Three-arm Phase III Trial Comparing Cisplatin Plus 5-FU (CF) Versus Docetaxel, Cisplatin Plus 5-FU (DCF) Versus Radiotherapy with CF (CF-RT) as Preoperative Therapy for Locally Advanced Esophageal Cancer (JCOG1109, NExT Study)

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A three-arm Phase III trial was started in November 2012. Preoperative chemotherapy with cisplatin plus 5-fluorouracil is the current standard treatment for locally advanced esophageal cancer in Japan, while preoperative chemoradiotherapy with cisplatin plus 5-fluorouracil is the standard in Western countries. Preoperative chemotherapy with docetaxel, cisplatin plus 5-fluorouracil is another promising regimen. The purpose of this study is to confirm the superiority of docetaxel, cisplatin plus 5-fluorouracil over cisplatin plus 5-fluorouracil and the superiority of cisplatin plus 5-fluorouracil with chemoradiotherapy over cisplatin plus 5-fluorouracil as preoperative therapy for squamous cell carcinoma of esophagus. A total of 501 patients will be accrued from 41 Japanese institutions within 6.25 years. The primary endpoint is overall survival and the secondary endpoints include progression-free survival, %R0 resection, response rate, pathologic complete response rate and adverse events.

Key words: esophageal cancer – preoperative chemotherapy – preoperative chemoradiotherapy – clinical trial – Phase III

INTRODUCTION

Worldwide, esophageal cancer is the fifth most common cause of cancer-related death for men and the eighth for women (1). For more than 30 years, the Japan Clinical Oncology Group (JCOG) has been conducting a series of multi-institutional clinical trials to establish new standard treatments for esophageal cancer (2). Locally advanced esophageal cancer, defined as clinical stage IB-IIIC in the 7th edition of Union for International Cancer Control (UICC)-TNM classification, accounts for more than half of all esophageal cancers in Japan, and these diseases have been the main target of JCOG
studies. In a randomized Phase III trial to compare post-operative chemotherapy with cisplatin plus 5-fluorouracil (5-FU) (CF) to surgery alone (JCOG9204), the superiority of post-operative chemotherapy in disease-free survival was demonstrated (3). In the following randomized Phase III trial (JCOG9907), the survival benefit of preoperative chemotherapy with CF over post-operative chemotherapy with the same regimen was confirmed (4). Therefore, preoperative chemotherapy has become the current Japanese standard treatment for locally advanced esophageal cancer.

In Western countries, on the other hand, survival benefits from preoperative chemoradiotherapy over surgery alone have been demonstrated in several clinical trials (5), and now it is accepted as the standard treatment for locally advanced esophageal cancer. However, many Asian physicians are reluctant to introduce these Western evidences directly to their clinical practice because the Western evidences came from trials where the majority of the enrolled patients had adenocarcinoma and the protocol-defined surgery was mostly transhiatal esophagectomy at least in part. The prognosis observed in the Western trials were usually poorer than that in Asia, and Asian physicians believe that their transthoracic esophagectomy with regional lymphadenectomy can achieve better local control (6). In addition, adenocarcinoma occupies only 1.5% of all esophageal cancers in Japan and a series of JCOG trials have included only squamous cell carcinoma. Nevertheless, the fact that local recurrences were observed among not a few patients in JCOG9907 indicates the possible need for more intensive local control. Thus, the first purpose of this trial is to investigate whether preoperative chemoradiotherapy with radical surgery is effective even for ‘Eastern’ esophageal cancer.

Reinforcement of systemic control with more intensive preoperative chemotherapy is another strategy to improve survival for locally advanced esophageal cancer. Docetaxel is one of the most promising drugs for esophageal cancer and recently preoperative chemotherapy with docetaxel plus CF (DCF) has been investigated in some exploratory trials. Hara et al. (7) conducted a feasibility study of this regimen for 44 patients with locally advanced esophageal cancer and showed a good response rate (60.0%) with no treatment-related death. Thus, the second purpose of this trial is to investigate whether DCF has better survival benefits over CF as a preoperative chemotherapy for locally advanced esophageal cancer.

Based on these backgrounds, we have launched a three-arm randomized controlled trial to confirm the superiority of DCF and the superiority of CF-RT in overall survival over CF as preoperative therapy for locally advanced esophageal cancer.

The JCOG Protocol Review Committee approved this study protocol in November 2012 and patient enrollment was started in December 2012. In each institution, approval by the institutional review board is obtained before starting patient accrual. This trial was registered at the UMIN Clinical Trials Registry as UMIN000009482 (http://www.umin.ac.jp/ctr/index.htm).

**PROTOCOL DIGEST OF THE JCOG1109**

**OBJECTIVES**

The purpose of this study is to confirm the superiority of DCF and the superiority of CF-RT in overall survival over CF as preoperative therapy for locally advanced esophageal cancer.

