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ORIGINAL ARTICLE

Comparison of efficacy of stereotactic body radiotherapy and thoracoscopic surgery in the treatment of early-stage non-small cell lung cancer

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Summary

Purpose: *To observe and compare the efficacy and safety between stereotactic body radiotherapy and thoracoscopic surgery in the treatment of early-stage non-small cell lung cancer (NSCLC).*

Methods: *The clinical data of 106 early-stage NSCLC patients admitted to the Thoracic Surgery Department of the hospital from February 2014 to February 2016 were retrospectively analyzed. Among these patients, 53 received stereotactic body radiotherapy (SBRT group), and 53 underwent video-assisted thoracoscopic surgery (VATS group). The clinical data of all patients were collected. The short-term response rate, Karnofsky performance status (KPS) score, changes in serum tumor marker levels before and after surgery and adverse reactions were compared between the two groups. Besides, all patients were followed up, and the overall survival (OS) and progression-free survival (PFS) were recorded.*

Results: *The levels of serum carcinoembryonic antigen (CEA), cytokeratin 19 fragment (CYFRA21-1) and neurone specific enolase (NSE) were decreased in both groups after treatment, and the differences were not statistically significant between the two groups. The patients tolerated well with SBRT, without evident myelosuppression or adverse hematological effects. In SBRT group, there were 7 cases of radioactive skin reaction, 2 cases of grade I radiation esophagitis and 4 cases of radiation pneumonitis (including 3 cases of grade I radiation pneumonitis and 1 case of grade II radiation pneumonitis). In VATS group, there were 3 cases of incision infection, 2 cases of pulmonary infection, 5 cases of pulmonary atelectasis, 1 case of pulmonary leakage and 1 case of deep vein thrombosis of lower extremity. The 3-year OS and PFS were 79.2% (42/53) and 67.9% (36/53) and 83.0% (44/53) and 77.4% (41/53) in SBRT group and VATS group, respectively. Kaplan-Meier survival showed no statistically significant differences in the OS and PFS between the two groups (log-rank).*

Conclusion: *SBRT achieves better RR and DCR, similar OS and PFS to those of typical thoracoscopic surgery, and good patient tolerance in the treatment of early-stage NSCLC, which is a safe and effective treatment means.*

Key words: *stereotactic radiotherapy, thoracoscopic surgery, non-small cell lung cancer, early stage, efficacy*

Introduction

Primary lung cancer is one of the most common tumors, of which non-small cell lung cancer (NSCLC) accounts for 75-80%. As to the treatment of early-stage NSCLC, surgery is a preferred method, and the postoperative stage I and II 5-year overall survival (OS) rates are 60-70% and 29-51%, respectively [1,2]. Stereotactic body radiotherapy (SBRT) is a non-invasive treatment method for patients who are unable or unwilling to undergo surgery due to advanced age or severe combined internal medicine diseases including heart and lung diseases. The method applies high-dose and

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low-segment radiation therapy to local tumors under precise image-guided techniques, with a local control rate of >95% [3,4]. At present, SBRT has become the standard treatment means for early-stage NSCLC patients who refuse surgical treatment or who are unable to undergo surgery. Moreover, SBRT is superior to surgery to some extent for patients at high surgical risk. Non-randomized trial studies have manifested that the local control rate and OS of SBRT are comparable to those of lobectomy [5-7]. Furthermore, SBRT achieves a relatively high local control rate and low toxicity for patients with peripheral lung metastases [8-10]. However, the comparative studies of the clinical efficacy of thoracoscopic surgery and SBRT in treating early-stage NSCLC are rare so far.

In this study, the clinical data of 106 early-stage NSCLC patients admitted to our Department from February 2014 to February 2016 were retrospectively analyzed. Among them, 53 patients underwent SBRT and the other 53 received video-assisted thoracoscopic surgery (VATS). The overall response rate (ORR), disease control rate (DCR), progression-free survival (PFS) and OS as well as common adverse reactions in patients were observed and recorded. The clinical efficacy and safety of the two treatment regimens were compared.

