Announcement and Request for Application
Pilot Grants for Clinical and Translational Research

Background
Sun Yat-sen University ("SYSU") is a top-ranked, multidisciplinary higher education institution in China with a medical school, 4 schools of health sciences and 8 affiliated teaching hospitals. In March 2013, SYSU entered into a two-year collaboration agreement with The Johns Hopkins University ("JHU") and Johns Hopkins Medicine International ("JHI") to enhance clinical and translational research. The focus of the collaboration is:

- Offering education and training programs to SYSU clinical investigators and research professionals
- Advising SYSU on development of clinical and translational research infrastructure
- Collaborating on clinical research projects. In 2013, 5 pilot grants were awarded to Johns Hopkins faculty to establish collaborative research projects in SYSU.
- Establishing JHU fellowship programs for SYSU visiting researchers and faculty

2014-2015 Request for Applications for Clinical and Translational Research Pilot Projects
SYSU and JHU seek to develop a multidisciplinary network of research collaborations between our respective institutions. To facilitate this collaboration, we are inviting JHU faculty members to submit proposals for funding pilot projects that leverage the experience and expertise of JHU investigators as well as focus on clinical and translational research projects of interest to SYSU faculty. An important element of the proposals should be targeted at sharing research expertise with SYSU and include a collaborative development plan to expand research in China beyond the pilot phase. Priority will be given to studies that already have funding at SYSU. Please see the attached list of currently funded projects at SYSU that are looking for collaborators from JHU. In addition to this list, independent new proposals will also be considered and will be passed to SYSU to look for potential collaborators and funding there.
Grant and Eligibility Information
Applicants to the grants must satisfy the following requirements:

- The applicant must be a full-time Johns Hopkins faculty member with a primary appointment in the Johns Hopkins University.
- JHU investigator must demonstrate desire and commitment to extending research activities to China.
- A faculty member can only submit one application.

Please refer to the attached list of currently funded clinical and translational research projects in SYSU that are looking to collaborate with JHU. The potential projects can be either an extension or optimization of those existing projects or independent new proposals that will be posted in SYSU to seek collaborative partners. The selection process will be made by a joint committee of JHU and SYSU faculty members. The proposals will be judged on the basis of scientific approach and innovation, and on the likelihood of developing successful collaboration with SYSU investigators.

The JHU/SYSU Pilot Grant initiative provides five $50,000/year grants for JHU faculty. The pilot grant funding period is from September 1, 2014 to August 31, 2015. The grants are generally funded for one year. Future funding may be available. There will be no indirect costs charged. JHU principal investigator salary, time and travel can be included in the budget. Applications may use this mechanism to supplement existing projects if sufficient justification of the added value obtained by the proposed SYSU collaboration is provided.

Submission Information
Applications must be submitted by May 1st, 2014. The proposal (font Arial 11) should not exceed THREE (3) pages (excluding cover letter, abstract, appendix and budget) and format of the application is as follows:

- Cover letter with contact information and the school of affiliation. Please indicate whether the proposal is for collaboration with an existing SYSU project or a new independent application.
- Scientific abstract
- Goal of the project
- Rationale for collaboration with SYSU
- Pertinent experience and/or preliminary data
- Scientific plan with statistical plan if needed
- Anticipated barriers
- Anticipated milestones
- Budget: A detailed itemization of costs and justification of each item
• Documentation of Institutional Review Board approval (projects need not be approved at the time of application)
• Appendix: NIH-type biosketch of investigator, current other support (NIH format), any supplemental figures (maximum 2 pages)

All applications must be submitted electronically in a single file of PDF format to Associate Director of Research for the Johns Hopkins and SYSU collaboration:

Zhiping Li, MD
Email: zhipingli@jhmi.edu
Phone: 410-502-1559

Contact Information
For scientific and research inquiries regarding the grants, please contact:
Zhiping Li, MD
Associate Professor of Medicine
Director of Hepatology
Assistant Director for International Medical Education
Email: zhipingli@jhmi.edu
Phone: 410-502-1559

For general information regarding the collaboration between SYSU, JHU and JHI and/or background information of SYSU and its affiliated hospitals, please contact:
Chengda Zhang
Senior Associate
Johns Hopkins Medicine International
Email: zhangchengda@jhmi.edu
Phone: 410-464-6550
Applicant name: Dan Liang
Affiliated hospital: Zhongshan Ophthalmic Center
Project name: Efficacy and safety of subantimicrobial dose doxycycline for moderate to severe and active Graves' orbitopathy: a randomised, multicenter, double blind double dummy, positive-controlled trial.