**STUDY SETTING**

A multi-institutional three-arm open label randomized Phase III study.

**FUNDING**

This study was supported by the National Cancer Center Research and Development Fund (23-A-16, 23-A-19).

**ENDPOINTS**

The primary endpoint is overall survival in all randomized patients. Overall survival is defined as the number of days from randomization to death from any cause, and it is censored at the last day the patient is alive. The secondary endpoints are progression-free survival (PFS), %R0 resection, response rate, pathologic complete response rate and adverse events.

PFS is defined as the number of days from randomization to progression or death from any cause, and it is censored at the latest day the patient is alive without any evidence of progression. Disease progression during preoperative therapy is not regarded as an event of PFS if R0/R1 resection is conducted. In cases of R2 resection, radiologically confirmed progression after surgery is regarded as a PFS event (8).

Adverse events include those during preoperative therapy, surgical morbidity, late radiation toxicity and serious adverse events.

**ELIGIBILITY CRITERIA**

**INCLUSION CRITERIA**

(i) Histologically proven squamous cell carcinoma, adenocarcinoma or basaloid cell carcinoma.
(ii) All lesions are located in the thoracic esophagus.
(iii) Clinical stages IB, II and III (excluding T4) based on the 7th UICC-TNM classification.
(iv) 20–75 years of age.
(v) ECOG performance status of 0 or 1.
(vi) Measurable lesions not required.
(vii) No prior therapy against esophageal cancer except for complete resection by endoscopic mucosal resection/endoscopic submucosal dissection with either pM1/M2 disease or pM3 disease without vascular infiltration.
(viii) No prior chemotherapy, radiotherapy or hormonal therapy against any cancers except for hormonal therapy for prostate cancer with more than 5 years of disease-free interval.
(ix) Adequate organ function.
(x) R0 esophagectomy is expected by open (or laparoscop-
ic) thoracotomy and laparotomy.
(xi) Written informed consent.

**Exclusion Criteria**

(i) Synchronous or metachronous (within 5 years) double
cancers, except for intramucosal tumor curatively
resected by local therapy.
(ii) Active infection requiring systemic therapy.
(iii) Positive hepatitis B surface antigen, hepatitis C virus
antibody or human immunodeficiency virus antibody.
(iv) Pregnant or lactating women or women of childbearing
potential.
(v) Psychiatric disease.
(vi) Patients requiring systemic steroid medication.
(vii) Requiring continuous administration of flucytosine,
phenytoin or warfarin potassium.
(viii) Iodine hypersensitivity.
(ix) Hypersensitivity for docetaxel, cisplatin or polysorbate
80-containing drugs.
(x) Diabetes mellitus with HbA1c of 6.5% or higher.
(xi) Severe emphysema or pulmonary fibrosis.
(xii) Poorly controlled hypertension.
(xiii) Unstable angina within 3 weeks or with a history of
myocardial infarction within 6 months.

**Randomization**

After the confirmation of the eligibility criteria, registration is
made by telephone, fax or web-based system to the JCOG
Data Center. Patients are randomized to any of the three arms
by minimization method balancing the arms with institution
and tumor depth (T1–2 versus T3). The three arms consist of
arm A (preoperative CF), arm B (preoperative DCF) and arm
C (preoperative CF-RT).

**Treatment Methods**

Patients in arm A receive two courses of preoperative CF (cis-
platin, 80 mg/m^2/day, day 1; 5-FU, 800 mg/m^2/day, days 1–5)
repeated every 3 weeks. Patients in arm B receive three
courses of preoperative DCF (docetaxel, 70 mg/m^2/day, day 1;
cisplatin, 70 mg/m^2/day, day 1; 5-FU, 750 mg/m^2/day, days
1–5) repeated every 3 weeks. Patients in arm C receive pre-
operative chemoradiotherapy (41.4 Gy/23 fractions) with two
courses of CF (cisplatin, 75 mg/m^2/day, day 1; 5-FU,
1000 mg/m^2/day, days 1–4) repeated every 4 weeks.

Radiotherapy in arm C is delivered with 6–10 MV photons
to a total dose of 41.4 Gy in 23 fractions over 5 weeks.
Three-dimensional treatment planning is required. The gross
tumor volume is defined as the volume of the primary tumor
and the metastatic lymph nodes measuring ≥5 mm along the
short axis. The clinical target volume (CTV) includes the
primary tumor with a 2-cm cranio-caudal margin, metastatic
lymph nodes and regional lymph nodes. The regional lymph
nodes include bilaterally supraclavicular fossae and superior
mediastinal lymph nodes for carcinoma of the upper thoracic
esophagus and mediastinal lymph nodes for carcinoma of the
middle or lower thoracic esophagus. Perigastric and celiac
axis lymph nodes are not included as elective regional lymph
nodes with consideration for anastomotic leak. The planning
target volume is defined as CTV plus a 0.5–1 cm margin in the
lateral direction and a 1–2 cm margin in the cranio-caudal
direction to account for respiratory organ motion and daily
set-up error.

