Original Article

Clinical Effect of the Cryoablation and Endostar on advanced non-small cell Lung Cancer

Ji-fu Liu MD, Bo Xu MB, Jing Zhao MM, Hui-feng Liu MD

Department of Thoracic Surgery, General Hospital of Beijing Military Region, PLA , N0 5 Nan Men Cang, 100700, Beijing, P.R.China

ABSTRACT **Object:** To investigate the curative effect of cryoablation combining with endostar applied locally for advanced non-small cell lung cancer (NSCLC). **Method:** This study was conducted from July 2007 to November 2008. One hundred and ninety-two patients with NSCLC were divided into two groups. In group 1, one hundred and two patients were treated continuously with cryocare system combining with endostar. Fifteen mg of endostar were injected into tumors before the cryoablation. In group 2, ninety patients were treated with cryocare system only. Two weeks after cryoablation, bronchial artery infusion chemotherapy was performed. Tumor size and hemoperfusion situation were evaluated within the next two months. **Results:** Patients' general condition(spirit condition, physical ability, body weight), appetite, chest distress, cough improved obviously in the above two groups. The tumors shrank by (35±15)% in group 1 and (25±12)% in group 2. The density of contrast-enhanced computer tomography (CT) in tumor area in the two groups was: 29±20HU before enhanced-CT scan and 31±14HU after enhanced-CT scan in group 1; 33±22HU before enhanced-CT scan and 38±16HU after enhanced-CT scan in group 2. There was significant difference between these two groups after enhanced-CT scan（P ＜0.05）.

Conclusion: The cryoablation combining with endostar applied locally for advanced NSCLC might reinforce curative effects.

Key Words: advanced lung cancer; targeted cryoablation therapy; endostar; anti-tumor drug.

The targeted cryoablation therapy for advanced NSCLC has demonstrated good effects; however the therapy hardly cover the tumor in the case that the tumor is big, which may affect the range and speed of tumor shrinking. To improve the effect, we treated the advanced NSCLC by cryoablation combining with endostar applied locally in the last two years, which is compared to the therapy of cryoablation only. Our results are as follows:Cryoablation combining Endostar for the target treatment of advanced NSCLC may raise a curative effect . The target area CT value changes of prior- and post-enhanced CT is an objective and useful index for definite effect.

CLINICAL DATA AND METHOD

One hundred and ninety-two patients with NSCLC, mostly accompanied with malignant pleural effusion, N3 lymph nodes and distant organs metastasis which are mainly in brain, bone, liver and adrenal gland, were diagnosed as clinical pathological stage IIIb and IV. The primary focuses in lung were treated with cryoablation. According to the size of the tumor, 1～4 cryo-hit in the tumor were given.

The detailed processes are in the following.Firstly, the temperature in the target region dropped rapidly to minus 136～145℃, lasting for 15～20 min, and then increased rapidly

The authors have no commercial,proprietary,or financial interest in the products or companies described in this article.

Corresponding author:Liu Ji-fu MD,Department of Thoracic Surgery, General Hospital of Beijing Military Region, PLA , N0 5 Nan Men Cang, 100700, Beijing, P.R.China,E-mail: liujf200809@sina.com,Tel:010 66721203, Mobile: 13910599873

ISSN:1538-5124/$-see front matter

to 25～33℃,lasting for 5 min. This is a cycle. Every focus requires two freezing-thawing cycles. The freezing ranged about 90%～100% of tumor.According to admitting order one hundred and ninety-two patients were divided into two groups . Patients in group 2 were treated with cryoablation only. Clinical data were in the following: Ninety patients including 68 male and 22 female ones with the age ranging from 30 to 84 and averaging 60.6±8.9. Tumor size ranged from 3㎝×2㎝ to 7㎝×6.5㎝. Karnofsky score ranged from 40 to 90, averaging 60±15. Group 1 received cryoablation and endostar locally applied, 15 mg of endostar was injected into tumor 5 min before cryoablation. Clinical data are in the followings: One hundred and two patients including 74 male and 28 female ones withthe age ranging from 28 to 90, and averaging 61.1±10.9 years. Tumor size ranged from 3㎝×3㎝ to 8 ㎝×7㎝. Karnofsky score ranged from 40 to 90, averaging 57±25. (Table1)

