An Exploratory Study of Reconstruction of Cervical Lymphatic System by Vascularized Lymphoid Tissue Transplantation During Head and Neck Squamous Cell Carcinoma Surgery

Informed Consent Form

2024/12/30

We invite you to participate in an exploratory study on the reconstruction of neck lymphatic system by vascularized lymphoid tissue transplantation during head and neck squamous cell carcinoma surgery. This study has been approved by the Medical Ethics Committee of Sun Yat-sen Memorial Hospital, Sun Yat-sen University.

Before you decide whether to participate in this study, please read the following information carefully. If you have read about the study in detail and decide to participate, you will need to sign this informed consent form.

I. Research background

Head and neck malignancies are the seventh most common malignancies in the world, 90% of which are Head and neck squamous cell carcinoma (HNSCC) . There are about 650,000 new cases of HNSCC in the world every year, including about 350,000 new cases in China every year, and 60% of patients are already locally advanced HNSCC when they are first diagnosed, requiring comprehensive treatment.

In the past 40 years, the 5-year survival rate of late-stage HNSCC has not been significantly improved, and still hovers around 50%, despite the use of combined treatment with surgery, chemoradiotherapy and targeted therapy. In addition, surgery and postoperative adjuvant radiotherapy often have a serious impact on the quality of life of patients, such as the

occurrence of head and neck lymphedema, oral mucositis, xerostomia, taste disorders, restricted mouth opening, dysphagia, aspiration and pharynx. At present, the standard treatment for oral squamous cell carcinoma recommended by guidelines is still a comprehensive treatment mode of surgery, supplemented by radiotherapy, chemotherapy, immunization and targeted therapy. Because solid tumors usually involve the lymphatic system and metastasize through regional lymphatic vessels and draining lymph nodes, neck lymph node dissection is necessary. The 2023 CSCO guidelines state that neck surgery for patients with locally advanced head and neck cancer should be performed with a modified benign or radical lymph node dissection. According to the National Comprehensive Cancer Network (NCCN) guidelines for head and neck cancer, the current surgical approach is mainly extended primary resection ± (ipsilateral or bilateral) neck lymph node dissection (guided by tumor location, depth of invasion, and imaging). Therefore, there is no clear evidence that cervical lymph node dissection can be avoided in patients with advanced head and neck cancer when neck lymph node dissection is part of the current standard surgical treatment.

Patients with Head and Neck cancer often develop secondary Head and Neck Lymphedema (HNL) after surgery, a progressive process that includes features such as lymphatic stasis, lymphatic vessel remodeling and dysfunction, inflammation, adipose tissue deposition, and eventual

fibrosis. Head and neck lymphedema can be divided into external edema and internal edema. External or internal edema may subside with time, and may also become a chronic disease, affecting the quality of life and social interaction of patients. At present, vascularized lymphatic transplantation has been widely used in the treatment of upper limb or lower limb lymphedema, and has achieved good results.

Although vascularized lymphatic transplantation has been studied in patients with head and neck cancer, there are no studies to prove its effect and efficacy.

We raise the clinical question that if more uninvolved lymph nodes in the neck can be preserved, or if autologous normal lymph nodes from other sites can be transplanted into the neck to form new lymphatic system pathways, it may reduce the incidence of head and neck lymphedema or alleviate symptoms in patients with head and neck cancer after surgery. We designed an exploratory clinical study to explore the effects of cervical lymphatic reconstruction on the incidence, degree and prognosis of postoperative head and neck lymphedema in patients with head and neck cancer.

II. Research purpose

1. Main objective: This study is a prospective and exploratory clinical study, which aims to study the extended primary resection, neck lymphatic dissection and vascularized lymphatic tissue chimeric flap

transfer repair for HNSCC patients, and postoperative radiotherapy/chemoradiotherapy according to the guidelines. The survival data of transplanted lymph nodes at 3 months, 6 months, 12 months and 24 months after comprehensive treatment of HNACC patients were evaluated by ultrasound, and the incidence and degree of lymphedema in head and neck within 2 years and the incidence and degree of lymphedema in upper limb of donor area within 2 years.

2. Secondary research objectives:

(1) 2-year disease-free survival (DFS)

(2) 2-year overall survival (OS)

(3) MR Detected the communication between the transplanted lymphoid tissue and lymphatic vessels in the surrounding tissue.