Abstract:
Background: Graves' orbitopathy (GO) constitutes a major clinical and therapeutic challenge. Glucocorticoids (GCs) represent the first line treatment. However, they are successful in 60-80% of patients with moderate-to-severe and active GO, and they often cause severe adverse events. Highly effective treatment for active Graves' orbitopathy (GO) with no/minimal side effects are not available now. Recent studies showed that subantimicrobial dose doxycycline possess anti-inflammatory activities in treating various autoimmune diseases, with minor side effects. Our preliminary pilot study showed that subantimicrobial dose doxycycline was effective in 61.5% of patients with moderate-to-severe and active GO. Hypothesis: subantimicrobial dose doxycycline might be a new effective treatment for moderate-to-severe and active GO, with minor side effects. Methods: Study Population: patients aged 18 to 60 years, presenting with untreated active and moderate-to-severe GO were recruited. All were euthyroid before the date of inclusion. Methods: This is a randomised, multicenter, double blind double dummy, positive-controlled trial. 146 patients were randomized to: group A: doxycycline (50 mg/d, 12 wk) plus placebo for prednisone; group B: prednisone (50 mg/d, 2 wk; 40 mg/d, 2 wk; 30 mg/d, 4 wk; 20 mg/d, 4 wk) plus placebo for doxycycline. All patients were examined at baseline and 4, 12, and 24 wk after the start of treatment. The primary endpoint of the study is the treatment response of the eye at 24 wk, which will be measured on the basis of improvement in Clinical Activity Score, diplopia, motility, soft tissue involvement, eyelid aperture and proptosis. The secondary endpoint includes the score of Quality of Life (GO-QoL) and adverse events. Statistical methods: We calculated the sample size necessary not to overlook a 25% difference in outcome (α=0.05, β=0.2, π1=60%, δ=0.25, lost rate 20%), a total of 146 patients were accordingly required. Chi-square test will be used to compare both the treatment response and rate of adverse events between two groups. T-test will be employed to compare the change of GO-QoL score between two group. All statistical tests were two-tailed, and P<0.05 were considered significant.

Project status and data collected: This project is conducted in six eye hospitals in China. A database has been established. We have successfully recruited 20 patients in the past 6 months.

Funding status description: This project was supported by grants from Sun Yat-Sen University Clinical Research 5010 Program (2012015), Science and Technology Program of Guangzhou (11BPP2Xaa2060017), Science and Technology Program of Guangdong Province (2012B061700085).

Expectation for the prospective collaborator at Johns Hopkins:
1. To promote collaboration between SYSU and JHU.
2. To recruit more patients and conduct the trial in a better way.

Other information and comments:
Applicant name: Mingguang He
Affiliated hospital: Zhongshan Ophthalmic Center of Sun Yat-sen University
Project name: The natural history and prophylactic treatment of Primary Angle-Closure Glaucoma

Abstract:
Primary angle-closure glaucoma (PACG) is a potentially detectable and preventable cause of blindness. It has been estimated that PACG accounts for approximately half of all glaucoma blindness worldwide. Based on 10 years of preparatory work in East Asia we have published data on prevalence and incidence, demographic and ocular biometric risk factors, efficacy of screening tests, and outcomes from prophylactic treatment by laser iridotomy. There is scientific equipoise on the feasibility of a structured screening programme for PACG, requiring that a clinical trial be performed. China is home to the majority of people with angle-closure glaucoma worldwide, and is the most appropriate location for such a trial. We propose to enroll participants from a screening survey of eye disease in 10,000 residents of Guangzhou City in southern China, aged 50 years and older. Pilot studies indicate 11% will be eligible. We calculate that 700 participants would be needed to complete the study to provide adequate power. Participants will be randomised to receive laser iridotomy in one eye, with the fellow remaining untreated as a control. Subjects will be followed over a five year period to identify three specific endpoints: 1) Elevated intraocular pressure (IOP) > 24 mmHg on two consecutive measurements on separate days; or 2) The development of any peripheral anterior synechiae (PAS); or 3) An episode of symptomatic ("acute") angle-closure. Management will be provided to current best international standards, with visual field and optic disc structure documented and monitored over the follow-up period. We have specifically chosen not to use these as outcome measures on the grounds of the strong association between IOP, PAS and glaucomatous optic neuropathy in angle-closure.

