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Original Article

Clinical effect of cold and heat ablation on patients with advanced lung cancer and its influence on immune function

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Abstract: Objective: This study was designed to explore the clinical effect of cold and heat ablation on patients with advanced lung cancer (LC) and its influence on immune function. Methods: Data of 104 cases of advanced LC treated between July 2015 and April 2017 in the First Affiliated Hospital of Hunan University of Chinese Medicine were retrospectively analyzed. Among them, 49 patients receiving argon helium cryoablation (AHC) were regarded as group A, and 55 patients receiving radiofrequency ablation (RFA) were regarded as group B. The short-term postoperative efficacy and local tumour control rate were compared between the two groups. The changes in immunoglobulin G (IgG), immunoglobulin A (IgA) and immunoglobulin M (IgM) were compared between the two groups before and after treatment. After treatment, the changes in carcinoembryonic antigen (CEA) and cytokeratin 19 fragment (CYFRA21-1) were compared between the two groups. During the treatment, the complications and incidence of adverse reactions were compared between the two groups. Cox regression analysis was applied to analyze the factors influencing the prognosis of patients. Results: There was no statistical difference in IgA, IgG and IgM between the two groups after treatment (P>0.05). There was no statistical difference in CEA and CYFRA21-1 between the two groups after treatment (P>0.05). There was no notable difference in disease control rate and response rate between the two groups at 3 and 6 months after operation (P>0.05). The incidence of pleural effusion in group A was obviously lower than that in group B (P<0.05). The incidence of intraoperative pain in group A was obviously higher than that in group B (P<0.05). Age, clinical stage, CEA and CYFRA21-1 were found to be independent prognostic factors impacting overall survival (P<0.05). Conclusion: AHC and RFA are minimally invasive procedures that lead to few complications in the treatment of advanced LC. Cold and heat ablation is a relatively safe and effective minimally invasive technique for tumour treatment, which is worthy of application and promotion in the clinical treatment of LC.

Keywords: Argon-helium cryoablation, radiofrequency ablation, advanced lung cancer, immune function

Introduction

Lung cancer (LC) is one of the malignant tumours with the highest morbidity and mortality in China. According to statistics, non-small cell lung cancer (NSCLC) accounts for 80-85% of LC, and it is a primary cause of death in patients with malignant tumours worldwide [1]. According to the statistics released by the National Cancer Center in January 2019 [2], the incidence and mortality of LC in China ranked the first in 2015. It has been reported that the 5-year survival rate in LC patients in China is only 19.8%, which is much lower than 32.9% in Japan and 25.1% in Korea [3]. One reason for this gap is the large number of advanced cases of LC in China, because of a high rate of late diagnosis [4]. Currently, the treatment methods for LC are surgery and drug therapy, and drug therapy includes chemotherapy, radiotherapy, targeted therapy, immunotherapy and interventional therapy [5].

Surgery is the first choice for the early treatment of LC. However, only about 20% of patients with LC can be found early and undergo radical

surgical resection because of the insignificant early symptoms [6]. Accordingly, most patients are in the advanced stage at the time of diagnosis. Although radiotherapy and chemotherapy have achieved good clinical results, the quality of life of patients is greatly affected by serious adverse reactions after treatment [7]. Over the past few years, the advent of the corresponding targeted drugs has obviously prolonged the survival time and improved the prognosis of patients, but the application of targeted therapy is still limited by acquired drug resistance and side effects [8]. Therefore, it is still necessary to explore more effective, safe and low drug resistance treatment methods for NSCLC.

With the continuous improvement of minimally invasive techniques, microwave ablation, radiofrequency ablation (RFA) which focused ultrasound ablation and argon helium cryoablation (AHC) are gradually applied in clinic [9, 10]. Tumour ablation has been recommended by NCCN and ESMO guidelines for malignant tumours such as hepatocellular carcinoma and NSCLC [11]. RFA can not only cause coagulation necrosis of tumours, but also expose tumour antigens, forming tumour necrosis factor (TNF) and interleukin (IL) to stimulate the immune response [12]. Additionally, a series of experiments have shown that tumour necrosis release tumour antigens after cryoablation, which induces specific immune response and improves the immune function of tumour patients through the processes of adsorption and presentation of antigen presenting cells [13].

