Original Article

Standard treatment-refractory/ineligible small cell lung cancer treated with drug-eluting beads bronchial arterial chemoembolization: a retrospective cohort study

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Background: Patients with small cell lung cancer (SCLC) are prone to developing refractoriness to standard treatment, and some patients are ineligible for systemic therapy owing to comorbidities or poor pulmonary function. The prognosis of patient with standard treatment-refractory/ineligible (STRI)-SCLC remains poor. This retrospective cohort study aimed to investigate the efficacy and safety of drug-eluting beads bronchial arterial chemoembolization (DEB-BACE) for the treatment of SRTI-SCLC and to identify the predictors of overall survival (OS).

Methods: A total of 18 patients with STRI-SCLC who received DEB-BACE were included. Treatment response, adverse events, progression-free survival (PFS), and OS were evaluated. Further molecular targeted therapy or immunotherapy was administered as a second-line treatment or beyond for those patients who had not received these regimens previously. Univariate and multivariate Cox analyses were used to explore the predictors of OS for STRI-SCLC treated with DEB-BACE.

Results: The overall disease control rate at 3 months after DEB-BACE was 77.8% (14/18); of these patients who experienced disease control, partial response and stable disease were achieved in 2 patients (11.1%) and 12 patients (66.7%), respectively. There were 7 patients (38.9%) who received anlotinib after DEB-BACE. No severe DEB-BACE-related or anlotinib-related adverse events were observed. The median PFS was 5.0 months; the 6- and 12-month PFS rates were 55.6% (10/18) and 11.1% (2/18), respectively. The median OS was 9.0 months; the 6- and 12-month OS rates were 77.8% (14/18) and 33.3% (6/18), respectively. Postoperative anlotinib [hazard ratio: 0.302; 95% confidence interval (CI): 0.098–0.930; P=0.037] was identified as the predictor of OS in patients with STRI-SCLC treated with DEB-BACE.

Conclusions: DEB-BACE is an effective and well-tolerated approach for patients with STRI-SCLC. Postoperative anlotinib is the predictor of OS and may indicate a better prognosis for patients with STRI-SCLC.

Keywords: Small cell lung cancer (SCLC); drug-eluting beads (DEBs); chemoembolization; anlotinib; survival

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Introduction

Primary lung cancer is a neoplasm with a high cancer incidence and mortality rate worldwide (1). In 2021, more than 810,000 new cases and 710,000 lung cancer deaths were estimated in China, where small cell lung cancer (SCLC) accounts for 15% of the new diagnoses, and three-quarters of the patients are accompanied by distant metastases when diagnosed (2). The criteria from the Veterans Administration Lung Study Group (VALSG) classifies SCLC as limited stage (LS) or extensive stage (ES) according to whether or not a tumor is confined to a single radiotherapy field (3). The standard treatments for SCLC include chemoradiotherapy, immunotherapy, and surgery, but the prognosis for patients remains poor, with a median overall survival (OS) of 13 months (4). It was reported that the median OS for LS-SCLC is 15–20 months, while that for ES-SCLC is 10–12 months (5,6). Although about 60% of patients with SCLC respond to first-line chemotherapy, almost all patients eventually develop refractoriness, with some eventually benefitting from second-line therapy or/and programmed cell death-ligand 1 (PD-L1) blockade (7,8). Moreover, it was reported that 30–50% of patients with lung cancer present with poor performance status and cannot tolerate systemic therapy owing to its toxicity (9). The treatment options for patients with standard treatment-refractory/ineligible (STRI) SCLC remain limited.

Bronchial arterial chemoembolization (BACE) is being increasingly applied in lung cancer treatment. BACE can prolong the actuation duration of chemotherapeutic drugs, elevate local drug concentration, and induce tumor necrosis via the embolization of tumor-feeding arteries (10). As a novel polyvinyl alcohol-based microsphere, drug-eluting beads (DEBs) bind drug molecules through reversible electrochemical bonds, which can deliver chemotherapeutic drugs continuously and embolize tumor-feeding arteries permanently, conferring advantages of higher local drug concentration and a lower rate of systemic toxicity (11). Since 2019, authors have investigated the feasibility and effectiveness of DEB-BACE in non-small cell lung cancer (NSCLC) (12-15). In 2021, one study included 23 patients with advanced lung cancer patients, including 2 patients with SCLC, treated with DEB-BACEs who experienced a median OS of 15.6 months (16). Lin *et al.* (17) analyzed 11 refractory patients with LS-SCLC treated with DEB-BACE but without sequential systemic therapy and reported promising results of 5.1 months for median progression-free survival (PFS) and 9.0 months for the median OS. Furthermore, 2 studies attempted DEB-BACE combined with molecular targeted therapy (such as anlotinib) or immunotherapy in patients with NSCLC and found that these regimens were promising approaches (18,19). However, to our knowledge, few studies have examined DEB-BACE for the treatment of STRI-SCLC. Therefore, a retrospective cohort study was conducted to investigate the efficacy and safety of DEB-BACE for the treatment of SRTI-SCLC, and to identify the predictors of OS. We present the following article in accordance with the STROBE reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-22-530/rc).

