



Drug-eluting beads-transcatheter arterial chemoembolization with or without iodine-125 treatment is effective and tolerable in treating advanced non-small cell lung cancer patients: a pilot study

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Background: This study aimed to explore the efficacy and safety of drug-eluting beads-transcatheter arterial chemoembolization (DEB-TACE) with or without iodine-125 (¹²⁵I) seed implantation in treating advanced non-small cell lung cancer (NSCLC) patients.

Methods: A total of 25 advanced NSCLC patients underwent DEB-TACE were consecutively enrolled, among which 17 cases also received ¹²⁵I seed implantation post DEB-TACE treatment. Treatment response, overall survival (OS), biochemical indexes and safety profiles were recorded and analyzed.

Results: Zero (0.0%), 13 (54.2%), 9 (37.5%) and 2 (8.3%) patients realized complete response (CR), partial response (PR), stable disease (SD) and progression disease (PD) respectively, and the objective response rate (ORR) and disease control rate (DCR) were 54.2% and 91.7%. The median OS was 12.6 (95% CI: 7.8–17.5) months. No difference of treatment response or OS was observed between DEB-TACE treatment alone and DEB-TACE plus ¹²⁵I seed implantation. Predictive factors analysis revealed that tumor size correlated with worse OS. Besides, chest distress grade and dyspnea grade were decreased after DEB-TACE procedure, while clinical symptoms were not changed after ¹²⁵I seed implantation. The common adverse events (AEs) were fever (32.0%), pain (12.0%) by DEB-TACE treatment, and common AE was pain (26.7%) by ¹²⁵I seed implantation.

Conclusions: DEB-TACE with or without ¹²⁵I seed implantation is effective and tolerable in treating advanced NSCLC patients.

Keywords: Drug-eluting beads-transcatheter arterial chemoembolization (DEB-TACE); non-small cell lung cancer (NSCLC); treatment response; overall survival (OS); safety profiles

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Introduction

Lung cancer is the most frequently diagnosed cancer and the leading cause of cancer death which accounts for 11.6% of total cancer cases and 18.4% of total cancer deaths all around the world (1,2). According to a recent cancer statistic report, there are 2,093,876 new cases and 1,761,007 lung cancer deaths in 2018 (1). Non-small cell lung cancer (NSCLC) is the most prevalent subtype of lung cancer that approximately 85% of lung cancer cases are NSCLC patients (3). Among the various alternative treatments for NSCLC, surgery is mainly used to treat early-staged NSCLC patients, whereas most NSCLC patients are diagnosed at advanced stage (3,4). Radiotherapy [such as iodine-125 (^{125}I) seed implantation] exhibits favorable treatment efficacy in majority of patients, whereas it is mainly served as an adjuvant therapy or palliative treatment due to the high recurrence rate (5). Targeted therapies (such as epidermal growth factor receptor tyrosine kinase inhibitors) and immunotherapies (such as anti-programmed death 1 antibody) provide great survival benefits for advanced NSCLC patients (6,7). However, there are still some patients who have no chance to receive these treatments partly due to lacking mutations, high cost or drug resistance (8). As for platinum-based systemic chemotherapy, it is commonly used as a palliative treatment which might decrease NSCLC patients' quality of life and bring in psychological disorders due to its systemic adverse events (AEs) (9,10). Therefore, exploring additional and effective treatment strategies is still critical to improving the survival of NSCLC patients.

Drug-eluting beads-transcatheter arterial chemoembolization (DEB-TACE) is a locoregional treatment strategy, and the microspheres not only delivery chemotherapeutic drugs to tumor tissues long-lastingly via the feeding arteries, but also block blood supply of tumor tissues, which then cause tumor ischemia and necrosis (11,12). Accumulating evidences have illustrated that DEB-TACE is an effective method to not only improve survival, but also decrease fatal AEs in unresectable liver cancer patients, whereas there is still limited information regarding the efficacy and safety of DEB-TACE in other cancer patients (13,14). As for lung cancer, one previous study enrolls 17 metastatic lung cancer patients who are about to receive DEB-TACE plus radiofrequency (RF) ablation, and reveals that the DEB-TACE plus RF ablation is feasible, effective and safe in these unresectable lung cancer patients (15). However, that previous study focuses on

the metastatic lung cancer patients, and the sample size is relatively small. More importantly, there is no more study reporting the application of DEB-TACE in treating advanced NSCLC patients. Therefore, we conducted the current study to explore the efficacy and safety of DEB-TACE with or without ^{125}I seed implantation in treating advanced NSCLC patients.

