

Received: 2019.01.30
Accepted: 2019.04.26
Published: 2019.08.30

Concurrent Bronchial Artery and Posterior Inferior Cerebellar Artery Microcatheter Interventional Chemotherapy for Adenocarcinoma of the Lung with Solitary Cerebellar Metastasis

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Statistical Analysis C
Data Interpretation D
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Source of support:

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This study was supported by Health Commission of Binhai New District, Tianjin, China (No: 2015BWKZ005)

Background: Lung cancer with intracranial metastasis requires concurrent treatment of the primary lung tumor and the secondary brain tumor. This study aimed to investigate the short-term clinical efficacy of concurrent bronchial artery and posterior inferior cerebellar artery microcatheter interventional chemotherapy for the treatment of adenocarcinoma of the lung with solitary cerebellar metastasis.



Material/Methods: Seventeen patients with adenocarcinoma of the lung with solitary cerebellar metastasis received concurrent microcatheter interventional chemotherapy via the bronchial artery and posterior inferior cerebellar artery. Two cycles of treatment with teniposide (VM-26), carmustine (BCNU), carboplatin (CBP), and pirarubicin (THP) were performed every four weeks.

Results: Four patients (23.53%) achieved a complete response (CR), five patients (29.41%) achieved a partial response (PR), seven patients (41.18%) had stable disease (SD), and only one patient (5.88%) developed progressive disease (PD). The objective response rate (ORR) and disease control rate (DCR) were 52.94% (9/17) and 94.12% (16/17), respectively. Four patients (11.76%) developed grade 1/2 chemotherapy toxicity, which included three cases (8.82%) of gastrointestinal toxicity and one case (2.84%) of granulocytopenia, but no grade 3/4 toxicity was found. During microcatheter interventional chemotherapy, three patients (8.82%) developed intracranial complications, including two cases (5.88%) of cerebrovascular spasm and one case (2.94%) of cerebral edema.

Conclusions: In 17 patients with adenocarcinoma of the lung with solitary cerebellar metastasis, concurrent microcatheter interventional chemotherapy via the bronchial artery and posterior inferior cerebellar artery was safe and showed short-term efficacy.

MeSH Keywords: **Chemotherapy, Adjuvant • Graft vs. Tumor Effect • Lung Neoplasms**

Full-text PDF: <https://www.medscimonit.com/abstract/index/idArt/915470>

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Background

Worldwide, lung cancer remains the leading cause of cancer-related death [1], and about half of patients have metastatic disease when first diagnosed [2]. Brain metastases from lung cancer are common and difficult to manage [3]. The most common site of brain metastases is the cerebral hemisphere, followed by the cerebellum, and brainstem. The symptoms of cerebellar metastases are atypical in the early stage of the disease. When the tumor grows to about 1–2 cm, the patients may only have the symptom of dizziness or mild ataxia. The prognosis of patients with brain metastasis from lung cancer is poor. The median survival time is only 1–2 months [4]. Whole brain radiotherapy or systemic chemotherapy for metastatic brain disease is limited, and radiation can result in cognitive impairment [5,6]. The cerebellum is located in the posterior fossa, adjacent to important nerves, blood vessels, and the brain stem. Radiation for the metastatic disease can result in edema and can be life-threatening or result in disability. Therefore, management of cerebellar metastasis from adenocarcinoma of the lung is a challenge for the oncologist or the neurologist.

Interventional intra-arterial chemotherapy for intracranial metastases can prolong the median survival to seven months in patients with brain metastases from lung cancer [7]. However, concurrent microcatheter interventional chemotherapy in the treatment of adenocarcinoma of the lung and solitary cerebellar metastasis has been rarely reported in the literature.

Therefore, this study aimed to investigate the short-term clinical efficacy of concurrent bronchial artery and posterior inferior cerebellar artery microcatheter interventional chemotherapy for the treatment of adenocarcinoma of the lung with solitary cerebellar metastasis.

Material and Methods

Patients

The study was approved by the Medical Ethics Committee of Tianjin TEDA hospital. The research complied with all the relevant national regulations, institutional policies and was in accordance with the tenets of the Helsinki Declaration. The Institutional Review Board of Tianjin TEDA Hospital approved the study. All study participants provided written informed consent.