This research was designed to analyse the short-term curative effect and the difference of immune function after AHC and RFA in patients with advanced LC, so as to provide a basis for the optimization and further application of minimally invasive treatment of LC.

Methods and materials

Clinical data

Data of 104 cases of advanced LC treated between July 2015 and April 2017 in The First Affiliated Hospital of Hunan University of Chinese Medicine were retrospectively analysed. Among them, 49 patients receiving AHC were regarded as group A, and 55 patients receiving RFA were regarded as group B. This study was approved by the Medical Ethics Committee of The First Affiliated Hospital of Hunan University of Chinese Medicine.

Inclusion and exclusion criteria

Inclusion criteria: ① patients who were diagnosed with primary LC by histological or cytological examinations before surgery; ② patients with surgically unresectable advanced LC; ③ patients with intrapulmonary metastatic carcinomas that had been controlled and the number of metastases did not exceed 3; ④ patients whose lesions could be treated locally by AHC or RFA; ⑤ patients whose T cell subsets were detected in peripheral blood before and after operation; ⑥ patients with complete clinical data.

Exclusion criteria: ① patients who were treated with EGFR-TKIs targeted drugs; ② patients with severe coagulation dysfunction; ③ patients who had taken drugs affecting immune function within 3 months before treatment; ④ patients with cardiopulmonary insufficiency or liver and kidney insufficiency; ⑤ patients with expected survival time less than 3 months.

Main instruments and equipment

CRYO-HITTM low temperature refrigeration system (Ualil Medical, Israel) and Cool-tip radiofrequency ablation system (American, Weili) were applied.

Therapeutic schemes

According to the preoperative enhanced CT and/or PET/CT examinations, the location and number of tumours, the surrounding organs, blood vessels, nerves, etc. were determined, and a reasonable needle insertion path and ablation range were worked out. Based on the location of the tumour and the basic situation of the patient, an appropriate body position was selected, labelled line was affixed, and CT scan was conducted to determine the location of the tumour, the puncture point, the angle and depth of the needle insertion. The doctor carried out routine disinfection and wore sterile gloves. The 2% lidocaine (5 ml) was extracted with a syringe, and local infiltration anaesthesia was performed layer by layer along the puncture point. Simultaneous injection and retraction were performed so as to not inject the

anaesthetic into the bloodstream during local anaesthesia.

AHC procedures: A number of argon-helium cryoprobes with a diameter of 1.47 mm were used to test the needle in vitro and ensure the normal operation of the cryoprobes. According to the preoperative plan, the needles were inserted in a step-by-step manner and distributed in accordance with the appropriate situation. After the needles were inserted to the ideal position, three-dimensional reconstruction was carried out if necessary, and the spatial position of the cryoprobes was defined. The distance between the cryoprobes and blood vessels, trachea, nerves and gastrointestinal tract was carefully evaluated to avoid possible damages caused by cryoablation. The basic principle of needle placement was that the distance between the needle and the great vessel and trachea was generally 5 mm to 10 mm, and the distance between each needle was kept between 10 mm and 20 mm. ECG was adopted for monitoring the vital signs of patients. The argon-helium cryotherapy system was connected and frozen at maximum pressure. Meanwhile, sterile gloves were filled with warm water to protect the skin of the surgical area. CT scan was performed every 6 to 8 min to monitor the size of the ice ball, and coronal and sagittal reconstructions were performed when necessary to understand the extent of ablation and the relationship between ice ball and major organs. The ablation range was determined to be ideal, and then rewarming for 1 to 2 min was used as one treatment cycle. Generally, 2 cycles were appropriate. At the end of the operation, CT scan showed that the lesion site was a large area of ground-glass density. The ablation of the tumour was completed, that is, the ablation range was ideal, so the treatment cryoprobes could be withdrawn. The puncture site was covered with sterile dressing, and CT scan was carried out to check whether there was bleeding or pneumothorax after operation. Patients with postoperative pain were given symptomatic treatment such as dezocine and kyffin.

