# Phase Ⅱ study of docetaxel, cisplatin, and fluorouracil for metastatic esophageal cancer

**Ying-Feng Peng[1)] , Motohiro Imano[1)] , Haruhiko Imamoto[1)] , Hitoshi Shiozaki[1)]**
**Shigeyuki Tamura[2)] ,Kenji Kobayashi[3)] , Toshio Shimokawa[4)] ,**
**Yukinori Kurokawa[5)] ,Hiroya Takiuchi[6)] ,Toshimasa Tsujinaka[5)] ,**
**Hiroshi Furukawa[7)]**

**Osaka GI Cancer Chemotherapy Study Group(OGSG),Japan**

**1) Department of Surgery, Kinki University 2) Department of Surgery, Kansai Rosai Hospital 3) Department of Surgery, Kinki Central Hospital**
**4) Graduate School of Medicine and Engineering, University of Yamanashi**
**5) Department of Surgery, National Osaka Medical Center**
**6) Osaka medical Uviversity 7) Department of Surgery, Sakai Municipal Hospital**

# Background

- Metastatic esophageal cancer patients have a poor prognosis.

- Phase Ⅱ studies of fluorouracil and cisplatin (CF) for localized esophageal cancer have shown high response rate(57～66%).

- The results of phase Ⅱ studies of CF for unresectable or metastatic esophageal cancer, response rate of 33～35%, have been unsatisfactory. (Table1)

- The standard regimen has been CF.

- New active regimens are required to improve the prognosis for metastatic esophageal cancer.

- **Phase Ⅲ trial of docetaxel, cisplatin, and fluorouracil (DCF) has shown superior efficacy versus CF in advanced gastric cancer.[1)]**

- **Phase Ⅲ trial of DCF has shown longer survival versus CF as an induction chemotherapy in unresectable head and neck cancer.[2)]**

- **These data led the authors to conclude that DCF can be a new standard regimen for metastatic esophageal cancer.**

- **The purpose of this study was to evaluate the efficacy and tolerability of DCF in the treatment of metastatic esophageal cancer.**

# Table 1 Phase Ⅱ trials of CF-based chemotherapy for esophageal cancer

| Authors | Patients | Regimen | Histology | Response rate | Median OS | 1-year survival |
|---|---|---|---|---|---|---|
| Hilgenberg AD [3] | 35 resectable | C:100mg/m$^2$ day4 F:1000mg/m$^2$ day1-4 /21days 2 cycles ⇒surgery | sq | 57% | N/A | N/A |
| Ajani JA [4] | 34 localized | C:20mg/m$^2$ day1-5 F:1000mg/m$^2$ day1-5 /21days 2 cycles ⇒surgery or CRT | sq | 66% | 28months | N/A |
| Iizuka T [5] | 39 advanced | C:70mg/m$^2$ day1 F:700mg/m$^2$ day1-5 /21days | sq | 35.9% | 9.2months (responders) | N/A |
| Hayashi K [6] | 36 advanced | C:20mg/m$^2$ day1-5 F:800mg/m$^2$ day1-5 /28days | sq | 33% | 6.7months | 27.8% |