Methods

Patient criteria

All patients with STRI-SCLC who underwent DEB-BACE between April 2019 and April 2021 in Beijing Hospital, National Center of Gerontology, Institute of Geriatric Medicine, Chinese Academy of Medical Sciences were included and selected in this retrospective cohort study. The study protocol was conducted as per the protocols of the Declaration of Helsinki (as revised in 2013). The institutional review board of Beijing Hospital, National Center of Gerontology, Institute of Geriatric Medicine, Chinese Academy of Medical Sciences approved this study. Informed consent was waived due to the retrospective nature of the study design. Patients were included if they (I) were aged no less than 18 years; (II) had histopathological subtypes of SCLC that were diagnosed before DEB-BACE; (III) were ineligible for or were refractory to standard treatments, including chemoradiotherapy, immunotherapy, surgery, or molecular targeted therapy; (IV) had an Eastern Cooperation Oncology Group (ECOG) score of 0–2 (20); and (V) intended to undergo DEB-BACE. Patients were excluded if (I) sequential interventional therapies were performed, such as those including ablation or implantation of radioactive seeds; (II) they had incomplete data; (III) their estimated OS was less than 3 months; (IV) their follow-

up time was less than 12 months; or (V) they were lost to follow-up.

Patients who had poor performance status owing to severe comorbidities (cardiovascular, pulmonary, hepatic, or kidney diseases, etc.) were considered intolerant to systemic therapy, which was determined by the multidisciplinary treatment team. All patients underwent positron emission tomography or computed tomography (CT) scans before undergoing DEB-BACE. The tumor stage was identified via the clinical tumor-node-metastasis staging system (eighth edition) and the VALSG 2-method staging system (3,21). Laboratory examinations occurring fewer than 4 days before DEB-BACE were also collected.

DEB-BACE procedure

DEB-BACE procedures were performed under the guidance of digital subtraction angiography (15). After Seldinger's technique was applied via the femoral artery approach, a 5-French pigtail catheter (PIG Impress; Merit Medical Systems, Inc., Jordan, UT, USA) was used to detect the origins of bronchial arteries. Then, a 5-French cobra (CB 1 Impress; Merit Medical Systems) or left gastric catheter (Radifocus; Terumo Corporation, Tokyo, Japan) was used to evaluate and select the tumor-feeding arteries, including the non-bronchial systemic arteries. Super-selective catheterization with a 1.98-French microcatheter (Masters PARKWAY SOFT; Asahi Intec Co., Nagoya, Japan) was initially performed and followed by bronchial artery infusion (BAI) chemotherapy via the microcatheter, with the chemotherapeutic regimens of etoposide (100–200 mg; Qilu Pharmaceutical Co., Jinan, China) or/and nedaplatin (40–100 mg; Lubei, Qilu Pharmaceutical Co.) for patients who had not received systemic chemotherapy of etoposide and platinum (EP), and irinotecan (40–80 mg; Aili, Jiangsu Hengrui Medical Co., Lianyungang, China) for patients who were refractory to EP. Sequentially, the 300–500 μm CalliSpheres microspheres (Jiangsu Hengrui Medical Co.) were used for chemoembolization. The loaded drugs were irinotecan (80 mg; Hengrui Medical Co.) for patients who developed refractoriness to EP or pirarubicin (30 mg; Adriamycin, Shenzhen Main Luck Pharmaceutical Inc., Shenzhen, China) for patients who had not received EP or who developed refractoriness to second-line systemic chemotherapy. Before chemoembolization, the CalliSpheres microspheres were mixed with the drugs at a temperature of 23–28 ℃ for 30 minutes and shaken every 5 minutes, and then the iodixanol (100 mL: 65.2 g/32 g iodine; Hengrui Medical Co.) was added at a 1:1 ratio. The chemoembolization was performed slowly and carefully in tumor-feeding arteries to avoid ectopic embolization and was terminated when the absence of additional tumor staining or stasis/near stasis of tumor-feeding arteries was observed. The repeated DEB-BACE/BAI was performed on demand at least 1 month after the first procedure, especially for the patients who showed a limited response to the initial procedure. Of these patients, DEB-BACE was performed for those with abundant tumor staining, while BAI alone was performed for those without abundant tumor staining.

Further management and assessments

Radiotherapy was performed for patients with brain or bone metastases. For patients who had received EP and developed refractoriness to DEB-BACE, second-line systemic chemotherapy was considered, and concomitant radiotherapy was performed as demanded. For patients who had not received molecular targeted therapy or immunotherapy, the anlotinib (Fukewei; Chia-Tai Tianqing Pharmaceutical Co., Nanjing, China) or durvalumab (IMFINZI; AstraZeneca, Cambridge, UK) was considered as a second-line treatment or beyond. For patients who had received anlotinib before DEB-BACE and showed refractoriness, continuing with anlotinib was waived after DEB-BACE. The detailed protocols were as follows: (I) anlotinib was administered orally at least 2 weeks after DEB-BACE and was continued until the occurrence of disease progression or intolerant adverse events (AEs), with an initial dose of 12 mg/d on a 1-week-on and 1-week-off treatment schedule and essential dose adjustments if necessary; and (II) durvalumab was administered intravenously and maintained every 4 weeks with the dose of 1,000 mg until the occurrence of disease progression or intolerant AEs.

