treatment planning in clinical practice. In summary, tumor size in advanced refractory lung cancer appears to significantly influence patient prognosis.

The efficacy of iodine-125 seed therapy has been well-established in prostate cancer and spinal metastases (20,21). In a study by Cheng *et al* (22), six patients with NSCLC received iodine-125 seed implantation. A total of five patients achieved CR, and one achieved PR 1 month after implantation, with an ORR of 100%, a median OS of 26 months, and a median PFS of 12 months. In another study by Sui *et al* (23), three patients with advanced NSCLC treated with iodine-125 seed brachytherapy and anti-programmed cell death protein-1 antibodies achieved CR or PR. Moreover, compared with conventional whole-body radiotherapy, iodine-125 seed implantation reduces radiation exposure to surrounding tissues, minimizes treatment-related side effects, and is suitable for inoperable patients or those unable to tolerate systemic chemotherapy (24). However, iodine-125 seed therapy has limitations, particularly in addressing the complex tumor-blood supply system.

BACE has also been assessed for treating advanced lung cancer (25). In a study by Zhu *et al* (26), BACE combined with apatinib improved outcomes in patients with lung cancer. Among the 47 patients who underwent the BACE procedure, the observation group had a median PFS of 322 days, compared with 209 days in the control group (P<0.05), with 1-year survival rates of 76.19 and 46.15%, respectively (P<0.05). However, traditional embolization materials such as polyvinyl alcohol (PVA) particles and gelatin sponge particles have limitations. PVA particles may cause incomplete embolization due to uneven size distribution, whilst gelatin sponge particles, being short-acting embolic agents, may result in tumor recurrence or complications (27,28).

8Sphere microspheres are a novel type of embolic material made from a macromolecular cross-linked polymer, with PVA as the main chain. These microspheres have a regular spherical shape and the ability to compress, which allows them to travel further within blood vessels. These properties enable precise distribution in the blood supply artery of a tumor during embolization, resulting in terminal embolization with a stable and predictable effect (11). In a study by Zhang *et al* (29), 15 patients with uterine fibroids underwent uterine artery embolization using 8Spheres microspheres, with no serious adverse effects. At 6 months post-surgery, the volumes of the uterus and dominant smooth muscle tumors notably decreased from 340.0±35.8 and 100.6±24.3 cm^3, respectively (baseline) to 266.6±30.9 and 56.1±17.3 cm^3. These results indicate the efficacy and safety of 8Spheres microspheres in solid tumor embolization. Furthermore, 8Spheres microsphere embolization is also associated with minimal adverse effects. In a study by Zhou *et al* (30), partial splenic artery embolization using 8Spheres microspheres in patients with hepatocellular carcinoma and hypersplenism not only achieved permanent vascular embolization but also markedly reduced inflammatory responses, resulting in a lower incidence of fever and pain. The enhanced therapeutic efficacy of the combined

Table III. Univariate Cox analysis of different characteristics based on overall survival.

Variable	B	SE	Wald	P-value	HR	95.0% CI for HR Lower	Upper
Age (>60 vs. ≤60 years)	0.298	0.358	0.692	0.405	1.347	0.668	2.716
Sex (Female vs. male)	0.191	0.316	0.364	0.546	1.210	0.651	2.249
Group (Control vs. test)	0.654	0.324	4.081	0.043	1.924	1.020	3.631
ECOG PS[a]			0.375	0.829			
0	Ref.						
1	0.294	0.736	0.159	0.690	1.341	0.317	5.672
2	0.110	0.774	0.020	0.887	1.117	0.245	5.089
Pathological type (SCC vs. AC)	0.255	0.322	0.629	0.428	1.291	0.687	2.427
TNM stage (IVA vs. IIIB)	0.161	0.314	0.263	0.608	1.175	0.635	2.175
Maximum tumor diameter (>53 vs. ≤53 mm)	0.849	0.324	6.853	0.009	2.336	1.238	4.410

[a]ECOG is a multi-categorical index and ECOG=0 is the reference group. B, partial regression coefficient; SE, coefficient standard error; Wald, Wald test value; HR, hazard ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; PS, Performance Status; SCC, squamous cell carcinoma; AC, adenocarcinoma; TNM, tumor-node-metastasis.