Seventeen patients with histologically confirmed adenocarcinoma of the lung with solitary single cerebellar metastasis confirmed on imaging were prospectively included in this study. All the 17 cases received concurrent microcatheter interventional chemotherapy for the treatment of adenocarcinoma of the lung and solitary cerebellar metastasis.

The study inclusion criteria were a diagnosis of adenocarcinoma of the lung, confirmed by histology or cytology (Figure 1), and a solitary cerebellar metastasis confirmed by magnetic resonance imaging (MRI), no history of previous treatment, and a Karnofsky Performance Scale (KPS) score of >60. Patients were excluded from the study if they had other types of lung cancer, including small cell or squamous cell lung cancer, the presence of multiple brain metastases, and treatment with neoadjuvant radiotherapy or chemotherapy. The demographic and clinical characteristics of the 17 cases included in this study are shown in Table 1.

Concurrent microcatheter interventional chemotherapy

The patients received concurrent microcatheter interventional chemotherapy for adenocarcinoma of the lung and solitary cerebellar metastasis using digital subtraction angiography (DSA). Intra-arterial infusion chemotherapy for the intracranial metastatic tumor was combined chemotherapy regimens of teniposide (VM-26), carmustine (BCNU), carboplatin (CBP), and pirarubicin (THP). Individualized dosing of chemotherapy drugs was given according to the patient's body surface area.

The Seldinger method was used to puncture the right femoral artery, and a 6F sheath was inserted. A 5F JL4.5 catheter was placed near the mesenteric artery from the abdominal aorta. Ondansetron, an anti-nausea medication, was slowly infused into the mesenteric artery. Bilateral bronchial arteries or related intercostal arteries were selected. The lung tumor was identified in the chest using computed tomography (CT) imaging (Figure 2A). An Echelon-10 45° microcatheter was guided by a SilverSpeed-14 microwire to select the branches of the bronchial artery, avoiding the contralateral branches or intercostal arteries. Tumor staining was seen using microcatheterography (Figure 2B). The microcatheter was guided by a SilverSpeed-14 microwire that could penetrate into the tumors for angiography and perfusion therapy (Figure 2C, 2D). Bronchial artery infusion chemotherapy was performed for patients whose catheters could not reach the tumors. Etoposide (VP-16), THP, and cisplatin (DDP), diluted with 20 ml saline or glucose, were perfused with a high-pressure syringe using 2 ml/min volumes. During perfusion, attention given to the X-ray findings of the head position of the catheter or microcatheter, including displacement. Timely repeat angiography was performed to ensure the accuracy of identification of the perfused vessels.

A 5F single-curved catheter was used for cerebral angiography. Microcatheters were super-selected according to the blood supply of the areas of the tumor on brain MRI to reach the branches of the posterior inferior cerebellar artery in the intracranial segment of the vertebral artery (Figure 3A, 3B). During the use of the microcatheter, 0.3% papaverine solution was perfused into the catheter at 6 ml/min to prevent

