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Original Article

Association between Chinese Medicine Therapy and Survival Outcomes in Postoperative Patients with NSCLC: A Multicenter, Prospective, Cohort Study*

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ABSTRACT **Objective:** To evaluate the association between Chinese medicine (CM) therapy and disease-free survival (DFS) outcomes in postoperative patients with non-small cell lung cancer (NSCLC). **Methods:** This multiple-center prospective cohort study was conducted in 13 medical centers in China. Patients with stage Ⅰ, Ⅱ, or ⅢA NSCLC who had undergone radical resection and received conventional postoperative treatment according to the National Comprehensive Cancer Network (NCCN) guidelines were recruited. The recruited patients were divided into a CM treatment group and a control group according to their wishes. Patients in the CM treatment group received continuous CM therapy for more than 6 months or until disease progression. Patients in the control group received CM therapy for less than 1 month. Follow-up was conducted over 3 years. The primary outcome was DFS, with recurrence/metastasis rates as a secondary outcome. **Results:** Between May 2013 and August 2016, 503 patients were enrolled into the cohort; 266 were classified in the CM treatment group and 237 in the control group. Adjusting for covariates, high exposure to CM was associated with better DFS [hazard ratio (HR) = 0.417, 95% confidential interval (CI): 0.307–0.567)]. A longer duration of CM therapy (6–12 months, 12–18 months, >24 months) was associated with lower recurrence and metastasis rates (HR = 0.225, 0.119 and 0.083, respectively). In a subgroup exploratory analysis, CM therapy was also a protective factor of cancer recurrence and metastasis in both stage Ⅱ–ⅢA (HR=0.50, 95% CI: 0.37–0.67) and stage ⅢA NSCLC postoperative patients (HR = 0.48, 95% CI: 0.33–0.71), DFS was even longer among CM treatment group patients. **Conclusions:** Longer duration of CM therapy could be considered a protective factor of cancer recurrence and metastasis. CM treatment is associated with improving survival outcomes of postoperative NSCLC patients in China. (Registration No. ChiCTR-OOC-14005398)

KEYWORDS Chinese medicine, non-small cell lung cancer, postoperative care, cohort study, disease-free survival

According to the epidemiological data of GLOBOCAN 2018,[1] lung cancer is still the most commonly diagnosed cancer type (2,093,876 cases, 11.6% of total cases) and the leading cause of cancer death (761,007 cases, 18.4% of total cancer deaths) worldwide. In recent years, the incidence of lung cancer has increased substantially in China and is likely to continue to rise for the next few decades at least.[2] Of all lung cancers, non-small cell lung cancer (NSCLC) accounts for approximately 80%–85% of cases.[3] For patients with early-/middle-stage NSCLC, the standard treatment recommendation of the National Comprehensive Cancer Network (NCCN) guidelines is still surgical resection.[4] However,

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postoperative recurrence and metastasis are the most important factors that affect NSCLC patient survival. More than 30% of postoperative lung cancer patients with stage Ⅰ disease die within 5 years because of recurrence or metastasis and the 5-year survival rate of stage ⅡA, ⅡB, ⅢA patients is 60%, 53% and 36%, respectively.[5] To reduce the recurrence and metastasis rates among high-risk patients, a platinum-based adjuvant chemotherapy strategy was recommended as the standardized treatment for postoperative NSCLC patients according to the International Adjuvant Lung Cancer Trial (ILAT) study.[6] The ILAT study enrolled 1,867 cases and showed that 5-year disease-free survival (DFS) and 5-year survival were only improved by 5.1% (44.5% *vs*. 39.4%) and 4.1% (40.4% *vs*. 44.5%) with adjuvant chemotherapy after resection. Thus, a regimen consisting of two platinum-based therapies are recommended as the adjuvant chemotherapy for postoperative NSCLC patients, although DFS and survival rate were not improved by much.

