Research Article

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Efficacy and Safety of Chinese Medicine in the Treatment of Patients with Pulmonary Nodules-A Multicenter Open Label Randomized Controlled Study: A Study Protocol for a Randomized Controlled Trial

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ABSTRACT

As the popularity of early screening of tumors, more and more people have detected pulmonary nodules, of which about 3.48% was lung cancer. However, false positive rates accounted for 1.4-23.3% according to trials reported. Therefore, pulmonary nodules may be over treated. In the clinical practice, we found that traditional Chinese medicine treatment makes some patients' lung nodules shrink or even disappear but this effect needs to be approved. Therefore, we design this global network randomized controlled study (RCT) study to explore the efficacy and safety of traditional Chinese medicine in the treatment of pulmonary nodules. This study is a multicenter, open, prospective, randomized, controlled study. In this study, participants will be randomly assigned to traditional Chinese medicine or routine treatment observation group. About 166 patients with pulmonary nodules will be registered within 12 months and followed up for at least 2 years. The important feature of this clinical trial is to provide services to patients with pulmonary nodules worldwide by combining online and offline diagnosis and treatment, excluding interference factors such as region, climate, environment, eating habits etc. At the same time, it also will save costs and improves patient compliance. This trial design will also conduct subgroup analysis on the population of traditional Chinese medicine in the treatment of pulmonary nodules and establish a mathematical model to analyze the dominant population of traditional Chinese medicine in pulmonary nodules and the predictive factors of curative effect.

Keywords: Pulmonary nodules; Chinese medicine; Randomized controlled trail; Lung cancer

INTRODUCTION

There were 19.29 million new cancer cases all over the world in 2020, including 4.57 million new cancer cases in China, accounting for 23.7% of the world, To add, it is estimated that there are 9.96 million global cancer deaths, including 3 million cancer deaths in China, accounting for 30% of the total cancer deaths, according to the international agency for research on cancer (IARC) of the World Health Organization (Reference). In 2020, lung cancer cases and deaths were ranked the first of cancer in China [1-2]. The 5-year survival rate of lung cancer patients was only about 16% due to the fact that most of the patients were diagnosed advanced stage of cancer initially [3].

Due to the enhancement of public awareness of physical examination, the early screening of high-risk groups of tumors, the improvement of computerized tomography (CT)

resolution and the assistance of artificial intelligence, the detection rate of pulmonary nodules has been significantly improved. Lung nodules can be found in more than 60% of patients with chest CT examination [4,5]. Based on the screening of 14506 randomly enrolled people in Shanghai, the detection rate of pulmonary nodules was 29.89%, and 3.48% of the nodules were lung cancer [6,7]. Based on the prospective study using low-dose CT to screen pulmonary nodules in northern China, about 26% of patients were screened for pulmonary nodules, including 23% of multiple pulmonary nodules [8]. These data were similar to the screening results of other countries in the world, and these screening were reported to reduce the mortality of lung cancer by 20%-44% [9,10]. The density and size of nodules were closely related to the probability of malignant transformation of nodules [11-13]. Based on a large number of clinical data, many benign and malignant prediction models of single pulmonary nodules have been discussed [14-16]. It is mainly related to gender, old age, increased nodule diameter, previous family history of tumor, smoking history and other factors. There are also many studies on the relationship between the diameter as well as number of nodules and the probability of malignant transformation of nodules. However, this is still controversy [17-21].

Preventing overdiagnosis and false positives from simultaneously identifying clinically significant lung cancer is the core challenge of lung nodule screening. Two large randomized controlled trials based on low-dose CT for lung cancer screening in high-risk population NELSON and *the national lung screening trial (NLST*) showed false positive rates of 1.4 and 23.3%, respectively [22,23]. Therefore, pulmonary nodules may be over treated. Pulmonary nodules have attracted the attention of the whole society, and even caused anxiety because of the possibility or potentiality of lung cancer. For these patients, how to avoid over treatment and insufficient treatment, and appropriate treatment is facing great challenges. At present, pulmonary nodules less than 10mm are mainly suggested for regular examination [24], and surgery or ablation treatment is required when cancer is highly suspected. However, postoperative complications and the decline in quality of life need to bear that brought by excessive surgery for those who are confirmed to be benign nodules after surgery. There is also the possibility of recurrence of pulmonary nodules [25].