Methods

Patients

Twenty-five advanced NSCLC patients underwent DEB-TACE or DEB-TACE combined with ^{125}I seed implantation in Lishui Central Hospital between January 2016 and May 2018 were consecutively recruited in this study. The inclusion criteria were as follows: (I) diagnosed as NSCLC confirmed by pathology examination; (II) TNM stage III, which was assessed according to the Union for International Cancer Control (UICC) system (7th edition); (III) age above 18 years; (IV) underwent DEB-TACE or DEB-TACE combined with ^{125}I seed implantation therapy; (V) Eastern Cooperative Oncology Group (ECOG) score ≤ 2 . Patients were excluded if they had the following conditions: (I) coagulation dysfunction; (II) allergic to chemotherapy agents used in the TACE therapy; (III) severe infection, serious heart, kidney or liver dysfunction; (IV) life expectancy less than 12 months; (V) history of TACE or ^{125}I seed implantation treatment; (VI) pregnant or lactating women.

Ethics statement

The current study protocol was approved by Ethics Committee of Lishui Central Hospital, and the study was performed according to the Declaration of Helsinki and Good Clinical Practice guidelines as defined by the International Conference on Harmonisation. Written informed consents were collected from all patients or their family members before enrollment.

Baseline data collection

Baseline characteristics of patients were collected after enrollment, including age, gender, history of smoke, tumor location, tumor size, histologic type, pathological differentiation, ECOG score and history of treatment. Besides, following baseline data were also collected: clinical

symptoms (including cough, hemoptysis, chest distress, chest pain and dyspnea), hematological indexes [including white blood cell (WBC), red blood cell (RBC), absolute neutrophil count (ANC), hemoglobin (Hb) and platelet (PLT)] and tumor markers [including carcinoembryonic antigen (CEA), carbohydrate antigen 125 (CA125), 2-phospho-D-glycerate hydrolase (NSE), squamous cell carcinoma antigen (SCCAg), cytokeratin 19 fragment (Cyfra21-1)].

Treatment

After the eligibility of DEB-ATCE therapy was confirmed, patients received the DEB-TACE voluntarily, and then the response to DEB-TACE therapy was evaluated at 1 month post the treatment. For patients with incompletely necrotic tumors, ^{125}I seed implantation was administered if they were willing to receive, and others who were unwilling to receiving the ^{125}I seed implantation, systemic chemotherapy or radiotherapy was given according to the disease status and personal willingness.

DEB-TACE procedure

Chest computed tomography (CT) plain scan and enhanced scan were performed to determine the size and blood supply of the tumors, and to exclude the contraindication of vascular intervention before the operation. The patient was lying on the digital subtraction angiography (DSA) operating table with routine disinfection of bilateral inguinal skin. Under local anesthesia by 5 mL 2% lidocaine, the femoral artery was percutaneously punctured with Seldinger technique using 5F catheter sheath. Subsequently, 5F Cobra catheter (COOK, Bloomington, Indiana, USA) was selectively inserted into bronchial artery. Then bronchial arteriography was performed to detect the supplying artery of tumor using 300 mg/mL iohexol at an injection rate of 1–2 mL/s (total volume was 3 to 8 mL). If the supplying artery of tumor was found being in common trunk with spinal artery, esophageal artery or intercostal artery, Terumo Progreat 3F microcatheter (Terumo Corporation, Shibuya-ku, Tokyo, Japan) was superselectively placed in the tumor supplying artery by avoiding spinal artery, esophageal artery and intercostal artery. Next, 300–500 μm CalliSpheres[®] microspheres (CSM) (Jiangsu Hengrui Medicine Co., Ltd., Jiangsu Province, China) loaded with 1.0 g gemcitabine was injected at the speed of 1 mL/min into the tumor supplying artery under perspective monitoring and followed by

60 mg (30 mg/m²) cisplatin infusion, with an average infusion dose of 53.2 \pm 7.1 mg. The embolization was stopped when the tumor staining was disappeared. After embolization, angiography was conducted again to detect whether there was extravasation of contrast medium and incomplete embolization of tumor artery. When procedures of DEB-TACE were finished, the microcatheter was pulled out, and the wound was pressed for hemostasis and then bandaged.

^{125}I seed implantation procedure

In the present study, ^{125}I seed with radiation activity of 0.7–0.9 mCi was provided by Seeds Biological Pharmacy (Tianjin) Ltd. (Seeds Biological Pharmacy (Tianjin) Ltd., Tianjin, China), which was implanted using HGGR-3000 Radioactive Seed Treatment-Planning System (TPS) (Zhuhai Hokai Medical Instruments Co., Ltd., Zhuhai, Guangdong, China). Before seed implantation, patients' clinical data were input into TPS to calculate the number, radiation activity and location of ^{125}I seed. And CT scan was performed to determine the location, direction and depth of the needle insertion during operation. With 2% lidocaine local anesthesia, patients were required to hold breath, then an 18-gauge needle was gradually inserted into the tumor. After confirming the puncture needle in right position by CT scan, the turntable seed implantation gun was used to evenly implant ^{125}I seed into the tumor at an interval of 0.5–1.0 cm, layer by layer. For tumors with residual thickness less than 1.0 cm, the ^{125}I seed was evenly implanted with a 0.5 cm interval centered on the largest layer of the tumor. If the tumor was large, seed implantation was carried out by more times. The median number of implanted ^{125}I seed was 49 (range, 28–70), and the median matched peripheral dose (MPD) was 89.31 Gy (range, 72.63–105.99 Gy). CT scan was performed immediately after seed implantation to confirm the implantation status of seed and detect whether complications (such as pneumothorax and hemothorax) occurred. After the operation, the needle was pulled out, and the wound was bandaged under pressure.