In China, at least 70% of cancer patients are treated with Chinese medicine (CM). After completing surgery, adjuvant chemotherapy, or radiotherapy, some Chinese patients are willing to undergo CM for further recovery. Although the effects of CM remain elusive, there have been some inspiring results of clinical trials with evidence-based methods.[7,8] CM integrated with adjuvant chemotherapy for NSCLC can reduce postoperative recurrence and metastasis rates[9] and improve quality of life.[10] Meanwhile, in *in vivo* and *in vitro* experiments, CM was also indicated to have regulatory effects on the immune microenvironment and inhibit tumor metastasis with few side effects.[11,12] However, current clinical studies are mostly focused on an integrative strategy that combines CM with Western medicine (WM), rendering its effects controversial. The efficacy of CM alone on the prognosis of cancer patients has not yet been clearly illustrated. Moreover, since tumors are prone to recurrence and metastasis, the current guidelines recommend that patients should be reviewed regularly after resection with or without adjuvant chemotherapy. However, interventional therapy with WM was only recommended if visible lesions upon imaging are found. At present, there is no suitable treatment for non-visible tumor lesions after resection. This cohort study was designed to evaluate the association between CM therapy and survival outcomes in postoperative NSCLC patients.

METHODS

Diagnostic, Inclusion and Exclusion Criteria

Patients with stage Ⅰ–ⅢA NSCLC diagnosed by pathologic or cytologic examination according to the 2002 AJCC Cancer Staging Manual (6th edition),[13] aged 18 to 75 years, who had undergone a complete resection of all lesions to R0 and had finished conventional postoperative adjuvant therapy according to the clinical guidelines for NSCLC of the National Comprehensive Cancer Network (NCCN), with an Eastern Cooperative Oncology Group (ECOG) score of 0–2, were eligible.

Patients with clinically significant cardiac dysfunction, renal dysfunction, hepatic dysfunction, active infection, or neurologic or psychiatric disorders were excluded.

Study Design

This was a prospective, multicenter cohort study in which a total of 503 patients with stage Ⅰ–ⅢA NSCLC were recruited to examine the effects of an adequate course of CM as the main exposure factor. The recruited patients were divided into a CM treatment group and a control group according to their wishes. Eligible patients were recruited from the following 13 medical centers in China: Guang'anmen Hospital, China Academy of Chinese Medical Sciences; Cancer Hospital of Shanxi Province; The First Affiliated Hospital of Guangzhou University of Chinese Medicine; Affiliated Hospital of Chinese Academy of Medical Sciences of Hunan Province; Cancer Hospital of Zhejiang Province; Cancer Hospital of Liaoning Province; Dalian Hospital of Traditional Chinese Medicine; Wuxi Hospital of Traditional Chinese Medicine; Anhui Provincial Hospital; The Xinjiang Uygur Autonomous Region Institute of Traditional Chinese Medicine; Shenzhen Baoan District Hospital of Traditional Chinese Medicine; The Fourth Hospital of Qinhuangdao; and Chongqing Cancer Institute. All participants have provided written informed consents.

Before the start of the clinical trial, a researchers' handbook was developed as standard for clinical trials at various centers to specify the details of clinical trials, such as the method of syndrome differentiation, course of treatment, selection method of CM and

selection method of Chinese patent drugs. Every researcher at each hospital was trained in a unified way to ensure consistency in the CM treatment methods administered to patients by different research centers.

Trained Good Clinical Practice (GCP)-certified research staff performed interviews to collect data on herbal use and clinical outcomes and completed case report forms during the clinical visits. Patients received follow-up according to NCCN clinical guidelines, with clinical visits every 3 months. For patients who occasionally missed clinical visits, telephone follow-ups were performed by trained research staff.

This trial has been reviewed and approved by the Ethics Committee of Guang'anmen Hospital, China Academy of Chinese Medical Sciences (No. 2013EC093-05), and has been registered in the Chinese Clinical Trial Registry (registration No. ChiCTR-OOC-14005398).