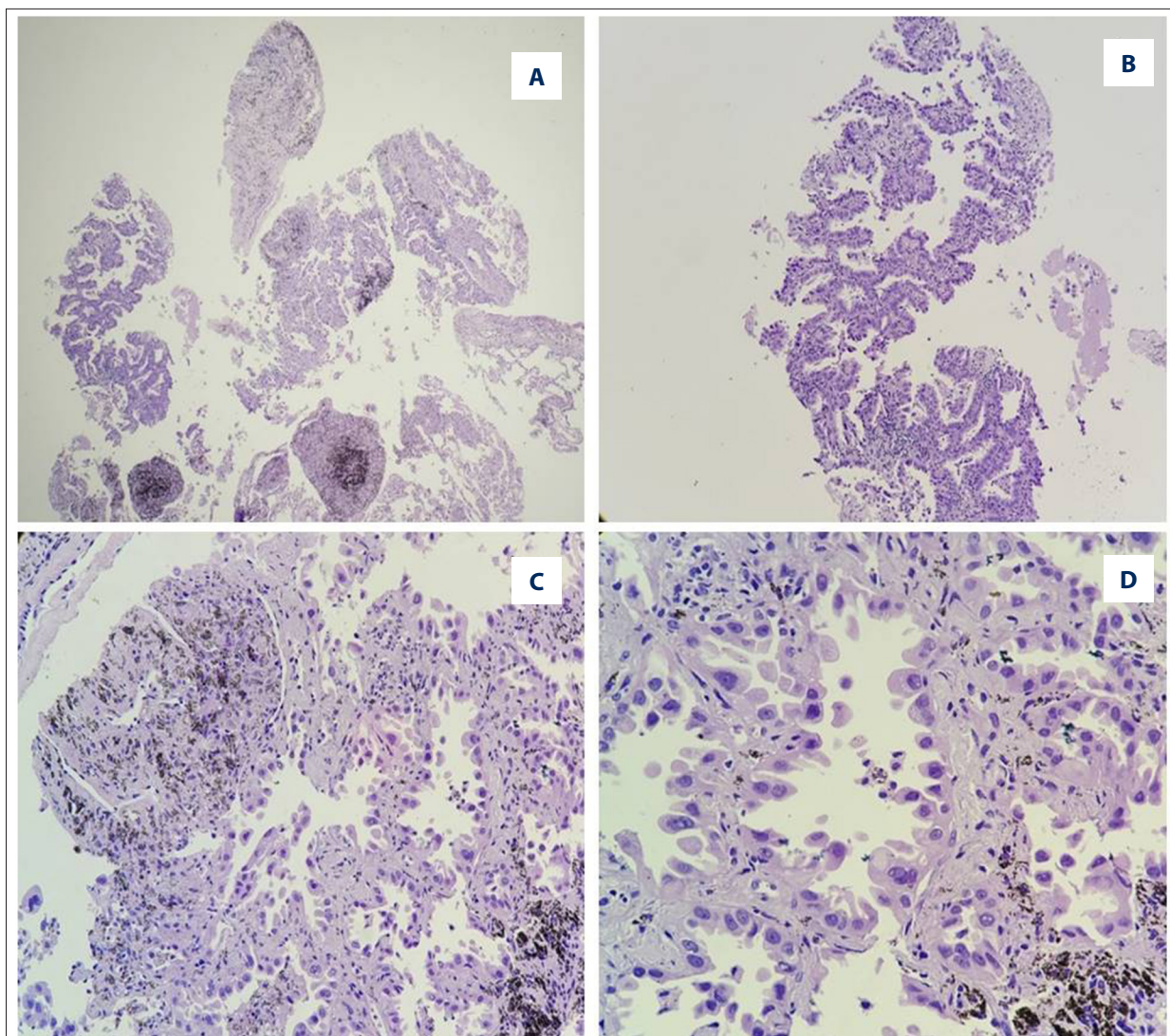


Figure 1. Photomicrographs of the histology of adenocarcinoma of the lung. Photomicrographs of the histology of adenocarcinoma of the lung. (A) Hematoxylin and eosin (H&E). Magnification $\times 40$. (B) H&E. Magnification $\times 100$. (C) H&E. Magnification $\times 200$. (D) H&E. Magnification $\times 400$.

cerebral vasospasm. Then, 30 ml of 20% mannitol, 10 mg of dexamethasone, 20 ml saline or glucose were used to dilute the VM-26, BCNU, THP, and CBP, which were perfused into the catheter at a rate of 3 ml/min. Vasospasm of the vertebral artery was observed during perfusion, and the dose of papaverine was adjusted. After perfusion, the microcatheter and the intermediate catheter were withdrawn slowly, and the arterial sheath was pulled out to ensure hemostasis.

Evaluation of the tumor response

The objective response (OR) after microcatheter interventional chemotherapy was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) [8]. The objective response rate (ORR) included the complete response (CR),

the partial response (PR), stable disease (SD), and progressive disease (PD). The objective response rate (ORR)=CR+PR. The Disease Control Rate (DCR)=CR+PR+SD. The ORR was evaluated according to the cerebellum metastatic lesions.

Chemotherapy-associated toxicity

Chemotherapy-associated toxicity was evaluated according to Common Terminology Criteria Adverse Events (CTCAE) version 5.0 from the National Cancer Institute (NCI).

Evaluation of intracranial complications

The evaluation of cerebrovascular complications during and after the procedure had three components. First, the presence of

Table 1. Demographic and clinical characteristics of the 17 patients with primary adenocarcinoma of the lung and solitary cerebellar metastases.