Assessments

Dynamic enhanced CT scan, clinical symptom examination and hematological examination were performed at 1 month after DEB-TACE and ^{125}I seed implantation respectively. Tumor response to the DEB-TACE therapy and ^{125}I seed implantation was assessed according to the modified

Response Evaluation Criteria in Solid Tumors (mRECIST), which was classified as complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). Moreover, objective response rate (ORR) was defined as CR+PR, and disease control rate (DCR) was defined as CR + PR + SD. Besides, adverse events occurred at 1 week after DEB-TACE and ^{125}I seed implantation were also recorded according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 respectively, and were categorized as pain, fever, nausea, vomit and others (16).

Follow up

In the first 3 months after treatment, all patients were followed up every month and then every 3 months until death or last follow-up (2018/10/28), with a median follow-up time of 9.1 months. Overall survival (OS) was calculated from the date of DEB-TACE therapy to the date of death or last follow-up.

Statistical analysis

Among enrolled 25 patients, there was 1 patient missing data of treatment response, therefore, a total of 24 patients were included in the analysis of response treatment; in addition, among 17 patients who underwent DEB-TACE combined with ^{125}I seed implantation, 2 patients were excluded from the analysis of clinical symptoms, hematological indexes, tumor markers and adverse events after ^{125}I seed implantation due to missing data. And all 25 patients were included in the survival analysis without missing data. For normally or approximately normal distributed continuous variable, it was presented as mean value \pm standard deviation; as for skewed or unknown distributed continuous variable, it was expressed as median (25th–75th quantiles), and the comparison between prior treatment and post treatment was determined by Wilcoxon signed rank test. Both ordered and unordered variable categorical variables were presented as count (percentage), and the comparison of ordered categorical variable between prior treatment and post treatment was determined using Wilcoxon signed rank test. OS was demonstrated by use of Kaplan–Meier method and comparison between subgroups was determined by log-rank test. SPSS 22.0 statistical software (SPSS Inc., Chicago, IL, USA) was used for statistical data processing, and GraphPad Prism 6.01 software (GraphPad Software Inc., San Diego, CA, USA)

was used for figures making. P value <0.05 was considered significant.

Results

Characteristics in advanced NSCLC patients

In totally 25 NSCLC patients, there were 19 male and 6 female, and the mean age was 67.3 ± 9.8 years. The number of patients with smoking history was 13 (52.0%) and the mean tumor size was 6.0 ± 2.5 cm. Meanwhile, 10 (40.0%) patients were squamous cell carcinoma, 12 (48.0%) patients were adenocarcinoma and 3 (12.0%) patients were mixed carcinoma. And the number of patients with ECOG score 0, 1, and 2 was 10 (40.0%), 14 (56.0%) and 1 (4.0%), respectively. Besides, 17 (68.0%) patients also received combined ^{125}I seed implantation after DEB-TACE treatment, and the interval between the two treatments was 38.6 ± 29.5 days. Other characteristics of NSCLC patients were listed in *Table 1*.

Treatment response rates in advanced NSCLC patients

Treatment response was assessed in 24 NSCLC patients, among whom 7 patients received DEB-TACE and 17 patients received DEB-TACE plus ^{125}I seed implantation. The number of patients achieved CR, PR, SD and PD were 0 (0.0%), 13 (54.2%), 9 (37.5%) and 2 (8.3%) respectively at 1 month after DEB-TACE or DEB-TACE plus ^{125}I seed implantation, and the ORR and DCR were 13 (54.2%) and 22 (91.7%) (*Figure 1A*). For patients received DEB-TACE treatment, the CR, PR, ORR and DCR were 0 (0.0%), 4 (57.1%), 4 (57.1%) and 7 (100.0%) respectively at 1 month after treatment; for patients received DEB-TACE plus ^{125}I seed implantation, the CR, PR, ORR and DCR were 0 (0.0%), 9 (52.9%), 9 (52.9%) and 15 (88.2%) respectively at 1 month after treatment; no difference of CR, PR, ORR or DCR was discovered between the two groups (all $P>0.05$) (*Figure 1B*).