DEB-BACE-related AEs were analyzed as per the criteria from the Society of Interventional Radiology (22). AEs of anlotinib and immunotherapy were graded on the basis of the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0 (23). As described previously (15), CT scans were performed every 1 to 3 months. Treatment response was classified as a complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) according to Response Evaluation Criteria in Solid Tumors version 1.1 (24). The disease control rate (DCR) was defined as CR, PR, or SD. OS was the interval from the first DEB-BACE administration to death or the last follow-up (April

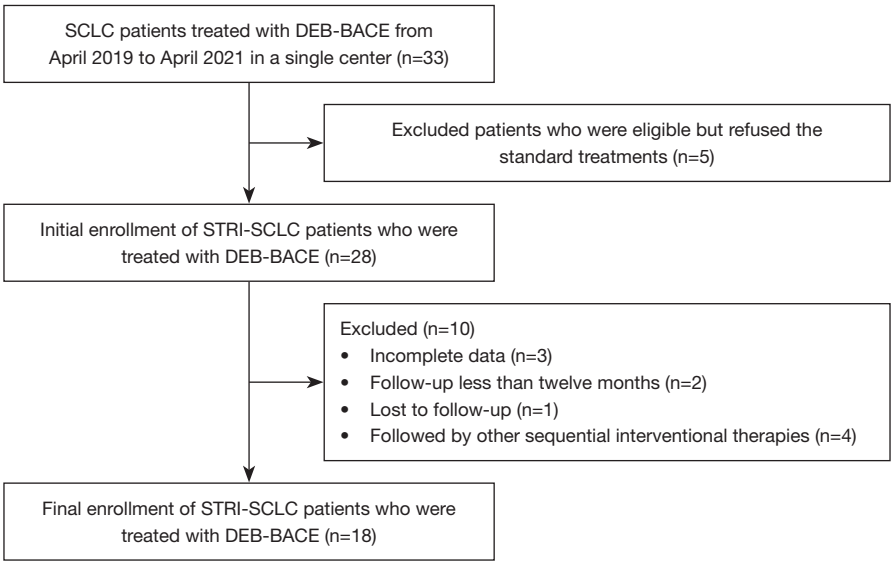

Figure 1 Patient selection flowchart. STRI-SCLC, standard treatment-refractory/ineligible small cell lung cancer; DEB-BACE, drug-eluting beads bronchial artery chemoembolization.

30, 2022). PFS was the interval from the first DEB-BACE administration to the time of objective progression, including local progression or/and distant metastases. For patients who did not die or progress, the censoring date was defined as the last clinical assessment date.

Statistical analysis

Statistical analyses were performed using SPSS 25.0 for Windows (IBM Corp., Armonk, NY, USA). Categorical variables are described as frequencies and percentages, and continuous variables are described as the mean ± standard deviation. The Kaplan-Meier method was used to explore the PFS and OS for patients STRI-SCLC treated with DEB-BACE. The predictors of OS were evaluated using univariate and multivariate Cox analyses. The detailed procedures were as follows: (I) variables with P values <0.05 in the univariate analyses were entered as candidate variables into stepwise Cox proportional hazards analyses, and (II) the variables with P values <0.05 in the multivariate analyses were identified as the predictors for OS.

Results

Patient characteristics

A total of 18 patients with SCLC were included (*Figure 1*). There were 11 patients (61.1%) who developed refractoriness to standard treatment, including 2 patients (11.1%) with EP, 2 patients (11.1%) with concurrent chemoradiotherapy, 2 patients (11.1%) with EP plus PD-L1 blockade, and 5 patients (27.8%) with EP and second-line therapy of anlotinib or/and programmed cell death-1 (PD-1) blockade. There were 7 patients (38.9%) who were ineligible for standard treatment owing to cardiovascular or/and pulmonary diseases and poor performance status. Detailed demographic characteristics are presented in *Table 1*. For further treatment, radiotherapy was performed for 5 patients (27.8%) with brain or bone metastases, second-line chemotherapy was performed for 4 patients (22.2%) who developed refractoriness to DEB-BACE (including 2 patients who underwent concurrent chemoradiotherapy), and anlotinib was administered as a second-line treatment or beyond for 7 patients (38.9%).

