# A prospective open controlled study of creatine combined with curcumin in the intervention of early cachexia in upper gastrointestinal tumors.

NCT number：05856500

Date：May 12, 2023

Nanjing Drum Tower hospital

The Affiliated Hospital of Nanjing University Medical School

# Informed consent

## Instructions for Subject

Dear Madam/Sir：

We are going to conduct a non-randomized controlled clinical trial, namely "Prospective and open controlled study of creatine combined with curcumin in the Intervention of early cachexia in upper digestive tract tumors". You may be eligible for enrollment in this trial; therefore, we invite you to participate in this trial, sponsored by the Clinical Nutrition Department of Drum Tower Hospital Affiliated to Medical School of Nanjing University. The main researchers are Xiaotian Chen and Shuan Wang.

This informed consent will explain to you the purpose, procedure, benefits, risks, inconvenience or discomfort, and major issues of the study. It will also explain to you other treatment options available to you and your right to withdraw from the study at any time. Please read carefully and make a careful decision on whether to participate in the study. This informed consent may contain some words or information that you do not understand. Please be sure to consult your study physician and you will be answered until you are satisfied. Before deciding, you may take the unsigned informed consent form home to consider or discuss it with your family, friends, or anyone you choose. If you decide to participate in this study, please sign and date this informed consent form. Your signature will not deprive you of any legal rights and interests. The original signed informed consent will be kept with the researcher, and the other copy will be kept by you.

**Background**

A very common phenomenon in many tumor patients is that they clearly know the importance of nutrition, but they just lose their appetite, don't want to eat, or force themselves to eat, and their body become thinner, weaker, and weaker. This phenomenon is medically known as cancer cachexia (CAC). It is a common complication of various advanced malignant tumors. Its clinical manifestations include weight loss, muscle atrophy, fatigue, loss of appetite, anorexia, sense of bloating, anemia, edema, hypoproteinemia, etc. CAC can seriously affect patients' quality of life, affect patients' tumor treatment effect, and even directly shorten the survival time of patients. The incidence of CAC in gastric cancer, pancreatic cancer, colon cancer and other digestive system tumors was significantly higher than other tumors.

The pathogenesis of CAC is very complex. The two core points are inflammatory states and metabolic disorders, which lead to increased protein decomposition and continuous muscle reduction. Energy consumption increased, but the body synthesis ability decreased; Eventually, the body will lose weight. The treatment of cachexia includes various strategies including nutrition, medicine and

physical exercise. Although nutritional therapy is the basic treatment in the tumor cachexia intervention measures, a common clinical problem is that even if the patient is provided with sufficient energy and protein, the body still cannot enter the normal protein anabolic process, the muscle will continue to lose, the body weight will continue to lose, and the patient will gradually appear fatigue and weakness. And so far, there is no effective drug to correct this state of cachexia. The main purpose of this study is how to make basic nutrients play a normal role in the synthesis of tumor cachexia, keep the muscle and weight loss or less loss, and reverse the development of tumor cachexia.

Curcumin is a plant polyphenolic compound that has anti-inflammatory properties. Creatine is a naturally occurring amino acid derivative in the body that can also be taken from food. Creatine supplementation improves muscle mass and function. Therefore, creatine is widely used in sports fitness and sarcopenia treatment. Some published clinical studies have also confirmed the positive effects of oral curcumin or creatine alone on patients with cachexia. However, although oral curcumin alone can improve internal environment such as inflammation, it is not ideal in terms of increasing lean body mass. Based on this, we speculated that the combination of the two may play a better and more stable synergistic effect in the treatment of tumor cachexia and delay the progression.

There are three stages of cachexia: early cachexia, cachexia, and refractory cachexia. In this study, creatine combined with curcumin was intended to intervene in patients with upper digestive tract tumors complicated with cachexia since adequate nutrition. In addition, it was considered that once the tumor cachexia developed to the refractory cachexia, both clinical and nutritional treatment would be difficult to achieve effect, so the study object was limited to the early cachexia. The main purpose of this study is to find out whether the combination of the two can improve the inflammatory state and metabolic state of the early cachexia, so as to make the basic nutrition play a role, improve the nutritional status, and eventually reverse tumor cachexia. This will have extremely important clinical significance for improving the clinical treatment effect of patients, improving the quality of life of patients with cancer, and even extending the survival period.

**Purpose**

(1) To study whether creatine combined with curcumin can improve the inflammatory state of the cachexia in the early stage of upper gastrointestinal tumors, correct the disorder of nutritional metabolism, and improve the nutritional status.

(2) To study whether creatine combined with curcumin can improve the quality of life and prognosis of early cachexia in upper digestive tract tumors, to provide a nutritional intervention mode for early cachexia in the clinic.

