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Efficacy and safety of CalliSpheres drug-eluting bead bronchial arterial infusion chemoembolization vs. bland embolization in advanced lung cancer with hemoptysis: A multicenter retrospective study

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ABSTRACT

Massive hemoptysis is a life-threatening complication in patients with advanced primary lung cancer, and effective, safe treatments are crucial. This study aimed to investigate the efficacy and safety of CalliSpheres drug-eluting bead bronchial arterial infusion chemoembolization (DEB-BACE) for managing this condition. A retrospective analysis included 144 patients with advanced primary lung cancer and massive hemoptysis treated at multiple hospitals from January 2019 to January 2023. Patients undergoing bronchial artery embolization were divided into two groups: the observation group (n=76) received CalliSpheres DEB-BACE with epirubicin, and the control group (n=68) received 8spheres blank embolization. Both groups achieved successful hemostasis, with no statistically significant difference in success rates (observation group: 88.16%, control group: 86.76%). However, the observation group had a significantly longer median duration without hemoptysis (96 days vs. 50 days). Two months post-therapy, the observation group showed higher objective response rates (82.89% vs. 38.24%) and disease control rates (92.11% vs. 66.18%) compared to the control group. Adverse reactions were manageable and similar between groups, with no serious complications observed. By January 31, 2024, the observation group had significantly longer median overall survival (11 months vs. 7 months). The DEB-BACE treatment demonstrates safety and efficacy in managing massive hemoptysis in patients with advanced lung cancer. However, the superiority of this approach over bland embolization remains to be established through well-designed prospective studies. Future research is anticipated to provide a definitive comparison and further validate the role of DEB-BACE in clinical practice.

Keywords: Malignant lung tumors; massive hemoptysis; bronchial arterial infusion chemoembolization; drug-eluting bead embolization microspheres

INTRODUCTION

Massive hemoptysis is a common emergency in lung cancer and is also one of the leading causes of death in advanced lung cancer. The condition of massive hemoptysis is critical and dangerous, and most patients die from shock and asphyxia(1). Bronchial artery embolization (BAE) is one of the most effective treatments for lung cancer with hemoptysis and has been widely used in clinical practice(2). However, due to the use of traditional embolization materials - gelatin sponge particles or polyvinyl alcohol (PVA) embolization microspheres - the tumor necrosis rate after embolization is low, and the incidence of re-bleeding is high, which affects the hemoptysis control rate, tumor remission rate, and long-term survival rate of patients(3). To address these limitations, we have turned to a new embolization material: drug-loaded embolization microspheres. When applied in bronchial arterial infusion chemoembolization (BACE), this technique is referred to as drug-eluting beads bronchial arterial infusion chemoembolization (DEB-BACE), which has dual functions of vascular embolization and sustained, slow release of chemotherapy drugs. The mechanism of DEB-BACE treatment lies in its dual impact on tumor vasculature through drug-eluting microspheres: on the one hand, the microspheres physically embolize the tumor vessels, rapidly reducing tumor volume; on the other hand, the chemotherapeutic agents they carry create a high-concentration local drug environment, continuously inhibiting the growth of tumor cells(4). This combination of local and systemic therapy not only improves treatment outcomes but also reduces the side effects associated with systemic chemotherapy, offering a new treatment option for patients with advanced lung cancer. Treating lung cancer with BACE has yielded favorable clinical outcomes(5, 6). DEB-BACE, as an emerging therapeutic approach, has demonstrated efficacy and safety in treating patients with advanced lung cancer in numerous clinical studies(7, 8). DEB-BACE combines the hemostatic effects of BAE with the chemotherapeutic benefits of drug-eluting beads, potentially transforming the management of massive hemoptysis in advanced lung cancer. The clinical significance of DEB-BACE extends beyond its direct hemostatic actions. It represents a strategic shift toward a more comprehensive treatment approach that addresses both the acute bleeding episode and the underlying malignancy. Given the poor prognosis associated with advanced

lung cancer and massive hemoptysis, the introduction of a treatment modality that can offer both immediate and long-term benefits is of paramount importance. However, there are few reports on the use of DEB-BACE in the treatment of advanced lung cancer with massive hemoptysis. This study aims to investigate the safety and efficacy of DEB-BACE in treating advanced primary lung cancer with massive hemoptysis.