Table 1 Patient's basic condition

Group	Sex		Age	Tumor size(㎝)
	M	F		
Group1	74	28	61.1±10.9	3-8
Group2	68	22	60.6±8.9	3-7

The above two groups received bronchial artery infusion chemotherapy (90mg of cis-platinum and 16mg of mitomycin) one week after the treatment. Patients with brain metastasis received r- ray treatment in two weeks. Index observation: Two months later, chest enhanced-CT rechecked. The changes of tumor size by measuring the maximal diameter of tumor and that of CT value pre- and post -enhanced-CT within tumor, the improvement of patient's general situation and symptoms were recorded.

Statistical analysis: Statistical analysis was performed using statistical package SPSS 11.0, the data were analysed by x2 test, and P<0.05 was considered statistically significant.

RESULTS

Almost all the patients recovered after treatment. The symptoms of appetite, chest distress, cough and general condition were greatly improved. There was no significant difference between these two groups. In group 1 one patient who died of dyscrasia and exhaustion 3 weeks after treatment was excluded. Tumor size shrinking: Tumors in group 1 shrank about 25%～56%, averaging (35±15)%. Among them 15 cases shrank above 50%. Patients who got partial remission (PR) accounted for 14.7%. Tumors in group 2 shrank about 23%～48%, averaging (25±12)% with no patient shrank above 50%. There was significant difference between the two groups（P＜0.05）.

Density of tumor area: patients in two groups all received enhanced-CT scan after treatment. In group 1, CT value was about 25～32HU before enhancement, averaging 29±20HU; about 27～35HU after enhancement, averaging 31±14HU. In group 2, CT value was about 24～45HU before enhancement, averaging 33±22HU; about 29～46HU after enhancement, averaging 38±16HU. There was significant difference on CT value of post-enhancement between the two groups (P＜0.05). (Table 2) Complications: 10 patients had pneumatothorax after treatment, 4 patients of which treated with thoracic close drainage, the others recovered with thoracentesis. No haemothorax happened.

DISCUSSION

The morbility and mortality of lung cancer now rank the top of cancers. The symptomatic relief time of patients with advanced NSCLC was only 2～7 months by using second-line chemotherapeutics[1]. Recently, cryoablated targeted therapy using Cryocare system for advanced NSCLC has been reported [2,3]. However there is no satisfactory method to assess the cryoablation effect by far. The changes of CT value between prior- and freeze-up were used as curative effect index [4], which can only reflect cryoablation coverage in fact but not curative effect. We combined cryoablated targeted therapy with local application of anti-tumor drug to see whether this kind of treatment can improve curative effect for advanced NSCLC. Our research had received some promising results.

The changes of tumor volume could be used as an index of curative effect. In early stages after treatment, the interior of tumor started bleeding, exudation and edema because of the intervene of cryo-hit, leading to tumor volume getting bigger than before, so we cannot use tumor size as curative effect index in this period, although tumor cells had already been necrosis. One month after treatment, swelling tumor tissue became regression and necrosis tumor tissue became fibrosis, tumor volume began to

Table 2 Two groups therapy results

Group	Tumorshrinking (%)	PR(%)	CT Value(HU)	
			Pre-E	Post-E
Group1	35±15※	14.7	29±20	31±14※
Group2	25±12	0.0	33±22	38±16

PR: partial responed; Pre-E : Pre-enhanced CT; Post-E : Post-enhanced CT ※P＜0.05

shrink, in this period the shrinking extent of tumor was a useful index. In our study, we found that shrinking extent of tumor in group 1 was bigger than that in group 2, indicating targeted cryoablation therapy combining with local application of anti-tumor drug can produce additive action on curative effect.