**1.Conditions of participation in the study/trials**

Inclusion Criteria:

(1) Men and women aged between 18 and 80; (2)Advanced tumors of the upper digestive tract (patients with untreatable or postoperative recurrence of esophageal and gastric cancer III-IV) are clearly diagnosed; (3) Meet the diagnostic criteria of early cachexia (anorexia and metabolic changes, involuntary body mass reduction ≤5% within 6 months); (4) Radiotherapy, chemotherapy or immunotherapy in our hospital; (5)Understand and fill in a variety of rating scales; (6) Informed consent, voluntary participation in this study.

Exclusion Criteria:

(1) Neoadjuvant chemotherapy patients;(2) Patients with intestinal obstruction or gastrointestinal bleeding who need complete fasting and parenteral nutrition; (3) Severe heart, lung and renal insufficiency; (4) Coagulopathy; (5) with diabetes and other metabolic diseases; (6) The expected survival time is less than 1 month; (7)Patients with cognitive dysfunction or poor coordination;(8) Allergy to creatine or curcumin; (9) People with a history of drug abuse; (10) Other conditions that doctors or researchers deem unsuitable for study participation.

**2.Number of people in research/trials**

152 subjects will be enrolled.

**3. Is it necessary to participate in and complete the test?**

Whether or not you participate in this study is of your own free will. If you decide to participate, you will be asked to sign an informed consent form and will receive a copy of this informed consent form. If you are enrolled in the study, you may still request withdrawal at any time if your withdrawal will not affect your standard care.

**4.Research/test process**

Detection items and time schedule

| Classification | Item | 0 | 0.5m | 1m | 3m |
|---|---|---|---|---|---|
| Serological indicators | blood routine | √ | – | √ | √ |
| | biochemical set | √ | – | √ | √ |
| | prealbumin | √ | – | √ | √ |
| | transferrin | √ | – | √ | √ |
| Body composition | CT scans skeletal muscle index at L3 | √ | – | √ | √ |

| | | | | | |
|---|---|---|---|---|---|
| index | cross section | | | | |
| | BIA measures muscle mass | √ | – | √ | √ |
| Inflammatory metabolic indicators | Serum insulin | √ | – | √ | √ |
| | IL-6 | √ | – | √ | √ |
| | TNF-α | √ | – | √ | √ |
| | lactic acid | √ | – | √ | √ |
| | PETCT（SUV） | p. r | – | p. r | – |
| Physical measurements | Weight | √ | √ | √ | √ |
| | grip strength | √ | √ | √ | √ |
| | skin fold thickness | √ | √ | √ | √ |
| | upper arm circumference | √ | √ | √ | √ |
| nutrition assessment | intake | √ | √ | √ | √ |
| | PG-SGA score | √ | √ | √ | √ |
| Questionnaire Survey | Functional Assessment of Anorexia/Cachexia Therapy（FAACT） | √ | √ | √ | √ |
| | ADL evaluation scale | √ | √ | √ | √ |

Clinical data of patients with advanced esophageal cancer and gastric cancer combined with early cachexia were collected. Abdominal CT scan was performed to measure skeletal muscle area and density at L3 cross section, and skeletal muscle index was obtained after height correction. Meanwhile, body composition and bone mineral density were measured. Routine examination and nutritional indexes were determined, including blood routine, biochemical set, prealbumin, transferrin; Inflammatory metabolic markers including serum insulin, IL-6, TNF-α, lactic acid, and PETCT were assessed for metabolism. NRS2002 and PG-SGA scores were performed. According to the standard

body weight, dietitians formulated a diet for all enrolled subjects. According to the ESPEN guidelines, the dietary energy intake was 30 to 35kcal/kg·d, the protein intake was 1.0 to 2.0g/kg·d, and the insufficient portion was given oral nutrition supplement and/or whey protein powder supplement. Or enteral nutrition supplementation for patients requiring tube feeding. The enrolled subjects were divided into group A control group and Group B intervention group according to the patients' own wishes by non-randomization principle.

Group A intervention group: Basic nutritional support was provided.

Group B control group: In addition to basic nutrition, oral creatine powder 5g qd, curcumin capsule 2g bid, intervention time 1 month.

The intake, complications and survival were followed up by telephone at 3 weeks; physical indicators, nutritional assessment, anorexia, and anorexia fluid quality Questionnaire (FAACT) and QoL scale were followed up at 2 weeks; nutritional serum indicators, body composition indicators, inflammatory metabolism indicators, physical indicators, nutritional assessment, FAACT and QoL scale were reviewed at 4 weeks. Evaluation of effect. The long-term survival, re-hospitalization and hospitalization expenses were investigated 3 months later. To evaluate the effect of creatine combined with curcumin on improving the nutritional status, metabolic level and clinical prognosis of the early stage of upper gastrointestinal neoplasm. Note: Weight is calculated by standard weight: Standard weight (kg) = height (cm)-105.