Grouping and Intervention

Patients were divided into CM treatment and control groups according to their wishes. Patients in the CM treatment group received continuous CM therapy for more than 6 months or until disease progression. Patients in the control group received CM therapy for less than 1 month or received no CM.

Treatment was administered according to the Diagnostics of Traditional Chinese Medicine and Clinical Practice Guidelines of Chinese Medicine in Oncology.[14] Based on the syndrome characteristics, postoperative patients with adjuvant chemotherapy were divided into the following syndrome types, i.e., qi-blood deficiency syndrome (main manifestations: laziness of breath, fatigue, spontaneous sweating, palpitation, insomnia, pale or yellowish complexion and weakness of pulse), weakness of Pi (Spleen) and Wei (Stomach) syndrome (main manifestations: loss of appetite, nausea, fatigue, dietary indigestion, limb weakness, pale complexion, loose stool, pale tongue and deficiency of pulse). Modified Bazhen Decoction (八珍汤) or modified Buzhong Yiqi Decoction (补中益气汤) were chosen for the above two syndromes respectively to supplement qi and blood, invigorating Pi and Wei, and for those with both syndromes the two decoctions were both used. Each sub-center purchases Chinese herbal medicines individually. The quality of Chinese herbal medicine has passed the national quality test, which achieves uniform standards. The drug dosages were all within the Pharmacopoeia dosage range. Chinese patent medicines were unified distributed by Guang'anmen Hospital.

When patients had obvious qi deficiency syndrome (main manifestations: fatigue, lack of breath and laziness, weak cough and asthma, pale complexion, sweating, eating less, abdominal distension, shortness of breath, frequent nocturnal urination and weakness of pulse), Shenyi Capsule (参一胶囊, 20 mg orally, twice a day; Jilin Yatai Pharmaceutical Co. Ltd., China) was used together with a herb decoction. When patients had fire syndrome (main manifestations: bitter taste, fever, dark yellow urine, constipation, cough and spit yellow phlegm, red face and eyes, thirst, fondness of cold drink, bleeding, red tongue and rapid pulse), Yifei Qinghua Granules (益肺清化颗粒, 20 g orally, 3 times a day; Beijing Huashen Pharmaceutical Co. Ltd., China) was taken instead. One course of treatment was 3 months for either group. The patients were revisited every 3 months.

All CM physicians in this study were certificated senior physicians who had attended medical school for 5 years and had over 3 years of clinical training and experience. All physicians received extensive training regarding the study protocol.

Covariates

Patients' basic information, including age, sex, Eastern Cooperative Oncology Group (ECOG) scores and smoking habits were obtained at the baseline assessment. Disease and treatment information including TNM stage, duration of herb use and whether they had undergone chemotherapy, as well as cycles of chemotherapy completed as confounders were also collected.

Outcome Measurements

The primary outcome was DFS, defined as the time from surgery to disease recurrence or metastasis after the last outcome evaluation. Considering all the clinical factors that might affect the prognosis of stage Ⅰ–ⅢA patients postoperative NSCLC patients, the Cox proportional hazards regression model to control relevant covariates. Possible clinical factors

were established including grouping (CM/WM), age (≤44 years/45–59 years/≥60 years), sex (male/female), smoking habits (yes/no), pathology (squamous cell carcinoma/non squamous cell carcinoma), ECOG (0/1/2), TNM (ⅠA/ⅠB/ⅡA/ⅡB/ⅢA), radiotherapy (yes/no), chemotherapy regimen (non-chemotherapy/paclitaxel+platinum/gemcitabine+platinum/pemetrexed+platinum/yinorelbine +platinum), strategy and cycles of chemotherapy (4 cycles/others) and duration of CM therapy (0 month/6–12 months/12–18 months/18–24 months/>24 months).

