The efficacy of drug-eluting beads bronchial arterial chemoembolization loaded with gemcitabine for treatment of non-small cell lung cancer

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Keywords
Bronchial arterial chemoembolization; CalliSpheres® beads; gemcitabine; non-small cell lung cancer.

Abstract

Background: Drug-eluting beads bronchial arterial chemoembolization (DEB-BACE) can embolize the tumor-feeding artery and also be loaded with antitumor drugs, which can be released slowly into the local tumor environment. The effect of DEB-BACE in patients with lung cancer remains unclear. We evaluated the efficacy and safety of DEB-BACE with gemcitabine-loaded CalliSpheres beads in patients with non-small cell lung cancer (NSCLC).

Methods: From May 2017 to December 2018, six patients with NSCLC who were ineligible or refused to receive standard treatment underwent DEB-BACE with gemcitabine-loaded CalliSpheres beads. The primary endpoint was the objective response rate (ORR). The secondary endpoints were progression-free survival (PFS), overall survival (OS), and quality of life. Safety was evaluated by the occurrences of adverse events and serious adverse events.

Results: All patients were treated with DEB-BACE loaded with gemcitabine (800 mg) using CalliSpheres beads. Five patients also received transarterial infusion with nedaplatin (80–100 mg). Of the six patients, five underwent a second session of DEB-BACE, with intervals of one month between the first and second session. The median follow-up time was 16.5 months (7.0–23.0 months). ORR and disease control rate were 50.0% and 100.0%, 50.0% and 83.3%, 50.0% and 66.7% respectively at 2, 4, and 6 months after DEB-BACE. One patient maintained a partial response and the other five had progressive disease, of whom two patients died and the other three remained alive receiving targeted therapy, radiotherapy, transarterial infusion or thermal ablation. The median PFS was 8.0 months (4–23 months), and the 6- and 12 month PFS rates were 66.7% and 16.7%, respectively. The median OS was 16.5 months (7–23 months), and the six and 12 month OS rates were 100.0% and 66.7%, respectively. Hemoptysis, cough and dyspnea disappeared after DEB-BACE in four patients. Global quality of life, physical and emotional functioning were all significantly improved at two months (P < 0.05). There were no serious adverse events.

Conclusions: DEB-BACE with gemcitabine-loaded CalliSpheres beads is a feasible and well-tolerated treatment for patients with NSCLC who are ineligible or refuse to receive standard treatment.

Introduction

Lung cancer is the leading cause of cancer-related deaths in men and women worldwide.1 Historically, it has been divided into small cell lung cancer and non-small cell lung cancer (NSCLC), of which NSCLC accounts for approximately 85.0% of all new lung cancer cases.2 The standard therapy for NSCLC includes surgery, chemotherapy, and radiotherapy. However, adverse events (AEs) such as radiation pneumonia, secondary bronchial stenosis, gastrointestinal reaction, myelosuppression, and
immune pneumonia may lower the patient’s quality of life and affect prognosis.\textsuperscript{5} Furthermore, patients with advanced age, heart disease, emphysema, or pulmonary interstitial fibrosis cannot tolerate the standard treatment, while patients with lesions adjacent to important organs such as the aorta and heart are at increased risks of surgery-related AEs. In addition, there is no effective treatment for patients with local tumor progression after initial chemotherapy and radiotherapy.\textsuperscript{4}