Adverse events

There were 5 patients (27.8%) who developed DEB-BACE-related AEs. Among these, 2 patients (11.1%) with moderate AEs received a pharmacological intervention. Detailed DEB-BACE-related AEs are presented in *Table 2*. The primary anlotinib-related AEs consisted of fatigue, hand-foot syndrome, and hypertension. There were 3 patients (42.9%, 3/7) who presented with moderate AEs but for whom the dose of anlotinib was not adjusted. Among

Table 1 Clinical characteristics of patients with STRI-SCLC treated with DEB-BACE

Variables	SCLC patients (n=18)
Age (years)	68.4±8.6
Gender	
Male	16 (88.9)
Female	2 (11.1)
ECOG score	
1	9 (50.0)
2	9 (50.0)
Comorbidity	
Hypertension	11 (61.1)
Cardiovascular diseases	5 (27.8)
TNM stage	
III	8 (44.4)
IV	10 (55.6)
VALSG stage	
LS	10 (55.6)
ES	8 (44.4)
Causes of undergoing DEB-BACE	
Ineligible for standard treatment	7 (38.9)
Refractory to standard treatment	11 (61.1)
Treatment history	
Previous chemotherapy	11 (61.1)
Previous radiotherapy	7 (38.9)
Previous anlotinib	4 (22.2)
Previous immunotherapy	5 (27.8)
Radiological features	
Tumor diameter (cm)	6.5±3.1
Location	
Lower or middle lobe	6 (33.3)
Upper lobe	12 (66.7)
Emphysema	6 (33.3)
Extrapulmonary metastases	7 (38.9)
Malignant pleural effusion	7 (38.9)
Number of metastases	
<2	14 (77.8)
≥2	4 (22.2)
Tumor number	
1	14 (77.8)
≥2	4 (22.2)
Laboratory examinations	
WBC ($\times10^9$/L)	5.0±1.5
Hb (g/L)	108.9±32.1
PLT ($\times10^9$/L)	241.6±99.7
PT (s)	11.4±0.9
NSE (ng/mL)	68.6±92.4
Postoperative treatments	
Chemotherapy	4 (22.2)
Radiotherapy	7 (38.9)
Anlotinib	7 (38.9)
Immunotherapy	5 (27.8)
DEB-BACE related factors	
Diameter of microsphere (μm)	
300–500	18 (100.0)
Loaded drug	
Irinotecan	10 (55.6)
Pirarubicin	8 (44.4)
BAI drugs	
Nedaplatin	11 (61.1)
Etoposide	8 (44.4)
Irinotecan	4 (22.2)
Embolized arteries	
BA	15 (83.3)
BA + NBSA	3 (16.7)
Number	1.2±0.4
DEB-BACE/BAI cycles	2.0±1.2

Frequencies and percentages are reported for categorical variables, and the mean ± standard deviation is reported for continuous variables. STRI-SCLC, standard treatment-refractory/ineligible small cell lung cancer; SCLC, small cell lung cancer; ECOG, Eastern Cooperative Oncology Group; TNM, tumor-node-metastasis; VALSG, Veterans Administration Lung Study Group; LS, limited stage; ES, extensive stage; DEB-BACE, drug-eluting beads bronchial artery chemoembolization; WBC, white blood cell; Hb, hemoglobin; PLT, platelet; PT, prothrombin time; NSE, neuron-specific enolase; BAI, bronchial artery infusion chemotherapy; BA, bronchial artery; NBSA, non-bronchial systemic artery.

Table 2 Details of DEB-BACE-related complications in patients with STRI-SCLC

Variables	SCLC patients (n=18), n (%)
Mild adverse event	
Chest congestion or pain	3 (16.7)
Fever	2 (11.1)
Myelosuppression	3 (16.7)
Moderate adverse event	
Chest congestion or pain	2 (11.1)
Fever	2 (11.1)
Severe adverse event	–

DEB-BACE, drug-eluting beads bronchial artery chemoembolization; STRI-SCLC, standard treatment-refractory/ineligible small cell lung cancer.

Table 3 Clinical outcomes of patients with SRTI-SCLC treated with DEB-BACE

Variables	SCLC patients (n=18)
Response, n (%)	
CR	–
PR	2 (11.1)
SD	12 (66.7)
PD	4 (22.2)
DCR (%)	77.8 (14/18)
PFS status, n (%)	
Progression-free	2 (11.1)
Progression or death	16 (88.9)
OS status, n (%)	
Survival	3 (16.7)
Death	15 (83.3)
Median PFS (months), mean ± SD	5.0±7.9
Median OS (months), mean ± SD	9.5±8.8
6-month PFS rate (%)	55.6 (10/18)
12-month PFS rate (%)	11.1 (2/18)
6-month OS rate (%)	77.8 (14/18)
12-month OS rate (%)	33.3 (6/18)

STRI-SCLC, standard treatment-refractory/ineligible small cell lung cancer; DEB-BACE, drug-eluting beads bronchial artery chemoembolization; CR, complete response; PR, partial response; SD, stable disease; PD, progression disease; DCR, disease control rate; PFS, progression-free survival; OS, overall survival.

these, the grade 1 AEs of fatigue and hypertension were observed in 1 patient (14.3%, 1/7), and the grade 2 AEs of hand-foot syndrome were observed in 2 patients (28.6%, 2/7). Neither severe AEs of DEB-BACE nor anlotinib were found. In terms of durvalumab-related AEs, only 1 patient (14.3%, 1/7) developed the grade 3 AE of pneumonia, which led to the discontinuation of immunotherapy.