Project status and data collected:
The clinical trial has recruited patients with anatomical narrow angles in both eyes primarily from a population-based study in Guangzhou City since 2008, aiming to determine if laser peripheral iridotomy prevents the development of PACG. LPI was done in one randomly chosen eye while the untreated eye was used as control. All the subjects were followed up frequently. A total of 11991 subjects underwent screening tests, and 1113 qualified people were enrolled to the study after two rounds of recruitments. LPI was received by 889 subjects with written informed consents and randomized grouping. Follow-up examinations were carried out at 2 weeks, then 6, 18, 36 months post laser, and the corresponding response rates in the follow-up were 99.6%, 97.5%, 95.6% and 89.7% respectively. In 2012, we applied for extension of follow-up period thus the follow-up visits would be at 2 weeks, 6, 18, 36, 54 and 72 months post LPI. Ethical approval was obtained from the Ethical Review Board of Sun Yat-sen University and the Ethical Committee of Zhongshan Ophthalmic Center. The follow-up visits at 54 months post LPI is ongoing among 734 subjects from first round recruitment, and 472 of them have completed.
**Funding status description:**

The baseline and follow-up data collection for the trail was funded by Sun Yat-sen University 5010 Clinical Research Project (2008~2018, 2 million RMB) and the Fight for Sight Foundation in UK (2008-2015, about 23 thousand pounds). The current requested fund will be used for family history data collection, DNA extraction and GWAS analysis.

**Expectation for the prospective collaborator at Johns Hopkins:**

We would like our collaborator to be responsible and willing to dedicate himself/herself to the study. Normally, our prospective collaborators should spend at least 10% of his/her time on the project, supervising the overall implementation of the study and contributing his/her ideas to the collective discussion. He/she is preferred to be responsive to the research dynamics, especially in the field of glaucoma, so that he/she knows when and how to better our study.

**Other information and comments:**
Abstract: Type 1 diabetes mellitus (T1D) is a lifelong disease which requires long-term treatment and patients with T1D are potentially suffer a number of diabetic complications. Because of the features of the disease, diabetes registries have emerged in many countries and greatly enhanced the clinical and epidemiology research of T1D. However, most of these studies were established in high-incidence countries with Caucasian population, and basic demographic/clinical characteristics of Chinese patients with T1D remain unclear due to a lack of similar studies in China. We therefore conducted this study to characterize the features of Chinese patients with T1D. The specific aims are 1) investigate demographic and clinical characteristics of Chinese patients with T1D; 2) assess metabolic control, other cardiovascular disease risk-factor control and diabetic complications in these patients; 3) develop an appropriate management model for Chinese patients with T1D; and 4) establish an associated biobank for future studies. To our knowledge, this study is the first large-scale T1D registration study in China, and it is also a first step in the development of a nation-wide T1D registry system. In this multicenter, hospital-based registration study, patients with T1D from 21 cities in Guangdong Province were registered. Patients were invited to the study site for an enrollment visit, and then return for a follow-up visit at 6, 12, 24, 36, 48 and 60 months after their baseline visit. Baseline and follow-up data were collected through a web-based registry system. Screening of retinopathy, nephropathy and cardiovascular disease were conducted in local centers. Patients’ HbA1c, C-peptide, type 1 diabetes autoantibodies, etc., were measured centrally. The economic burden of T1D and the quality of life of patients with T1D were also evaluated.

Project status and data collected:
The study was set up in June 2010. The enrollment will end in December 2016. As described above, both baseline and follow-up data were collected through a web-based registry system. Some preliminary results are as below.
1) The demographic and clinical features at onset of patients with T1D
As of July 2013, 4,519 patients diagnosed with T1D were registered (48.2% female). The median age was 31.3 (interquartile range [IQR]: 21.7, 42.3) years, duration of T1D was 3.7 (1.2, 7.0) years, age at diagnosis was 26.4 (17.0, 36.6) years, body mass index (BMI) at onset was 18.5(16.5, 21.1) kg/m². Obese, overweight, normal weight and underweight patients were in 1.2%, 5.7%, 65.2% and 27.9%, respectively. Prevalence of diabetic ketoacidosis (DKA) at onset was 48.3%.
2) Metabolic control in patients with T1D
Improving diabetes care remainsa challenge in T1D patients. The median (IQR) of HbA1c level was 8.7 % (7.1%-11.1%), and 24.7% of patients achieved the age-specific target level. A total of 69.7% and 55.3% met the target of blood pressure and LDL-C controls, respectively.
3) Diabetic Nephropathy in Chinese patients with T1D
Urine albumin-to-creatinine ratio (UACR) was used for diabetic nephropathy screening. Normal UACR, microalbuminuria and macroalbuminuria were observed in 78.1%, 16.5% and 5.4% of the patients, respectively. Multivariate logistic regression models showed that the major risk factors for albuminuria were duration of T1DM (P=0.008) and HbA1c (P=0.006).
4) Acute complications in Chinese patients with T1D
The incidence of DKA and severe hypoglycemia was 26.4 (22.4, 31.0) and 68.8 (62.2, 76.0) /100 patient-years, respectively.