Bronchial arterial chemoembolization (BACE) is a palliative treatment option for lung cancer. Studies have shown that the bronchial artery is the main feeding artery for lung tumors.\textsuperscript{6} BACE can increase the local drug concentration and improve the curative effect via the ‘first pass effect’, with milder adverse reactions than systemic chemotherapy.\textsuperscript{5} Seki \textit{et al.} conducted a retrospective study of 16 patients with unresectable pulmonary metastases from renal cell carcinoma who were treated by BACE with superabsorbent polymer microspheres (SAP-MS), and found objective response rates (ORRs) of 38.8%, 44.9%, and 38.8% after 1, 3, and 6 months, respectively.\textsuperscript{6} Kennoki \textit{et al.} recently found a response rate and five-year survival rate of 28.6% and 49.5%, respectively, among 14 patients with a total of 29 unresectable pulmonary or mediastinal breast cancer metastases who underwent BACE using SAP-MS, after transarterial infusion of a combination of 2–4 types of antitumor drugs.\textsuperscript{7} Conventional transarterial chemoembolization (TACE) often uses emulsions of lipiodol with chemotherapeutic drugs, which do not reside long in the tumor tissues and thus reduce the local antitumor drug concentration, and may cause systemic AEs.\textsuperscript{6} Drug-eluting beads TACE (DEB-TACE) has recently been used as a novel drug delivery and embolization system with the ability to not only embolize the tumor-feeding artery, but also be loaded with chemotherapeutic drugs and release them slowly into the local environment.\textsuperscript{9,10} Several clinical studies showed that doxorubicin-loaded DEB-TACE resulted in higher local drug concentration and lower rate of systemic toxicity.\textsuperscript{10} CaliSphere\textsuperscript{®} beads (CB) is the first DEB product in China, and has just been introduced into clinical use in the last two years, mostly in patients with hepatocellular carcinoma.\textsuperscript{11,12} However, to the best of our knowledge, the clinical efficacy and safety of CB have not been assessed in patients with NSCLC. The current study therefore aims to evaluate the short-term clinical efficacy and safety of DEB-BACE using gemcitabine-loaded CB for the treatment of NSCLC.

\section*{Methods}

\section*{Ethical approval}

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of Beijing Hospital. Written informed consent was obtained from all patients.

\section*{Study design and population}

This was an retrospective observational study conducted in six patients with NSCLC who underwent DEB-BACE using gemcitabine-loaded CB between May 2017 and December 2018. The indications for DEB-BACE were as follows: age \(\leq 80\) years; NSCLC (pathological diagnosis); initial treatment; postoperative recurrence or local progression after standard treatment; ineligible or refused to receive surgery, chemotherapy, or radiotherapy due to heart disease, emphysema, pulmonary interstitial fibrosis, etc; Eastern Cooperative Oncology Group (ECOG) performance status \(\leq 2\); estimated survival time \(\geq 6\) months; and no other life-threatening diseases. The exclusion criteria were: extensive, uncontrolled extrapulmonary metastatic lesions such as liver, bone and brain metastasis; current or past other malignancy without curative treatment; white blood cell count <3.0 \(\times 10^9/\text{L}\), platelets <50.0 \(\times 10^9/\text{L}\), or hemoglobin <90 g/L; liver dysfunction (alanine aminotransferase and/or aspartate aminotransferase > twice the upper normal limit); renal dysfunction (serum creatinine >2.0 mg/L); coagulopathy (international normalized ratio >1.5) or known bleeding disorders, or undergoing anticoagulant treatment; active infection; pregnant or breastfeeding; and allergic to contrast agent.

\section*{Data collection}

Baseline data for all patients were collected from medical records and included demographic features (age, sex), past history of illness (hypertension, diabetes, coronary heart disease, stroke, etc.), clinical features (symptoms, signs), tumor features (lesion size, histopathology, staging), DEB-BACE treatment (cycless, antitumor drugs), routine blood indexes (white blood cell count, hemoglobin, platelets), kidney function indexes (blood creatinine, blood urea nitrogen), liver function indexes (alanine aminotransferase, aspartate aminotransferase), tumor markers (carcinoembryonic antigen [CEA]), imaging data (contrast-enhanced computed tomography [CT], bone scan or positron emission tomography-CT, if necessary), and previous treatments (surgery, chemotherapy, radiotherapy, targeted therapy, thermal ablation, etc.).