RFA procedures: The radiofrequency electrode needle was used and inserted into the planned depth in a step-by-step manner according to the planned needle insertion angle along the positioning point. If necessary, three-dimensional reconstruction was performed to determine the position of the needle tip. The distance between the needle and blood vessels, trachea, nerves and gastrointestinal tract was carefully observed. After the needle was determined to enter the ideal position, the RFA system was turned on (the power mode was 120 W and the ablation time was 12 min). ECG was adopted to monitor the vital signs of patients. During ablation, normal saline was injected through the pinhole gap of the electrode needle to prevent the tissue from charring. Basic principles: The edge of the ablation focus was 5-10 mm beyond the edge of the tumour. At the end of the operation, CT scan showed that the lesion site was a large area of ground-glass density. The ablation of the tumour was completed, that is, the ablation range was ideal, so the radiofrequency electrode needle could be withdrawn. Needle-track ablation should be done before withdrawal of the radiofrequency electrode to reduce the probability of neoplasm seeding or bleeding. The puncture site was covered with sterile dressing, and CT scan was performed to check whether there were complications such as bleeding and pneumothorax. Electrocardiogram was used for monitoring for 24 hours after operation, and patients with mild complications were given symptomatic treatment.

The edge of the ablation focus was 5-10 mm beyond the edge of the tumour. When the tumour is large (≥5 cm), multiple or multi-point ablation was performed. When the tumour is near the pleura, the path was designed to avoid direct puncture of the tumour, and the needle was inserted along the long axis of the tumour as far as possible. When the tumour is near the major organs, artificial isolation techniques (artificial pneumothorax, artificial water injection, etc.) were applied, and the operation was stopped when the ablation edge was approximate 5 mm away from the major organ. When patients had neurological symptoms, the operation should be stopped immediately, and the radiofrequency needle or probe was withdrawn from the vicinity of the nerve track area. When there was nerve injury during the operation, trophic nerve treatment and other drugs were given after the operation.

Detection of immune indexes

The venous blood (3 ml) was drawn from patients at 1 day before treatment and two

weeks after treatment. Immunoturbidimetry was used for detecting the levels of immunoglobulin G (IgG), immunoglobulin A (IgA) and immunoglobulin M (IgM) in the serum.

Detection of tumour markers

The venous blood of the patients was drawn at 1 day before treatment and two weeks after treatment, placed statically for 30 min and centrifuged at 1500 g for 15 min. The supernatant was obtained. The levels of carcinoembryonic antigen (CEA) and cytokeratin-19-fragment (CYFRA21-1) were detected by the Roche E602 electrochemiluminescence instrument.

Efficacy evaluation

The efficacy was evaluated according to the modified RECIST [14]. Complete response (CR): after operation, the lesions showed low density and no enhancement shadow in arterial phase; partial response (PR): in contrast to the baseline, more than 70% of the lesions showed low density and no enhancement shadow in arterial phase at one month after operation; progressive disease (PD): the necrosis of the ablated lesions was not obvious or new lesions appeared; stable disease (SD): after ablation, the necrotic area of the lesion was less than 70%, which did not meet the above conditions. Objective response rate (RR) % = (CR+PR) cases/total cases × 100%. Disease control rate (DCR) = (CR+PR+SD) cases/total cases × 100%.

Clinical efficacy evaluation also included local control rate and overall survival (OS) rate. The local control rate was determined according to the absence of enhanced lesions in the ablation area in enhanced CT scan. The death of patients was the end point of follow-up.

Outcome measures

Primary outcome measures: The short-term postoperative efficacy and local tumour control rate were compared between the two groups. The changes in IgA, IgG and IgM were between the two groups compared before and after treatment. After treatment, the changes in CEA and CYFRA21-1 were compared between the two groups.

Secondary outcome measures: The clinical data of the two groups were compared. During the treatment, the complications and incidence of adverse reactions were compared between the two groups. Cox regression analysis was conducted to analyse the factors influencing the prognosis of patients.

Statistical analysis

All the experimental data in this research were statistically analysed using SPSS 20.0 analysis software. The measuring materials with a normal distribution were expressed by mean value ± standard deviation (mean ± SD). T test was applied to compare measuring materials with normal distribution and homogeneity of variance. The counting data were statistically described by frequency (N) and percentage (%). Kaplan-Meier was used for survival analysis, and the survival rate was compared by Log-rank test. Cox regression analysis was applied to analyse the factors affecting the prognosis. The difference was statistically significant when $P<0.05$.