MATERIALS AND METHODS

Case data

Patients with advanced primary lung cancer complicated by massive hemoptysis who were admitted to the Affiliated Hospital of Jining Medical College, Linyi Tumor Hospital, and Linyi People's Hospital in Shandong Province from January 2019 to January 2023 were included as research subjects. Inclusion criteria: (1) Age between 18 and 80 years, both genders; (2) Diagnosis of stage IIIc or IV primary lung cancer with massive hemoptysis (defined as > 500ml in 24 hours or > 100ml in a single episode) based on medical history, clinical manifestations, and auxiliary examinations; (3) no systemic chemotherapy or radiotherapy during interventional treatment; (4) computed tomography angiography (CTA) or angiography indicating bronchial or other systemic arteries involved in the tumor’s blood supply. In emergency cases, some patients did not undergo CTA but were promptly treated with angiography and embolization; (5) Karnofsky Performance Status (KPS) score ≥60; (6) the expected survival time of more than three months. Exclusion criteria: (1) Severe cardiopulmonary dysfunction and coagulation abnormalities; (2) requirement for endotracheal intubation and mechanical ventilation during the procedure; (3) Active infection, iodine allergy, or other contraindications to angiography; (4) tumor-feeding artery sharing a common trunk with the spinal artery, where selective catheterization is not feasible. In cases of lung cancer with hemoptysis, the responsible vessels primarily originate from the bronchial arteries, accounting for up to 90% of cases. This is different from hemoptysis caused by other conditions, such as lung abscesses or tuberculosis, which were excluded from this study. The inclusion and exclusion process is illustrated in the study flowchart (Figure 1). A total of 144 patients were ultimately enrolled. Following comprehensive preoperative discussions, the treatment team determined the appropriate treatment plan (DEB-BACE or

BAE) based on each patient's specific clinical condition, treatment preferences, and financial considerations. Patients were then assigned to either the observation group (76 cases) or the control group (68 cases), according to the type of interventional embolization material used. There were no statistically significant differences in age, gender, tumor location, or tumor size between the two groups (all $P > 0.05$). For a detailed comparison of patient demographics and tumor characteristics between the groups, refer to Table 1.

Treatment

Control group (BAE): Under local anesthesia, a modified Seldinger technique was used to puncture the right femoral artery. A 5F pigtail catheter was introduced into the thoracic aorta through a 5F vascular sheath to obtain images of the thoracic aorta. Then, 5F Cobra, MIK, and TIG catheters were used for bronchial arteriography. Angiography of the intercostal arteries, internal thoracic arteries, branches of the thyrocervical trunk, phrenic arteries, and left gastric arteries was performed when necessary to identify the responsible vessels. The microcatheter (Progreat 2.7F) was further superselected to the offending artery, and non-offending vessels, such as the spinal artery, were confirmed to be avoided through repeated angiography. According to the angiographic results, 8spheres (300-500 μm) were used for embolization, and larger microspheres (500-700 μm) were used for special angiography. Angiography was then performed to determine the degree of vascular embolization. Angiographic endpoints included stasis or near stasis of the blood lumen in the embolized vessel or loss of substantial tumor staining.