\section*{DEB-BACE procedures}

Percutaneous right femoral artery puncture with a modified Seldinger technique was performed under local anesthesia. A 5F-pigtail catheter (Terumo, Japan) was introduced through a 5-F vascular sheath to the thoracic aorta to obtain a thoracic aortogram. A 5F-Cobra catheter (Terumo, Japan) was then introduced and bronchial artery angiography was
performed to identify the tumor-feeding artery. If no definite tumor-feeding artery was identified, angiography of the internal thoracic artery and intercostal artery was performed to confirm the tumor-feeding artery. A 2.6-F microcatheter (Asahi, Japan) was then advanced super-selectively into the tumor-feeding artery through a coaxial hydrophilic guidewire. CalliSpheres beads (300–500 μm, Jiangsu Hengrui Medicine Co. Ltd., Jiangsu, China) were used as the carrier to load gemcitabine (800 mg). If the patient had not previously received platinum-based chemotherapy, nedaplatin (80–100 mg) was initially infused via a microcatheter. The CBs were first mixed with gemcitabine for 30 minutes at 23°C–28°C, with shaking for 30 minutes every five minutes. After loading, ioxidanol, as a nonionic contrast agent, was mixed with the CB-gemcitabine (at a volume ratio of 1:1). The CB-gemcitabine was then injected manually into the tumor-feeding artery, slowly and carefully, under fluoroscopic monitoring to avoid reflux into nontarget vessels. Subsequent angiography was performed to identify the extent of vascular occlusion. The angiographic endpoint included stasis or near-stasis of embolized vessel, or nonvisualization of parenchymal tumor blush. If one bottle of CB was insufficient, Embosphere microspheres (Merit, American) were used to complete the embolization. DEB-BACE was repeated in patients without local tumor progression or serious adverse events one month after the first session. Patients were reviewed by contrast-enhanced CT (head, chest and abdomen) every eight weeks after the second DEB-BACE, and bone scan or positron emission tomography-CT were performed if necessary.

**Primary endpoint**

The primary endpoint was the ORR, according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST), assessed by contrast-enhanced CT after DEB-BACE treatment. The OR was defined as CR plus PR, and disease control (DC) was defined as CR, PR, plus SD.

**Secondary endpoints**

The secondary endpoints were progression-free survival (PFS), overall survival (OS), and quality of life evaluated by QLQ-C30 questionnaire. The QLQ-C30 evaluates self-assessed health status and social, physical, and emotional functioning, based on 30 items, grouped into five functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning), three symptom scales (fatigue, nausea and vomiting, and pain), and six single questions (evaluating the severities of dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties).

**Safety evaluation**

AEs and serious AEs (SAEs) were recorded during the follow-up period, according to the Common Terminology Criteria for Adverse Events (CTCAE) (version 4.0).

**Follow-up**

Patients were followed up by outpatient visit or phone calls with the last follow-up date on 31 March 2019. Death was confirmed through registrations at the Department of Civil Affairs of China.

**Statistical analyses**

All patients were included in the analysis according to the intention-to-treat analysis. Data were expressed as the mean ± standard deviation, median (25th–75th quantiles), or count (%). Differences among groups were analyzed by Student’s t-test, χ² test, or Wilcoxon’s rank-sum test. Kaplan-Meier survival analysis was used to evaluate PFS and OS. A P-value <0.05 was considered significant. Data processing was performed using STATA software (version 12.0; StatCorp, College Station, TX, USA).

**Results**

**Patient characteristics**

The study included six men (median age 70.5 years, range 56–74 years). The patient characteristics are shown in Table 1. Two patients were diagnosed with adenocarcinoma and the other four with squamous cell carcinoma. Lymph node metastases were present in four patients, located in the mediastinum in three and in the ipsilateral hilum in one. Three patients presented with hemoptysis, one with cough and dyspnea, and two with no specific symptoms. Four patients refused standard therapies including surgery, chemotherapy, and radiotherapy due to cardiac insufficiency, coronary heart disease or emphysema, one had acute cerebral infarction within one month before the diagnosis of lung cancer, and one had lesion progression after six cycles of chemotherapy and one course of radiotherapy. Serum levels of CEA were elevated in one patient (10.8 ng/mL) and normal in the other five patients.