Results

Comparison of clinical data

By comparing the clinical data of patients in both groups, it was found that there was no statistical difference in the age, sex, smoking history, pathological type, tumour size and clinical stage between the two groups ($P>0.05$, **Table 1**).

Changes in immune function indexes after treatment

The changes in IgA, IgG and IgM were compared between the two groups before and after treatment. The results showed that there was no significant difference between the two groups before treatment ($P>0.05$). After treatment, the IgA, IgG and IgM in both groups increased significantly ($P<0.001$). Further comparison showed no significant difference in IgA, IgG and IgM between the two groups after treatment ($P>0.05$, **Figure 1**).

Changes of tumour markers in patients after therapy

By comparing the changes in tumour markers after treatment, it was found that there was no statistical difference in CEA and CYFRA21-1 between the two groups before treatment

Table 1. Comparison of patients' clinical data

Factors	Group A (n=49)	Group B (n=55)	χ^2 value	*P* value
Age			0.715	0.397
≥60	35	35		
<60	14	20		
Sex			0.227	0.633
Male	29	30		
Female	20	25		
Smoking history			0.473	0.491
Yes	30	30		
No	19	25		
Pathological types			0.358	0.549
Adenocarcinoma	33	40		
Non-adenocarcinoma	16	15		
Tumour size			0.457	0.498
≥3 cm	21	20		
<3 cm	28	35		
Clinical stage			1.417	0.234
Stage IIIb	28	25		
Stage IV	21	30		

(P>0.05), but after treatment, CEA and CYFRA21-1 of the two groups obviously decreased (all P<0.001). Further comparison revealed that there was no statistical difference in CEA and CYFRA21-1 between the two groups after treatment (P>0.05, **Figure 2**).

Comparison of short-term efficacy

The clinical efficacy was evaluated at 3 months and 6 months after operation. The results revealed no statistical difference in DCR and RR between the two groups at 3 months (P>0.05, **Table 2**) and 6 months after operation (P>0.05, **Table 3**).

Complications and adverse reactions during treatment

During the treatment, the complications of the two groups was statistically analysed, and the patients with pleural effusion in group A were obviously fewer than those in group B (P<0.05, **Table 4**). In addition, we statistically analysed the adverse reactions in both groups and found that more patients in group A showed intraoperative pain than those in group B (P<0.05, **Table 5**).

Prognostic analysis of patients with LC

At first, we compared the survival rates of patients received different surgical methods. In our research, we found no statistical difference in OS between the two groups (P>0.05, **Figure 3**). Then, the survival data of patients were collected, and the prognosis of patients was statistically analysed by univariate Cox regression analysis. Univariate analysis found that age, clinical stage, CEA, CYFRA-21-1 were factors affecting the prognosis of patients. Further multivariate analysis showed that age, clinical stage, CEA, CYFRA21-1 were independent prognostic factors affecting OS (P<0.05, **Table 6**).

Discussion

LC as one of the primary diseases that seriously threaten human life, greatly impacts the physical and mental aspects of the patients [15]. Surgical resection is the primary treatment. Because of the old age of patients, basic diseases and high surgical risks, less than 30% of patients with LC can receive surgical resection [16]. The commonly used treatment scheme for advanced LC is comprehensive treatment based on radiotherapy and chemotherapy. For most patients, the single treatment mode is a major problem for the treatment of LC [17].