Observation group: The conditions for puncture catheterization, arteriography, and superselection of offending vessels by microcatheter (Progreat 2.7F) were the same as those in the control group. Preparation of CalliSpheres Drug-Eluting Microspheres: CalliSpheres drug-eluting microspheres (1g/vial, Suzhou Hengrui Kalisen Biopharma Co., Ltd., National Medical Products Administration of China approval number 20153771072) were aspirated along with saline using a 20 mL syringe. The syringe was then placed vertically for 2 to 3 minutes to allow the microspheres to settle, after which the supernatant was expelled as much as possible. Epirubicin hydrochloride, at a dosage of 40 to 60 mg, was dissolved in 5 mL of

sterile water for injection. A three-way stopcock was used to connect the syringe containing the microspheres (20 mL) with the one containing the epirubicin solution (5 mL), and the epirubicin solution was slowly injected into the syringe with the microspheres. The syringe containing both the microspheres and the chemotherapeutic agent was then capped with a needle hub, and the mixture was gently agitated every 5 minutes for a total of 30 minutes to allow for drug absorption. The epirubicin-loaded microspheres were subsequently mixed with the non-ionic contrast agent iohexol at a 1:1 ratio and left to stand for 5 minutes before use. After superselection to the offending artery, the drug-loaded microspheres were injected intermittently and slowly into the offending artery. Angiography was subsequently performed to determine the degree of vascular embolization, and the embolization endpoints were the same as above.

Postoperative management: Conventional treatments such as oxygen inhalation, blood transfusion, anti-inflammatory therapy, rehydration therapy, and monitoring were administered. When the condition was stable, patients were transferred to the medical oncology department or related departments to continue anti-tumor treatment.

Efficacy evaluation and adverse reaction observation

Hemoptysis control: (1) Technical success: successful superselection to offending vessels and effective embolization; (2) Clinical success: after BAE/BACE, hemoptysis was completely stopped or significantly reduced (partial cessation); (3) Clinical failure: persistent hemoptysis without reduction after the operation, or recurrent hemoptysis during hospitalization after temporary reduction or cessation, with the hospital stay ranging from 1 to 7 days; (4) Time without hemoptysis: time from surgery to recurrence of hemoptysis or death. Tumor response: Two months after the first treatment, chest-enhanced computed tomography (CT) was reexamined, and efficacy was evaluated according to the response evaluation criteria in solid tumors (mRECIST). The efficacy was categorized as complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). The objective response rate (ORR)=(CR+PR)/ total cases ×100%, and the disease control rate (DCR)=(CR+PR+SD)/ total cases ×100%. Survival: Overall survival (OS) was defined as the time from the initiation

of treatment to death or the last follow-up. Adverse events: According to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (9), adverse events were graded on a scale from 0 to 4.

Follow-up

Follow-up methods included inpatient treatment, outpatient clinic visits, and telephone consultations. During the treatment period, each return to the hospital for treatment was considered a follow-up visit. After the completion of treatment, follow-ups were scheduled every 2 to 3 months. The follow-up period concluded on January 31, 2024, with no cases lost to follow-up.

Ethical statement

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Ethical approval for this study was obtained from the Medical Science Research Ethics Committee of Linyi Cancer Hospital (Approval Number: [2019]106), and the study was conducted in accordance with the approved guidelines. Informed consent was obtained from all participants or their legal guardians.

Statistical analysis

SPSS 20.0 software was used for statistical analysis. Qualitative data were expressed as the number of cases and percentages, and comparisons between groups were analyzed using the chi-square test or Fisher's exact probability method. Quantitative data conforming to a normal distribution were expressed as $\bar{x}\pm s$, and comparisons between groups were made using the independent sample t-test. The Kaplan-Meier method was used for survival analysis, and the log-rank test was used to compare survival rates. A P value < 0.05 was considered statistically significant.

