A Randomized Phase II Trial of Preoperative Exercise to Reduce Operative Risk in Gastric Cancer Patients with Metabolic Syndrome: Adjuvant Exercise for General Elective Surgery (AEGES) Study Group

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This study is conducted to evaluate the efficacy and safety of preoperative exercise in patients with T1N0/T1N1/T2N0 gastric cancer and metabolic syndrome, which has emerged as a global health care issue. The primary endpoint is an incidence of perioperative complications and the secondary endpoints are weight change, change in high density lipoprotein cholesterol, operation time, intraoperative blood loss, number of dissected lymph nodes. The sample size is 86 (43 for surgery alone and 43 for exercise group) to select promising treatment for Phase III trial in a randomized Phase II setting.

Key words: preoperative exercise – gastric cancer – metabolic syndrome

INTRODUCTION

Perioperative complications greatly affect treatment results of surgery. Although the surgical outcome is improving due to advancement of surgical skills, devices and medical treatment including intensive care, mortality of gastric cancer surgery has still been reported to be as high as 5–10% (1,2) in the western countries. This can be partly explained by their high incidence of obesity. Recently, the incidence of obesity, especially of which from visceral fat accumulation such as metabolic syndrome (MetS) is increasing also in Japan.

Tsujinaka et al. (3) reported in 2007 that obesity is the risk factor in gastrectomy for stomach cancer. He indicated increased body mass index (BMI) is associated with long operative time, intraoperative blood loss, and incidence of surgical complications in a prospective gastrectomy trial. Especially, pancreatic fistula and abdominal abscess were significantly associated with increased BMI in D2 subgroup. These complications deteriorate physical conditions and QOL, consequently require long hospital stay and high medical expenses in Japan. However, there has been no study to minimize such preoperative surgical risk of obesity.

The optimal treatment for obesity is controversial. Diet restriction and/or exercise are the most common methods for long-term control. Particularly, visceral fat is likely to be reduced by exercise without diet control (4), whereas diet restriction alone may risk physical condition before surgery. In this study, the effect of preoperative exercise for gastric cancer with MetS will be verified, comparing surgery alone.

PROTOCOL DIGEST OF THE STUDY

OBJECTIVE

The objective is to evaluate the efficacy and safety of preoperative exercise for gastric cancer with MetS. This protocol was approved by the institutional review board of Kanagawa Cancer Center.
RESOURCES
Research grant from the non-profit organization: Epidemiological and Clinical Research Information network (ECRIN) and Kanagawa Health Foundation.

ENDPOINTS
The primary endpoint is incidence of perioperative complications. The secondary endpoints are weight change, change in HDL cholesterol concentration, operation time, intraoperative blood loss, and number of dissected lymph nodes.

ELIGIBILITY CRITERIA

INCLUSION CRITERIA
(i) Histologically confirmed gastric cancer (except for small cell carcinoma).
(ii) Clinical stage T1N0/T1N1/T2N0, P0, H0, M0 (Japanese Classification of Gastric Carcinoma, the 13th edition (5)).
(iii) Age 20–75 at registration.
(iv) ECOG PS0.
(v) Can walk 200 m on the flat floor and can go up two consecutive stairs without rest.
(vi) No ischemic change in the treadmill ECG (within 6 weeks before registration).
(vii) None or one cardiac risk in the following check list (within 4 weeks before registration).
(a) History of ischemic heart disease.
(b) History of heart failure.
(c) History of cerebrovascular disease.
(d) Insulin therapy for diabetes.
(e) Preoperative serum creatinine 2.0 mg/dl.
(viii) Two or less respiratory risks in the following check list (within 4 weeks before registration).
(a) Current smoker within 8 weeks of registration.
(b) Serum albumin <3.0 g/dl.
(c) Serum blood urea nitrogen (BUN) ≥30 mg/dl.
(d) COPD (FEV1.0 of <80% of predicted).
(ix) No liver disease or Child-Pugh A (within 4 weeks before registration).
(x) Suffice the following laboratory data (within 2 weeks before registration).
(a) Hb ≥9.0 g/dl.
(b) pH ≥7.38 × 10⁻³/mM³.
(c) AST <100 IU and ALT <100 IU.
(xi) Suffice the following three criteria (within 4 weeks before registration).
(a) Waist circumference (WC).
1) Male with his height ≥160 cm: WC ≥85 cm.
2) Female, or Male with his height <160 cm: WC ≥80 cm.
(b) Excessive intraabdominal fat measured with a specially designed software for CT scan.
(c) Applicable to >1 item of the following.
1) TG ≥150 mg/dl and/or HDL cholesterol <40 mg/dl.
2) Systolic blood pressure ≥130 mmHg and/or Diastolic blood pressure ≥85 mmHg
3) FBS ≥110 mg/dl.
(Medication for hyperlipidemia, hypertension, or diabetes mellitus (DM) is regarded as having each item irrespective of the laboratory data.)