The psychological symptoms of pulmonary nodules on patients during follow up is mainly anxiety, tension and worries, which highly influence physical health and life quality, even work and family life [26]. It's the actual and strong demand of patients with pulmonary nodules to find a non-invasive and safe treatment method that can not only treat patients' psychological symptoms, but also treat pulmonary nodules. Traditional Chinese medicine plays a dominant role in regulating the body constitution, by which to improve the microenvironment in which nodules grow in the body. In the clinical practice of traditional Chinese medicine, we found that pulmonary nodules of some patients disappeared in 1-3 months after taking traditional Chinese medicine. Previous studies had also reported the clinical results of traditional Chinese medicine in the treatment of pulmonary nodules showing that they can dissipate nodules to a certain extent [27,28]. However, the design of clinical trial and the level of evidence need to be improved. In addition, it is of great significance to find patients benefiting from traditional Chinese medicine and the efficacy prediction factors to avoid the waste of medical resources. Based on this, and thanks to the development of internet diagnosis and treatment technology, we designed this global network RCT study to clarify the efficacy and safety of traditional Chinese medicine in the treatment of pulmonary nodules, and to clarify the features of dominant pulmonary nodule population and the factors that affect the efficacy and prognosis.

METHODS

This study is a multicenter, open, prospective, randomized, controlled study to compare between the effectiveness of traditional Chinese medicine and routine treatment on patients with pulmonary nodules. In this study, participants will be randomly assigned to traditional Chinese medicine group or routine treatment observation group. About 166 patients with pulmonary nodules will be registered within 12 months and followed up for at least 2 years.

Aim

To confirm the effectiveness of traditional Chinese medicine intervention in the treatment of pulmonary nodules. We hypothesize that traditional Chinese medicine can shrink pulmonary nodules and reduce the rate of malignant transformation.

Study design

Participants: The cases included in this study are diagnosed as pulmonary nodules with chest CT examination. All patients should sign the requirement of informed consent, or provide consent online or by phone. The registered participants will be contacted by phone or Wechat to inform them about the study and provide an opportunity to opt out for data collection purposes.

Enrollment

1. Lung nodules are confirmed by CT scanning, between 6mm to 8mm as the diameter of the nodules, and the age is between 18 and 70 years old.
2. After thoracic surgery to evaluate the risk of nodule malignancy and the feasibility of surgery, all the cases were judged to be patients who could be followed up regularly.
3. Blood routine and biochemical tests are within the normal range.
4. Not receiving or more than 2 weeks after the end of previous treatment.

Case exclusion criteria

1. Those who are participating in other clinical trials or unwilling to cooperate with the investigators of this study.
2. Incomplete data affect the evaluation of curative effect.
3. Previous allergy, liver injury, or other serious adverse reactions to traditional Chinese medicine.
4. Patients with mental disease, dementia and other mental or cognitive disorders who cannot cooperate with the investigation and research.
5. Pregnant or lactating women
6. Patients with dysfunction of liver, kidney or heart; immune system diseases, such as AIDS, systemic lupus erythematosus, rheumatism, etc. tumor history etc.
7. Patients who plan to undergo surgery or ablation and other interventions for nodules.

Rejection criteria

1. Those who fail to meet the inclusion criteria.
2. Those who meet the inclusion criteria but fail to implement the test plan after inclusion
3. Patients with poor compliance, who fail to take medicine according to the study protocol.

Case shedding criteria

1. Self withdrawal during the study
2. Those who quit the study or lost the follow-up due to other reasons.
3. Those who have serious adverse events, complications, special physiological changes caused by drugs or other emergencies, and are not suitable to continue the research.
4. Combined medication, especially the combination of drugs that have a greater impact on the study drug, affects the effectiveness and safety evaluators.

Prevention measures for exfoliation cases

Regularly follow up by telephone or wechat and resolve the existing problem that may influence compliance.

Diagnostic criteria

Diagnostic criteria for pulmonary nodules: Pulmonary nodules refer to quasi-circular or irregular lesions with a diameter of less than or equal to 3 cm in the lungs. Imaging manifestations are shadows with increased density and lesions with clear or unclear boundaries, which can be single or multiple [29,30]. In this project, we focus on nodules between 6-8mm.

Research plan

Grouping and randomization: Patients with pulmonary nodules who meet the inclusion criteria and accept to participate are informed of the relevant research contents and required to sign the consent form SPSS 22.0 statistical software was used to generate random numbers and grouping numbers. The included subjects will be randomly divided into treatment group and control group as the ratio of 1:1.

Interventions: All the cases were judged to be patients who could be followed up regularly by thoracic surgery rather than surgery treatment, so there is no western medicine treatment required following guidelines.

Control group: follow-up with chest CT at certain time point following the guideline. The patients will be followed up every 3 months until 3 years.

Treatment group: patients in this group will be treated with Chinese medicine. From the first day after joining the group, Chinese medicine will be given twice a day for 3 months, which is mainly based on Qingqihuatan decoction and with revision according to syndrome differentiation personally, and then followed up every 3 months until 3 years.