Clinical outcomes

Detailed clinical outcomes are presented in *Table 3*. In a mean follow-up of 20.5±9.2 months, the median PFS and OS were 5.0 (*Figure 2A*) and 9.5 (*Figure 2B*) months, respectively. The 6- and 12-month PFS rates were 55.6% (10/18) and 11.1% (2/18), respectively, while the 6- and 12-month OS rates were 77.8% (14/18) and 33.3% (6/18), respectively. There were 2 patients (11.1%) who achieved PR at 3 months after DEB-BACE (*Figure 3A-3H*). The overall DCR was 77.8% (14/18) at 3 months after DEB-BACE. The patients who received postoperative anlotinib as a second-line treatment or beyond had a median PFS and OS of 9.0 and 14.0 months, respectively.

Predictors of OS for patients with STRI-SCLC treated with DEB-BACE

Detailed results of univariate and multivariate analyses are presented in *Table 4*. Postoperative anlotinib (hazard ratio: 0.302; 95% confidence interval (CI): 0.098–0.930; P=0.037) was identified as the predictor of OS in patients with STRI-SCLC treated with DEB-BACE. The estimated median OS was 15.0 months for patients with postoperative anlotinib, compared with 7.0 months for those patients without it (*Figure 4*).

Discussion

SCLC originates from the precursors of neuroendocrine cells and is characterized by rapid growth, high sensitivity to chemotherapy, and easily developing refractoriness (25). In a systemic review, Johal *et al.* (26) found that the therapeutic patterns and prognosis of SCLC has remained unchanged over the past two decades, which may be attributable to its rapid doubling time, genomic instability, and increased vascularity (27). For LS-SCLC, the standard treatment is chemotherapy with concurrent radiotherapy, which is preferred to EP, while surgery is also considered for early-stage patients (28). For ES-SCLC, the combination of EP

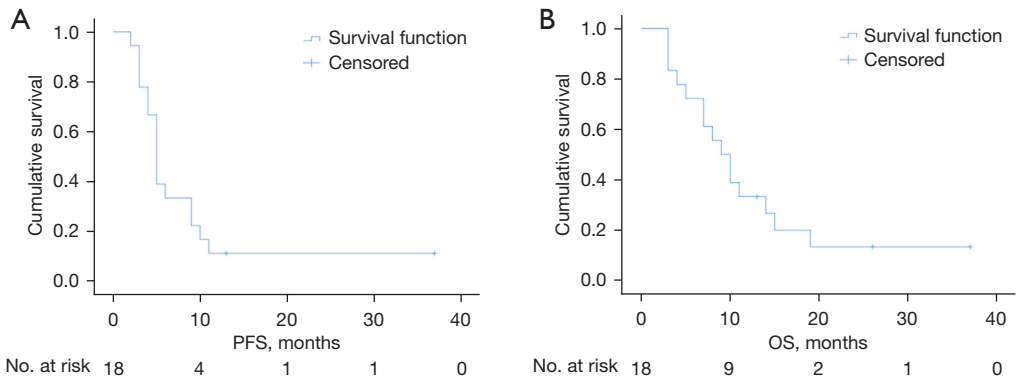

Figure 2 Kaplan-Meier curves showing the PFS and OS of STRI-SCLC treated with DEB-BACE. (A) The median PFS was 5.0 months. (B) The median OS was 9.5 months. PFS, progression-free survival; OS, Overall survival; STRI-SCLC, standard treatment-refractory/ineligible small cell lung cancer; DEB-BACE, drug-eluting beads bronchial artery chemoembolization.