EXCLUSION CRITERIA
(i) Disable to exercise because of musculoskeletal disease.
(ii) History of injury such as fracture within 6 months before registration.
(iii) History or current therapy of bronchial asthma.
(iv) History of severe pneumonia or bronchitis within 6 months before registration.
(v) History or current therapy of arrhythmia to be treated.
(vi) History of acute myocardial infarction within 6 months before registration.
(vii) Uncontrolled DM (Insulin-treated patient is also applicable, if control of serum glucose level is good.)

REGISTRATION
An eligibility checking report form is sent to the registration center at the Medical Administration Course of Master’s Degree Program, Nagoya University. Eligible patients are centrally randomized to either Arm A (surgery alone) or Arm B (exercise followed by surgery), stratified by the operation approach (open gastrectomy or laparo-assisted gastrectomy) and allocated by five factors: age, sex, numbers of factors regulating MetS, institution, and existence of circulatory/respiratory risk. The accrual has started since January 2007.

TREATMENT METHODS
The enrolled patients will start following protocol treatment within 14 days after registration.

Arm A: Surgery alone
Open or laparoscopy-assisted gastrectomy (LAG).

Arm B: Exercise followed by surgery
Exercise: The training program is composed of three components: aerobic exercise, resistance training, and stretch.
Main training is aerobic exercise such as treadmill, bicycle ergometer, swimming dance, jogging, and so on. Aerobic training is performed 3–7 days per week. The strength of the training is set by maximal heart rate reserve [Karvonen method (6)] or Borg’s scale (7) for rating of perceived exertion. The expected energy expenditure of exercise is 30 kcal/kg/week. Resistance training is performed 1–2 days per week. Stretch should be performed before and after aerobic training. Total energy
expenditure is measured by calorie counter (Lifecorder, Suzuken, Japan).
Open or LAG will be performed within 7 days after completing 4 weeks of protocol exercise.

FOLLOW-UP

Physical and blood examinations of the patients are scheduled to be checked up weekly to monthly until a month after finishing the protocol. Follow-up survey for postoperative status and survival is performed at a year after the operation.

STUDY DESIGN AND STATISTICAL METHODS

This study was designed to evaluate (i) whether preoperative exercise for gastric cancer patients with MetS is effective and safe enough compared with surgery alone, and (ii) whether it is suitable for promising test arm in Phase III trial. In the prospective gastrectomy trial JCOG 9501 study (3), incidence of perioperative complications in D2 gastrectomy for obese gastric cancer patients was approximately 35%, whereas that for non-obese patients was approximately 20%. Therefore, the exercise is expected to decrease the incidence of morbidity from 35 to 20% by improving excessive intraabdominal fat condition. However, the incidence of surgical morbidity for obese gastric cancer patients only in early stage is not accurately known because the extent of lymph node dissection in gastrectomy for early cancer stage is not always the same with D2 dissection. Then we must certify not only the safety and effectiveness of new treatment (Arm B) but also those of standard treatment (Arm A), compared with historical control for each. The comparison of effectiveness between Arms A and B will be done when both arms are judged to be effective. Assuming that incidence of perioperative complications in Arm B (P1) is 20%, the sample size is calculated to be 40 per treatment arm (80 in total) under 0.1 alpha error and 0.8 power. Taking a few dropout and ineligible patients into account, the final sample size is decided to be 86 in total.

Randomization is controlled by five strata: age (<60/over 60), sex, number of MetS defining factors (excluding WC), institution, with or without cardiovascular/respiratory risk. Furthermore, LAG is also included in this study as another stratification factor for assessing the interaction between surgical approach and treatment effect. Statistical analysis will be performed both per protocol and intention-to-treat set.

UNIVERSITY HOSPITAL MEDICAL INFORMATION NETWORK (UMIN) REGISTRATION

This study protocol was registered to the UMIN Clinical Trial Registry (UMIN-CTR) on 07 February 2007 (http://www.umin.ac.jp/ctr/index-j.htm).

PARTICIPATING INSTITUTIONS

Approximately nine Japanese institutions and hospitals participate in this trial.

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Conflict of interest statement

None declared.

References