Funding status description: This study was supported by the Sun Yat-sen University Clinical Research 5010 Program (Grant No. 2007030), the Guangdong Provincial Department of Science and Technology (Grant No. 2010B031500008), and unrestricted research grants from Novo Nordisk, Sanofi–Aventis, Bayer, Johnson & Johnson and Medtronic.

Expectation for the prospective collaborator at Johns Hopkins: Through this project we are looking forward to bringing together the methodological expertise at Johns Hopkins (i.e. epidemiology, biostatistics, behavioral science) and clinical and cultural expertise at SYSU (i.e. endocrinology, nursing, health coach) to take maximum advantage of the large dataset and lay the foundation for future clinical trials.

Other information and comments:
Applicant name: Zhu Jiayuan
Affiliated hospital: the First Affiliated Hospital of Sun Yat-Sen University
Project name: Multicenter Clinical Randomized Controlled Trials on Rapid Construction of Tissue-engineered Skin for Repairing Wounds

Abstract:
A wound comprises a break in epithelial continuity and disruption of structure and function of underlying tissues, the treating and repairing is always a great challenge in clinical practice. The complex healing process make the wound easy to get a tendency of nonhealing and result in a heavy burden of life quality. Nowadays surgical repairing is still the main method, such as traditional split-thickness skin graft, flap transplantation or tissue-engineered substitute transplantation. However, none of these methods could have effective and satisfy outcomes. Because none of these treatments could repair skin on both structure and function. Therefore, as a new treating technology the tissue-engineered skin has been widely used recently and shows good response. As a consequence, we provide a quick and effective method to rebuilt complete structure and function of the skin based on tissue-engineered skin technology. This method is composite of skin grafting over human acellular dermal matrix scaffold we used before with skin basal cell as seed cells, moreover it was finished in the surgery without culturing the cells and could greatly reduce the time. To further test the efficacy and safety of this new method, we propose a prospective randomized controlled multicenter trial to compare this method with traditional skin graft. If this method could actually increase wound take rate, improve the skin quality and restore skin function in some extent, it should resolve the problem of wound repair to a large extent.

Project status and data collected:
Recruiting
2013.08-2020.08

Funding status description:
Sun Yat-Sen University Clinical Research 5010 Program

Expectation for the prospective collaborator at Johns Hopkins:
Treating and repairing wounds is always a great challenge in clinical practice all over the world. Now we suggested a new method that rapid construction of tissue-engineered skin is expected to solve this problem effectively, restore the structure and function of the skin, to achieve the ideal tissue engineering skin in practice, moreover it has strong feasibility. If we can collaborate with Johns Hopkins, to expand the clinical trials to abroad, it is expected to promote the method and solve the global problem.

Other information and comments:
No.
Abstract:
Lumbar disc herniation (LDH) is a common pathological process leading to spinal surgery. Open discectomy used to be a widespread procedure for surgical treatment for symptomatic LDH. Currently, with rapid progress of endoscopic techniques, several minimal invasive endoscopic surgeries have been developed to perform discectomy. Percutaneous transforaminal endoscopic discectomy (PTED) and microendoscopic discectomy (MED) are two widely used minimal invasive surgical procedures, and both of them has been proved to be comparable to conventional open discectomy. However, the clinical outcome might be dramatically different from each other due to the difference in surgical approaches and iatrogenic injury caused by operation.

In this study, a multicenter randomized controlled trial will be performed to evaluate the effectiveness of two minimal invasive endoscopic discectomy, PTED and MED, for the treatment of symptomatic LDH. We will conduct the study at 3 affiliated hospitals of Sun Yat-Sen University.

Two groups of patients will be investigated; 1) patients diagnosed with lumbar disc herniation undergoing PTED, and 2) patients diagnosed with lumbar disc herniation undergoing MED.

The primary endpoints of the study will be changes in Oswestry Disability Index (ODI) as measured at pre- and post-operation, 1 month, 3 months, 6 months, and annually thereafter. Secondary outcomes include Visual Analog Scale (VAS), the SF-36 Health Survey, as well as post-operative radiological assessment. Treatment effect is defined as the difference in the mean change from baseline between the two groups.

On the basis of the results of this trial we will, for the first time, have scientific evidence as to the relative effectiveness of PTED versus MED for minimal invasive surgical treatment for symptomatic lumbar disc herniation.

Project status and data collected:
This project has been registered at clinicaltrial.gov (NCT01997086). For more detail, please refer to the website:

The project started at November 2013. Twenty eight patients with LDH has been enrolled in this project and followed up with primary/secondary endpoints, including 18 PTED and 10 MED. Fifteen of them has been followed up for 1 month. According to primary endpoint (Oswestry Disability Index), the effectiveness of PTED was better than that of MED in the early stage after surgical operation. However, whether the advantage of PTED could be maintained at a long time, the present project will answer this question with long-term follow up result.