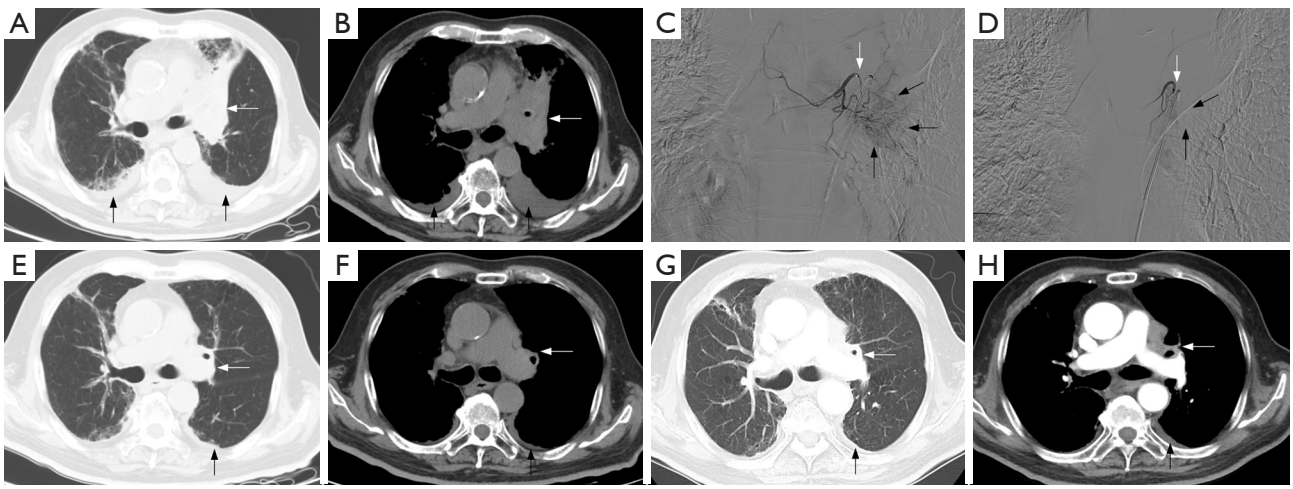

Figure 3 A typical case of STRI-SCLC treated with DEB-BACE. (A,B) An SCLC patient with a primary tumor stage of IIIB and LS who has received first-line concurrent chemoradiotherapy. Despite prophylactic cranial irradiation being performed, the occurrence of brain and liver metastases confirms the progression of the tumor stage to ES. The second-line combination therapy of anlotinib plus PD-1 blockade did not achieve satisfactory efficacy. The CT scans revealed the presence of an enlarged central SCLC (white arrow) and bilateral pleural effusion (black arrow). (C) DEB-BACE was performed, with the super-selective catheterization being performed via a microcatheter (white arrow). Sequential angiography revealed that the left bronchial artery was the tumor-feeding artery and showed the presence of abundant tumor staining (black arrow). (D) The chemoembolization was performed by 300–500 μm CalliSpheres microspheres loaded with irinotecan (80 mg) via the microcatheter (white arrow). The angiography presented with the disappearance of tumor staining (black arrow). There were 2 cycles of DEB-BACE performed for this patient in total. (E,F) The CT reexamination at 3 months after DEB-BACE showed a significant reduction of tumor size (white arrow), pleural effusion (black arrow), and a PR in response. (G,H) The 6-month contrast-enhanced CT scans revealed a continued decrease in the tumor (white arrow) and pleural effusion (black arrow). STRI-SCLC, standard treatment-refractory/ineligible small cell lung cancer; DEB-BACE, drug-eluting beads bronchial artery chemoembolization; LS, limited stage; ES, extensive stage; PD-1, programmed cell death-1; CT, computed tomography; PR, partial response.

Table 4 Univariate and multivariate Cox proportional hazards analyses for OS in STRI-SCLC treated with DEB-BACE

Variables	Univariate analysis		Multivariate analysis	
	Median OS (95% CI)	P value*	HR (95% CI)	P value**
Age (years)		0.325		–
<65	8.0 (0.000–20.002)		–	
≥65	9.0 (5.605–12.395)		–	
ECOG score		0.218		–
1	14.0 (4.239–23.761)		–	
2	7.0 (4.078–9.922)		–	
TNM stage		0.892		–
III	8.0 (5.228–10.772)		–	
IV	10.0 (0.703–19.297)		–	
VALSG stage		0.231		–
LS	9.0 (5.901–12.099)		–	
ES	5.0 (0.000–13.316)		–	
Tumor diameter (cm)		0.367		–
<6	9.0 (5.763–12.237)		–	
≥6	10.0 (0.000–22.831)		–	
Location		0.492		–
Lower or middle lobe	10.0 (1.598–18.402)		–	
Upper lobe	8.0 (1.210–14.790)		–	
Loaded drug		0.856		–
Irinotecan	9.0 (1.252–16.748)		–	
Pirarubicin	8.0 (3.842–12.158)		–	
DEB-BACE/BAI cycles		0.879		–
1	9.0 (1.799–16.201)		–	
≥2	8.0 (2.908–13.092)		–	
Postoperative radiotherapy		0.610		–
Yes	10.0 (4.868–15.132)		–	
No	9.0 (2.526–15.474)		–	
Postoperative anlotinib		0.025		0.037
Yes	15.0 (10.655–19.345)		0.302 (0.098–0.930)	
No	7.0 (3.873–10.127)		1.000	
Postoperative immunotherapy		0.612		–
Yes	10.0 (6.562–13.438)		–	
No	9.0 (4.706–13.294)		–	

*, log-rank test was used; **, Cox proportional hazards regression analysis was used. OS, overall survival; STRI-SCLC, standard treatment–refractory/ineligible small cell lung cancer; DEB-BACE, drug-eluting beads bronchial artery chemoembolization; ECOG, Eastern Cooperative Oncology Group; TNM, tumor-nodes-metastasis; VALSG, Veterans Administration Lung Study Group; LS, limited stage; ES, extensive stage; BAI, bronchial artery infusion chemotherapy; CI, confidence interval; HR, hazard ratio.