**Treatments**

Patients were all treated with gemcitabine-loaded DEB-BACE. Five patients also received transarterial infusion with nedaplatin. Of the six patients, five underwent a second session of DEB-BACE, with an interval of one month between the first and second session of DEB-BACE. One patient...
| Patient | Age | Gender | Symptom            | CEA (ng/mL) | TACE indication                                                                 | Lesion characteristics                                                                 | Treatment                                                                 | Follow-up treatment          | Follow-up (month) |
|---------|-----|--------|--------------------|-------------|----------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|----------------------------------------------------------------------------|-------------------------------|-------------------|
| 1       | 63  | Male   | No symptom         | 2.2         | Acute cerebral infarction occurs within one month                                 | Left upper lobe with atelectasis, squamous cell carcinoma, 2.7 cm x 2.3 cm, ipsilateral hilar lymph node metastasis, T2N1M0, stage IIIB | BACE: DEB-BACE loaded with gemcitabine (800 mg) using CB (300–500 μm)† Infusion: nedaplatin (100 mg)† | Transarterial infusion‡ | 14                |
| 2       | 56  | Male   | Hemoptysis         | 4.1         | Lesion progressed after six cycles of chemotherapy (albumin paclitaxel+ platinum) and one course of radiotherapy | Right upper lobe, squamous cell carcinoma, 2.6 cm x 2.1 cm, ipsilateral mediastinal lymph node metastasis, T1N2M0, stage IIA | BACE: DEB-BACE loaded with gemcitabine (800 mg) using CB (300–500 μm) | _                      | 7                 |
| 3       | 69  | Male   | Hemoptysis         | 2.6         | Refused chemotherapy and radiotherapy                                             | Right lower lobe, squamous cell carcinoma, 4.2 cm x 3.4 cm, T2bN0M0, stage IIA          | BACE: DEB-BACE loaded with gemcitabine (800 mg) using CB (300–500 μm)§ Infusion: nedaplatin (100 mg)§ | Targeted therapy            | 11                |
| 4       | 72  | Male   | Cough and dyspnea  | 4.6         | Refused chemotherapy and radiotherapy                                             | Right lower lobe, adenocarcinoma, 3.1 cm x 2.0 cm, contralateral mediastinal lymph node metastasis, T2N2M0, stage III | BACE: DEB-BACE loaded with gemcitabine (800 mg) using CB (300–500 μm)§ Infusion: nedaplatin (80 mg)§ | Targeted therapy            | 23                |
| 5       | 74  | Male   | No symptoms        | 10.8        | Refused chemotherapy and radiotherapy                                             | Right lower lobe, squamous cell carcinoma, 2.0 cm x 2.0 cm, ipsilateral mediastinal lymph node metastasis, T1N2M0, stage IIIA | BACE: DEB-BACE loaded with gemcitabine (800 mg) using CB (300–500 μm)§ Infusion: nedaplatin (100 mg)§ | Transarterial infusion and microwave ablation after PD | 19                |
| 6       | 73  | Male   | Hemoptysis         | 1.31        | Refused chemotherapy and radiotherapy                                             | Left lower lobe, adenocarcinoma, 2.3 cm x 2.1 cm, T1N0M0, stage IIA                    | BACE: DEB-BACE loaded with gemcitabine (800 mg) using CB (300–500 μm)§ Infusion: nedaplatin (100 mg)§ | Radiotherapy and targeted therapy after PD | 19                |

†Patient underwent a second treatment two months after the first treatment. ‡Patient underwent a second treatment one month after the first treatment. §Two months after the second BACE treatment.
refused the second session of DEB-BACE because of economic factors. Two months after the second session of DEB-BACE, one patient was treated with one session of transarterial infusion with gemcitabine 1000 mg and nedaplatin 100 mg, one patient was treated with anlotinib 12 mg/day, and one patient was treated with gefitinib 250 mg/day (Table 1).