Characteristic	n/ $\bar{x}\pm s$
Gender, n (%)	
Male	10 (58.82%)
Female	7 (41.18%)
Age (years)	57 (35–73)
Brain tumor diameter (cm)	
Range	0.5–3.0
<2cm	15 (88.24%)
2~3 cm	2 (11.76%)
KPS	
60	3 (17.65%)
70	6 (35.29%)
80	5 (29.41%)
90	3 (17.65%)
T	
T1	2 (11.76%)
T2	10 (58.82%)
T3	5 (29.41%)
T4	0 (0.00%)
N	
N0	0 (0.00%)
N1	4 (23.53%)
N2	8 (47.06%)
N3	5 (29.41%)
M	
M0	0 (0.00%)
M1	17 (100.00%)

T – primary tumor; N – lymph node; M – metastasis.

stroke was evaluated as irreversible ischemia or hemorrhage, confirmed by brain CT or MRI imaging. Second, cerebral vasospasm or transient cerebral ischemia that could completely recover in a short time after treatment, without cerebral lesions, as determined by CT or MRI. Third, cerebral brain edema, evaluated by CT or MRI before and after microcatheter interventional chemotherapy.

Statistical analysis

Data were analyzed using STATA version 11.0 statistical software (<http://www.stata.com>), Measurement data were expressed as the mean \pm standard deviation (SD). Comparison of the data before and after treatment was made based using the paired

t-test of the sample mean. Numerical data were expressed with a relative number, and comparison of the data before and after treatment was analyzed by the chi-squared (χ^2) test. A P-value <0.05 was considered to be statistically significant.

Results

Microcatheter interventional chemotherapy

Of the 17 patients with adenocarcinoma of the lung with solitary cerebellar metastasis who received microcatheter interventional chemotherapy, the lung tumor was reached in nine patients. A further eight cases received bronchial artery pulmonary perfusion chemotherapy because of the difficulty in microcatheter intubation in the inner part of the tumor. For the 17 cases that had solitary cerebellar metastasis, in 13 cases the angiographic catheter entered the extracranial segment of the vertebral artery smoothly. The microcatheter microwire was superselectively perfused through a single-curvature angiographic catheter. In four cases, the opening of the vertebral artery was tortuous (two cases), slim (one case), and stenosed (one case). The 6 F guided catheter was used to support the subclavian artery. A microwire and microcatheter guided the 5F intermediate catheter through the tortuous stenosis. The guide tube arrived at the V2-V3 segment of the vertebral artery to provide stable support. The micro guidewire guided the microcatheter to perform a superselection of the branches of the posterior inferior cerebellar artery.

Objective response (OR)

All 17 patients received two cycles of microcatheter interventional chemotherapy. The objective response rate (ORR) was evaluated according to the metastatic cerebellar lesion. Of the included 17 cases, four patients (23.53%) achieved a complete response (CR) (Figure 4), five patients (29.41%) achieved partial response (PR) (Figure 5), seven patients (41.18%) achieved stable disease (SD) and only one patient (5.88%) developed progressive disease (PD). The objective response rate (ORR) and disease control rate (DCR) were 52.94% (9/17) and 94.12% (16/17), respectively.

Chemotherapy-associated toxicity

Four (11.76%) grade 1/2 chemotherapy-associated toxicity events were observed in the 34 chemotherapy cycles, and no grade 3/4 toxicity occurred. Of the four toxicity events, three cases (8.82%) were grade 1/2 gastrointestinal reactions, and one case (2.84%) was grade 1/2 granulocytopenia.