OS and factors affecting OS in advanced NSCLC patients

The median OS was 12.6 (95% CI: 7.8–17.5) months and the accumulating OS at 12th month was 47.6% in NSCLC patients (*Figure 2A*), besides, no difference of OS was found between patients receiving DEB-TACE and patients receiving DEB-TACE plus ^{125}I seed implantation ($P=0.148$) (*Figure 2B*). In addition, we further investigated

Table 1 Characteristics of NSCLC patients

Characteristics	Values (total n=25)
Age (years)	67.3±9.8
Gender (male/female)	19/6
History of smoke, n (%)	13 (52.0)
Tumor location, n (%)	
Left	13 (52.0)
Right	12 (48.0)
Tumor size (cm)	6.0±2.5
Histologic type, n (%)	
Squamous cell carcinoma	10 (40.0)
Adenocarcinoma	12 (48.0)
Mixed carcinoma	3 (12.0)
Pathological differentiation, n (%)	
Well	0 (0.0)
Moderate	2 (8.0)
Poor	23 (92.0)
ECOG score, n (%)	
0	10 (40.0)
1	14 (56.0)
2	1 (4.0)
History of treatment, n (%)	
Interventional therapy	1 (4.0)
Systematic chemotherapy	19 (76.0)
Targeted therapy	23 (92.0)
Combined with ¹²⁵ I seed implantation, n (%)	17 (68.0)
The interval between DEB-TACE and ¹²⁵ I seed implantation (days)	38.6±29.5

Data were presented as mean value ± standard deviation or count (percentage). ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small-cell lung cancer; ¹²⁵I, iodine-125.

the correlation of baseline characteristics with OS in these NSCLC patients, and found that NSCLC patients with tumor size ≤5 cm presented with higher OS compared with patients with tumor size >5 cm (P=0.023) (Table S1). However, no association of age (P=0.828), gender (P=0.652), history of smoke (P=0.906), tumor location (P=0.461), histologic type (P=0.051), pathological differentiation

(P=0.146), ECOG score (P=0.094), previous chemotherapy (P=0.224) or previous targeted therapy (P=0.453) with OS was observed in NSCLC patients.

Clinical symptoms before DEB-TACE treatment and at 1 month after DEB-TACE treatment in advanced NSCLC patients

The chest distress grade (P=0.013) and dyspnea grade (P=0.025) were decreased at 1 month after DEB-TACE treatment than that before treatment. However, no difference of cough grade (P=0.308), hemoptysis grade (P=0.564) or chest pain grade (P=1.000) was observed in NSCLC patients before DEB-TACE and at 1 month after DEB-TACE treatment (Table 2).

Hematological indexes and tumor markers before DEB-TACE treatment and at 1 month after DEB-TACE treatment in advanced NSCLC patients

At 1 month after DEB-TACE treatment, median values of RBC (P=0.044), Hb (P=0.007) and PLT (P=0.042) were declined, while median value of ANC (P<0.001) was elevated compared to that before DEB-TACE treatment (Table 3). Whereas there was no difference in other hematological indexes or tumor markers in NSCLC patients before DEB-TACE and at 1 month after treatment (all P>0.05).

Adverse events within 1 week after DEB-TACE treatment in advanced NSCLC patients

As for adverse events by DEB-TACE operation, 3 (12.0%), 8 (32.0%), 1 (4.0%), 1 (4.0%) and 8 (32.0%) NSCLC patients occurred pain, fever, nausea, vomit and other adverse events respectively within 1 week after DEB-TACE treatment (Table 4).

Clinical symptoms before ¹²⁵I seed implantation and at 1 month after ¹²⁵I seed implantation in advanced NSCLC patients

There was no difference of cough grade (P=0.783), hemoptysis grade (P=0.317), chest distress grade (P=0.317), chest pain grade (P=1.000) or dyspnea grade (P=1.000) in NSCLC patients before ¹²⁵I seed implantation and at 1 month after ¹²⁵I seed implantation (Table 5).