**5.Participating in the study requires your cooperation**

- Provide accurate medical history and current condition information.
- Tell research is responsible for the doctor you have any health problems during the study period.
- Research is responsible for the doctor you tell any new drugs, drugs during the study period, to survive, nutrition, or herbs.
- Unless the study doctor is responsible for licensing, should not be taking any drug or treatment, including prescription and over the counter when buying drugs (including vitamins and herbal medicine).
- According to the doctor's advice, taking the study drug supervision as required.
- Every time in your follow-up, please return the unused drugs and all returned empty package to study doctor.
- Drugs, room temperature storage research will study drug kept out of reach of children, not to study drug to anyone.
- Don't participate in other clinical trials.
- Appropriate precautions (during the study period and final dose within 30 days).

- Follow researchers and research the doctor's guidance.
- There is any unclear you can ask at any time.

**6.If you don't participate in this trial, other treatment options are available**

You may choose not to participate in this study, which will not have any adverse effect on your access to the appropriate treatment. We will still inform you of the relevant follow-up precautions. Basic nutritional therapy is required for subjects with early malignant upper digestive tract tumors and will be provided even if you choose not to participate in this study.

**7. Possible side effects, risks, and discomfort of participating in the trial**

Your study doctor will monitor creatine and curcumin for side effects. If you experience any side effects or discomfort during the study, it is vital that you report them to the study physician immediately. The research doctor may give you other medications to control side effects. If you or your study physician determines that you cannot tolerate these side effects, the study may be discontinued entirely, and you may withdraw from the study.

In this study, no definite adverse reactions have been reported for the two oral health foods, and a few of them may cause nausea, vomiting or abdominal distension, which disappear automatically after discontinuation.

**8. Test items**

Blood samples and abdominal CT scans will be collected for this study. The collection of blood samples may cause temporary discomfort and/or bruising. The total amount of blood collected during the study was about 15 ml/time. In this study, the nutritional status of the subjects was assessed by CT scan. The preoperative CT examination was routine and did not increase the risk of radiation exposure. The CT examination 6 months after the operation was also routine and did not increase the risk of radiation exposure. The PETCT will be examined according to the clinical needs and will be informed in detail by the clinician and the nuclear Medicine doctor prior to the examination. The determination of body composition and bone mineral density had no adverse effects on human body.

**9. Women with reproductive potential**

If you are breastfeeding, pregnant, or think you may be pregnant or trying to become pregnant, and the study drug has unknown risks for a nursing or non-delivered baby, you cannot participate in this trial. Before you can participate in this trial, you will need to undergo a pregnancy test to make sure you are not pregnant.

To participate in this study, you must be on birth control. If you are sexually active, you should use a contraceptive method acceptable to you, the study physician, and the sponsor. You must continue contraception until 30 days after the last dosing of the study drug.

It is critical that you tell the study doctor immediately if you become pregnant or suspect that you may become pregnant at any time during the study. If you are pregnant, you will be discontinued from the study and the study doctor will discuss with you that you should do. The study doctor will provide

you with his or her contact information, and you may also be asked questions about pregnancy and the baby after the study is completed.

**10. Possible benefits of participating in the trial**

Participating in this study has the potential to control your disease, delay its progression, improve its outcome, and improve its nutritional status. Or you do not benefit directly from participating in this study. The information you gain from participating in this study may be of guiding significance for patients to receive relevant treatment in the future.

**11. New information during the study/trial**

It is possible that new information about the drug under study will emerge during the research project. If new information becomes available, your study physician will inform you and discuss with you whether you wish to continue participating in the study. If you decide to discontinue your participation in the study, your study physician will arrange for subsequent treatment. If you decide to continue to participate in the study, you may be asked to sign a new informed consent form. Or if your study physician thinks it would be in your best interest to withdraw from the study, he or she will explain why and arrange for subsequent treatment.

**12. Your rights**

Participation in the study is entirely up to you. You may withdraw your informed consent at any time without giving a reason. Whether you make the decision to participate or not, it will not lead to prejudice against you or affect your medical care. If you do not participate in the study, or drop out of the study, there are many alternative treatments that you do not have to choose to participate in to treat your disease. If you need to withdraw from the study, for your safety and objective evaluation of the effects of the drug, please cooperate with the study doctor to complete the relevant evaluation and laboratory examination after the study.