Funding status description:
This project was supported by the Sun Yat-sen University Clinical Research 5010 Program (Grant number 20130006).
Expectation for the prospective collaborator at Johns Hopkins:

1) Study design.
2) Study protocol: how to conduct a blinded protocol for a surgical intervention; how to conduct an effective follow up et al.
3) Calculations, Statistics and Bias: how control bias and manage data.
4) Results publication: how to present our clinical data.

Other information and comments:
No.
Applicant name: Li Zhang

Affiliated hospital: State Key Laboratory of Oncology in South China, Sun Yat-sen University Cancer Center

Project name: A Randomized, Multicenter Phase III Clinical Trial Comparing Gemcitabine and Cisplatin With 5-Fluorouracil and Cisplatin in the Treatment of Recurrent or Metastatic Nasopharyngeal Carcinoma.

Abstract: Nasopharyngeal carcinoma (NPC) is highly sensitive to both radiotherapy and chemotherapy. Nowadays, the regimen of 5-Fluorouracil plus cisplatin (FP) is widely used in recurrent or metastatic (R/M) NPC patients, but the response period is usually short and the adverse reaction is frequent and badly tolerable. Several small phase II trials suggest gemcitabine plus cisplatin (GP) has promising efficacy and better tolerability. Unfortunately, there is no head to head comparison study to evaluate these two regimens in this setting. This phase III trial will evaluate the efficacy and safety of GP versus FP as first-line therapy in patients with R/M NPC. The population consists of R/M NPC patients that failed the radical radiotherapy or chemotherapy-naive advanced NPC (stage IV). Eligible patients will be randomized in a 1:1 ratio to receive either GP (gemcitabine 1,000 mg/m2 on days 1, 8, cisplatin 80 mg/m2 on day 1, every 3 weeks) or FP regimens (5-Fluorouracil 4,000 mg/m2 CIV over 96 hours, cisplatin 80 mg/m2 on day 1, every 3 weeks) for 4 to 6 cycles. The primary endpoint is progression free survival (PFS). Secondary endpoints include overall survival (OS), objective response rate (ORR), safety and quality of life. According to previously reported, it was assumed that the median PFS would be 4 months in the FP group and 6 months in the GP group. To detect a hazard ratio of 0.67, and a two-sided significance level of 5%, with a power of 80%, accommodating for a maximum drop-out rate of 5%, the necessary sample size was calculated to be 198 patients per group. Therefore, the trial plans to enroll 362 patients.

Project status and data collected: Thus far, 210 patients at 22 sites in China have been enrolled. One hundred and twenty patients have completed the chemotherapy. The trial has been registered in clinicaltrials.gov (NCT01528618) and all data are recorded in an electronic data capture system.

Funding status description: This trial is funded by the Sun Yat-Sen University Clinical Research 5010 Program.

Expectation for the prospective collaborator at Johns Hopkins: 1. Statisticians on data analysis, sample size/ power calculation 2. Oncologist on nasopharyngeal carcinoma 3. Researchers on translational medicine

Other information and comments:
Applicant name: Ping Lan
Affiliated hospital: Sixth Affiliated Hospital
Project name: Randomized Open-label Phase III Study Comparing Perioperative FOLFIRI Versus Adjuvant FOLFIRI in Resectable Advanced Colorectal Cancer Failed to Oxaliplatin-containing Treatment.

Abstract:
Colorectal cancer (CRC) is one of the most leading causes of cancer death in China. Although multiple treatment modalities including surgery, radiotherapy and chemotherapy have been developed, the prognosis of advanced CRC still remains poor. While around 30% of resectable advanced CRC could be cured, the appropriate treatment strategy is uncertain. This study is designed to compare perioperative FOLFIRI versus adjuvant FOLFIRI in resectable advanced CRC who exposed to oxaliplatin in open-label, phase III mode.

Project status and data collected:
The project is recruiting participants.
84 participants have been recruited. Clinical characteristics, tumor resection details, chemotherapy toxicity, life quality and survival status of all the participants were collected. Furthermore, tumor specimens, blood samples and RNA samples of the tumors were well collected and stored. The preliminary analysis of the data is ongoing.

Funding status description:
The study is partly funded by 5010 project of Sun Yat-sen University.

Expectation for the prospective collaborator at Johns Hopkins:
1. Anticipate recruitment from Johns Hopkins Hospitals for this study.
2. Seek advice and training on translational research specifically for this phase III trial.