Methods

General data

This study was approved by the Ethics Committee of Gansu Provincial Hospital. Signed written informed consents were obtained from all participants before the study entry. A total of 106 operable stage I-II NSCLC patients admitted to our hospital from February 2014 to February 2016 were enrolled in this study and definitely diagnosed through biopsy or cytology. Exclusion criteria: Patients who had no measurable lesions, were intolerable to surgery, or had severe cardiopulmonary dysfunction, tumor metastasis during treatment, a Karnofsky performance status (KPS) score of <60 points, an estimated survival time of <3 months, cognitive dysfunction or mental illness, or those who were unable to cooperate in the treatment. The general characteristics of patients in the two groups before treatment (Table 1) showed no statistically significant differences (p>0.05). This study was approved by the Ethics Committee of our hospital. All patients enrolled complied with the Declaration of Helsinki, were informed of this study and signed the informed consent. Based on the treatment received, these patients were divided into SBRT group (n=53) and VATS group (n=53). In SBRT group, there were 33 males and 20 females aged 43-75 years (mean 60.3±9.0), and the diameter of tumor target area was 1-5 cm (mean 2.32±0.81). As to TNM stage there were 39 cases in stage I NSCLC and 14 in stage II NSCLC. In

Table 1. Baseline characteristics of the studied patients

Parameters	*SBRT group (n=53)* *n (%)*	*VATS group (n=53)* *n (%)*	*p value*
Age (years), mean±SD	60.3±9.0	58.7±10.3	0.396
Gender			
Male	33 (62.3)	37 (69.8)	0.539
Female	20 (37.7)	16 (30.2)	
Histological type			0.573
Squamous cell carcinoma	26 (49.1)	23 (43.4)	
Adenocarcinoma	21 (39.6)	26 (49.1)	
Others	6 (11.3)	4 (7.5)	
Clinical stage			0.698
IA	22 (41.5)	20 (37.7)	
IB	17 (32.1)	15 (28.3)	
II	14 (26.4)	18 (34.0)	
KPS score			0.366
≥80	38 (71.7)	42 (79.2)	
<80	15 (28.3)	11 (20.8)	
Location of tumor			0.830
Left upper lobe	19 (35.8)	23 (43.4)	
Left lower lobe	9 (17.0)	7 (13.2)	
Right upper lobe	11 (20.8)	13 (24.5)	
Right middle lobe	6 (11.3)	4 (7.5)	
Right lower lobe	8 (15.1)	6 (11.3)	
Tumor target diameter, mean±SD	2.32±0.81	2.43±0.77	0.475

SBRT: stereotactic body radiotherapy, VATS: video-assisted thoracoscopic surgery, KPS: Karnofsky performance status

VATS group, there were 37 males and 16 females aged 40-74 years (mean 58.7±10.3), and 35 cases in stage I NSCLC and 18 cases in stage II NSCLC, with the diameter of tumor target area of 1-5 cm (mean 2.43±0.77).

Therapeutic regimens

SBRT group: The 4D-computed tomography (CT) respiration control technique was used for simulation after position fixation. The scanning range was from the lower edge of the mandible to 5 cm below the costophrenic angle, and both the thickness and spacing were 3 mm. The 4D-CT was employed to track the motion of tumors and other internal organs during breathing. On PET-CT, gross tumor volume (GTV) referred to the primary tumor lesion, and clinical target volume (CTV) was equivalent to GTV. The internal target volume (ITV) was determined based on the range of motion and deformation information of GTV in the respiratory cycle. ITV + 3 mm outward = planning target volume (PTV). The above indexes were delineated. The planned CT scan and contour of each patient were input into the tomotherapy (TOMO) system, and treatment plans were developed. For peripheral lung cancer, the dosage was 5 times/week, 1 time/d, 10 Gy/time, for 5 times (the total dose was 50 Gy), while for central lung cancer, it was 5 times/week, 1 time/d, 6 Gy/time, for 10 times (the total dose was 50 Gy). During treatment, all plans were fully evaluated, and the dose on the organ at risk (OAR) should not exceed the tolerance dose. The 90% isodose line covered 100% of the PTV. The dose on OAR around the PTV should not exceed the tolerance dose. The total dose and contralateral dose should be small as far as possible. Besides, esophagus: ≤32.5 Gy, trachea and bronchus: ≤32.5 Gy, heart: ≤35 Gy, and brachial plexus: ≤30 Gy. For peripheral lung cancer, the average radiation dose was ≤6 Gy for spinal cord and <6 Gy for lungs, while in terms of central lung cancer, it was ≤13 Gy for spinal cord and <12 Gy for lungs.