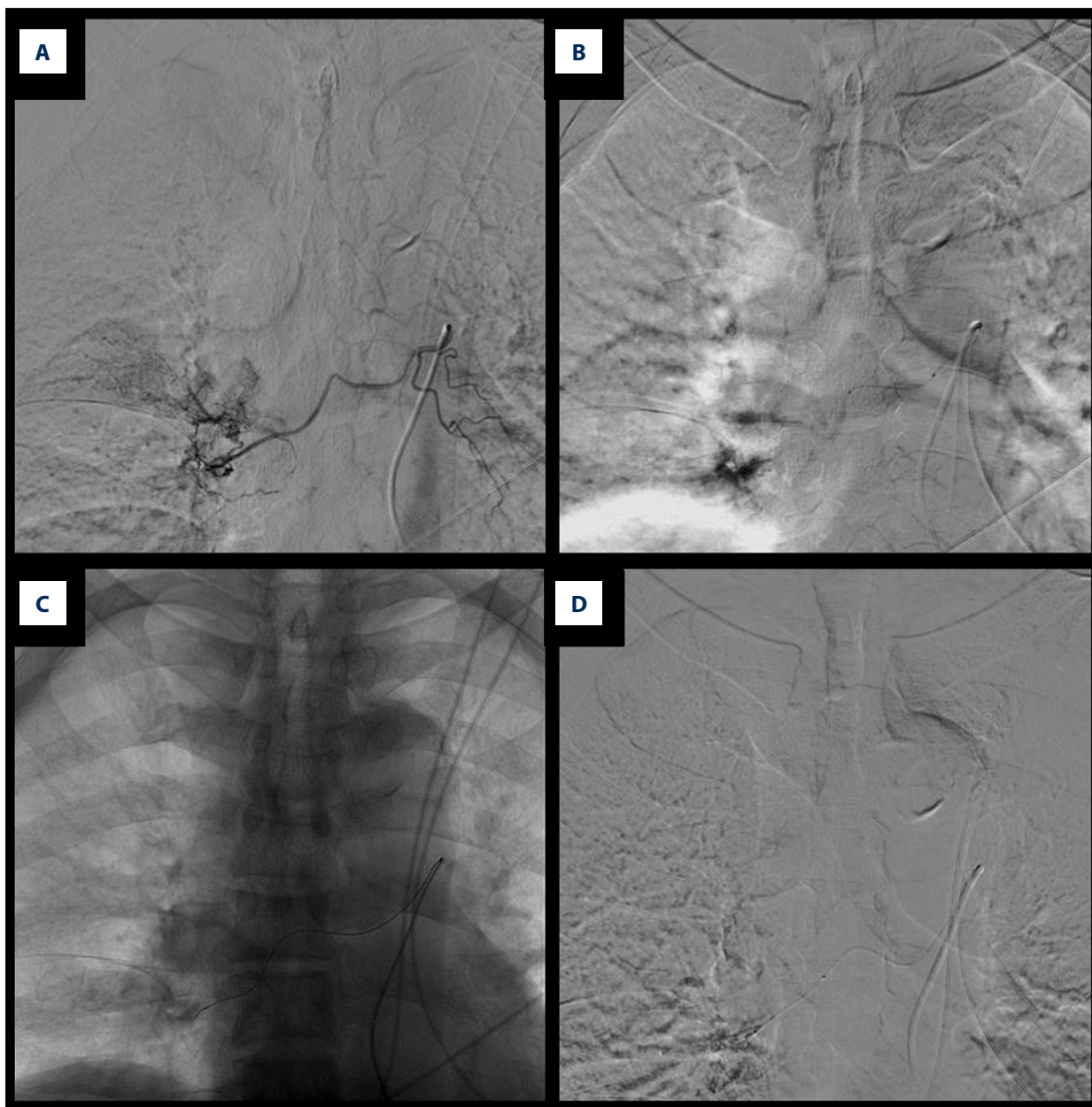


Figure 2. Imaging during microcatheter interventional chemotherapy for adenocarcinoma of the lung. **(A)** Bronchial arteriography shows abnormal blood vessels in the right upper lobe of the lung. **(B)** After superselective microcatheterization, the tumor is clearly identified. **(C)** The microcatheter guided by the microwire penetrates into the tumor. **(D)** Microcatheter angiography of the tumor identifies the adenocarcinoma of the lung.

Intracranial complications

A total of three (8.82%) intracranial complications were found during the microcatheter interventional chemotherapy. There were two cases (5.88%) of cerebrovascular spasm and one case (2.94%) of cerebral edema. No postoperative ischemic or hemorrhagic stroke occurred during treatment. Cerebral vasospasm occurred in the vertebral artery with contrast medium retention during the procedure. Cerebral vasospasm occurred

in the position of catheter adjustment and papaverine infusion. Cerebral edema was reduced with mannitol treatment after microcatheter interventional chemotherapy.