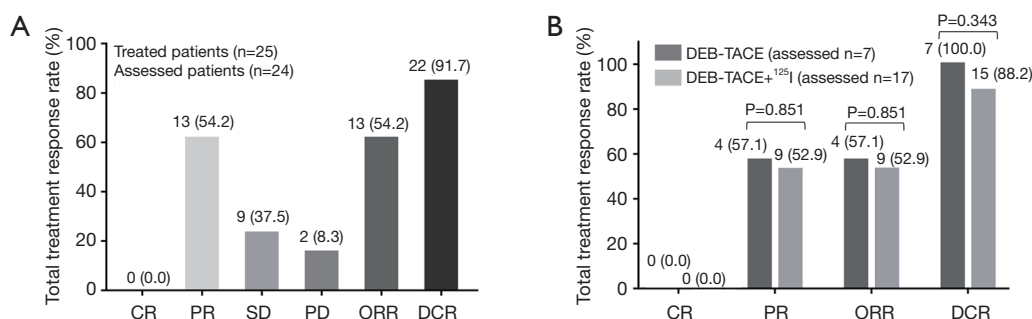


Figure 1 Treatment response of NSCLC patients. (A) Treatment response was evaluated in 24 patients, among which 7 patients received DEB-TACE and 17 patients received DEB-TACE plus ¹²⁵I seed implantation. The number of patients realized CR, PR, SD and PD were 0 (0.0%), 13 (54.2%), 9 (37.5%) and 2 (8.3%) respectively after DEB-TACE or DEB-TACE plus ¹²⁵I seed implantation, and the ORR and DCR were 13 (54.2%) and 22 (91.7%). (B) In patients received DEB-TACE treatment, the CR, PR, ORR and DCR were 0 (0.0%), 4 (57.1%), 4 (57.1%) and 7 (100.0%), respectively; in patients received DEB-TACE plus ¹²⁵I seed implantation, the CR, PR, ORR and DCR were 0 (0.0%), 9 (52.9%), 9 (52.9%) and 15 (88.2%), respectively. The clinical responses were similar between patients received DEB-TACE and patients received DEB-TACE plus ¹²⁵I seed implantation. Comparison between prior treatment and post treatment was determined using Wilcoxon signed rank test. $P < 0.05$ was considered significant. DEB-TACE, drug-eluting beads-transcatheter arterial chemoembolization; ¹²⁵I, iodine-125; CR, complete response; PR, partial response; SD, stable disease; PD, progression disease; ORR, objective response rate; DCR, disease control rate.

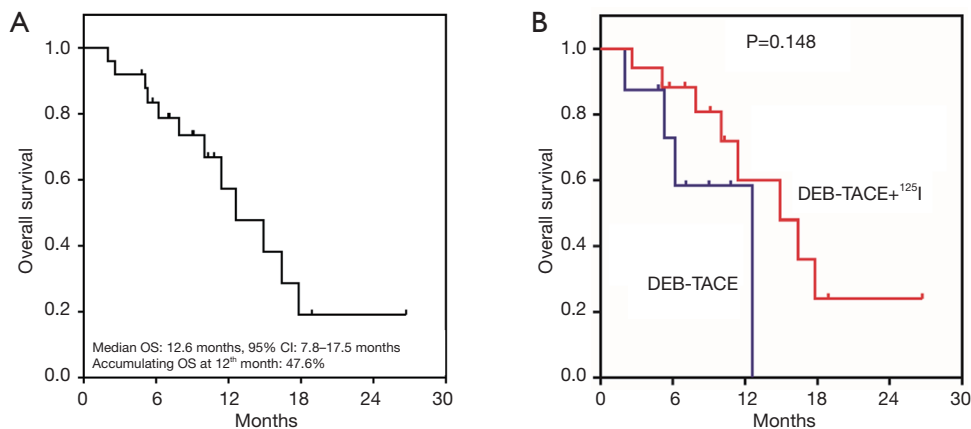


Figure 2 OS of NSCLC patients. (A) Median OS was 12.6 (95% CI: 7.8–17.5) months and accumulating OS at 12th month was 47.6%, and (B) no difference of OS was found between the two groups. OS was demonstrated by Kaplan-Meier method. OS, overall survival; NSCLC, non-small cell lung cancer; DEB-TACE, drug-eluting beads-transarterial chemoembolization; ¹²⁵I, iodine-125.

Hematological indexes and tumor markers before ¹²⁵I seed implantation and at 1 month after ¹²⁵I seed implantation in advanced NSCLC patients

The values of WBC ($P=0.085$), RBC ($P=0.859$), ANC ($P=0.086$), Hb ($P=0.859$), PLT ($P=0.139$), CEA ($P=0.593$), CA125 ($P=1.000$), NSE ($P=0.785$), SCCAg ($P=0.465$) and Cyfra21-1 ($P=1.000$) were similar in NSCLC patients before ¹²⁵I seed implantation and at 1 month after ¹²⁵I seed

implantation (Table 6).

Adverse events within 1 week after ¹²⁵I seed implantation in advanced NSCLC patients

4 (26.7%) patients occurred pain and 8 (53.3%) patients occurred other adverse events within 1 week after ¹²⁵I seed implantation, while no patient occurred fever, nausea or vomit (Table 7).

Table 2 Clinical symptoms before and at one month after DEB-TACE

Clinical symptoms	Before DEB-TACE (n=25)	One month after DEB-TACE (n=25)	P
Cough grade, n (%)			0.308
No	10 (40.0)	8 (32.0)	
Mild	9 (36.0)	16 (64.0)	
Moderate	4 (16.0)	1 (4.0)	
Severe	2 (8.0)	0 (0.0)	
Hemoptysis grade, n (%)			0.564
No	22 (88.0)	23 (92.0)	
Mild	3 (12.0)	2 (8.0)	
Moderate	0 (0.0)	0 (0.0)	
Severe	0 (0.0)	0 (0.0)	
Chest distress grade, n (%)			0.013
No	15 (60.0)	22 (88.0)	
Mild	7 (28.0)	3 (12.0)	
Moderate	3 (12.0)	0 (0.0)	
Severe	0 (0.0)	0 (0.0)	
Chest pain grade, n (%)			1.000
No	23 (92.0)	22 (88.0)	
Mild	1 (4.0)	3 (12.0)	
Moderate	1 (4.0)	0 (0.0)	
Severe	0 (0.0)	0 (0.0)	
Dyspnea grade, n (%)			0.025
No	19 (76.0)	24 (94.0)	
Mild	6 (24.0)	1 (6.0)	
Moderate	0 (0.0)	0 (0.0)	
Severe	0 (0.0)	0 (0.0)	