VATS group: Video-thoracoscope-assisted pulmonary lobectomy was carried out with double-lumen tracheal cannula and one-lung ventilation anesthesia. A surgical incision (1.5 cm) was made on the 6th or 7th intercostal space of the midline of the operation side, and a thoracoscope was placed. Then, an incision (6-8 cm) on the 4th or 5th intercostal space of the ipsilateral midline was made as an operation hole. Next, the diseased lung lobe was resected, followed by left and right thoracic lymphadenectomy. Lastly, catheterization and sternal closure were performed after endothoracic water test.

Observation indexes

Short-term efficacy: The efficacy [complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD)] was evaluated according to response evaluation criteria in solid tumor (RECIST) at 6 months after treatment in the patients in SBRT group. ORR: The proportion of patients whose tumor volume reduced to the predetermined value for the minimum duration, ORR= CR + PR. Disease control rate (DCR): The percentage of the number of patients with PR, CR and SD after treatment in the number of evaluable cases, DCR= CR + PR + SD.

The KPS score was utilized to evaluate the functional status of the two groups of patients before treatment and 4 weeks after treatment. The score ranges from 0 to 100 point (s). The higher the score, the better the functional status. The fasting venous blood was collected before treatment and 4 weeks after treatment. An electrochemiluminescence immunoassay analyzer (Elecsys2010, Roche) was used to measure the levels of serum lung cancer-related tumor markers [carcinoembryonic antigen (CEA), neurone specific enolase (NSE), and cytokeratin 19 fragment (CYFRA21-1)].

Adverse reactions caused by radiation therapy were assessed or graded according to RTOG acute radiation injury grading standards and late radiation injury grading standards. Acute reactions referred to radiation therapy responses occurring from the 1st to 9th day of treatment. Late radiation reactions referred to radiation reactions occurring after 3 months from the day on which the radiation therapy was started.

Survival follow-up: All patients were followed up, and the OS and PFS were recorded. The patients lost to follow-up were deemed as censoring from the date of loss of follow-up. OS: The time from the start of randomization to death (for any reason). PFS: The time from the start of randomization to the progression of the tumor (in any aspect) or death (for any reason).

Statistics

SPSS 22.0 (IBM, Armonk, NY, USA) was used for statistical analyses. Measurement data were expressed as mean ± standard deviation, and t-test was employed for comparison between groups. Enumeration data were expressed as ratio (%), and x^2 test was used for comparison between groups. P<0.05 suggested that the difference was statistically significant. The survival curves were plotted using the Kaplan-Meier method, and log-rank test was used to assess differences among groups. P<0.05 indicated that the difference was statistically significant.

Results

Short-term efficacy

After treatment, there were 40 cases (75.5%) with CR, 10 cases (18.9%) with PR, 3 cases (5.6%) with SD and 0 case with PD among 53 patients in SBRT group, with a response rate (RR) of 94.3% (50/53) and a DCR of 100%.

Comparisons of the levels of serum tumor markers

Before treatment, the mean CEA level was 43.81±21.13 ng/mL and 45.08±20.31 ng/mL in the two groups, respectively, without statistically significant difference (p=0.753). After treatment, the serum CEA level was evidently lowered in the two groups, showing statistically significant difference (21.12±21.04 ng/mL *vs.* 23.84±19.18 ng/mL, p=0.488). The level of mean CYFRA21-1 in the two groups was 14.31±1.47 ng/mL and 13.85±1.96

ng/mL, respectively, before treatment, without statistically significant difference (p=0.175). This level was decreased in both groups after treatment without exhibiting statistically significant difference (6.81±1.93 ng/mL and 7.34±1.12 ng/mL, p=0.087). The mean NSE level before treatment was 36.11±5.73 ng/mL and 34.88±4.23 ng/mL in the two groups, respectively (p=0.212). After treatment, the mean NSE level was clearly decreased in the two groups, which was 21.61±3.66 ng/mL and 19.82±4.33 ng/mL, respectively, and the difference was not statistically significant (p=0.077) (Figure 1).