RESULTS

Hemoptysis control status

A total of 311 offending vessels were found in 144 patients across the two groups. The offending vessels exhibited: (1) arterial tortuosity and dilatation with significant tumor staining (100%, 144/144); (2) contrast agent spillover (4.17%, 6/144); and (3) arteriovenous and arterio-arterial shunting (6.25%, 9/144). The offending vessels included the left bronchial artery in 31.25% (45/144), the right bronchial artery in 56.94% (82/144), bilateral bronchial arteries in 9.72% (14/144), and other vessels in 2.08% (3/144). All 144 patients were successfully treated with arterial embolization, resulting in a technical success rate of 100% (144/144). Among the 144 patients who underwent arterial embolization, 125 achieved clinical success in hemostasis, with a success rate of 86.81%. This included 67 cases (88.16%) in the observation group. The clinical success rate was 86.76% in the control group and 88.16% in the observation group, with no significant difference between the two groups (χ^2 = 0.064, P = 0.801). Among the 19 patients with failed hemostasis, four achieved cessation of bleeding following medical hemostatic treatment. Twelve patients underwent re-interventional treatment, of whom eight exhibited recanalization of the offending vessels and underwent re-embolization. Four patients had suspected blood supply from the ipsilateral internal mammary artery and underwent embolization. Three patients discontinued treatment and died within three days after discharge. The median hemoptysis-free duration was 96 days (95% CI: 92.01-99.99) in the observation group and 50 days (95% CI: 39.69-60.31) in the control group, with the difference being statistically significant (χ^2=91.667, P < 0.001), as shown in Figure 2.

Tumor response after interventional operation

Enhanced chest CT was re-examined two months after the first intervention, and the tumor response was evaluated using the Response Evaluation Criteria in Solid Tumors (mRECIST). In the observation group, there were 12 cases of CR, 51 cases of PR, 7 cases of SD, and 6 cases of PD, resulting in an ORR of 82.89% (63/76) and a DCR of 92.11% (70/76). In the control group, there were 0 cases of CR, 26 cases of PR, 19 cases of SD, and 23 cases of PD, with an ORR of 38.24% (26/68) and a DCR of 66.18% (45/68). The ORR and DCR in the observation group were significantly higher than those in the control group (χ^2=30.322, P < 0.001; χ^2=15.002, P = 0.001). For details, refer to Table 2.

Survival analysis

As of January 31, 2024, the follow-up period ranged from 2 to 25 months, with an average of (9.96 ± 5.31) months. Except for three patients who were discharged and died outside the hospital due to unsuccessful interventional hemostasis, the remaining 141 patients completed follow-up with no cases left. The median OS was 11 months (95% CI: 8.8413.16) in the observation group and 7 months (95% CI: 5.938.07) in the control group, with a statistically significant difference (P<0.001) (Figure 2 and Figure 3). Data for the hemoptysis-free survival curves and overall survival curves of the two groups can be found in Supplementary Table 1 and Supplementary Table 2, respectively.

Adverse reactions

The primary intervention-related adverse reactions in both groups were chest pain (39/144), followed by fever (33/144). Other adverse reactions included cough, nausea and vomiting, and fatigue, all of which were ≤ Grade II; there were no occurrences of Grade III-IV adverse reactions. All symptoms were significantly alleviated within three to seven days after symptomatic treatment. There were no severe complications such as spinal cord injury or ectopic cerebral embolism. The incidence of adverse reactions between the two groups showed no statistically significant difference (all P > 0.05). Refer to Table 3 for details.

DISCUSSION

The literature reports that tumor lesions in lung cancer patients can damage pulmonary vessels, causing ruptures in the vessel walls, which can lead to hemoptysis (10, 11). When lung cancer is accompanied by hemoptysis, traditional treatment generally involves conservative measures such as pharmacological hemostasis, but the bleeding often recurs after a short period. Surgical procedures are often not feasible due to the advanced stage of the tumor, poor physical condition of the patient, significant trauma, and high risk. BAE is a minimally invasive interventional technique that involves the injection of embolic agents into the culpable artery to occlude the bleeding vessel and achieve hemostasis (12). Traditional embolic materials include gelatin sponges, coil springs, and polyvinyl alcohol particles, which aim solely to stop bleeding and have minimal impact on the tumor. However, due to

the tumor's persistence and continued growth, it becomes the primary cause of recurrent hemoptysis (13). Therefore, to achieve better hemostasis and simultaneously control the tumor, causing it to necrotize and shrink, it is essential to prolong patient survival and improve quality of life (14).