Discussion

Primary lung cancer with intracranial metastasis requires concurrent treatment of the primary lung tumor and the secondary

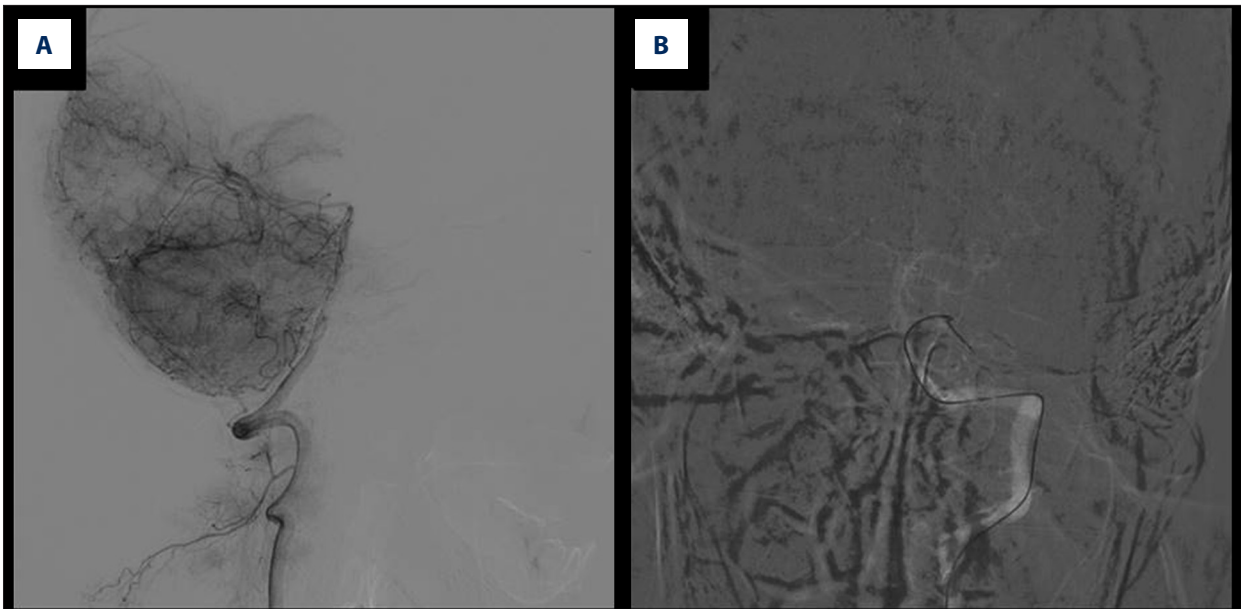


Figure 3. Microcatheter interventional chemotherapy for solitary cerebellar metastasis from adenocarcinoma of the lung. (A) Vertebral artery angiography shows abnormal branching of posterior inferior cerebellar artery and the metastatic tumor. (B) Microwire-guided superselective microcatheter in the posterior inferior cerebellar artery.