Comparison of quality of life after treatment

The mean KPS score before treatment was 72.37±5.19 points and 73.22±6.43 points, respectively, in the two groups, displaying no statistically significant difference (p=0.456). After treatment, the KPS score was elevated in both groups to some extent, i.e. 83.71±6.27 points and 81.65±7.78 points, respectively, but without statistically significant difference (p=0.136) (Table 2).

Comparisons of adverse reactions

SBRT therapy was well tolerated in patients with early-stage NSCLC, and no adverse reactions requiring the discontinuation of therapy occurred during the radiotherapy. Routine blood examinations were conducted regularly during the radiotherapy, and no obvious myelosuppression or adverse hematological reactions was/were observed. In SBRT group, 7 cases of radioactive skin reaction, 2 cases of grade I radiation esophagitis, 0 case of grade II or above acute radiation esophagitis, and 4 cases of radiation pneumonitis (including 3 cases of grade I radiation pneumonitis and 1 case of grade II radiation pneumonitis) were observed, 6 patients reported mild fatigue during radiotherapy, no grade IV acute radiation reaction occurred, and no patients had chest pain, hemoptysis or rib fracture. In VATS group, there were 3 cases of incision infection, 2 cases of pulmonary infection, 5 cases of pulmonary atelectasis, 1 case of pulmonary leakage and 1 case of lower extremity deep vein thrombosis. The specific adverse reactions in the two groups of patients are shown in Table 3.

Follow-up results of patient survival

After treatment, all 106 patients were followed-up for 6-60 months (mean 28.9±8.8) till February 2019. During the follow-up, the 1-year OS and PFS were 94.3% (50/53) and 92.5% (49/53) in SBRT group and 96.2% (51/53) and 94.3% (50/53) in VATS group. The 2-year OS and PFS in SBRT group and VATS group were 86.8% (46/53) and 81.8% (43/53) and 90.6% (48/53) and 86.8% (46/53), respectively. The 3-year OS and PFS were 79.2% (42/53) and

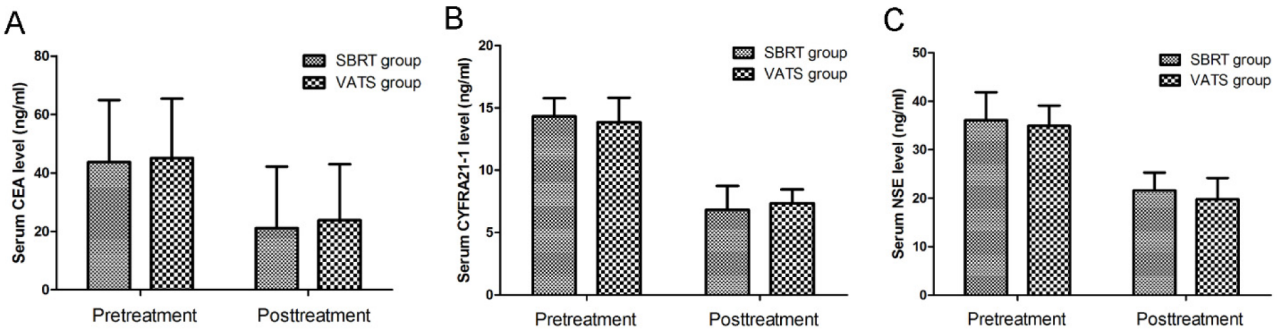

Figure 1. Comparison of serum NSCLC biomarkers level before and after treatment of patients in the two studied groups. **A:** The difference between pretreatment CEA levels of patients in SBRT group and VATS group had no statistical significance (p=0.753). The difference between posttreatment CEA levels of patients in SBRT group and VATS group had no statistical significance (p=0.488). **B:** The differences between pretreatment CYFRA21-1 levels and posttreatment CYFRA21-1 levels of patients in SBRT group and VATS group had no statistical significance (p=0.175, p=0.087). **C:** The differences between pretreatment NSE levels and posttreatment NSE levels of patients in SBRT group and VATS group had no statistical significance (p=0.212, p=0.077). SBRT: stereotactic body radiotherapy; VATS: video-assisted thoracoscopic surgery; CEA: carcinoembryonic antigen; CYFRA: cytokeratin fragment; NSE: neurone specific enolase.