Data were presented as count (percentage). Comparisons were determined by Wilcoxon signed rank test. $P < 0.05$ was considered significant. DEB-TACE, drug-eluting beads-transcatheter arterial chemoembolization.

Discussion

Accumulating evidences reveal that chemoembolization is effective for the treatment of lung cancer (17,18). For instance, a prospective cohort study observes that 8 (34.8%) cancer patients with unresectable lung metastases achieve PR and 6 (26.1%) patients achieve SD after transpulmonary chemoembolization (the suspension of mitomycin and lipiodol is injected into the feeding artery, followed by embolization with microspheres) (19). In another prospective cohort study, 52 unresectable lung

cancer patients receive transpulmonary chemoembolization, among whom 16 (30.8%) patients achieve PR, 11 (21.2%) patients achieve SD, and 25 (48.1%) patients achieve PD; and the median OS is 21.1 (95% CI: 4.2–38) months (20). These previous studies have identified the efficacy of chemoembolization in lung cancer treatment. DEB-TACE uses microspheres to act both as drug carriers and embolization agents, which not only release chemotherapeutic drugs to tumor tissues in a sustained manner, but also block blood supply of tumor (12,13).

Table 3 Hematological indexes and tumor markers before and at 1 month after DEB-TACE

Items	Before DEB-TACE (n=25)	One month after DEB-TACE (n=25)	P
WBC ($\times 10^9/L$)	6.7 (5.5–7.8)	6.9 (6.0–9.0)	0.095
RBC ($\times 10^{12}/L$)	3.9 (3.7–4.2)	3.6 (3.5–4.2)	0.044
ANC (%)	66.9 (60.0–73.1)	77.5 (72.3–87.2)	<0.001
Hb (g/L)	122.0 (112.0–132.0)	117.0 (106.0–125.5)	0.007
PLT ($\times 10^9/L$)	248.0 (181.0–317.0)	208.0 (166.5–296.0)	0.042
CEA (ng/mL)	3.2 (2.2–10.0)	3.0 (1.6–12.2)	0.502
CA125 (U/mL)	41.7 (14.8–201.1)	83.4 (18.9–182.2)	0.859
NSE (U/mL)	18.9 (15.2–35.2)	13.4 (11.4–55.1)	1.000
SCCAg (ng/mL)	1.2 (0.8–4.4)	0.9 (0.5–7.5)	0.753
Cyfra21-1 (ng/mL)	6.0 (3.9–12.2)	5.7 (3.3–22.3)	0.594

Data were presented as median (25th–75th quantiles). Comparisons were determined by Wilcoxon signed rank test. $P < 0.05$ was considered significant. DEB-TACE, drug-eluting beads-transcatheter arterial chemoembolization; WBC, white blood cell; RBC, red blood cell; ANC, absolute neutrophil count; Hb, hemoglobin; PLT, platelet; CEA, carcinoembryonic antigen; CA125, Carbohydrate antigen 125; NSE, 2-phospho-D-glycerate hydrolase; SCCAg, squamous cell carcinoma antigen; Cyfra21-1, cytokeratin 19 fragment.

Table 4 Adverse events occurred within one week after DEB-TACE treatment

Adverse events	Patients (n=25)
Pain, n (%)	3 (12.0)
Fever, n (%)	8 (32.0)
Nausea, n (%)	1 (4.0)
Vomit, n (%)	1 (4.0)
Others, n (%)	8 (32.0)

Data were presented as count (percentage). DEB-TACE, drug-eluting beads-transcatheter arterial chemoembolization.

These features enable DEB-TACE to be more effective in treating liver cancer patients compared with other chemoembolization methods (21). As for the feasibility of DEB-TACE in lung cancer treatment, one previous study recruits 17 metastatic lung cancer patients who are about to receive DEB-TACE plus RF ablation, and discovers that DEB-TACE plus RF ablation is effective and safe in these patients (15). However, that previous study focuses on the metastatic lung cancer patients but not advanced NSCLC patients. In the current study, we discovered that NSCLC patients who received DEB-TACE or DEB-TACE plus ^{125}I seed implantation achieved an ORR of 54.2% and a DCR of 91.7%, and the median OS was 12.6 (95% CI: 7.8–17.5) months, indicating the favorable treatment efficacy