Total or subtotal thoracic esophagectomy and regional lymph-
phadectomy with right thoracotomy is performed within 56
days of completion of preoperative therapy. Transhiatal eso-
ophagectomy is not allowed. Thoracoscopic esophagectomy is
acceptable but only the surgeons credentialed by the study
chair can be responsible for thoracoscopic surgery. Regional
lymph nodes for upper thoracic disease include both cervical
ganglionic (parasophageal, paratracheal, subcarinal and
mediastinal) lymph nodes. Those for middle and lower
disease include thoracic and perigastric nodes.

**Follow-up**

All randomized patients are followed up for at least 5 years
after primary accrual is completed while the analysis of
primary endpoint is performed at 3 years after accrual comple-
tion. Tumor markers (carcinoembryonic antigen and squa-
mous cell carcinoma) are evaluated at least every 3 months for
the first year, every 6 months from the second to the fifth year
and every year afterwards. Enhanced computed tomography
for the cervix, chest and abdomen is evaluated at least 6
months for the first 5 years.

**Study Design and Statistical Analysis**

This three-arm randomized trial is designed to confirm the su-
periority of preoperative DCF and the superiority of preopera-
tive CF-RT over preoperative CF in terms of overall survival.
We assumed 3-year survival with preoperative CF to be 63%
and expected a 10% increase in 3-year survival for preopera-
tive DCF and preoperative CF-RT. According to the
Schoenfeld and Richter’s method (9), the sample size was cal-
culated as 161 patients per arm with a study-wise one-sided
alpha level of 5%, a power of 70% for each pair-comparison,
an expected accrual period of 6.25 years and a follow-up
period of 3 years. One-hundred and seventy events were
expected for each pair-comparison. We adjusted for multipli-
city due to two pair-comparisons with the Bonferroni method
to maintain the study-wise one-sided alpha level of 5%. The
total sample size was set at 501 patients considering some
patients lost to follow-up. Only when the superiorities of both
preoperative DCF and CF-RT over preoperative CF are
demonstrated, the direct comparison between preoperative
DCF and CF-RT is to be conducted with a one-sided alpha of
5% in a closed testing procedure.
All statistical analyses will be conducted at the JCOG Data Center.

**INTERIM ANALYSIS AND MONITORING**

We plan to conduct two interim analyses, taking multiplicity into account using the Lan-DeMets method with O’Brien and Fleming type alpha spending function. The first interim analysis will be conducted after half of the planned number of patients are enrolled and the second interim just before the planned patient accrual is completed. The Data and Safety Monitoring Committee of the JCOG will review the interim analysis reports independently from the group investigators and group statistician. If the superiority of only one of the test arms is demonstrated with an adjusted alpha level, the study will be terminated. If the superiorities of both test arms are demonstrated over the preoperative CF arm, the study will be continued only with the two test arms. If either of the test arms is terminated because of futility, the study will be continued with the other two arms.

In-house monitoring will be performed every 6 months by JCOG Data Center to evaluate and improve study progress, data integrity and patient safety.

**PARTICIPATING INSTITUTIONS (FROM NORTH TO SOUTH)**

Hokkaido University, Iwate Medical University, Tohoku University, Ibaragi Prefectural Central Hospital, Tochigi Cancer Center, Saitama Cancer Center, National Cancer Center Hospital East, Chiba Cancer Center, Chiba University, Tokyo Dental College Ichikawa General Hospital, National Cancer Center Hospital, Tokyo Women’s Medical University, National Hospital Organization Tokyo Medical Center, Keio University, Showa University, Tokyo Medical and Dental University, Cancer Institute Hospital, Toranomon Hospital, Tokai University, Yokohama Municipal Citizen’s Hospital, Niigata Cancer Center, Niigata University, Toyama University, Shizuoka Prefectural General Hospital, Shizuoka Cancer Center, Aichi Cancer Center, Kyoto University, Osaka University, Osaka Medical Center for Cancer and Cardiovascular Disease, National Hospital Organization Osaka Medical Center, Osaka City General Hospital, Osaka Medical College, Kobe University, Hyogo Cancer Center, Hiroshima University, Hiroshima City Asa Hospital, National Hospital Organization Shikoku Cancer Center, Kochi Medical Center, National Hospital Organization Kyushu Cancer Center, Kurume University, Kyushu University.

**Conflict of interest statement**

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**References**