The process of rapid freezing and thawing of cryo-hit not only led to tumor cells burst into death, but also cause injury to endothelial cells of tumor capillaries and result in thrombopoiesis, which worsen avascular necrosis of tumor. The local application of endostar may aggravate the destructiveness of uncovered tumor tissue and surrounding capillaries. Dynamic enhanced-CT scan, which can objectively and scientifically evaluate the capillary density and blood supply of tumor by using of CT value changes, is a useful observational method. The CT value changes of target area between prior- and post-enhanced-CT scan can reflect the capillary density and blood supply of tumor. Tateishi studied the Standard uptake value (SUV)of FDG-PET, relative blood supply of enhanced-CT and capillary density of operative specimens and found that the 3 indexes had significant correlation[5].

Romaneehsenperformed cryoablation to tumor model in mice and observed the relationship between imaging features post-enhanced-MRI and histopathologic changes[6]. Tumor blood supply was good before cryoablation. After the treatment, tumor area showed no enhanced feature. There was only narrow strip of enhancement around the tumor like hyperemia feature, but no enhanced feature in tumor area. These results suggested that enhanced imaging in the post-treatment was a scientific index which can objectively reflect tumor blood supply. Our research took enhanced-CT scan as an index of curative effect and compared CT value of target area of group 1 to group 2. Our results indicated that there was significant difference between these two groups and capillary destruction of tumor area was more apparent in group 1, which were in accordance with that of enhanced-MRI in animal experiment [6].

All patients in our research received bronchial artery infusion chemotherapy after cryoablation. The management played a role in curing biggish endobronchial tumor and metastatic mediastinal lymph nodes, and compensated the treatment to the positions where the cryo-hit cannot reach, and kept the treatment method of both groups to be conformity and made the curative effect to be comparable. The follow-up time is not long enough, but the results can represent near-term curative effect. Long-term effect follow-up is ongoing.

Although Karnofsky score between two groups had no significant difference, the improvement of respiratory symptoms, physical activity and appetite can also objectively reflect the curative effect. The observation to symptom changes should be further detailed and graded, quantitative standards is better for judgment.

In one word, cryoablation combining with endostar applied locally, which can aggravate the destructiveness of tumor capillaries and worsen the necrosis of tumor cells, is better for local control to advanced NSCLC.

REFERENCES

1. de Ma rinis F, Pereira JR, Fossella F, et al. Lung Cancer Symptom Scale outcomes in relation to standard efficacy measures: an analysis of the phase III study of pemetrexed versus docetaxel in advanced non-small cell lung cancer. J Thorac Oncol. 2008, 3:30-36.
2. Liu Ji-fu, Li Ying-chun, Wu Shan-shan, et al. Probe into cryo-ablation treatment of advanced pulmonary neoplasms. Chinese J of Clin Oncol and Rehabil. 2006，13:355～357.
3. Zhang Zong-cheng, Li Kai-bin, Jiang Jian-xiao, et al. Clinnical observation of cryo-care system treatment for advaced lung cancer. J of Oncol Clin. 2003，8:193～194.
4. Chen Shu-chang, Chen Jian-min, Chen Hua, et al. Cryo-care system target combined with chemotherapy for advanced non-small cell lung cancer. Shan Dong Medicine. 2007,47:56～57.
5. Tateishi U, Nishihara H, Tsukamoto E, et al. Lung tumors evaluated with FDG-PET and dynamic CT: the relationship between vascular density and glucose metabolism. J Comptu Assist Tumor. 2002, 26:185-190.
6. Romaneehsen B, Anders M, Rohrl B, et al. Cryotherapy of malignant tumors: studies with MRI in an animal experiment and comparison with morphological changes. Rofo, 2001, 173:632-638.