Table 2. Comparison of KPS score before and after treatment of patients in the two studied groups (mean±SD)

KPS score	*SBRT group*	*VATS group*	*p value*
Pretreatment	72.37±5.19	73.22±6.43	0.456
Posttreatment	83.71±6.27	81.65±7.78	0.136

SBRT: stereotactic body radiotherapy, VATS: video-assisted thoracoscopic surgery

67.9% (36/53) in SBRT group and 83.0% (44/53) and 77.4% (41/53) in VATS group. The survival curves (Figure 2) using Kaplan-Meier method and log-rank test revealed that the OS and PFS exhibited no statistically significant differences between the two groups (p=0.777, p=0.440).

Discussion

Surgery is the standard treatment method for early-stage NSCLC, with a relatively high 5-year OS. VATS, a brand-new minimally invasive surgery, provides imaging assistance within the field and provides light source support in the surgery under direct vision so as to magnify and observe lesions and surrounding lesions from multiple angles. Besides, it creates small chest wall trauma, which not only keeps the integrity of the chest wall, but also promotes the recovery of postoperative cardiopulmonary function. In addition, it has the following advantages: small surgical incision, quick recovery and few complications [11,12]. However, some NSCLC patients cannot tolerate the surgery or refuse the surgical treatment because of advanced age and concurrent diseases, and their prognosis is poor. SBRT, mainly based on the principle of ray geometry focusing, accurately and stereoscopically quantifies cancer tissues. Compared with conventional radiotherapy, SBRT is characterized by high precision, high dose, high therapeutic gain ratio and low normal tissue irradiation around the target, which can reduce the number of fractions and single treatment dose, relieve the damage to surrounding normal tissues, help shorten the treatment course and avoid the accelerated re-proliferation of tumor cells. Moreover, it has a wide application scope and brings no pain [13,14]. The results of a multicenter phase II clinical trial RTOG0236 in the United States have suggested that SBRT is the first choice for peripheral stage I NSCLC for patients that cannot tolerate surgery [15]. In a multicenter and retrospective clinical study jointly conducted in Germany and Austria, 582 patients definitely diagnosed with stage I NSCLC from 13 research institutes from 1998 to 2011 were treated by SBRT and followed-up, and the results revealed that the 3-year local PFR and 3-year OS were 79.6% and 47.1% respectively, none of the patients had severe radiotherapy toxicity, and the radiotherapy-related side effects were within acceptable limits. This study demonstrated that SBRT is effective and relatively safe in the treatment of patients with stage I NSCLC [16]. A meta-analysis by Grutters et al [17] has proved that SBRT improves the local control rate in patients with stage I NSCLC, and its long-term efficacy prolongs the OS of patients.

Table 3. Comparison of adverse reactions of patients in the two studied groups

Adverse reactions	*SBRT group n (%)*	*VATS group n (%)*
Incision infection	0 (0)	3 (5.7)
Pulmonary infection	0 (0)	2 (3.8)
Pulmonary atelectasis	0 (0)	5 (9.4)
Pulmonary air leakage	0 (0)	1 (1.9)
Deep venous thrombosis	0 (0)	1 (1.9)
Radiation dermatitis	7 (13.2)	0 (0)
Radiation esophagitis	2 (3.8)	0 (0)
Radiation pneumonia	4 (7.5)	0 (0)

SBRT: stereotactic body radiotherapy, VATS: video-assisted thoracoscopic surgery.