Data collection

Baseline: Patients should complete the basic information description within 7 days after randomization, which include case collection, such as patient's gender, age, height, weight, smoking history, tumor history, nodule size, nodule location, nodule density, burr sign (if the patient has multiple pulmonary nodules, the nodule with the largest diameter will be recorded), tumor markers, immune function index evaluation, quality of life evaluation, physical fitness score, and symptoms score.

Efficacy evaluation indicators

Main efficacy evaluation indicators: The changes of the maximum diameter and density (solid part) of nodules are evaluated by CT to prognosis the risk of pulmonary nodules. Criteria for determining the size of nodules: the diameter of nodules is determined according to the chest CT before and after treatment, which is divided into cured, significantly effective, effective and ineffective, as follows: cured (maximum diameter reduction rate, nodules completely disappear), significantly effective (maximum diameter reduction rate ≥ 50%), effective (maximum diameter reduction rate < 50% and ≥ 25%), and ineffective (maximum diameter reduction rate < 25%).

According to the measurement requirements of the 2017 Fleischner guidelines for pulmonary nodules [31], select a suitable position in the axial position, and measure at the largest level of the position. Average the long axis and short axis of the nodules and take the average value of the two. Some solid nodules are measured by referring to the above methods, and the diameters of solid components and sub solid components are measured respectively, with the change of solid component diameter as the reference basis for density change [32].

Secondary observation index

1. Comparative evaluation of malignant risk: This study uses the Mayo model recommended by the guidelines to evaluate the malignant risk of pulmonary nodules [33]. The probability of malignant risk =ex/ (l+ex), x= - 6.8272+ (0.0391 * age (year)) + (0.7917 * smoking history) + (1.3388 * history of extrapulmonary malignant tumors) + (0.1274 * nodule diameter (mm)) + (1.0407 * Burr) + (0.7838* location). Formula Description: e is the natural logarithm, and those with smoking history are counted as 1, otherwise it is 0; Those who have a history of extrapulmonary malignant tumor for more than 5 years are counted as 1, and vice versa is 0; If there is burr sign in the nodule, it is 1, otherwise it is 0; If the nodule is located in the upper lobe of the lung, it is counted as 1, and if it is not in the upper lobe, it is counted as 0.
2. T lymphocyte classification count (cd3+, cd4+, cd8+, cd4/cd8).

Safety observation

1. Blood routine and urine routine: one week before and after treatment;
2. Liver function, renal function and electrocardiogram: before and after treatment.

Data collection and management

Data elements will be collected and managed by investigators, including baseline data of patients, information related to intervention treatment, and observation index results, and will be safely transmitted to the Cancer Hospital of the Chinese Academy of Medical Sciences to ensure quality control and analysis.

STATISTICAL ANALYSIS

Sample size estimation

The effective rate of nodule shrinkage of the research object is the observed outcome index. According to the literature review, it is estimated that the effective rate of the intervention group is 31.25%, and the effective rate of the control group is 9.37% [28], with two sides α=0.05, the assurance is 90%. The sample size is calculated according to the following sample size calculation formula:

$$n = \frac{2\bar{p}\bar{q}\left(z_{\alpha} + z_{\beta}\right)^{2}}{(p_1 - p_2)^{2}}$$

(N represents the required sample size of each group. P1 and P2 represent the estimated effective rate of the two groups. P: average effective rate; α: class I error probability; β: class II error probability; 1- β: test efficiency.)

According to the calculation, n=72 cases can be obtained. Considering the 1:1 randomized grouping, that is, 72 subjects need to be studied in the intervention group and the control group and considering 15% of the loss of follow-up and refusal of follow-up, at least 83 subjects need to be studied in the intervention group and the control group, with a total of at least 166 subjects included.

Efficacy and safety evaluation and analysis

Statistical software Spss22.0 will be used to statistically process the data. For the evaluation and analysis of efficacy and safety, CMH will be used as the categorical variable- χ 2 tests, Fisher's exact probability method or Wilcoxon rank sum test of hierarchical data to compare the differences between groups. Continuous variables will be tested by group t test or Wilcoxon rank sum test. Except for special points, all statistical tests are bilateral tests, and the difference judged can be considered to be statistically significant if $p<0.05$. We will also explore subgroup analysis to explore the differences in efficacy, such as the impact of smoking history, nodule density, nodule size, demographic characteristics and geographical region on efficacy. We will also use regression analysis to model the main results and try to find out the characteristics and predictors of the dominant group of people who benefit from the treatment of pulmonary nodules with traditional Chinese medicine.

Missing data

For the missing data caused by the loss of follow-up of subjects, it is planned to use all available information before death or loss of follow-up and use multiple imputation to explain the missing data.

Research team and quality control

The research team, including researchers, clinicians and supervisors, has undergone strict professional training. Researchers and patients should fully understand the purpose and content of the study. All cooperation activities follow the principle of PCORI participation [34]. All the above personnel actively participated in the design and implementation of the trial, including the design of monitoring scheme, the selection of observation indicators and follow-up methods. During regular follow-up, researchers should lead patients to return to the hospital on time and ensure the integrity of the data and the authenticity of the content. Data should be immediately finished record and upload.