The secondary outcomes were rates of recurrence and metastasis for years 1 and 2. The recurrence and metastasis of the disease were confirmed by imaging data (CT, MRI or PET-CT). Tumor markers in blood and ctDNA or other detection methods were not used as the criteria for judging the recurrence and metastasis of the disease. Outcome data with case report forms (CRFs) were collected at each follow-up, including information of cancer relapse and metastasis and survival outcomes.

Follow-Up

During outpatient or telephone follow-up period, the status of patients, including DFS, whether they received continuous CM therapy and details of the main adverse reactions during treatment were collected. Imaging and blood tests were performed every 3 months. After grouping, patients who did not attend follow-up appointments in the outpatient clinic or who could not be contacted by telephone more than 3 times (no answer, shutdown, refusal to answer), were considered drop-out cases. The last follow-up time (August 31, 2016) was used to calculate the outcome indicator. Adverse events were monitored by Common Terminology Criteria for Adverse Events (CTCAE) v4.0.

Statistical Analysis

Statistical analysis was conducted using Statistical Analysis System version 9.2 developed by SAS, USA. The 'full analysis set' analysis included all participants. Patient characteristics were summarized in descriptive statistics. Either two-sample *t*-tests or Wilcoxon rank sum tests for continuous data and Chi-squared test or Fisher's exact test for categorical data were conducted after the test for normality. The rates of tumor recurrence and metastasis were assessed using the Kaplan–Meier method, with the log-rank test used to evaluate significance.[15] The Cox proportional hazards model was used to assess the prognostic values of variables. A significance level of 5% was used throughout the analysis.

RESULTS

Characteristics of Study Participants

From May 1, 2013 to March 31, 2016, 503 patients were enrolled into the cohort. Among the participants, 266 were categorized into the CM treatment group and 237 were categorized into the control group. There was no statistically significant difference between the two groups with respect to age, sex, pathologic type, or ECOG score. However, those in the CM treatment group were more likely to have stage Ⅰ cancer than those in the control group (42.8% *vs*. 17.7%; *P*<0.001). Additionally, more patients in the control group had stage Ⅲ cancer than those in the CM treatment group (48.1% *vs*. 29.3%; *P*<0.001). During follow-up, 2 cases (0.4%) in the control group were lost, while in the CM treatment group 1 case (0.8%) was lost. The mean time of herb administration in the CM treatment group was 18.5 months and 0.1 months in the control group (Table 1, Figure 1).

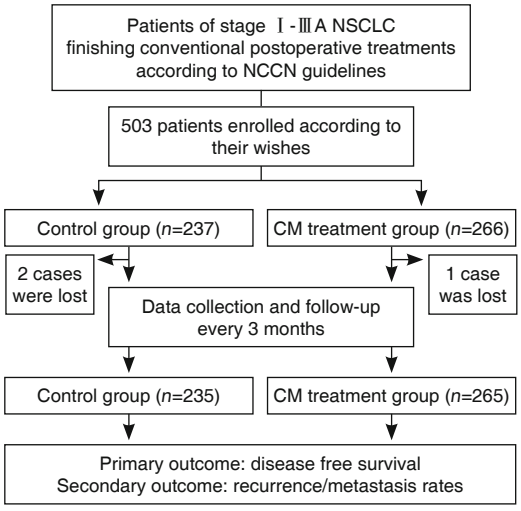

Figure 1. Study Flow Diagram of NSCLC Patients

DFS

The control group reached a median DFS of 656 days while the CM treatment group did not. DFS in the CM treatment group was much longer than that in the control group [*P*<0.0001; hazard ratio (HR)=0.3825, 95% confidence interval (CI): 0.29–0.50; Figure 2]. Over the course of the 3-year follow-up period, 64 patients in the CM treatment group experienced cancer relapse, compared with 133 patients in the control group (24.1% *vs*. 56.1%; *P*<0.05).