### Primary endpoint

The ORRs and DC rates (DCRs) at 2, 4, and 6 months after DEB-BACE are shown in Table 2.

| Response | 2M (%) | 4M (%) | 6M (%) |
|----------|--------|--------|--------|
| CR       | 0(0)   | 0(0)   | 0(0)   |
| PR       | 3(50.0)| 3(50.0)| 3(50.0)|
| SD       | 3(50.0)| 2(33.3)| 1(16.7)|
| PD       | 0(0)   | 1(16.7)| 2(33.3)|
| ORR      | 3(50.0)| 3(50.0)| 3(50.0)|
| DCR      | 6(100.0)| 5(83.3)| 4(66.7)|

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

### Secondary endpoints

The median follow-up time was 16.5 months (7.0–23.0 months), and no patients were lost to follow-up. One patient was PR during the follow-up period and the other five had PD, including two patients died and three patients who remained alive receiving targeted therapy, radiotherapy, transarterial infusion or thermal ablation subsequently. The median PFS was 8.0 months (4–23 months), and the 6- and 12-month PFS rates were 66.7% and 16.7%, respectively. The median OS was 16.5 months (7–23 months), and the 6- and 12-month OS rates were 100.0% and 66.7%, respectively (Figs 2–3).

### Symptom improvement

Among the three patients with hemoptysis on admission, the hemoptysis disappeared after DEB-BACE. In one patient with cough and dyspnea before DEB-BACE, these symptoms were relieved one month after DEB-BACE. The tumor size decreased after treatment (Fig 1).

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**Table 2** Local tumor response according to mRECIST criteria (n = 6)

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**Figure 1** CT scan and left bronchial artery angiography of a 63-year-old patient with NSCLC diagnosed within one month after acute cerebral infarction. (a) PET-CT showing tumor (arrow) in left upper lobe with atelectasis, (b) CT performed two months after the second session showed reduction of tumor size (arrow) and remission of atelectasis, (c) Left bronchial artery angiograph showing the tumor with abnormal staining before embolization, (d) Left bronchial artery angiograph showing the abnormal tumor staining subsided after embolization.
Quality of life

The quality of life was significantly improved at two months after the first session compared with baseline, including improvements in global quality of life, physical functioning, and emotional functioning. Moreover, patients were significantly less affected by fatigue, nausea and vomiting, dyspnea, and insomnia after DEB-BACE (P < 0.05) (Table 3).

Safety

There were no SAEs, including catheter-related AEs, treatment-related deaths, nontarget embolization, or hematological and nonhematological toxicities of grade 3 or more. Only one patient (16.7%) had a fever of grade 1 and one patient (16.7%) had chest pain of grade 1, both of which were transient and well controlled with oral anti-inflammatory drugs.

Discussion

The results of the current study showed that DEB-BACE using CB had good short-term clinical efficacy in patients with NSCLC. Furthermore, the treatment could improve quality of life with no SAEs. DEB-BACE using gemcitabine-loaded CB thus appears to be a feasible and well-tolerated treatment option for patients with NSCLC who are ineligible or refuse to receive standard treatment because of poor physical condition or local tumor progression after standard therapy.

DEB-BACE is a novel drug delivery and embolization system for patients with lung cancer. Compared with standard treatments such as surgery, chemotherapy, radiotherapy, and targeted therapy, BACE can embolize the tumor-feeding artery, thereby blocking the blood and nutrient supply to the tumor. Meanwhile, slow release of an antitumor drug by the DEB-BACE method can increase the local tumor drug concentration and drug retention time, whilst reducing the systemic drug concentration.16 DEB-BACE can therefore provide a more constant antitumor drug concentration in local tumor tissues, resulting in more effective tumor necrosis, thereby alleviating clinical symptoms and improving the treatment response.17,18 Xiang et al. found that the ORRs were significantly elevated in patients with hepatocellular carcinoma receiving DEB-TACE at 1 month (68.0%), 3 months (100.0%), and 6 months (100.0%), while DEB-TACE was also an