C: cisplatin, F: fluorouracil, P: Paclitaxel sq: squamous cell carcinoma

# Methods

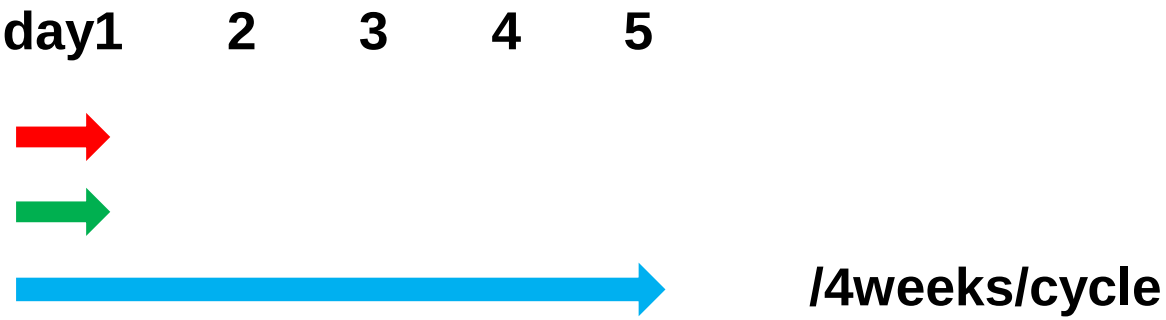
## Study design

- A multi-center collaborative phase Ⅱ trial .
- The sample size was calculated from an expected response rate of 55% and a minimum of 35% with an α error of 0.05 and a β error of 0.2, using Simon's two-stage minimax design.
- The estimated sample size was 41 and adding 10% of expected ineligible cases.
- A total of 45 patients were required.

## Participants

- Major inclusion criteria:
  - Histologically proven esophageal cancer and measurable metastatic lesions according to RECIST criteria (Stage Ⅳa, Ⅳb)
  - No prior chemotherapy, radiotherapy or surgery
  - Performance status of 0-2(ECOG scale)
  - Life expectancy of 3 months or longer
  - Between 20 and 75 years old
  - Adequate hepatic, renal, and hematologic function

# Treatment




Docetaxel(60mg/m$^2$) over 1 hour
Cisplatin(70mg/m$^2$) over 2 hours
5-FU(600mg/m$^2$) continuous infusion

- This regimen was designed based on the phase Ⅰ study in head and neck cancer[7] .
- Treatment continued until disease progression, unacceptable toxicity, death, or consent withdrawal.

## Assessments

- The primary end point was response rate (RR).
- The secondary end points were tolerability, overall survival (OS) and progression free survival (PFS) .
- Response rate was assessed using RECIST.
- The incidence and severity of all adverse events were assessed using NCI-CTC version 2.0

## Statistical analysis

- Statistical analysis was conducted using statistical software R2.9.0

# Results

## Patients

- A total of 21 patients with metastatic esophageal cancer were enrolled between July 2004 and October 2007.
- Patients' baseline characteristics are shown in Table2.
- Patients received a median of 2 treatment cycles (range, 1 to 7 cycles).
- The reasons for leaving the protocol were shown in Table3.

## Efficacy

- All of participants were evaluable for efficacy.
- The RR was 38.1% while the disease control rate (DCR) was 66.6% (Table4).
- The median OS was 12.3 months and 1-year survival was 55.7% (Figure1).
- The median PFS was 3.7 months (Figure2).

## Tolerability

- Hematological and gastrointestinal toxicities were the main adverse events (Table5).

# Table 2 Patients' baseline characteristics

| Characteristics | No. |
|---|---|
| **Sex** | |
| Male | 15 |
| Female | 6 |
| **Age (years)** | |
| Median | 62 |
| Range | 55-73 |
| **Performance status** | |
| 0 | 19 |
| 1 | 2 |
| 2 | 0 |
| **Primary tumor site** | |
| Upper thoracic | 2 |
| Middle thoracic | 12 |
| Lower thoracic | 7 |

| Characteristics | No. |
|---|---|
| **Primary tumor (T)** | |
| T1 | 0 |
| T2 | 5 |
| T3 | 13 |
| T4 | 3 |
| **Nodal stage (N)** | |
| N0 | 1 |
| N1 | 20 |
| **Distant metastasis (M)** | |
| M1a | 6 |
| M1b | 15 |
| **Sites of metastases** | |
| Lung | 3 |
| Lymph nodes | 17 |
| Liver | 0 |
| Other | 1 |

## Table 3 Reasons for leaving the protocol

| Reasons | No. |
|---|---|
| Disease progression | 7 |
| Toxicity | 4 |
| Patient's refusal | 4 |
| Surgical resection | 3 |
| Other disease | 0 |
| Others | 3 |