of DEB-TACE in NSCLC patients. The possible reasons for the good efficacy of DEB-TACE in treating advanced NSCLC patients were as follows: (I) the sustained release of chemotherapeutic drugs by microspheres enabled the long-lasting tumoricidal efficacy, thus NSCLC patients who were treated by DEB-TACE exhibited favorable response and OS; (II) the microspheres also embolized feeding artery completely, leading to tumor ischemia and necrosis, which enhanced the anti-tumor efficacy of chemotherapeutic drugs. Interestingly, we also observed that the treatment response and OS were similar after DEB-TACE or DEB-TACE plus ^{125}I seed implantation in NSCLC patients. The possible reasons may be due to: (I) The sample size was relatively small, causing the relatively low statistics power; (II) a proportion of NSCLC patients presented with incompletely necrotic tumors after DEB-TACE treatment and they subsequently received systemic chemotherapy or radiotherapy rather than ^{125}I seed implantation. These patients might achieve similar response and OS compared with patients treated with DEB-TACE plus ^{125}I seed implantation. Hence, the response or OS was of no difference after DEB-TACE treatment or DEB-TACE plus ^{125}I seed implantation in NSCLC patients. In addition, we used DEB-TACE loaded with gemcitabine combined with cisplatin in this study, which is not a consensus for NSCLC treatment, however, gemcitabine and cisplatin were both common therapeutics in NSCLC treatment. In addition,

Table 5 Clinical symptoms before and at one month after ¹²⁵I seed implantation

Clinical symptoms	Before ¹²⁵ I seed implantation (assessed n=15)	One month after ¹²⁵ I seed implantation (assessed n=15)	P
Cough grade, n (%)			0.783
No	8 (53.3)	5 (33.3)	
Mild	5 (33.3)	9 (60.0)	
Moderate	1 (6.7)	1 (6.7)	
Severe	1 (6.7)	0 (0.0)	
Hemoptysis grade, n (%)			0.317
No	15 (100.0)	14 (93.3)	
Mild	0 (0.0)	1 (6.7)	
Moderate	0 (0.0)	0 (0.0)	
Severe	0 (0.0)	0 (0.0)	
Chest distress grade, n (%)			0.317
No	11 (73.3)	12 (80.0)	
Mild	4 (26.7)	3 (20.0)	
Moderate	0 (0.0)	0 (0.0)	
Severe	0 (0.0)	0 (0.0)	
Chest pain grade, n (%)			1.000
No	13 (86.7)	11 (73.3)	
Mild	1 (6.7)	4 (26.7)	
Moderate	0 (0.0)	0 (0.0)	
Severe	1 (6.7)	0 (0.0)	
Dyspnea grade, n (%)			1.000
No	15 (100.0)	15 (100.0)	
Mild	0 (0.0)	0 (0.0)	
Moderate	0 (0.0)	0 (0.0)	
Severe	0 (0.0)	0 (0.0)	

Data were presented as count (percentage). Comparisons were determined by Wilcoxon signed rank test. P<0.05 was considered significant. ¹²⁵I, iodine-125.

DEB-TACE loaded with gemcitabine in treating NSCLC is also reported in a previous study (22).

The clinical symptoms of common AEs must be treated properly to avoid other life-threatening complications in NSCLC patients. According to previous studies, chemoembolization facilitates the alleviation of NSCLC patients' clinical symptoms (15,23). In addition, 7 (70%) patients present with pulmonary lesion shrinkage, revealing that chemoembolization alleviates clinical symptoms of lung

cancer patients (23). In accordance with this previous study, we found that DEB-TACE eased the clinical manifestations in advanced NSCLC patients, such as the chest distress grade and the dyspnea grade. The possible explanations for the results might derive from the sustained release of chemotherapeutic drugs and the complete embolization of feeding artery by microspheres. We also observed that the symptoms remained unchanged after ¹²⁵I seed implantation, which might be due to that: advanced NSCLC patients who

Table 6 Hematological indexes and tumor markers before and at 1 month after ¹²⁵I seed implantation

Clinical symptoms	Before ¹²⁵ I seed implantation (assessed n=15)	One month after ¹²⁵ I seed implantation (assessed n=15)	P
WBC (×10 ⁹ /L)	5.5 (4.4–7.3)	6.7 (5.5–9.1)	0.085
RBC (×10 ¹² /L)	3.7 (3.3–4.2)	3.6 (3.4–4.0)	0.859
ANC (%)	66.6 (57.9–73.2)	72.2 (61.8–79.6)	0.086
Hb (g/L)	111.5 (104.5–127.5)	113.5 (105.8–123.8)	0.859
PLT (×10 ⁹ /L)	225.0 (123.0–266.5)	221.5 (130.8–245.0)	0.139
CEA (ng/mL)	2.9 (1.8–4.0)	8.6 (2.0–285.1)	0.593
CA125 (U/mL)	19.8 (10.7–67.0)	67.9 (16.8–119.7)	1.000
NSE (U/mL)	16.7 (15.3–20.8)	19.2 (15.4–21.5)	0.785
SCCAg (ng/mL)	1.4 (0.9–4.9)	1.1 (0.5–12.7)	0.465
Cyfra21-1 (ng/mL)	5.2 (2.9–9.5)	7.9 (2.5–13.2)	1.000