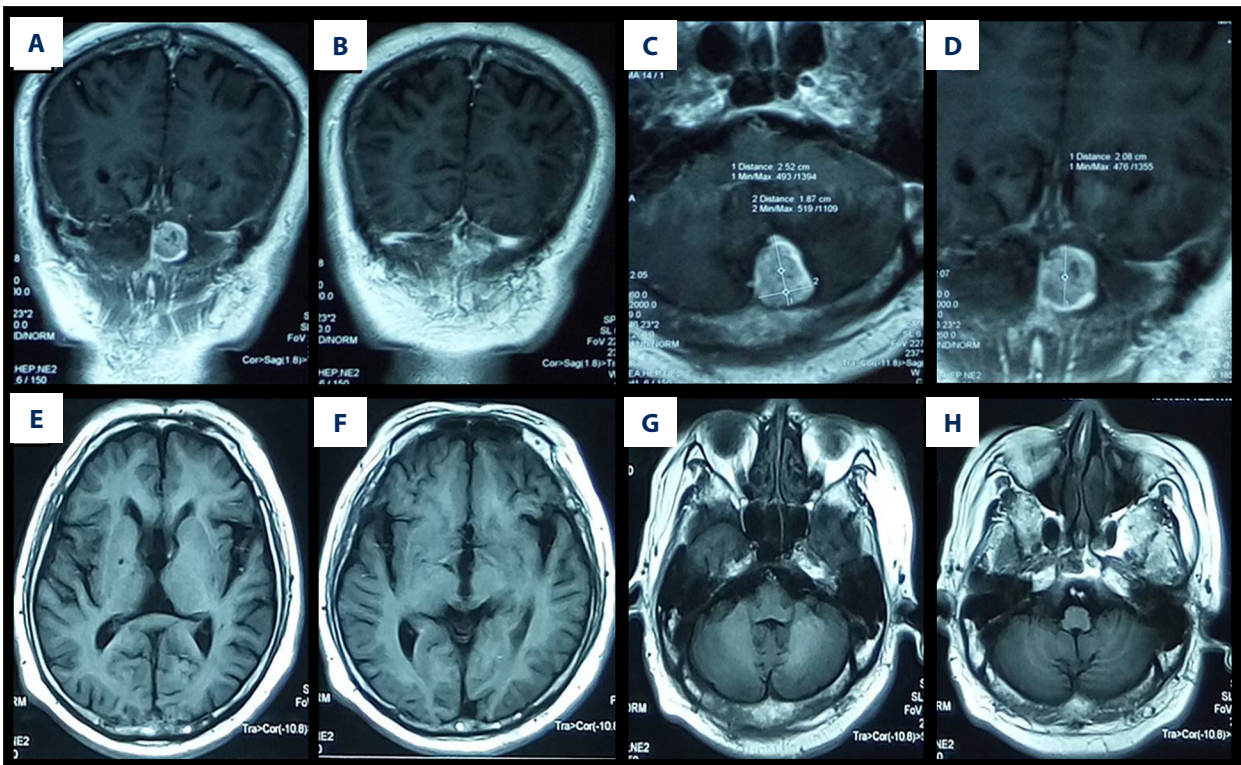


Figure 4. Computed tomography (CT) scan of a male patient who received microcatheter interventional chemotherapy for a solitary cerebellar metastasis. (A–D) Before treatment, a cerebellar metastasis was located in the left cerebellar hemisphere, 2.08×2.52 cm. (E, F) One month after two interventions, cranial magnetic resonance imaging (MRI) was repeated and cerebellar metastases showed a complete response (CR). (G, H) After treatment for one month, the metastatic cerebellar tumor had completely disappeared with a complete response (CR).

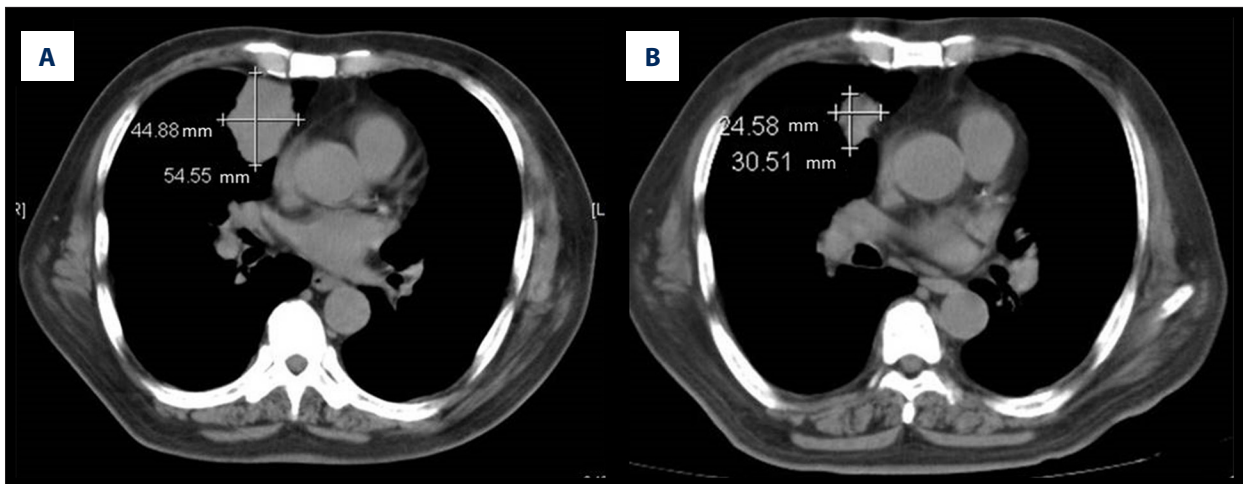


Figure 5. Computed tomography (CT) scan of adenocarcinoma of the lung. (A) Adenocarcinoma of the right lung before treatment with the tumor diameter of 54.55×44.88 mm. (B) After two cycles of treatment, the tumor showed partial response (PR), with the tumor diameter being 24.58×30.51 mm.

brain tumor. However, due to the anatomical characteristics of the bronchial artery, lung tumors are usually supplied by the intercostal artery, or the bronchial artery that originates from the intercostal artery, while the thoracic spinal artery and the intercostal artery often have the same origin [9,10]. Bronchial or intercostal arteries have small branches that communicate with the spinal artery. Therefore, when the injection pressure is high, or the injection speed is fast, complications may arise that include paraplegia [11]. Therefore, superselective perfusion with microcatheters can be used to avoid spinal cord injury [12–14]. However, it is difficult for some patients to have microcatheters sited during the treatment procedure.