Table 1. General Characteristics of NSCLC Patients at Baseline [Case (%)]

Index	CM treatment (266 cases)	Control (237 cases)	*P*-value
Age ($\bar{x} \pm s$, year)	56.6 ± 8.9	57.0 ± 9.0	0.618
Gender			
Male	142 (53.4)	146 (61.6)	0.063
Female	124 (46.6)	91 (38.4)	
Pathologic type			0.6913
Adenocarcinoma	211 (79.3)	162 (68.4)	
Squamous cell	47 (17.7)	68 (28.7)	
Others	8 (3.0)	7 (2.9)	
TNM stage			<0.0001
Ⅰ	114 (42.8)	41 (17.7)	
Ⅱ	74 (27.8)	81 (34.2)	
ⅢA	78 (29.3)	114 (48.1)	
ECOG grade			0.202
0	8 (3.0)	11 (4.6)	
1	188 (70.7)	173 (73.0)	
2	0	0	

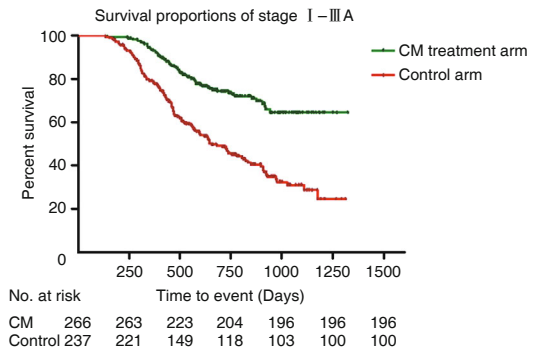

Figure 2. DFS of Stage Ⅰ–ⅢA NSCLC Patients in Two Groups

Cox Regression Analysis of Factors Affecting DFS

Results of Cox regression analysis showed that CM exposure was associated with better DFS (HR=0.417, 95% CI: 0.307–0.567) and the protective effect of CM therapy was extended along with the duration of application time (Table 2). The prognosis was also obviously related to the disease stage, but was not related to other factors statistically. Thus, a subgroup analysis according to TNM stage was conducted.

Subgroup Analysis of DFS and Recurrence/ Metastasis Rates by Stage

Considering the baseline differences in TNM staging between the two groups, we limited the stage parameter to stage Ⅱ–ⅢA then conducted a further subgroup exploratory analysis. There were 152 cases in the CM treatment group and 195 cases in the control group. The mean time of herb administration in the CM treatment group was 16.8 months and 0.1 months in the control group. There was no statistically significant difference between the two groups with respect to age, sex, location, pathologic type, TNM staging (ⅡA, ⅡB, ⅢA), ECOG score and adjuvant therapy (P>0.05). In this subgroup, DFS was significantly different between the two groups, with a median DFS of 582 days in the control group while median DFS was not reached in the CM treatment group (P<0.0001, HR=0.50, 95%CI 0.37–0.67; Figure 3).