Data were presented as median (25th–75th quantiles). Comparisons were determined by Wilcoxon signed rank test. P<0.05 was considered significant. ¹²⁵I, iodine-125; WBC, white blood cell; RBC, red blood cell; ANC, absolute neutrophil count; Hb, hemoglobin; PLT, platelet; CEA, carcinoembryonic antigen; CA125, Carbohydrate antigen 125; NSE, 2-phospho-D-glycerate hydrolase; SCCAg, squamous cell carcinoma antigen; Cyfra21-1, cytokeratin 19 fragment.

Table 7 Adverse events occurred within one week after ¹²⁵I seed implantation

Adverse events	Patients (assessed n=15)
Pain, n (%)	4 (26.7)
Fever, n (%)	0 (0.0)
Nausea, n (%)	0 (0.0)
Vomit, n (%)	0 (0.0)
Others, n (%)	8 (53.3)

Data were presented as count (percentage). ¹²⁵I, iodine-125.

received ¹²⁵I seed implantation also received DEB-TACE treatment before ¹²⁵I seed implantation, which meant that these patients presented with alleviated symptoms before ¹²⁵I seed implantation. Thus, it was difficult to realize improvement of symptoms after ¹²⁵I seed implantation. Besides, we performed DEB-TACE before ¹²⁵I radiation to diminish the risk of bleeding and to enhance the necrotic effect on tumor in NSCLC patients.

In order to further investigate its safety, we evaluated the AEs of NSCLC patients after DEB-TACE treatment. It showed that the most common AEs were mild fever and pain, implying that DEB-TACE was tolerable in treating NSCLC patients. Our results were in line with a previous study, which shows that pleural effusion, chest pain and

fever are common AEs after lung cancer patients being treated by DEB-TACE plus RF ablation, and no treatment-related lung function changes or treatment-related deaths are observed (15). In brief, the AEs of DEB-TACE was tolerable in advanced NSCLC patients.

There still remained some limitations in the present study. Firstly, our study was a single-center study with a relatively small sample size, hence further validation is needed in multi-central study with more NSCLC patients. Secondly, the comparison of efficacy and safety between DEB-TACE and other chemoembolization methods (such as conventional transcatheter arterial chemoembolization or transpulmonary chemoembolization) was not explored. Thirdly, the use of DEB-TACE from bronchial artery was not established, however, there have been studies illustrating that DEB-TACE was tolerable and effective in tumors supplied by bronchial arteries, including NSCLC (22,24,25). Fourthly, the grading of AEs was not performed in our study, however, the primary aim of ours was to assess the incidence of AEs; besides, the number of AEs was small and most of which were tolerable. Lastly, the feasibility of DEB-TACE in treating other types of lung cancer (such as small cell lung cancer) also needed to be investigated.

Conclusions

In conclusion, DEB-TACE with or without ¹²⁵I seed

implantation is effective and tolerable in treating advanced NSCLC patients, which provides a good option for advanced NSCLC treatment.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The current study protocol was approved by Ethics Committee of Lishui Central Hospital. Written informed consents were collected from all patients or their family members before enrollment.

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Supplementary

Table S1 Correlation of OS with clinical characteristics

Items	Mean OS (95% CI) (months)	P value
Age, years		0.828
<60	8.2 (4.7–11.8)	
≥60	14.2 (10.4–18.1)	
Gender		0.652
Female	10.5 (6.9–14.0)	
Male	14.8 (10.3–19.3)	
History of smoke		0.906
No	11.8 (8.1–15.5)	
Yes	14.0 (9.2–18.7)	
Tumor location		0.461
Left	15.4 (9.6–21.2)	
Right	11.6 (8.2–15.0)	
Tumor size, cm		0.023
≤5	19.0 (12.5–25.5)	
>5	10.4 (7.3–13.6)	
Histologic type		0.051
Squamous cell carcinoma	9.0 (5.6–12.4)	
Adenocarcinoma	17.4 (11.5–23.4)	
Mixed carcinoma	12.0 (0.7–23.4)	
Pathological differentiation		0.146
Moderate	–	
Poor	–	
ECOG score		0.094
0	7.7 (5.5–10.0)	
1/2	15.6 (11.4–19.7)	
Previous chemotherapy		0.224
No	16.3 (10.4–22.3)	
Yes	11.0 (6.3–15.6)	
Previous targeted therapy		0.453
No	15.2 (10.9–19.4)	
Yes	12.0 (10.9–13.2)	

Correlation was determined by Log-rank test. OS, overall survival; ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small cell lung cancer; ¹²⁵I, iodine-125.