III. Clinical research process

1. Sign informed consent

2. Conduct enrollment screening for clinical studies and improve various examinations, as follows:

1) Confirmed pathological diagnosis;

2) Blood routine and urine routine;

3) Serological examination: blood biochemistry, liver and kidney function, lipids, blood sugar, electrolytes; Electrocardiogram examination;

4) HPV DNA quantification

5) Chest X-ray;

6) Abdominal color ultrasound;

7) MRI/CT examination of maxillofacial and neck region;

8) Color ultrasound of cervical and axillary lymph nodes;

9) Blood immunocytology test;

10) nuclide lymphatic imaging;

11) Circulating tumor cell detection.

3. Study grouping and treatment

If you meet the eligibility criteria, you will be enrolled in the trial group and receive the appropriate treatment according to the study protocol.

Trial group:

The surgical methods were extended primary resection, neck lymph node dissection and free dorsal thoracic artery flap repair. Meanwhile, vascularized axillary lymph tissue was transplanted to reconstruct neck lymph nodes. Adjuvant chemotherapy/chemoradiotherapy was performed according to the CSCO guidelines for head and neck tumors.

4. Visit and follow-up

During the study period, you also have some corresponding responsibilities, such as visiting the hospital on time and accepting the protocol of examination until the end of the study. Check up every 3 months for the first 1 to 3 years after surgery, and at each visit, your doctor will schedule you for the following follow-up tests:

History and physical examination

Blood routine, urine routine, liver and kidney function, blood biochemistry, liver and kidney function, lipid, blood glucose, electrolyte,

Blood immunocytology;

Imaging examination: MRI/CT examination of maxillofacial region and neck region, color Doppler ultrasound of neck lymph nodes, nuclide lymphatic imaging;

circulating tumor cell detection;

head and neck lymphedema evaluation;

upper limb lymphedema evaluation;

recurrence and metastasis;

Quality of life assessment.

5. Collection and testing of remaining samples

In the course of this study, your doctor will collect the remaining blood, tissue, and other samples from your routine treatment with your consent, and collect 16ml of fresh venous blood with free DNA preservation tubes before surgery and at 1, 6, 12, and 24 months after surgery. The use of these specimens will not affect your disease diagnosis and treatment. Your sample will be sent to our laboratory for testing peripheral blood circulating tumor DNA. The above test results may help to better understand your disease.

6.need your cooperation to complete other matters

During the study, you are responsible for reporting to your doctor any

changes in your body and mind during the study, whether or not these changes are related to the study. Be sure to tell your doctor about any other medications you are currently using and that you are using during the study. During the study period, please do not use any other drugs for head and neck tumors, and if other treatments are required, please contact your doctor in advance for formal medical guidance.

IV. Alternative treatment

Participation in the study is completely voluntary, and if you do not participate, or opt out at any stage of the study, you will receive alternative treatment. Alternative treatment methods include: (1) standard surgical protocol, namely, extended resection of primary lesion + neck lymph node dissection + free flap repair; (2) Neoadjuvant immunochemotherapy, using albumin-paclitaxel + cisplatin/carboplatin +PD-1 inhibitors. You may discuss specific alternative treatments with your doctor before deciding whether to participate in the study.

V. Expenses related to this study

The expanded primary resection + neck lymph node dissection + free flap repair used in this study is the treatment recommended by clinical guidelines. Hematology and imaging examinations such as MR And CT are routine examination items, so the expenses need to be borne by you. In this study, transportation subsidies were provided to patients, and the payment method was 150 yuan for each postoperative visit. The fee for

preoperative and postoperative cervical lymph node ultrasonography is waived.

Participating in this study will not add to your financial burden.

VI. Possible benefits

Participating in this clinical study, your disease may be alleviated, but it may not achieve the expected effect; The treatment and examination you receive may not benefit you directly, but your participation will contribute to further medical research and understanding of this disease, and hopefully improve the diagnosis and treatment of this disease in the future.

VII. Possible risks

Diagnosis and treatment of any disease can involve discomfort and unpredictable risks.

Surgical risks, such as cardiovascular and cerebrovascular accidents, anesthesia accidents, bleeding, hematoma, flap crisis, flap necrosis, etc.

Risk of postoperative chemoradiotherapy, such as bone marrow suppression, fever, nausea, vomiting, heart function damage, liver and kidney function damage, etc.