Table IV. Multivariate Cox analysis of different characteristics based on overall survival.

Variable	B	SE	Wald	P-value	HR	95.0% CI for HR Lower	Upper
Group (Control vs. test)	0.829	0.333	6.212	0.013	2.291	1.194	4.396
Maximum tumor diameter (>53 vs. ≤53 mm)	1.002	0.334	9.011	0.003	2.723	1.416	5.238

B, partial regression coefficient; SE, coefficient standard error; Wald, Wald test value; HR, hazard ratio; CI, confidence interval.

treatment is likely due to multiple biological mechanisms. Vascular embolization with 8Spheres microspheres induces tumor hypoxia and the simultaneous inhibition of tumor cell proliferation and invasion (29). In a study by Chao *et al* (31), TACE was reported to be associated with the modulation of serum angiogenic, inflammatory and cell growth cytokines in patients with hepatocellular carcinoma (HCC). Additionally, the ischemic and hypoxic environment created by embolization may alter the immune microenvironment of the tumor, potentially enhancing the immune response against the tumor (32). In a previous study, hepatic artery embolization (HAE) was reported to enhance intratumoral and peritumoral programmed death-ligand 1 (PD-L1) expression in a rat HCC model. The hypoxia-inducible factor-1α pathway is a possible mechanism underlying increased intratumoral PD-L1 expression after HAE (32). Moreover, in a study by Kang *et al* (33), the iodine-125 seed promoted the apoptosis of cholangiocarcinoma cells and induced the activation of the ROS/p53 pathway in a dose-dependent manner. The combination of 8Spheres microsphere vascular embolization of the tumor blood supply and induction of tumor hypoxia, and iodine-125 seed implantation for radiation damage to the tumor, enhanced the therapeutic effect on the tumor. However, further studies are required to elucidate these mechanisms in more detail. In a single-arm pilot study by Chen *et al* (34), embosphere microsphere embolization combined with iodine-125 seeds was used to treat patients with locally advanced stage III NSCLC after radiotherapy failure. Among the 28 patients, the 6-month ORR and DCR were 71.42 and 92.86%, respectively, with no serious complications observed during follow-up. The median PFS was 8 months (95% CI, 7.3-8.8 months). In the present study, the ORR, DCR and median PFS in the combination therapy group were higher than those reported by Chen *et al*. We hypothesize that the improved treatment efficacy in the present study was associated with the superior size distribution, enhanced spherical stability and improved retention characteristics of the 8Spheres microspheres.

Compared with standard-of-care treatments, such as immunotherapy-based regimens and radiation therapy, the combined treatment of 8Spheres microsphere embolization and iodine-125 seed implantation offers several advantages. The minimally invasive nature of the procedure and the enhanced therapeutic effect due to the synergistic action of the two modalities make it a promising option for patients with

Table V. Univariate Cox analysis of different characteristics based on progression-free survival.

						95.0% CI for HR	
Variable	B	SE	Wald	P-value	HR	Lower	Upper
Age (>60 vs. ≤60 years)	0.228	0.355	0.410	0.522	1.256	0.626	2.519
Sex (Female vs. male)	0.276	0.314	0.775	0.379	1.318	0.712	2.439
Group (Control vs. test)	0.819	0.329	6.206	0.013	2.269	1.191	4.322
ECOG PS[a]			0.129	0.938			
0	Ref.						
1	0.247	0.736	0.113	0.737	1.281	0.303	5.420
2	0.188	0.770	0.060	0.807	1.207	0.267	5.455
Pathological type (SCC vs. AC)	0.403	0.323	1.562	0.211	1.497	0.795	2.818
TNM stage (IVA vs. IIIB)	0.222	0.312	0.508	0.476	1.249	0.678	2.302
Maximum tumor diameter (>53 vs. ≤53 mm)	0.763	0.325	5.511	0.019	2.146	1.134	4.059

[a]ECOG is a multi-categorical index and ECOG=0 is the reference group. B, partial regression coefficient; SE, coefficient standard error; Wald, Wald test value; HR, hazard ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; PS, Performance Status; SCC, squamous cell carcinoma; AC, adenocarcinoma; TNM, tumor-node-metastasis.