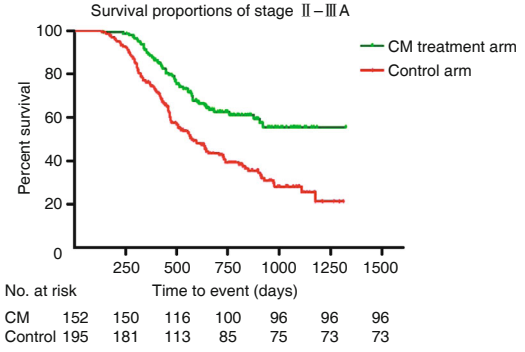

Figure 3. DFS of Stage Ⅱ–ⅢA NSCLC Patients in Two Groups

Table 2. Multivariable Cox Proportional Hazards Analysis

Parameters	Classification	Reference	X^2	*P*	HR (95% CI)
Grouping	CM	WM	0.0071	<0.0001	0.417 (0.307, 0.567)
TNM staging	ⅠA	ⅢA	16.3932	0.0002	0.331 (0.187, 0.587)
	ⅠB	ⅢA	17.3769	<0.0001	0.245 (0.137, 0.438)
	ⅡA	ⅢA	12.0783	0.1432	0.774 (0.550, 1.091)
	ⅡB	ⅢA	0.0071	0.0802	0.638 (0.386, 1.056)
Duration of CM therapy (Month)	6–12	0	0.0071	0.9328	0.980 (0.615, 1.563)
	12–18	0	16.3932	<0.001	0.225 (0.110, 0.464)
	18–24	0	17.3769	<0.001	0.119 (0.044, 0.324)
	>24	0	12.0783	0.0005	0.083 (0.020, 0.338)

Furthermore, among stage Ⅱ–ⅢA patients, the CM treatment group had significantly fewer events of cancer relapse than the control group by log-rank test (P<0.05; Table 3).

Table 3. Recurrence and Metastasis Events of Stage Ⅱ–ⅢA NSCLC Patients [Case (%)]

Group	Case	Year 1 events	Year 2 events
CM	152	16 (10.53)	51 (33.55)
Control	195	46 (23.59)	108 (55.38)
P		0.0010	<0.0001

Then we limited the stage parameter to stage ⅢA and conducted a further subgroup exploratory analysis. There were 78 cases in the CM treatment group and 114 cases in the control group; 28 cases relapsed in the CM treatment group and 76 cases in the control group (35.9% *vs*. 66.7%). The mean time of herb administration in the CM treatment group was 16.1 months and 0.1 months in the control group. There was no statistically significant difference between the two groups with respect to age, sex, location, pathologic type, ECOG score and adjuvant therapy (P>0.05). In this subgroup, DFS was also significantly different between the two groups, with a median DFS of 532 days in the low-exposure group while median DFS was not reached in the CM treatment group (P<0.0001, HR=0.48, 95%CI: 0.33–0.71; Figure 4).

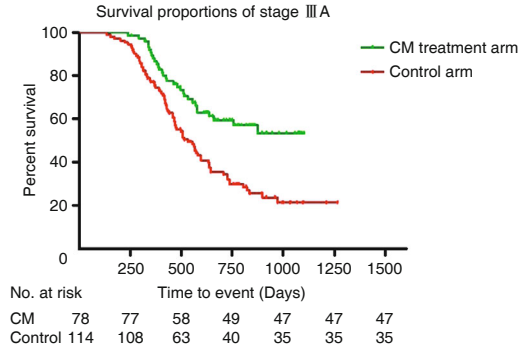

Figure 4. DFS of Stage ⅢA NSCLC Patients in Two Groups

Moreover, among these stage ⅢA patients, the CM treatment group had significantly fewer events of cancer relapse than the control group by log-rank test (P<0.05; Table 4).

Table 4. Recurrence and Metastasis Events of Stage IIIA NSCLC Patients [Case (%)]

Group	Case	Year 1 events	Year 2 events
CM	78	9 (11.54)	28 (35.90)
Control	114	26 (22.81)	72 (63.16)
P		0.0010	<0.0001

Safety and AEs

There were no statistically significant differences between the CM treatment group and the control group regarding incidences of adverse events, hepatorenal function, cardiac function and blood routine indexes.

DISCUSSION

NSCLC is a devastating disease with high incidence and mortality worldwide.[16] At present, surgical resection is the main treatment for early-stage lung cancer. Platinum-based chemotherapy is necessary and effective after surgery for patients with early-/middle-stage NSCLC and may reduce the risk of tumor recurrence in some cases.[17] However, the survival rate is only improved by 5% with adjuvant chemotherapy. Accordingly, new methods that could further reduce the recurrence and metastasis rates and improve survival for NSCLC patients have significant implications.