If you have any questions during the study, please feel free to consult your study physician.

**13. Costs of participating in the study/trial and treatment in case of test-related injuries**

You will be required to pay the regular treatment fee to participate in this study. The following fees are provided free of charge by the researcher (2975 yuan/person in total):

(1) Preparation expenses

A. Cost of enteral nutrition preparation: 50 yuan/person · day ×30 days =1500 yuan/person

B. Cost of health food:

Curcumin capsule 2 yuan/person · day ×30 days =60 yuan/person

Creatine powder 10 yuan/person · day x 30 days =300 yuan/person

(2) Nutrition management

A. Food electronic scale: 10 yuan/person

B. Food record book: 5 yuan/person

(3) Test and laboratory processing fees

A. Inspection fee (except body components): 1000 yuan/person.

B. Body composition determination: 50 yuan/person · times ×2 times =100 yuan/person.

If your health is harmed because of participating in this study, please inform the researcher and we will take necessary medical measures. In this study, creatine powder and curcumin capsules were mainly used, which belong to nutrition and health food. The oral dose was the conventional dose recommended by the instructions. No adverse reactions were reported, and no harm was found. As for some problems, we will deal with them according to the standard.

You take it orally as directed by the investigator.

Your bodily injury was not intentional.

Notify your researcher at the first sign of injury.

You followed the medical advice of the researchers.

**14. Privacy protection**

Any personal information and data obtained during the trial will be kept strictly confidential. Your blood samples will be identified by a study number, not your name, and information that can identify you will not be disclosed to members outside the study team unless your permission is obtained. All research members and sponsors are requested to keep your identity confidential. Your files will be kept in a locked cabinet and will be accessible to researchers only. To ensure that the study is carried out in accordance with the regulations, the government administration, the sponsor's authorized inspectors or the Ethics committee members will have access to the relevant information about your participation in the study facility as required, but they will ensure that your information will not be disclosed to other parties. Although the results may be published, your identity will not be revealed in these publications. The research data will be stored in Gulou Hospital Affiliated to the School of Medicine of Nanjing University.

By signing this written informed consent, you consent to the study physician's collection and processing of your personal information for the study (the "Study Data"), including your birth date, gender, and physical health data, which will remain available for use unless your informed consent is withdrawn. If you withdraw your informed consent, your personal data will no longer be used by the study physician and the sponsor, but personal data shared prior to the withdrawal of informed consent can still be used.

Study physicians will use the study data for clinical research.

You have the right to access personal data kept with the study physician and the sponsor, and you also have the right to request the correction of inaccuracies in your personal data; You have the right to withdraw your informed consent at any time. Please contact the study physician if you have any of the above requirements.

The data will not be transmitted to other countries and regions outside China.

**15. Treatment after the study**

After the study, your doctor will discuss your future treatment options with you.

**16. Contact information**

If a study-related injury occurs, or if you have any questions about the study or the drug under study, please contact:

Doctor's Name: Xiaotian Chen

Address: No. 321 Zhongshan Road, Gulou District

Tel: 13851752678

If you have any questions about subjects' rights and interests, please contact the Medical Ethics Committee of Gulou Hospital Affiliated to the School of Medicine of Nanjing University at 025-68182923

Informed Consent Signature page

Subject Informed Consent Statement:

• I have read the informed consent form and obtained the background, purpose, procedure, risks and benefits of this trial. I have enough time and opportunity to ask questions about this clinical trial and have received satisfactory answers.

• I understand that participation in the trial is voluntary.

• I permit the use and sharing of my medical information as described in the informed consent form.

• I know that I can withdraw from the trial at any time without loss of interest or other adverse consequences.

• I am willing to cooperate with researchers for relevant tests or treatments.

• I understand that the identity and privacy of individuals participating in this study will be strictly guarded.

• I was also told who to contact when I had questions or wanted further information.

• I will obtain a signed and dated copy of this informed consent.

Subject's signature (printed): _____ Contact number: _____

Subject's signature (handwritten): _____ Date: _____

Guardian signature (if applicable) (print), please indicate the relationship with the subjects directly): _____ contact phone number: _____

Guardian signature (handwriting): _____ date: _____

The researcher who performs informed consent states:

I or my research team have fully explained and explained to the subject the background, purpose, procedure, risks, and benefits of the clinical trial, and given him/her enough time to read the informed consent, discuss it with others and answer his/her questions about the study. I have given the subject

contact information in case of any problems; I have informed the subject (or guardian) that he/she may withdraw from the study at any time during the study period without any reason.

Investigator signature (printed): _____ Contact number: _____
Investigator signature (handwritten): _____ Date: _____