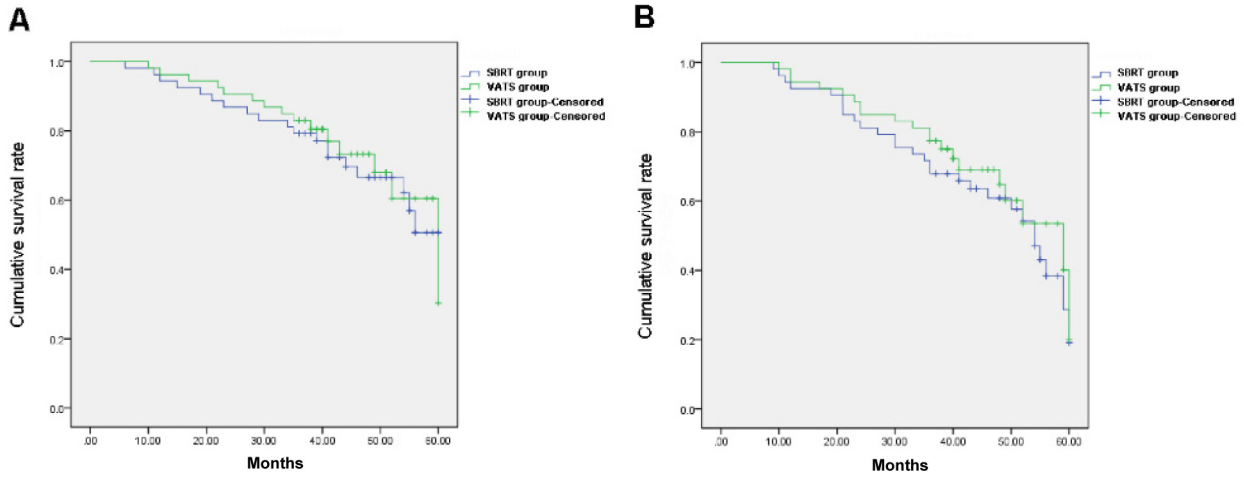

Figure 2. Kaplan-Meier survival curves of patients in SBRT group and VATS group. **A:** The difference between overall survival rate of patients in SBRT group and VATS group had no statistical significance (p=0.777). **B:** The difference between progression-free survival rate of patients in SBRT group and VATS group had no statistical significance (p=0.440).

At present, there are many clinical analyses on the efficacy of surgery and SBRT in the treatment of operable NSCLC, whereas prospective randomized controlled trials are still needed to compare the clinical efficacy of VATS and SBRT. Robinson et al [18] retrospectively analyzed the data of SBRT and surgery in treating stage I NSCLC and found that the median survival period of patients undergoing surgery and SBRT was 62.3 and 33.1 months, respectively. Crabtree et al [19] compared the efficacy of SBRT and surgery in the treatment of clinical stage I NSCLC and discovered that the 3-year local control rate of SBRT was 89%, and that of surgery was 96%. In this study, it was found that in 53 patients treated with SBRT, the RR was 94.3% (50/53), and the DCR 100%. There were no significant differences in the KPS score, CEA, NSE and Cyfra21-1 between the two groups. The 1-, 2- and 3-year OS and PFS were slightly higher in the VATS group than those in the SBRT group, but the differences were not statistically significant, which are basically consistent with the results reported in the literature. Moreover, this study explored the adverse reactions in the two groups of patients. Incision infection and pulmonary atelectasis were mainly observed in VATS group, while radioactive skin reaction, radiation pneumonitis and radiation esophagitis were prevailingly found in SBRT group. Besides, there was no death due to side effects in the two groups. Since the reactions were diverse between the two groups, statistical analysis was not carried out. However, Yuan et al [20] pointed out that the risk of treatment-related side effects or complications in the SBRT group is lower than in the surgery group.

The confounding factors in the efficacy comparison of SBRT and VATS are complex, including clinical stage, tumor size, radiotherapy dose, bronchioloalveolar carcinoma (BAC), pathological type, peripheral or central location of NSCLC, and the degree of operability in patients. Studies by Baba et al [21] and Ricardi et al [22] have shown no difference in local control rate between stage Ia and stage Ib tumors despite different tumor sizes. However, whether increased SBRT dose is beneficial for slightly larger tumors needs to be further studied. In comparison with other NSCLC subtypes, BAC is likely to have similar failure and survival patterns after SBRT treatment, and may also have increased risk of distant metastases [23]. The OS of patients with central lung tumor treated with SBRT is considerable, and the OS and local PFS are better in central NSCLC than those in peripheral NSCLC [24,25].

This study was a single-center retrospective study and had certain shortcomings: The sample size was small, the follow-up period was short, and the possible effects of many confounding factors on the efficacy were not excluded. In the future, further prospective multicenter randomized controlled trials with a large sample size are needed to support the results of this study, thereby providing references for selecting treatment options for early-stage NSCLC in clinical practice.

Conclusions

SBRT is able to achieve better RR and DCR in the treatment of early-stage NSCLC, with similar OS and PFS of patients to those of typical thoracoscopic surgery and good patient tolerance, which makes it a safe and effective treatment method.

Conflict of interests

The authors declare no conflict of interests.

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