Other information and comments:
Anyone can get more information from NCT02087475.
Applicant name: Wei-bin Liu

Affiliated hospital: Department of Neurology, the First Affiliated Hospital of Sun Yat-sen University

Project name: A prospective multi-center clinical study to compare the therapeutic efficacy of Azathioprine versus Leflunomide in the treatment of Myasthenia Gravis

Abstract:
Myasthenia Gravis (MG) is an intractable neurological disease. There are no consistent guidelines of treatments. In clinical practice, we found that immunosuppressive treatments improved the cure rate of MG after thymectomy, therefore we conducted a randomized controlled trial to validate the reliability of those treatments in multi-center. We recruited the patients after the thymectomy as our research objects. According to the principles of RCTs, participated patients in our study were randomly divided into two groups, one group receiving corticosteroids + azathioprine treatment, the other group receiving corticosteroids + leflunomide therapy. We established case report forms for each patient, and evaluated the therapeutic efficacy and side effects. We also established a database for further statistical analysis. Following our instructions, a statistical specialist evaluated the short-term and long-term efficacies of the treatments in each group. By analyzing the outcomes of this trail, we hope to propose suitable immunosuppressive treatments for the MG patients with different background (such as age, gender, subtypes). We also evaluated and controlled the acute toxicity (such as gastrointestinal side effects, liver and kidney dysfunction) and chronic toxicity (such as immune dysfunction, gonadal suppression) that occur in MG patients in two different groups. Through the prognostic analysis, we expect to find factors affecting MG’s prognosis. Ultimately, we hope to offer evidence to make guidelines for the individualized treatments of MG patients that could improve the cure rate.

Project status and data collected:
The present research is an open, random controlled and multicentre clinical trial. The trial lead by the MG Centre in department of neurology, the first affiliated hospital of Sun Yat-sen University and should enroll at least 390 cases, and all cases must satisfy the criteria (Inclusion Criteria, Exclusion Criteria and Exit Criteria) and followed-up.

Funding status description:
The study has been supported by “The Clinical Study of 5010 Plan of Sun Yat-sen University (NUM 2010003)”. 

Expectation for the prospective collaborator at Johns Hopkins:
The hope that we will cooperate with Johns Hopkins University and want to assign 1-2 doctors to Johns Hopkins University to study and co-publish articles.

Other information and comments: NO
Applicant name: Xiaoming Huang
Affiliated hospital: Sun Yat-sen Hospital of Sun Yat-sen University
Project name: Endoscopic Selective Neck Dissection for cN0 Head and neck cancer: a multicenter randomized controlled study

Abstract:
Objectives: To establish a new selective neck dissection method and sentinel lymph node biopsy in treating cN0 Head and neck cancer (cN0HNC) with endoscopy technique. To assess the cure rate of cN0 head and neck cancer, the postoperative survival rate, the postoperative complications, the functional preservation and the postoperative quality of life by compare with conventional technique.

Study design: Randomized parallel control

Inclusion criteria:
1. All patient were T1-2N0M0(AJCC2010) head and neck cancer(included oral squamous cell carcinoma, oropharyngeal squamous cell carcinoma, Laryngeal carcinoma, hypopharyngeal carcinoma, papillary thyroid carcinoma) evaluated by CT/MRI/US.
2. male and female aged 16 to 68 years old.
3. Zubrod-ECOG-WHO (ZPS) Grade:0-2; Karnofsky Performance Status (KPS) ≥60;
4. Patients provided voluntary informed consent to participate in the study.

Exclusion criteria:
1. History of radiotherapy in head and neck region;
2. History of operation in head and neck region;
3. Patient with distant metastasis disease;
4. Severe heart insufficiency, decompensated pulmonary, liver, renal functions, or other severe systemic disease;
5. Patient were receive other anti-cancer therapy;
6. Other situation which was recognized should be excluded by the researcher;
7. Patients or guardian do not agree to sign the informed consent;

Study execute time: From 2011-3-17 To 2020-12-31
Sample size: control group: 310; endoscopy group: 310

Project status and data collected:
This project was started from 2001-3-17. Until now we have recruited over 190 cN0HNC.

Funding status description:
Funding was support by Sun Yat-Sen University Clinical Research 5010 Program

Expectation for the prospective collaborator at Johns Hopkins:
We expect the prospective collaborator at Johns Hopkins could join us to develop an international mutilcenter randomized controlled study

Other information and comments:
Abstract:

**Background:** Gastric cancer is the second leading cause of cancer-associated death worldwide, with high incidence in China. The prognosis of advanced gastric cancer is quite poor. Although perioperative chemotherapy may help to prolong survival in cases of advanced disease, radical tumor resection remains the most effective treatment for curable gastric cancer. Nowadays, radical gastrectomy with extended (D2) lymphadenectomy has become the standard for treatment of advanced gastric cancer. However, this surgical procedure cannot achieve a radical tumor resection for most cases with advanced disease. Hence, a more extensive (D2 plus para-aortic nodal dissection, D4) lymphadenectomy along with gastrectomy has been performed in Japan and other Asian countries. A recent study by Sasako et al. indicated that a prophylactic D4 lymphadenectomy did not improve the prognosis of curable gastric cancer, but increased the blood loss and operation time compared with single D2 procedure. We reviewed our database, which had collected almost 2,000 gastric cancer cases since its establishment in 1994, and found that the D4 surgical procedure actually improved the prognosis of T4 tumor and tumor with lymph node metastasis at the second stations. To further confirm the results from our retrospective analysis, we performed a prospective study with multicenter, open-label, and randomized design in the affiliated hospitals of Sun Yat-sen University. This study would be helpful to improve the prognosis of patients with advanced gastric cancer, and find more efficient management for curable gastric cancer.

**Method:** This study, which started from January, 2011 and planned to close after ten years, has been approved by the ethic committee of Sun Yat-sen University, with written informed consent obtained from all enrolled subjects. Patients who had histologically proven gastric adenocarcinoma and confirmed lymph node metastasis to para-aortic nodes (<3 enlarged lymph nodes) were prospectively enrolled in this trial. A standard D2 lymphadenectomy or D4 procedure was randomly decided by a formal randomization program. The primary end point of this study was overall survival, defined as the time from randomization to death. The secondary end points were recurrence-free survival, postoperative complications, length of stay, and hospital charges. Recurrence-free survival was defined as the time from randomization to the first recurrence of cancer or death from any cause. The follow-up period would last for at least five years after the definitive operation.

**Significance:** This study would further confirm the efficacy of D2 plus para-aortic nodal dissection (PAND) procedure for management of advanced gastric cancer as compared with the classic D2 lymphadenectomy operation. Moreover, the therapeutic measures employed in current study may guide the future treatment of advanced gastric cancer in China.

**Project status and data collected:**

The project was first approved by the ethic committee of Sun Yat-sen University in 2010, and then supported by the funding of 5010 projects (Sun Yat-sen University) in 2011. Since the qualified subjects were quite limited in the affiliated hospitals of Sun Yat-sen University, we have recruited other 10 teaching hospitals in southern China to join this project. **This project is currently recruiting participants.** Up to the present, 39 eligible patients have underwent the
randomized operation for cancer elimination. Besides, another 40 patients has been enrolled and currently underwent preoperative chemotherapy prior to the definitive operation. The longest duration of follow-up visit last for 3 years. We would like to share our raw data if you are interested with this project and willing to provide your similar cases for us. More details about our collected data are attached at the end of this protocol.

**Funding status description:**
This project was mainly supported by the funding from Sun Yat-sen University (5010 Projects, a 10-year clinical research grants). In addition, other funding that supported this study were listed as follows:

4. The Science and technology foundation of Sun Yat-sen University (No. c03030303)

**Expectation for the prospective collaborator at Johns Hopkins:**
We look forward to this international collaboration. This project would also provide valuable information for the management of GC patients in the United States. As we know, D4 surgical procedure is rarely performed in the United States since most of patients are over-weight (BMI>25). No direct data for such population are available, without clear efficacy of D4 lymphadenectomy confirmed neither.

We hope that the cancer center of Johns Hopkins could recruit 30~40 eligible patients with curable gastric cancer annually and manage all enrolled subjects as our protocol described. Most importantly, we hope the prospective collaborator in Johns Hopkins could assign a high-trained surgical team to perform all surgical procedures as our team. To achieve this goal, we hope both teams could join an online or offline meeting every 3 to 6 months to share operation experience. At last, all enrolled data must be open for all collaborators. All data must be kept updated every half a year.

**Other information and comments:**
Applicant name: Prof. Lu Zhen-Hai

Affiliated hospital: Sun Yat-Sen University Cancer Center

Project name: Randomized Controlled Study on Optimize Neoadjuvant Chemoradiotherapy for Locally Advanced Rectal Cancer

Abstract: Although neoadjuvant chemoradiotherapy has significantly reduced the risk of local recurrence in locally advanced rectal cancer, systemic failure remains a predominant issue probably due to the insufficient control of systemic micro-metastasis in the neoadjuvant treatment. Induction chemotherapy is one of the most studied strategies. However, the efficacy of induction chemotherapy prior to neoadjuvant chemotherapy remains controversial. In our previous study, induction chemotherapy, gap chemotherapy combined with neoadjuvant chemoradiotherapy can improve response rate of rectal cancer patients, but the results have not been confirmed in clinical trial. Whether this new kind of treatment can optimize neoadjuvant therapy for locally advanced rectal cancer or not is still a big problem in clinical practice. This study will focus on how to optimize neoadjuvant chemotherapy.