In the present study, the rate of microcatheter placement in this study was only 52.94% or nine out of 17 patients. In the present study, the primary lung tumor and the metastatic cerebellar tumor were treated by femoral artery puncture, concurrently. The microcatheter and microwire can be reused for the primary lung lesions and cerebellar metastases, reducing procedural cost.

Microcatheter technology has been widely used in interventional perfusion chemotherapy and embolization for the treatment of hepatocellular carcinoma [15,16], and also renal cancer, lung cancer [17] and uterine cancer [18]. The superselective technique of the use of a bronchial artery microcatheter for lung cancer is not usually difficult, but some patients have variant anatomical characteristics of the bronchial artery that can introduce technical difficulties [19].

In the present study, 17 patients with adenocarcinoma of the lung with solitary cerebellar metastasis were treated. Four patients (23.53%) achieved a complete response (CR), five patients (29.41%) achieved a partial response (PR), seven patients

(41.18%) had stable disease (SD), and only one patient (5.88%) developed progressive disease (PD). The objective response rate (ORR) and disease control rate (DCR) were 52.94% (9/17) and 94.12% (16/17), respectively. However, the study sample size was relatively small, and the statistical power of the study was limited. Although the overall effective rate and disease control rate was not significantly better than those of patients with anterior circulation metastases treated with the same method, the complete response rate was significantly higher than those of patients with cerebral hemispheric metastases. This improved response may due to the small volume of the posterior cranial fossa. The posterior inferior cerebellar artery that originates from the vertebral artery supplies the cerebellar hemisphere. Therefore, the microcatheters could directly perfuse the tumor and increased the local drug concentration.

In this study, four patients (11.76%) developed grade 1/2 chemotherapy toxicity, which included three cases (8.82%) of gastrointestinal toxicity and one case (2.84%) of granulocytopenia, but no grade 3/4 toxicity was found. Therefore, superselective concurrent microcatheter interventional chemotherapy in the treatment of adenocarcinoma of the lung and solitary cerebellar metastasis was both safe and effective. Gao et al. [20] performed a clinical study of arterial interventional chemotherapy for brain metastases of lung cancer after opening the blood-brain barrier and found that the response rate in the treatment group was superior to the group who received radiotherapy.

For the treatment of solitary cerebellar metastatic disease, standard treatment is surgical resection and whole brain radiotherapy. Because cerebellar metastases are located in the posterior cranial fossa, adjacent to the brainstem and many important nerves and blood vessels, the risk of surgical resection is high. Whole brain radiotherapy alone has the drawback

of extensive radiation damage to brain tissue and poor curative effects, which may lead to neurological deficits. Previous studies have shown that the median survival time was no longer than six months for patients with metastatic brain disease treated with radiotherapy, and the primary lung lesions and cerebellar metastases could not be treated simultaneously [21]. In superselective microcatheter interventional chemotherapy, angiography can identify the extent of the tumor and the arterial blood supply. Microcatheters can access the inner part of the tumor where intravenous chemotherapy may not reach. Microcatheters in primary lung cancer can superselectively perfuse the bronchial arteries, and in cerebellar metastases, microcatheters can superselectively perfuse the posterior inferior cerebellar arteries.

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Conclusions

This study aimed to investigate the short-term clinical efficacy of concurrent bronchial artery and posterior inferior cerebellar artery microcatheter interventional chemotherapy for the treatment of adenocarcinoma of the lung with solitary cerebellar metastasis. The findings showed that in 17 patients with adenocarcinoma of the lung with solitary cerebellar metastasis, concurrent microcatheter interventional chemotherapy via the bronchial artery and posterior inferior cerebellar artery was safe and showed short-term efficacy. However, the long-term efficacy of superselective microcatheter interventional chemotherapy, combined with radiotherapy or other treatment modalities remains to be further evaluated by large-scale prospective randomized controlled clinical trials.

Acknowledgments

The authors thank Tianjin Tumour Hospital, Professor Guo, and Professor Xing for support and help with this study.