Pregnancy risk

Because we do not know the effects of the study drug on the fetus and on breastfed infants, it is important that you are not pregnant or breastfeeding when you join the study, and that you do not become

pregnant during the study. If you are pregnant, trying to become pregnant, or breastfeeding, you may not participate in this study.

If you are a female subject and are fertile, the study doctor will ask you to provide a urine sample for a pregnancy test before you begin the study.

If you are a female subject and are fertile, you must use a reliable contraceptive method for the duration of the study. A research doctor will be able to tell you which are acceptable methods of birth control. The following methods of contraception are recommended: condoms with or without spermicide (drugs that kill sperm), diaphragms or cervical caps with spermicide, or intrauterine birth control devices (small contraceptive devices installed in a woman's uterus). Emergency contraception taken after unprotected sex, such as the morning-after pill, cannot be used as a regular method of contraception. If you find a positive pregnancy test result while participating in a study, you should tell the study doctor immediately. You will need to stop taking the study medication immediately and will need to agree to further follow-up tests. If it is confirmed that you are pregnant, the study physician may ask you to withdraw from the study and terminate the pregnancy at your own expense; If you choose to continue the pregnancy, there may be an adverse pregnancy outcome, and the consequences and costs arising therefrom will be borne by you.

If you are a male subject: Participating in this study may damage your

sperm and harm the children you conceive during the study. The damage is currently unpredictable. If you have sex, you must consent to use medically approved birth control during the study. Medically approved birth control methods include surgical contraception (such as a vasectomy) or spermicidal condoms. Emergency contraception taken after unprotected sex, such as the morning-after pill, cannot be used as a regular method of contraception. Please inform your partner of the risks of this medication to the unborn baby. She should know that if she is pregnant, you need to tell your study doctor immediately, and she should tell her doctor immediately and agree to further follow-up tests. If it is confirmed that your partner is pregnant, the study doctor may order a termination of the pregnancy and the costs associated with such termination will be borne by you and your partner; If your partner chooses to continue the pregnancy, there may be an adverse pregnancy outcome, and the consequences and costs arising therefrom will also be borne by you and your partner.

VIII. Study the treatment and compensation of related injuries

In the event that an adverse event occurs that is attributable to the study drug and the diagnostic tests and treatments required for the study protocol, and that causes harm to you, your doctor will provide active treatment for you, and if a medical event occurs, it will be handled according to the medical event procedure.

IX. Confidentiality measures

The results of this clinical study are only used for scientific research purposes, so your participation in the study and your personal data during the study are confidential and will be protected in accordance with the law, your name and identity will not be disclosed, and your name will not appear in any research reports and public publications. Government administrative departments, hospital ethics committees, researchers, etc. have the right to access all your research data, including clinical observation sheets, trial data, etc., if necessary for their work.

X. Study termination

You may withdraw from the study at any time without a reason, and your decision will not have any impact on your continued medical treatment. Your doctor may also stop you from participating in the study for the following reasons:

You did not take your medication as directed and as required by the study physician;

progression of disease or intolerable adverse reactions, and the study doctor believes that continuing to participate in the study will endanger you;

You received a treatment not permitted in this study;

The study was stopped at the request of the study physician, ethics committee, or government administration.

When you withdraw from the study or the study is terminated, the study physician will discuss follow-up care with you.

XI. Rights

This clinical study has been reviewed and approved by the Medical Ethics Committee of Sun Yat-sen Memorial Hospital of Sun Yat-sen University, and the protocol design is in line with ethical requirements, which will ensure that your rights and interests are not infringed in this study.

Your participation in this clinical study is entirely voluntary, and you may refuse to participate or withdraw at any time without discrimination or retaliation, and your medical treatment and rights will not be affected. If you withdraw from a clinical study, for safety reasons, you should complete a number of appropriate medical tests at the time of withdrawal. If the doctor considers that you are unfit to continue to participate during the study period, the doctor has the right to discontinue your participation in the clinical study to protect your interests. In addition, during the study, you can always access information related to the study. If we learn any new information about the study, we will inform you in time so that you can decide whether to continue to participate in the study.

During the clinical study, in case of any discomfort or aggravation, please inform your study doctor immediately, and we will take appropriate medical measures in time; If you comply with the study protocol, the

investigator will aggressively treat any study-related adverse events that occur.