Building on the foundation of BAE, BACE incorporates the use of chemotherapeutic agents to maintain higher drug concentrations within tumor tissues for prolonged periods, thereby enhancing the cytotoxic effect against tumors. In recent years, BACE has emerged as a promising therapeutic modality for advanced lung cancer, particularly in patients with refractory lung cancer who present with symptoms of compression, hemorrhage, or disease progression following multiple lines of treatment (15). BACE has proven effective in achieving excellent outcomes and significantly improving patient quality of life and survival. DEB-BACE represents an innovative interventional treatment modality for lung cancer. The drug-eluting beads not only permanently embolize the tumor vessels but also gradually release the carried chemotherapeutic agents to destroy tumor cells, thus aiming to control tumor growth (16), which in turn ameliorates clinical symptoms and enhances quality of life (17). CalliSpheres beads, an indigenously developed drug-eluting bead in China, have been deployed in the treatment of lung cancer. A patient with locally advanced squamous cell lung cancer achieved a pathological Complete Response (pCR) after receiving DEB-BACE followed by curative surgical resection, indicating that DEB-BACE could be a neoadjuvant treatment option for locally advanced non-small cell lung cancer (NSCLC) (18). In a retrospective study by Liu et al., BACE was found to achieve better tumor treatment effects and improve quality of life compared to systemic chemotherapy in patients with advanced NSCLC (19). Fu and colleagues included 36 lung cancer patients with hemoptysis, with one group receiving conventional bronchial arterial chemoembolization (cBACE) using lipiodol, and the other receiving drug-eluting beads bronchial arterial chemoembolization (D-BACE). They found that D-BACE could achieve higher tumor response rates and longer hemoptysis-free survival compared to cBACE. However, it is important to note that lipiodol, as a liquid embolic agent, is not currently recommended for bronchial artery embolization due to its small particle size, which can damage the bronchial wall or esophagus and potentially lead to

severe extraterritorial injury complications. In our study, we chose blank microspheres as the control embolic material, which have been shown to have higher safety in BACE management. In the efficacy assessment of the control group patients, our results were superior to those of the control group in their study, suggesting that microspheres might be more suitable for bronchial artery embolization. Of course, in the observation group, the results of the two studies were largely consistent (14). Li's study suggests that after DEB-BACE treatment for non-small cell lung cancer, there is rapid tumor necrosis and effective reduction in tumor burden, with the addition of immune checkpoint inhibitors further enhancing tumor control efficacy (20). Our center was one of the first in China to carry out BACE treatments using CalliSpheres beads. In one of our prospective studies, we included 21 patients with intractable, recurrent NSCLC. Following the initial intervention, the ORR was 88.37%, the DCR was 95.35%, and the median survival time was 11.5 months (21). However, there are few reports on the use of DEB-BACE in the treatment of lung cancer with massive hemoptysis.

In this study, patients with advanced primary lung cancer and massive hemoptysis were treated with either DEB-BACE or BAE alone. The findings indicated that both groups achieved similar short-term clinical success rates in controlling hemoptysis. However, the observation group experienced a significantly longer duration without hemoptysis compared to the control group. Additionally, the observation group showed markedly higher ORR and DCR than the control group. For the treatment of hemoptysis by DEB-BACE and BAE, both approaches aim at embolization of the responsible blood vessels, which is technically similar. However, the differences in tumor control outcomes reflect the superior tumor necrosis effect of DEB-BACE. Short-term postoperative CT scans in some patients from the observation group revealed significant low-density necrosis and cavity-like necrosis in lung tumors, indicating that DEB-BACE effectively embolizes tumor-supplying arteries. Furthermore, the favorable drug-carrying properties of microspheres also contribute to the efficacy of tumor necrosis. When microspheres interact with chemotherapeutic drugs, they enhance the therapeutic effect, achieving the dual goals of controlling bleeding and suppressing tumor growth. A prospective cohort study comparing DEB-BACE with conventional BACE