Table VI. Multivariate Cox analysis of different characteristics based on progression-free survival.

						95.0% CI for HR	
Variable	B	SE	Wald	P-value	HR	Lower	Upper
Group (Control vs. test)	0.943	0.335	7.929	0.005	2.567	1.332	4.949
Maximum tumor diameter (>53 vs. ≤53 mm)	0.892	0.331	7.273	0.007	2.440	1.276	4.665

B, partial regression coefficient; SE, coefficient standard error; Wald, Wald test value; HR, hazard ratio; CI, confidence interval.

Table VII. Adverse events.

Adverse event	Test group (n=23)	Control group (n=22)	P-value
Pneumothorax	2 (8.7)	3 (13.6)	0.647
Hemoptysis	3 (13.0)	3 (13.7)	1.000
Chest pain	6 (26.1)	5 (22.7)	0.756
Fever	5 (21.7)	3 (13.6)	0.594
Nausea	2 (8.7)	2 (9.1)	1.000

Data are presented as n (%). Comparisons between two groups were determined by Fisher's exact test.

advanced refractory NSCLC. However, the combined treatment may not be suitable for all patients, and further studies are needed to determine the optimal indications and patient selection criteria.

The present study has several limitations. First, it was a retrospective analysis with a small sample size and a relatively short follow-up period, which could introduce selection bias. To more comprehensively evaluate the long-term efficacy and safety of the treatment regimen, larger-scale prospective randomized controlled trials are warranted. In future prospective studies, it is recommended that propensity score matching be incorporated. This approach can help adjust for potential confounders and further validate the findings obtained in the current study, thereby providing more robust and reliable evidence for clinical practice. Moreover, despite all patients receiving the same treatment, individual

variations in response could affect efficacy and safety. Whilst the present study reports follow-up data up to June 2024, long-term survival outcomes (such as 3-5 years follow-up) are crucial for evaluating the true efficacy of the treatment. Future studies should aim to provide long-term data on survival trends, late-onset adverse events and patterns of disease recurrence. This will further validate the clinical benefits of the combined treatment. In addition, future research should focus on more precise patient stratification and individualized treatment regimens so as to offer improved options for patients with refractory NSCLC. The current study used the sequence of seed implantation followed by embolization; however, future studies should evaluate the clinical outcomes of pre-seed implantation embolization. This modification may enhance tumor hypoxia and improve the efficacy of iodine-125 radiotherapy. Furthermore, genetic alterations (such as EGFR, ALK and KRAS mutations) were not systematically recorded in patient medical records, limiting the ability to stratify outcomes by molecular profiles. Future prospective studies should integrate comprehensive genomic profiling to refine prognostic models and identify biomarkers predictive of treatment response. Finally, although histological subtypes (adenocarcinoma vs. squamous carcinoma) and baseline ECOG performance status were balanced between groups, subgroup analyses stratified by these factors were not performed due to the small sample size. More extensive studies should explore whether treatment efficacy differs across histological subtypes or patient functional status.

In conclusion, the combination of 8Spheres microsphere embolization and iodine-125 seed implantation presents a promising treatment option for patients with advanced refractory NSCLC. The procedure is straightforward, minimally invasive and safe, making it a promising option for clinical application. Furthermore, this approach significantly enhances therapeutic efficacy, extends survival and is minimally invasive, meaning that it well-suited for clinical use. However, further research is required to evaluate its long-term effects and explore optimized treatment strategies.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

LR and HP conceived and designed this study. LR, LJ and YL participated in data collection and data curation (organizing and maintaining data). LJ, YL and HP analyzed the data. LR, LJ and HP drafted the manuscript and all authors reviewed it. YL and HP confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Institutional Ethics Committee of the First Affiliated Hospital of Chongqing Medical University (approval no. K2023-470). The requirement for informed consent for participation was waived due to the retrospective nature of the study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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