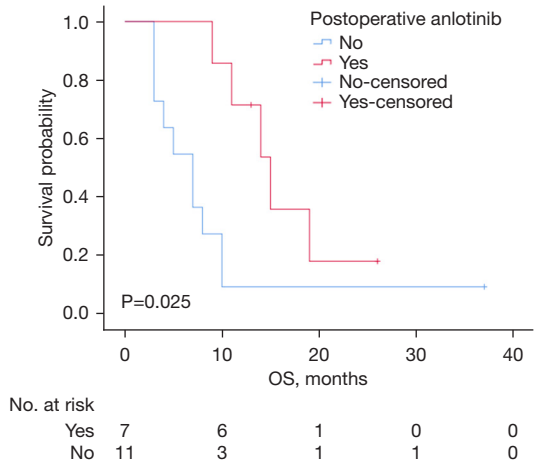

Figure 4 The estimated median OS was 15.0 months for patients with postoperative anlotinib compared with 7.0 months for those patients without postoperative anlotinib. OS, overall survival; STRI-SCLC, standard treatment-refractory/ineligible small cell lung cancer; DEB-BACE, drug-eluting beads bronchial artery chemoembolization.

and PD-L1 blockade (durvalumab or atezolizumab) was upgraded to the first-line treatment despite a reported median OS increase of about only 2 months, which was based on the results from the CASPIAN and IMpower133 trials (5,29). The prognosis for patients who are refractory to first-line chemotherapy remain exceedingly poor, with a median OS of 2 to 3 months reported for patients who do not receive further treatment and that of less than 6 months for patients who do receive second-line therapy (30). Topotecan is considered the standard second-line treatment, with response rates of 25% for platinum-sensitive patients and less than 10% for platinum-refractory patients (31). For the treatment beyond the second line, PD-1 blockade (nivolumab or pembrolizumab) has emerged as an appealing therapeutic option, with a response rate of 11.9% and a median duration of response of 17.9 months achieved by nivolumab monotherapy (32). Despite these results, the high incidence of AEs in SCLC treated with systemic therapy should not be neglected. In a systemic review, Amarasena *et al.* (33) found platinum-based chemotherapy to be significantly associated with high incidence rates of AEs for patients with SCLC, with AE's notably including nausea and vomiting (65.2%), leukopenia (42.1%), and thrombocytopenia (53.9%). For treatment-naïve patients with ES-SCLC, the combination therapy of PD-1/PD-L1 blockade and chemotherapy was found to result in a significantly higher incidence of ≥ grade 3 AEs than was chemotherapy alone (34). Moreover, 30–50% of lung cancer patients are ineligible for systemic chemotherapy owing to comorbidities or poor pulmonary function (9). It seems that an effective and well-tolerated approach would be highly meaningful for the treatment of patients with STRI-SCLC.

The foundation for BACE/BAI in SCLC stems from a report stating that 90% to 95% of SCLC arises from lobar or main bronchi and is predominantly fed by the bronchial artery (35). The chemotherapeutic drugs can be infused directly via the tumor-feeding arteries during BAI, providing higher local drug concentration, improved antitumor efficacy, and a lower incidence of systemic AEs than found in systemic chemotherapy (36). Owing to the embolization-induced tumor ischemia or necrosis and the drugs entering the tumor again through blood circulation, BACE administration can achieve both local and systemic chemotherapy to improve the curative effect (37). Uchiyama *et al.* (38) performed BAI for 40 patients with lung cancer and found that PR was observed in 8 of 9 (88.9%) SCLC patients. Further, Xiaobing *et al.* (39) attempted to explore the efficacy and safety of BACE in 187 advanced lung cancer patients with hemoptysis, including 21 patients with SCLC, and reported favorable results of 86.6% for the hemoptysis control rate and 12.0 months for the median OS.

Compared with conventional chemoembolization, DEB microspheres can release the loaded drugs more precisely and sustainably, further improving the local drug concentration and inducing tumor ischemia or necrosis while reducing systemic toxicity (11). In 2019, Bie *et al.* (12) were the first to attempt gemcitabine-loaded DEB-BACE in 6 patients with lung cancer and found favorable results of 8.0 months for median PFS and 16.5 months for median OS, despite a limited sample size. Several studies have reported a median PFS of 6.3–11.0 months and a median OS of 8.0–16.5 months in advanced NSCLC treated with DEB-BACE (12-15). In 2020, Zeng *et al.* (16) achieved a response rate of 78.3% and median OS of 15.6 months for 23 patients with lung cancer—including 2 patients with SCLC—treated with DEB-BACE, which indicates a potential efficacy for these patients. Moreover, Lin *et al.* (17) reported a median PFS of 5.1 months and a median OS of 9.0 months in 11 patients with recurrent/refractory SCLC treated with DEB-BACE. Similarly, our study revealed comparable results of 5.0 months for median PFS and 9.5 months for the median OS. However, some distinctions between the 2 studies should be noted. First, 38.9% of the

patients in our study were ineligible for systemic treatments owing to comorbidities, and 44.4% of the patients had ES-SCLC, which seems to indicate a worse prognosis when compared to the patients with recurrent/refractory LS-SCLC in Lin's study (17). Moreover, the therapeutic protocols in our study included further treatments of anlotinib or immunotherapy for patients without a treatment history of these regimens, while that was absent in Lin's study (17).