Table 3 Quality of life assessment with QLQ-C30

| Functional | Pretreatment | Follow-up (two months) | P-value |
|------------|-------------|------------------------|---------|
| Global quality of life | 57.7(50.0–66.7) | 66.7(66.7–83.3) | 0.016 |
| Physical functioning | 81.8(53.3–86.7) | 86.7(86.7–93.3) | 0.016 |
| Role functioning | 66.7(66.7–100.0) | 100(66.7–100.0) | 0.269 |
| Emotional functioning | 83.3(66.7–83.3) | 91.7(66.7–100.0) | 0.031 |
| Cognitive functioning | 83.3(66.7–100.0) | 100(83.3–100.0) | 0.162 |
| Social functioning | 66.7(66.7–100.0) | 100(83.3–100.0) | 0.081 |

| Symptom | Pretreatment | Follow-up | P-value |
|---------|-------------|----------|---------|
| Fatigue | 44.4(33.3–55.6) | 11.1(11.1–33.3) | 0.008 |
| Nausea and vomiting | 0(0–16.7) | 0(0–0) | 0.023 |
| Pain | 16.7(0–16.7) | 0(0–16.7) | 0.093 |
| Dyspnea | 33.3(33.3–66.7) | 0(0–33.3) | 0.006 |
| Insomnia | 33.3(0–66.7) | 0(0–33.3) | 0.023 |
| Appetite loss | 33.3(0–66.7) | 33.3(30–33.3) | 0.206 |
| Constipation | 0(0–16.7) | 0(0–0) | 0.317 |
| Diarrhea | 0(0–16.7) | 0(0–0) | 0.317 |
| Financial difficulties | 0(0–33.3) | 0(0–16.7) | 0.902 |

Values given as median (25th–75th quantiles).
independent factor predicting higher ORR (odds ratio = 12.00, 95% confidence interval: 1.05–136.79).\textsuperscript{11} Wu et al. found that DEB-TACE markedly increased the DCR at 3 and 6 months after the treatment of hepatocellular carcinoma.\textsuperscript{10} However, few studies have evaluated the efficacy of DEB-BACE in patients with lung cancer, although Kennoki et al. found that three sessions of BACE with SAP-MS decreased the tumor size and alleviated the symptoms in a patient with large lung cystic adenocarcinoma\textsuperscript{19} refractory to standard treatments.\textsuperscript{19} Meanwhile, five sessions of BACE with SAP-MS also reduced tumor size, decreased CEA levels, and improved physical condition in a patient with refractory stage IV NSCLC.\textsuperscript{20} Seki et al. found that BACE with SAP-MS was associated with ORRs of 38.8%, 44.9%, and 38.8% after 1, 3, and 6 months, respectively, in patients with unresectable pulmonary metastases from renal cell carcinoma.\textsuperscript{2} Thus, DEB-BACE is a feasible treatment option for patients with lung cancer refractory to standard treatment. In the current study, four patients refused all standard therapies due to cardiac insufficiency, coronary heart disease or emphysema, one had acute cerebral infarction, and one had lesion progression after standard therapies. The DCRs were 100.0%, 83.3% and 66.7%, respectively at 2, 4, and 6 months after DEB-BACE in patients with NSCLC, suggesting that DEB-BACE was associated with good short-term disease control.