(cBACE) in the treatment of patients with stage II-IV lung cancer showed that DEB-BACE resulted in better progression-free survival and overall survival rates (22). In the current study, the median OS for patients in the observation group was 10 months, which is lower than that reported in some studies (23, 24). This discrepancy is primarily attributed to differences in baseline characteristics, with a higher number of late-stage patients. Additionally, massive hemoptysis often indirectly exacerbates the condition, leading to a poorer prognosis - albeit still better than the OS in the control group. DEB-BACE enables the delivery of high concentrations of chemotherapeutic agents directly into tumor tissues, thereby slowing tumor progression and reducing the likelihood of recurrent bleeding by diminishing tumor angiogenesis. Additionally, DEB-BACE demonstrates a favorable effect on slowing tumor progression, which may actively contribute to prolonging the survival of patients with lung cancer. No severe complications, such as ectopic embolism, occurred in either group in this study. The use of microspheres with a diameter of 300-500 μm for embolization in lung cancer patients with massive hemoptysis was found to be safe, consistent with particle diameters reported in the current literature (25, 26). The main postoperative adverse reactions were chest pain and fever, all Grade I-II, with no Grade III-IV adverse reactions occurring. These reactions are believed to be related to post-embolization tumor swelling and necrosis and were alleviated shortly after medical treatment.

While our retrospective study provides valuable insights into the efficacy and safety of the treatment under evaluation, it is important to recognize its limitations. The design restricts control over confounding variables and may introduce biases. The lack of randomization could lead to selection bias. Although the sample size is sufficient to demonstrate significant differences, it may impact the generalizability of our findings. In our current analysis, we primarily relied on available data without estimating missing values. We acknowledge that this approach may have limitations. To address this and improve the quality of our future research, we plan to implement more sophisticated methods for handling missing data. These may include multiple imputation techniques or sensitivity analyses to assess the impact of missing data on our results. Additionally, since all patients were from hospitals in Shandong Province, China, this may limit broader applicability. Therefore, we acknowledge the need

for larger, prospective studies to validate our findings and to further explore the impact of the treatment in a broader patient population. Future research should focus on conducting large-sample, multicenter, prospective studies to overcome the limitations of our current study. Such studies will provide a more comprehensive understanding of the treatment's effectiveness and safety profile across diverse patient populations and clinical settings.

CONCLUSION

In summary, DEB-BACE, as a locoregional treatment approach, is safe and effective for the treatment of advanced lung cancer with massive hemoptysis, offering a promising therapeutic option for these patients. This retrospective study highlights the need for prospective research to validate the superiority of DEB-BACE over traditional embolization, as well as to investigate whether a particular subpopulation might benefit more specifically from this treatment.

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TABLES AND FIGURES WITH LEGENDS

Table 1. Comparison of general information between the two groups of patients [$\bar{x}$±s/n(%)]

Clinical characteristics	Observation group（*n*=76）	control group（*n*=68）	t/χ^2value	*P* value
Age	55.37±10.59	56.65±11.91	0.557	0.289
Gender			0.354	0.552
male	57	48		
female	19	20		
Pathological type			1.932	0.681
Squamous cell carcinoma	60	48		
adenocarcinoma	13	14		
Small cell lung cancer	3	6		
Tumor diameter(cm)	4.78±1.27	4.65±1.53	0.455	0.455
Extrapulmonary metastasis			0.448	0.503
Yes	51	42		
No	25	26		
Tumor staging			0.005	0.945
Stage IIIc	16	14		
Stage IV	60	54		
Location of the tumor			0.612	0.433
Central type	70	60		
Peripheral type	6	8		
Previous antineoplastic therapy			0.350	0.553
Yes	67	62		
No	9	6		

Table 2. Comparison of short-term clinical efficacy between the two groups [n (%)]