In the past 20 years, more local ablation techniques for LC have been applied in clinical practice, including RFA, microwave ablation, AHC, etc., all of which cause irreversible damage to tumour cells through extreme temperature to achieve the purpose of eliminating tumours [18]. RFA is an ablation technique that is widely used in the treatment of LC at present. The radiofrequency electrode is pierced into the tumour tissue, and the ions in the tumour tissue oscillate and rub against each other under the action of high-frequency alternating current. When the temperature reaches 60°C-100°C, it can cause coagulation necrosis of tumour cells, thus achieving the goal of destroying the tumour [19, 20]. AHC is designed to uses gas throttling effect to destroy tumour tissue through repeated rapid cooling and heating cycles [21]. When frozen, cell membrane can be destroyed, and intracellular proteins can be

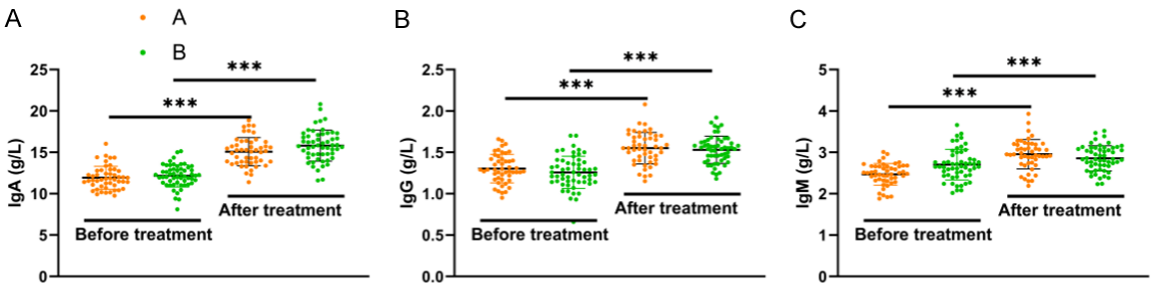

Figure 1. Comparison of changes in immune indexes before and after treatment. A. Changes in IgA before and after treatment. B. Changes in IgG before and after treatment. C. Changes in IgM before and after treatment. Note: *** means P<0.001, immunoglobulin (Ig).

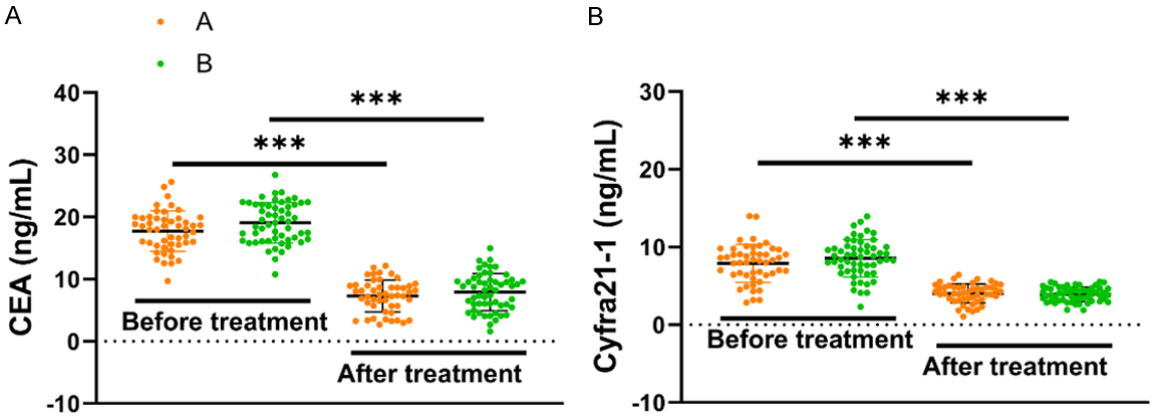

Figure 2. Changes of tumour markers in patients before and after treatment. A. Changes of CEA in patients before and after treatment. B. Changes of CYFRA21-1 in patients before and after treatment. Note: *** means P<0.001, carcinoembryonic antigen (CEA), cytokeratin 19 fragment (CYFRA21-1).

Table 2. Comparison of clinical efficacy after operation for 3 months

Groups	CR	PR	SD	PD	DCR	RR
Group A (n=49)	23 (46.94%)	12 (24.49%)	8 (16.33%)	6 (12.24%)	43 (87.76%)	35 (71.43%)
Group B (n=55)	24 (43.64%)	11 (20.00%)	11 (20.00%)	9 (16.36%)	46 (83.64%)	35 (63.64%)
χ^2 value					0.356	0.715
P value					0.550	0.397

Note: complete response (CR), partial response (PR), progressive disease (PD), stable disease (SD), response rate (RR) % = (CR+PR) cases/total cases × 100%, disease control rate (DCR) = (CR+PR+SD) cases/total cases × 100%.