The primary DEB-BACE-related AEs include postembolization syndrome (fever, chest pain, etc.), gastrointestinal reaction (anorexia, vomiting, etc.), and myelosuppression (12-17). It was reported that the quality of life could be improved in patients with NSCLC treated with DEB-BACE compared to those treated with systemic chemotherapy (40). Compared with the high incidence rate of AEs of up to 65.2% after systemic chemotherapy (31), a lower incidence and milder degree of AEs after DEB-BACE was found in our study. This may have occurred because (I) loaded drugs can be delivered continuously after DEB-BACE, which may lead to a high local drug concentration; (II) the permanent embolization of peripheral vessels prevents the reflux of chemotherapeutic drugs, which may significantly decrease the systemic drug concentration; and (III) tumor ischemia or necrosis induced by embolization may lead to local inflammation, which makes postembolization syndrome less likely to occur in systemic chemotherapy than in DEB-BACE. Which chemotherapeutic drug is optimal for loading in DEB-BACE remains debatable. Loading of cytotoxic drugs is based on hydrophilic swelling and ion exchange with positively charged molecules like doxorubicin and irinotecan. The efficacy of DEB microspheres loaded with doxorubicin or irinotecan has already been elaborated in liver cancer (41,42). For advanced NSCLC, pirarubicin and gemcitabine are the 2 most common drugs loaded in DEB microspheres, but the superior efficacy of these has not been demonstrated (12-15). Irinotecan is a topoisomerase I inhibitor and has the characteristics of less frequent dosing and a lower probability of myelosuppression (43). The combination of irinotecan and platinum was been used in the treatment of patients with ES-SCLC, while the monotherapy of irinotecan has been used as an alternative to topotecan in second-line treatment (43,44). In our study, the predominant drug loaded in the DEB microspheres was irinotecan, especially for those patients who developed refractoriness to first-line chemotherapy of EP.

Anlotinib is a multitargeted tyrosine kinase inhibitor that inhibits tumor angiogenesis and proliferative signaling. A phase 2 trial evaluated the efficacy of anlotinib as a third-line treatment or beyond for patients with SCLC who showed refractoriness to at least 2 lines of chemotherapy, reporting a median OS of 7.3 months, which was significantly higher than that of 4.9 months in the placebo group (45). Recently, another single-arm phase II trial reported a median PFS of 8.02 months and a median OS of 15.87 months for patients with ES-SCLC treated with anlotinib plus EP and proposed this regimen as a promising first-line treatment (46). Our study revealed a median PFS of 9.0 months and a median OS of 14.0 months for 7 patients with STRI-SCLC treated with DEB-BACE and anlotinib, which represents a superior result when compared to that from treatment of anlotinib alone described in a previous prospective study (45). This indicates that these regimens are promising approaches and can be tolerated by patients with STRI-SCLC. For patients with advanced NSCLC, Liu *et al.* (18) reported a median PFS of 8.4 months and a median OS of 18.4 months for those treated with DEB-BACE plus anlotinib and indicated that DEB-BACE concomitant with anlotinib is effective and well-tolerated by these patients. An identical result was also observed in the present study, in which postoperative anlotinib was analyzed as the predictor of OS in patients with STRI-SCLC treated with DEB-BACE. The potential mechanisms of the longer OS resulted from postoperative anlotinib were the following: (I) an embolization-induced hypoxic environment may increase the risk of recurrence and stimulate neovascularization of peritumoral tissue (18); and (II) anlotinib could inhibit the tumor angiogenesis and enhance the synergistic anticancer effects of DEB-BACE.

This study has several limitations that should be noted. First, we employed a retrospective design; thus, patient-related selection bias may be present. Second, although this study, to our knowledge, contains the largest number of SCLC cases treated with DEB-BACE reported thus far, the statistical power may be affected by the limited sample size, and the results should be validated with other data sets. Third, this study included patients with STRI-SCLC with different treatment histories, which complicates conclusions concerning the effect of further therapeutic strategies after DEB-BACE, with potential heterogeneity likely being present.

In conclusion, DEB-BACE is an effective and well-tolerated approach for treating patients with STRI-SCLC. Moreover, postoperative anlotinib is a predictor of OS and may indicate a better prognosis for patients with STRI-SCLC.

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Footnote

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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 study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The institutional review board of Beijing Hospital, National Center of Gerontology, Institute of Geriatric Medicine, Chinese Academy of Medical Sciences approved this study. Written informed consent from patients was waived for this retrospective analysis.

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