However, the ability of DEB-BACE to prolong PFS and OS remains controversial. Among 14 patients with unresectable pulmonary or mediastinal breast cancer metastases, two to 10 sessions of BACE using SAP-MS after transarterial infusion of a combination of two to four types of antitumor drugs (cisplatin plus fluorouracil, epirubicin plus mitomycin plus fluorouracil) was associated with a response rate of 28.6% (4 PD, 10 SD), a median OS time after the first BACE of 29 months, and a five-year survival rate of 49.5%.\textsuperscript{7} In a recent study of 62 patients with stage III-IV NSCLC, BACE combined with radioactive iodine-125 seed implantation was associated with a higher local control rate (90.0% vs. 59.3%), higher effective rate (74.0% vs. 40.6%), longer PFS time (12.6 vs. 8.2 months), and longer OS time (644 vs. 544 days) compared with BACE alone.\textsuperscript{21} Additionally, some patients with NSCLC are treated with radiofrequency ablation, and BACE combined with radiofrequency ablation was associated with a significantly higher short-term effective rate (93.0%), and 1, 2, and 3-year OS rates of 90.7%, 58.1%, and 20.9%, respectively.\textsuperscript{2} However, to the best of our knowledge, there have been no studies of CB in patients with NSCLC. DEB-TACE using CB could significantly increase the median time to disease progression in patients with hepatocellular carcinoma after five-years of follow-up (11.0 vs. 16.0 months),\textsuperscript{23} but several studies found that DEB-TACE provided no survival benefit over conventional TACE in hepatocellular carcinoma.\textsuperscript{24} In the current study, the median PFS and OS after DEB-BACE were 8.0 and 16.5 months, respectively. The 6- and 12-month PFS rates were 66.7% and 16.7%, and the 6- and 12-month OS rates were 100.0% and 66.7%, respectively. More studies are needed to confirm the effect of DEB-BACE on PFS and OS in patients with NSCLC.

Meanwhile, the PFS and OS in case 2 (4 and 7 months) and case 3 (6 and 11 months), who both died, were shorter. Case 2 was treated with several cycles of standard therapies before DEB-BACE and case 3 had larger tumor size (4.2 cm x 3.4 cm), suggesting that larger lesion size and more previous treatments such as chemotherapy and radiotherapy may predict poor therapeutic response to DEB-BACE. Moreover, all the other four cases alive received two sessions of DEB-BACE, and more sessions of treatment may predict better disease control. More therapeutic options such as transarterial infusion, targeted therapy and thermal ablation may further improve the prognosis. Chen et al. found that BACE combined with radioactive iodine-125 implantation was associated with a longer PFS time.\textsuperscript{21} Yang et al. showed that combined with radiofrequency ablation, BACE prolong the OS time.\textsuperscript{22} In the current study, case 5 was treated with microwave ablation and transarterial infusion and case 6 administered radiotherapy and targeted therapy after PD. Therefore, after the DEB-BACE or PD, patients can also be treated with other antitumor methods such as targeted therapy, transarterial infusion, thermal ablation and radioactive seed implantation.

We assessed quality of life before and after DEB-BACE and revealed that global quality of life, physical functioning, and emotional functioning were significantly improved, and patients were also significantly less affected by fatigue, nausea and vomiting, dyspnea, and insomnia at two months after treatment. This could be because BACE may also decrease the rate of systemic AEs whilst embolizing the vessel to achieve tumor ischemia. Kennoki et al. found that three sessions of BACE with SAP-MS lowered the ECOG-PS score from 3 to 0 in a patient with a large lung cystic adenocarcinoma.\textsuperscript{19} Furthermore, several studies have confirmed that BACE with SAP-MS did not increase the rate of SAEs.\textsuperscript{2,21,22} BACE combined with SAP-MS\textsuperscript{21,22} or DEB\textsuperscript{23} was therefore associated with a better performance status. In line with previous studies, we found that DEB-BACE was not associated with any SAEs, and only one patient each (16.7%) developed fever and chest pain (grade 1), both of which were transient and well controlled with oral anti-inflammatory drugs. DEB-BACE using gemcitabine-loaded CBs thus appears to be a safe treatment option for patients with lung cancer who are ineligible or refuse to receive standard treatment.
We acknowledge that this study had several limitations. It was a retrospective observational study with a small sample size, resulting in low statistical power. However, DEB-BACE using CB is a new therapeutic option for lung cancer, and the number of patients receiving this treatment is therefore very limited. All the patients enrolled in this study were from a single hospital, which could cause selection bias. Finally, the baseline features differed among the patients, which could result in compounding factors. More studies are therefore required to verify these findings.

In short, DEB-BACE with gemcitabine-loaded CalliSpheres® beads is a feasible and well-tolerated treatment option for patients with NSCLC who are ineligible or refuse to receive standard treatment. However, more studies are warranted to confirm these findings.

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Disclosure

There are no conflicts of interest with respect to the authorship, research, and publication of this paper.

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