Table 3. Comparison of clinical efficacy after operation for 6 months

Groups	CR	PR	SD	PD	DCR	RR
Group A (n=49)	23 (46.94%)	8 (16.33%)	11 (22.45%)	7 (14.28%)	42 (85.72%)	31 (63.27%)
Group B (n=55)	25 (45.45%)	10 (18.18%)	8 (14.55%)	12 (21.82%)	43 (78.18%)	35 (63.63%)
χ^2 value					0.984	0.001
P value					0.321	0.968

Note: complete response (CR), partial response (PR), progressive disease (PD), stable disease (SD), response rate (RR) % = (CR+PR) cases/total cases × 100%, disease control rate (DCR) = (CR+PR+SD) cases/total cases × 100%.

released, including cytokines and danger signals. Cytokines can promote the maturation of antigen presenting cells and lymphocyte proliferation, thus promoting immune response [22].

Table 4. Postoperative complications of patients

Complications	Pneumothorax	Haemorrhage	Pleural effusion
Group A (n=49)	10	8	1
Group B (n=55)	12	6	7
χ^2 value	0.030	0.652	2.041
P value	0.860	0.419	0.041

Table 5. Adverse reactions of patients

Adverse reactions	Intraoperative pain	Postoperative fever	Diarrhoea
Group A (n=49)	15	5	3
Group B (n=55)	6	7	4
χ^2 value	6.243	0.161	0.054
P value	0.012	0.697	0.815

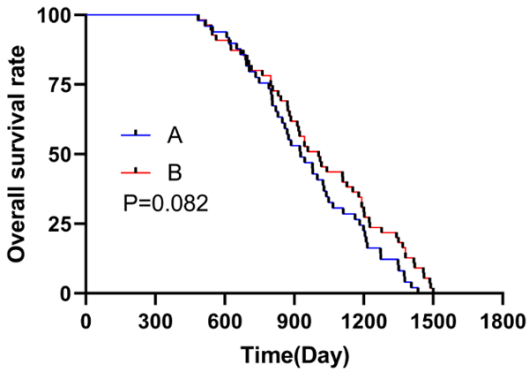

Figure 3. Comparison of overall survival after two different treatments. A: Group A. B: Group B.

Currently, there are few comparative studies on RFA and AHC in the treatment of LC, and the comparison of the two local treatment methods mainly focuses on liver tumours. A previous retrospective study revealed that the median survival time and progression-free duration of patients with complete ablation were obviously longer than those of patients with partial ablation after RFA and AHC, and it was found that complete ablation and incomplete ablation were closely related to mortality [23]. But there were only 9 cases of AHC in their study.

In the present study, we compared the clinical efficacy of patients between the two groups at 3 months and 6 months. Recent CT evaluation within 1 month to 3 months was defective, so the clinical efficacy of patients 6 months after treatment was observed simultaneously. During this period, the reactive hyperaemia and fibrous tissue hyperplasia in the focus and surrounding areas generally haven't disappeared, and the size of the ablation area is stable or gradually shrinks after 6 months, and there may be fibrosis, nodules and disappearance [24]. RR and DCR at 3 months and 6 months were not statistically different between the two groups treated with either RFA or AHC regimens, indicating that the two local ablations were both safe and effective in the treatment of LC. In addition, this research compared the OS of patients after treatment with the two methods. Through analysis, it was found that there was no difference in OS between the two groups after treatment. It showed that the two ablation methods in this research were effective in the control rate of LC, but did not affect the survival time of patients. The reason may be related to the combination of multiple fine needles with argon-helium knife, repeated ablation, good pain tolerance of patients during operation, frozen immune effect, etc. [25]. Therefore, we further studied the effects of two treatment methods on immune response and tumour markers.