Project status and data collected:
This project opened in February 1st. Nine rectal cancer patients enrolled in this project. None patient have finished the whole treatment course. Database had been set up and data is being collecting.

Funding status description:
The project is supporting by Sun Yat-Sen University 5010 research fund which will support 200,000 RMB total.

Expectation for the prospective collaborator at Johns Hopkins:
We look forward to cooperate with Hopkins to conduct a multi-center prospective randomized study.

Other information and comments:
Applicant name: Zhiwei Zhou

Affiliated hospital: Sun Yat-sen University Cancer Center

Project name: Pre-operative Chemoradiotherapy versus Chemotherapy Followed by Surgery and Adjuvant Chemotherapy in Patients with Locally Advanced Gastric Adenocarcinoma

Abstract: This is an open phase III, multicenter (nearly 30), randomized, comparative study to assess the superiority and safety of pre-operative chemoradiotherapy compared with chemotherapy followed by surgery and adjuvant chemotherapy in patients with locally advanced gastric adenocarcinoma. It is expected to enroll 620 ambulatory male or female participants having ECOG score <2, age 18-75 years old with histologically confirmed locally advanced (cT3N2M0, cT4aN+M0, or cT4bNanyM0, stage III A/B/C) gastric adenocarcinoma assessed by computer tomography (CT) and/or endoscopic ultrasound (EUS) that would be divided into two preoperative treatment groups, neoadjuvant chemotherapy (arm A) and chemoradiotherapy (arm B), in a ratio 1:1 respectively. The overall 5-year survival rate is expected to be from 30 to 40% by addition of the radiation treatment. CT evaluation would then be assessed 4 weeks after completion of neoadjuvant therapy, following which patients would be scheduled for total or subtotal gastrectomy, depending upon location of the tumor, plus D2 lymphadenectomy unless contraindicated by disease progression. The primary end point is to assess the disease free survival between arms A and arm B. The secondary end points are: 1) overall survival, 2) comparison of the preoperative treatment pathological response rate, 3) the resection rate (R0, R1, R2), 4) postoperative complications and safety between the two groups.

Project status and data collected: We have already enrolled 15 patients up to now, whereby 7 and 8 patients have been randomly assigned to arm A and B respectively. Of them, 4 have already completed the therapy and are under surveillance while the rest are still following their designated preoperative treatment plan. In the 7 patients who have already received preoperative CT evaluations, the results have been very promising showing PR and SD in 6 and one of the participating patients. Interestingly, one patient in arm B after surgical resection demonstrated pathological complete remission (PCR).

Funding status description: This phase III clinical trial is supported by Sun Yat-sen University with a total of 2 million Chinese Yuan fund, of which a grant of fifty thousand Chinese Yuan for international cooperation is allocated.

Expectation for the prospective collaborator at Johns Hopkins: Intellectually rigorous and methodologically sound, approach, implemented mainly through three operational activities: (1) solid team work spirit, (2) fairness of resources, and (3) reliable collaboration.

Other information and comments:
Principal Investigator: Prof. Zhiwei ZHOU, M.D, PhD; Email: zhouzhw@sysucc.org.cn
Project Communicator: Dr. Wei WANG, M.D, PhD; Email: wangwei@sysucc.org.cn
Applicant name: Zhong-yu Yuan
Affiliated hospital: Sun Yat-sen University Cancer Center
Project name: A randomized phase III (SYSUCC-001) trial assessing metronomic capecitabine therapy after standard chemotherapy for operable triple negative breast cancer (NCT01112826)

Abstract:
Triple negative (ER-/PR-/HER2-) breast cancer (TNBC), a disease with few treatment options, is an aggressive disease associated with poor overall prognosis and high probability of distant metastases, especially lung and brain. The primary objective of this study is to compare disease-free survival (DFS) of TNBC patients who were randomized to treatment with either standard adjuvant chemotherapy alone or standard adjuvant chemotherapy followed by 1 year of metronomic capecitabine therapy. The study is a multi-center, randomized, Control clinical trial. Recruitment to the study is currently ongoing with accrual of 424 patients planned.

Project status and data collected:
As of November 2013, 189 patients from eleven centers in China have been randomized (95 in capecitabine group, 94 in observation group). We reported the first safety data on 2013 St. Gallen Breast Cancer.

Funding status description:
From June 2012, this study was financially supported by Sun Yat-sun University Clinical Research 5010 Program.

Expectation for the prospective collaborator at Johns Hopkins:
We hope there will be more cancer center to recruit eligible TNBC patients.

Other information and comments:
We hope also the results from this trial will be able to provide a effective treatment to improve poor prognosis of TNBC.