RESULTS

We will implement this clinical trial in strict accordance with this protocol. This clinical trial will estimate the effectiveness and safety of Chinese medicine in treating pulmonary nodules. Positively, it might be possible to provide a non-invasive treatment scheme for patients with pulmonary nodules smaller than 8mm in addition to observation. And it might also aid in analyzing the characteristic factors of the people who can benefit from the advantages of traditional Chinese medicine, so as to provide guiding evidence for clinicians for Chinese medicine to be included in the multidrug therapy (MDT) treatment group of pulmonary nodules.

DISCUSSION

Due to the intensification of globally aging, it is estimated that the cancer burden will increase by 50% in 2040 compared with 2020, and the number of new cancer cases will reach nearly 30million per year. This is most significant in countries undergoing social and economic transformation. In nearly 100 countries around the world, cancer is the primary or secondary cause of premature death, of which the cumulative risk of cancer before the age of 75 is 21.4%, and the risk of death is 17.7%. Cancer is still an important cause threatening human health and life, among which lung cancer ranks first in the global cancer incidence rate and mortality [35].

Cancer prevention unanimously adopted as new cancer resolution at the World Health Assembly is increasingly admitted as its significance and application potential in reducing the burden of cancer in the future. Existing studies have shown that about 1/3 to 2/5 of new cases can be avoided by eliminating or reducing exposure to known lifestyle and environmental risk factors [35]. Some interventions have also been proved to be effective means of cancer prevention. Therefore, it is urgent to promote and implement primary cancer prevention. Researchers pointed out that cancer prevention could be achieved through the three-level prevention path [36]. In the theoretical system of disease prevention and treatment of traditional Chinese medicine, the idea of "prevention before disease" is the earliest source of the "prevention first" strategy followed by China's medical and health industry, which includes the meaning of "prevention before disease, prevention of change after existing disease, and prevention of relapse", which coincides with the concept of "three-level prevention" of cancer, and provides a theoretical basis for the prevention and treatment of lung cancer by traditional Chinese medicine [37]. Early intervention is of great significance in the evolution and development of pulmonary nodules. Therefore, in the follow-up period, it's worthy to seek ~~to~~ traditional Chinese medicine to slow down or even inhibit the growth rate of nodules and improve life quality, which may reduce the malignant probability of pulmonary nodules through the intervention of traditional Chinese Medicine.

The advantage of this clinical trial design is to take the lead in carrying out a multicenter, open, prospective, randomized, controlled trial to observe the efficacy of traditional Chinese medicine in the treatment of pulmonary nodules. At present, the diagnosis and treatment guidelines of pulmonary nodules less than 8mm were mainly focused on long-term observation and regular examination, without treatment intervention measures. Traditional Chinese medicine minimizes the occurrence and development of nodules or tumors through improving the constitution and adjusts the microenvironment, which is still lack of high-level clinical evidence at present. Another feature of this clinical trial is to provide services to patients with pulmonary nodules worldwide by combining online and offline diagnosis and treatment, excluding interference factors such as region, climate, environment, eating habits etc. At the same time, it also saves economic costs and improves patient compliance. This trial design will also conduct subgroup analysis on the effective population of traditional Chinese medicine in the treatment of pulmonary nodules and establish a mathematical model to analyze the features of these dominant patients and the predictive factors of curative effect.

There are also some limitations that cannot be determined in this protocol, such as the pathological nature of pulmonary nodules but the observation of tumor markers and immune indicators, combined with the changes of nodule size

and risk level, also reflect the curative effect of traditional Chinese medicine to a certain extent. At present, there is a consensus on that tumor markers can be used as one of the evaluation methods of differentiating benign and malignant lung nodules [30], and we should observe lung cancer for abnormally elevated or progressive tumor markers such as carcinoembryonic antigen (CEA), neuron specific enolase (NSE) [38-41]. The percentage of T cell subsets in peripheral blood is an index to judge the anti-tumor immunity of patients. Studies have shown that the cellular immune function of lung cancer patients is significantly inhibited [42], and the blood cd4/cd8 ratio of tumor patients is significantly lower than that of normal people, while the ratio of lung cancer lymph node metastasis group is significantly lower than that of non lymph node metastasis group. Many studies have shown that traditional Chinese medicine could adjust the immune system function of the body [43-45], so this is also one of the therapeutic goals we want to observe.

The theory of "pretreatment" in traditional Chinese medicine guides the clinic to treat cancer as a chronic disease, and participate in the whole process of cancer prevention and treatment. We carried out this study based on this concept and previous clinical practice experience.

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