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ORIGINAL ARTICLE

# Study of neoadjuvant chemoradiotherapy with combined S-1 and low-dose cisplatin for patients with clinical stage II/III esophageal cancer

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**KEYWORDS**
esophageal cancer;
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S-1

**Summary** *Background:* Trimodality therapy with surgery and neoadjuvant chemoradiotherapy (nCRT) has been developed to improve survival outcomes in advanced esophageal cancer. We hypothesized that the effect of surgery plus nCRT with oral fluoropyrimidine (S-1) and low-dose cisplatin will be effective with low toxic effects in patients with esophageal cancer as well as gastric cancer.
*Methods:* This cohort study included 28 Japanese patients who underwent nCRT plus esophagectomy for esophageal cancer in preoperative clinical Stage II/III. They received only one cycle of S-1 and low-dose cisplatin concurrently, followed by surgery 3–4 weeks after completion of nCRT (the doses of radiotherapy were 20 or 30 Gy). We examined the clinical efficacy and safety of nCRT plus esophagectomy.
*Results:* All patients had squamous cell carcinoma and they all completed nCRT and underwent esophagectomy. No treatment-related deaths were observed. The response rate to nCRT was 92.9%. The 1-year, 3-year, and 5-year overall survival rates were 84.4%, 67.0%, and 67.0%, respectively for Stage II/III.

Conflicts of interest: Kodai Takahashi, Hideto Ito, Masatoshi Hashimoto, Kazuhito Mita, Hideki Asakawa, Takashi Hayashi, Keiichi Fujino, and Yukihiro Hama have no conflicts of interest or financial ties to disclose.

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*Conclusion:* Toxicity of nCRT was acceptable, and the efficacy and prognosis were favorable, particularly as we performed only one cycle of neoadjuvant chemotherapy with low doses of radiotherapy.


## 1. Introduction

The prognosis of locally advanced esophageal cancer patients is poor. Trimodality therapy of surgical resection plus neoadjuvant chemoradiotherapy (nCRT) has been developed to improve survival outcomes of locally advanced esophageal cancer. Combination therapy appears to be more effective than either chemotherapy or radiotherapy alone because chemotherapeutic agents can act as radiosensitizers to improve locoregional control and prevent micrometastasis. Some previous reports have shown a survival benefit with the use of nCRT compared with surgery alone.[1–3]

Currently, the standard nCRT is fluorouracil (5-FU) and cisplatin in Japan. However, we administered oral fluoropyrimidine (S-1) and low-dose cisplatin for clinical Stage II/III esophageal cancer at our institution. S-1 has been approved in Japan for many malignancies, but limited data are available for esophageal cancer.[4] Recently, combination chemotherapy with S-1 and cisplatin has been widely studied in advanced gastric cancer.[5–7]

In 2008, an American Society of Clinical Oncology abstract showed that S-1 plus cisplatin was superior to continuous infusion of 5-FU plus cisplatin. Outside Asia, despite differences in S-1 dose and schedule from Asian trials, S-1 plus cisplatin was associated with fewer toxic effects, slightly improved survival, and equal efficacy when compared with 5-FU plus cisplatin.[8] Further, S-1 combined with low-dose cisplatin has been reported to be effective, with tolerable toxicity.[6]

We hypothesized that the effect of surgery plus nCRT with S-1 and low-dose cisplatin will be effective with low toxic effects in patients with esophageal cancer as well as gastric cancer. Therefore, the aim of this study was to clarify the efficacy and safety of nCRT plus esophagectomy for clinical Stage II/III esophageal cancer.

## 2. Materials and methods

### 2.1. Patients

All patients provided written informed consent. The study was approved by the Institutional Review Board to ensure the protection of patient privacy and confidentiality. The study was undertaken in accordance with the ethical standards of the World Medical Association Declaration of Helsinki.

This retrospective cohort study included 28 Japanese patients (5 females and 23 males; median age, $69.8 \pm 8.3$ years) who underwent nCRT plus esophagectomy for preoperative clinical Stage II/III esophageal cancer between January 2008 and April 2015 at our institution. All patients were staged preoperatively and postoperatively according to the tumor—node—metastasis classification of the American Joint Committee on Cancer Staging Version 7.[9] Prior to administering nCRT, all patients were staged by endoscopic ultrasound (EUS) and biopsy, computed tomography (CT), or positron emission tomography (PET). All pathological specimens from the initial endoscopic biopsies were read and confirmed by pathologists specializing in gastrointestinal malignancies. The eligibility criteria for this study were as follows: age $<$ 85 years, adequate organ function (white blood cell count $\geq$ 3500, hemoglobin $\geq$ 10 g/dL, aspartate aminotransferase/alanine aminotransferase $\leq 2 \times$ the upper limit of normal, platelet count $\geq$100,000/mm$^3$, serum creatinine $\leq$ 2.0 mg/dL), and a performance status of $<$2 at the time of admission. Exclusion criteria included the following: Patients with distant metastases and any previous palliative therapy or incomplete healing from previous major oncological surgery.

The patients received S-1 and low-dose cisplatin and nCRT concurrently, plus surgery. The medical data collected included those on patient characteristics, post-treatment characteristics, surgical outcome, clinicopathological findings, prognosis, and toxicity. Follow-up data were obtained from the patients' medical records and their referring physicians.

Postoperative complications were defined as complications occurring by postoperative Day 90. Postoperative mortality was defined as death occurring during hospitalization for the operation.

Toxicity was graded on the basis of the National Cancer Institute Common Terminology Criteria (NCI-CTC) guidelines.

Following nCRT and esophagectomy, postoperative pathological staging was compared to the initial staging to assess the effect of nCRT and subsequent downstaging or upstaging.

Pathological examinations included tumor detection and the assessment of invasion depth, metastatic lymph node number, and surgical margins. Tumor regression grades were defined by the Japan Esophageal Society as follows: Grade 3, markedly effective, with no viable cancer cells [pathological complete response (pCR)]; Grade 2, moderately effective, with viable cancer cells accounting for less than one-third of the tumor tissue (partial response); Grade 1, slightly effective, with viable cancer cells accounting for one-third or greater of the tumor tissue (low efficacy); Grade 0, ineffective, with no recognizable cytological or histological therapeutic effect (poor efficacy). Downstaging

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