Group	CR	PR	SD	PD	ORR	DCR
Observation Group(n=76)	12(15.78)	51(67.11)	7(9.21)	6(7.89)	63(82.89)	70(92.11)
Control Group(n=68)	0(0.0)	26(38.24)	19(27.94)	23(33.82)	26(38.24)	45(66.18)

Table 3. Incidence of treatment-related adverse reactions in the two groups [n (%)]

Adverse reaction	Observation group（*n*=76）			Control group（*n*=68）			χ^2 value	*P* value
	GradeI ~ II（n）	GradeIII ~ IV（n）	Incidence（%）	GradeI ~ II（n）	GradeIII ~ IV（n）	Incidence（%）		
fever	19	0	25.00	14	0	20.59	0.395	0.529
chest pain	22	0	28.95	17	0	25.00	0.283	0.595
cough	16	0	21.05	11	0	16.18	0.560	0.454
nausea/vomiting	9	0	11.84	6	0	8.82	0.087	0.768
fatigue	6	0	7.89	3	0	4.41	0.743	0.389

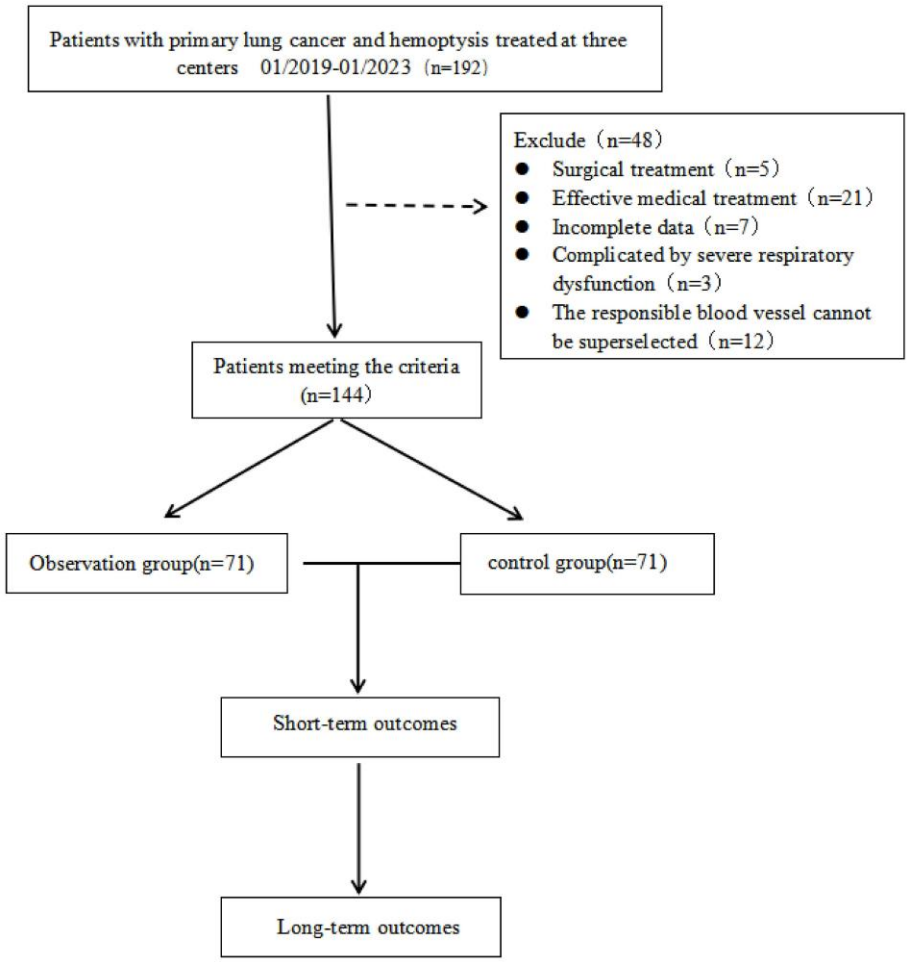
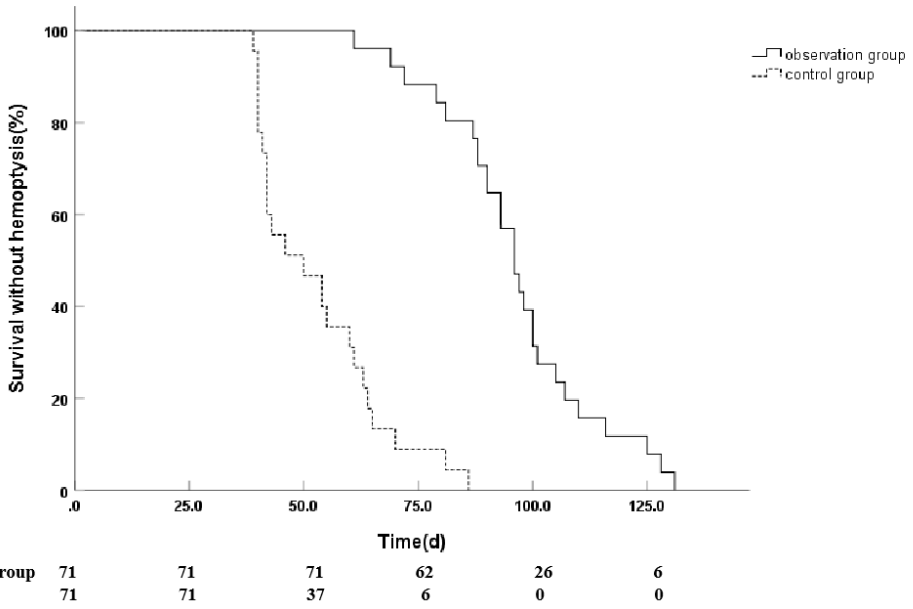
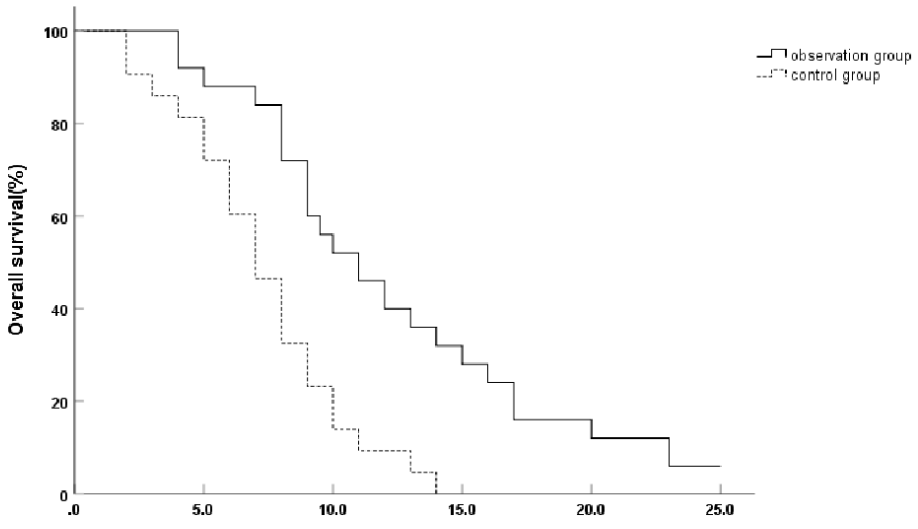


Figure 1. The study flow chart for inclusion and exclusion



NO.at risk						
Observation group	71	71	71	62	26	6
Control group	71	71	37	6	0	0

Figure 2. Hemoptysis-free survival curve of two groups of patients



NO.at risk						
Observation group	71	61	33	18	9	3
Control group	71	59	12	0	0	0

Figure 3. Overall survival curve of two groups of patients

SUPPLEMENTAL DATA

Supplementary data are available at the following link:

https://www.bjbms.org/ojs/index.php/bjbms/article/view/10808/3589

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