In this study, the changes in IgA, IgG and IgM were compared. After treatment, IgA, IgG and IgM in both groups increased notably, but the two groups were not greatly different in the levels after treatment. In terms of tumour markers, both treatment schemes reduced the levels of CEA and CYFRA21-1, but there was no difference between the two groups. This does not indicate that cryoablation has a stronger effect on immunity and curative effect than FRA in the treatment of LC, but the two schemes can both enhance the body's anti-tumour immune function and cellular immune function. Besides, we found that the incidence of pleural effusion in group A was lower than that in group B, while the incidence of intraoperative pain in group A was obviously higher than that in group B. Intraoperative and postoperative complications are related to the accuracy of puncture, tumour characteristics, ablation range and characteristics of ablation methods. Statistics revealed that the incidence of pleural effusion of patients treated by thermal ablation ranged from 1.3% to 60%, which was self-limiting in

Table 6. Cox regression analysis

Factors	Univariate Cox regression			Multivariate Cox regression		
	P value	HR value	95% CI	*P* value	HR value	95% CI
Age	<0.001	2.748	1.723-4.383	<0.001	2.402	1.498-3.852
Sex	0.675	0.919	0.619-1.364			
Smoking history	0.506	0.875	0.589-1.298			
Pathological type	0.775	0.939	0.612-1.443			
Tumour size	0.930	0.982	0.661-1.461			
Clinical stage	0.003	0.545	0.367-0.810	<0.001	0.477	0.316-0.719
IgA	0.305	1.076	0.936-1.236			
IgG	0.401	1.58	0.543-4.593			
IgM	0.909	0.967	0.547-1.712			
CEA	0.001	1.109	1.042-1.181	0.012	1.081	1.017-1.149
CYFRA21-1	<0.001	1.273	1.150-1.408	<0.001	1.241	1.115-1.383
Treatment method	0.084	1.423	0.954-2.122			

Note: carcinoembryonic antigen (CEA), cytokeratin 19 fragment (CYFRA21-1), cluster of differentiation (CD), immunoglobulin (Ig).

most cases, and could be treated conservatively [26]. Patients with moderate to massive pleural effusion need puncture aspiration or closed thoracic drainage, and the catheterization rate is less than 10%, which is consistent with our research results. Reactive pleural effusion is rare after RFA, but intraoperative pain is the most common adverse reaction of RFA. Univariate and multivariate analysis by Okuma et al. revealed that lesions with a distance of ≤1 cm from the chest wall were obviously related to the development of pain [27]. Because of its analgesic effect, cryotherapy is superior to RFA for tumours close to the pleura, which is well tolerated by patients and has low risk of bronchopleural fistula.

At the end of the research, we analysed the factors influencing the prognosis of patients, and found that age, clinical stage, CEA and CYFRA21-1 were independent factors influencing the prognosis. With the increase of age, the body function declines continuously, and the spontaneous recovery function is weak, which leads to the poor prognosis of elderly patients after treatment [28]. Clinical staging is one of the key bases for judging the severity of patients' illness and prognosis, and formulating treatment methods. Patients in stage IV not only have a high tumour burden, but also are often accompanied by metastasis to other organs, so their complications and mortality are also higher than patients in early stage [29]. CEA can be used to assist the diagnosis of tumours and judge the metastasis, recurrence and prognosis of tumours. The CEA level of patients with endpoint events was higher than that of patients without endpoint events at admission, and a higher CEA level can lead to poor prognosis of patients [30]. CYFRA21-1 has a high value in diagnosing NSCLC, monitoring the condition, and judging the curative effect and prognosis. The CYFRA21-1 level of patients with endpoint events was higher than that of those without endpoint events at admission, and the higher the level, the worse the prognosis [31].

In the present study, we determined the effect of AHC and RFA regimens in the treatment of patients with advanced LC, as well as their impact on patients' immune function. However, there are still some limitations in this research. First, we didn't conduct a prospective study. As a retrospective study, the grouping cannot be randomized, which may affect the analysis of results. Second, the indicators we tested in this study are limited. Finally, the sample size of this study is small. Therefore, we hope to carry out more clinical trials in the follow-up study to improve the conclusion.

To sum up, AHC and RFA are minimally invasive procedures that lead to few complications in the treatment of advanced LC. Cold and heat ablation is a relatively safe and effective minimally invasive technique for tumour treatment, which is worthy of application and promotion in the clinical treatment of LC.

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Disclosure of conflict of interest

None.

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