Previous clinical and experimental studies have revealed that CM has effects on tumor recurrence and metastasis prevention, as well as exceptional effects in enhancing immunity and improving clinical symptoms and quality of life.[18,19] Based on previous evidence, we hypothesized that CM therapy would be associated with improved DFS for postoperative NSCLC patients, which might further improve prognosis (Figure 5). The NCCN guidelines highlighted that NSCLC patients who finished adjuvant chemotherapy after surgery could only be reviewed regularly until recurrence and metastasis, without intervention methods. For the period that WM can only observe without treatment, CM can be used as an intervention therapy. Although CM is extensively used among NSCLC patients in China, little evidence has demonstrated the survival benefits and safety of CM in postoperative patients. Thus, further evidence is required to determine whether CM has advantages at this stage.

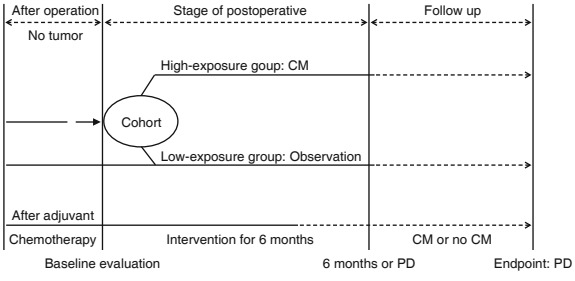

Figure 5. Study Flow Diagram

In this cohort study, we found that CM, based on syndrome differentiation, could improve prognosis

and longer duration of CM treatment was associated with improved DFS and less recurrence/metastasis among postoperative NSCLC survivors. In subgroup analyses, the effect of CM therapy on DFS was more evident for stage ⅢA patients. This multicenter prospective observational study provided the initial steps for evaluating the role of CM in NSCLC postoperative care.

In recent years, there have been controversial viewpoints regarding the effect of complementary and alternative medicine in cancer patients. Some study results showed that it may have a negative impact on prognosis[20] and although these observations were later demonstrated to be the result of treatment delays,[21] CM is still not recognized and accepted worldwide. Because of the complexity of composition formula of CM it is also difficult to promote its application. The Clinical Practice Guidelines of Chinese Medicine in Oncology[14] has been promoted and used as the standard guideline of tumor treated with CM in China. Therefore it was also selected as the treatment strategy for this current cohort study. Objective indicators of radiological examination were used for evaluation. The prospective study design explained the causal relationship between CM and prognosis.

Because this was an observational study, a direct causal inference between CM therapy and survival outcome could not be obtained. Unmeasured covariates such as education and income, as well as other health behaviors, including obesity and physical activity, may confound survival outcomes. Additionally, all surgery was performed in tertiary hospitals and thus may not have been undertaken using the same skills or techniques. This also produced some bias. Furthermore, we did not collect some disease information, such EGFR gene mutation status, because it was not part of the standard of care at the time at which the study was designed. Our measurements of duration of CM exposure were not specific and may be subject to participant recall bias. Another limitation of this study was the brevity of its follow-up period, as an analysis time point of 3 years was selected rather than 5 years or longer. However, despite these limitations, these findings can be used to spearhead future observational and interventional studies for postoperative patients. It can also provide some evidence-based medical evidence for the use of CM after NSCLC operation.

In the future, we will further design a randomized controlled trial based on the results of this study and will fix the patients' stage, the prescription, drug, dosage, course of treatment and administration of CM in an attempt to definitively determine its curative effects.

Conflict of interest

None to declare.

Author Contributions

LHS, HW and ZY are the main investigators regarding study data accrual and study design. WXQ and WYT contributed to data statistics and writing the article. WXQ and ZJB contributed to study monitoring and acquisition of data. LJ, LLZ, JYL, WSY, XY, ZHL, SQJ, LP, WW, YJL, LG, LJ, FHT and ZMY were responsible for data-processing support. All authors have read and approved the final version of the manuscript.

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