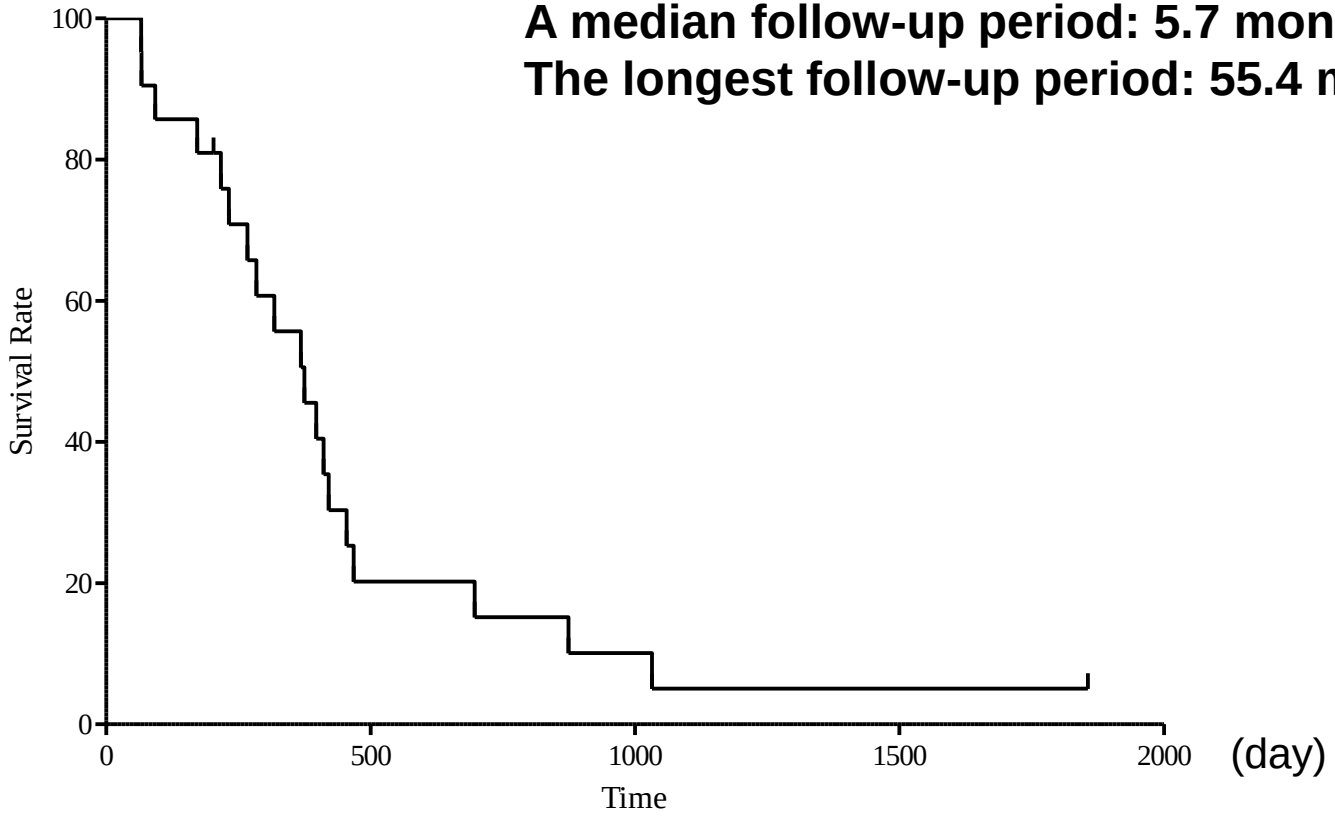
## Table 4　Tumor responses

| CR | PR | SD | PD | NE | RR<br>*P* *<br>95% CI | DCR<br>95% CI |
|---|---|---|---|---|---|---|
| 2 | 6 | 6 | 7 | 0 | 38.1%<br>0.820<br>[18.1－61.6%] | 66.6%<br>[43.0－85.4%] |

* p value at the minimum response rate of 35%

Statistical analysis: exact binomial test

# Figure 1　Overall survival

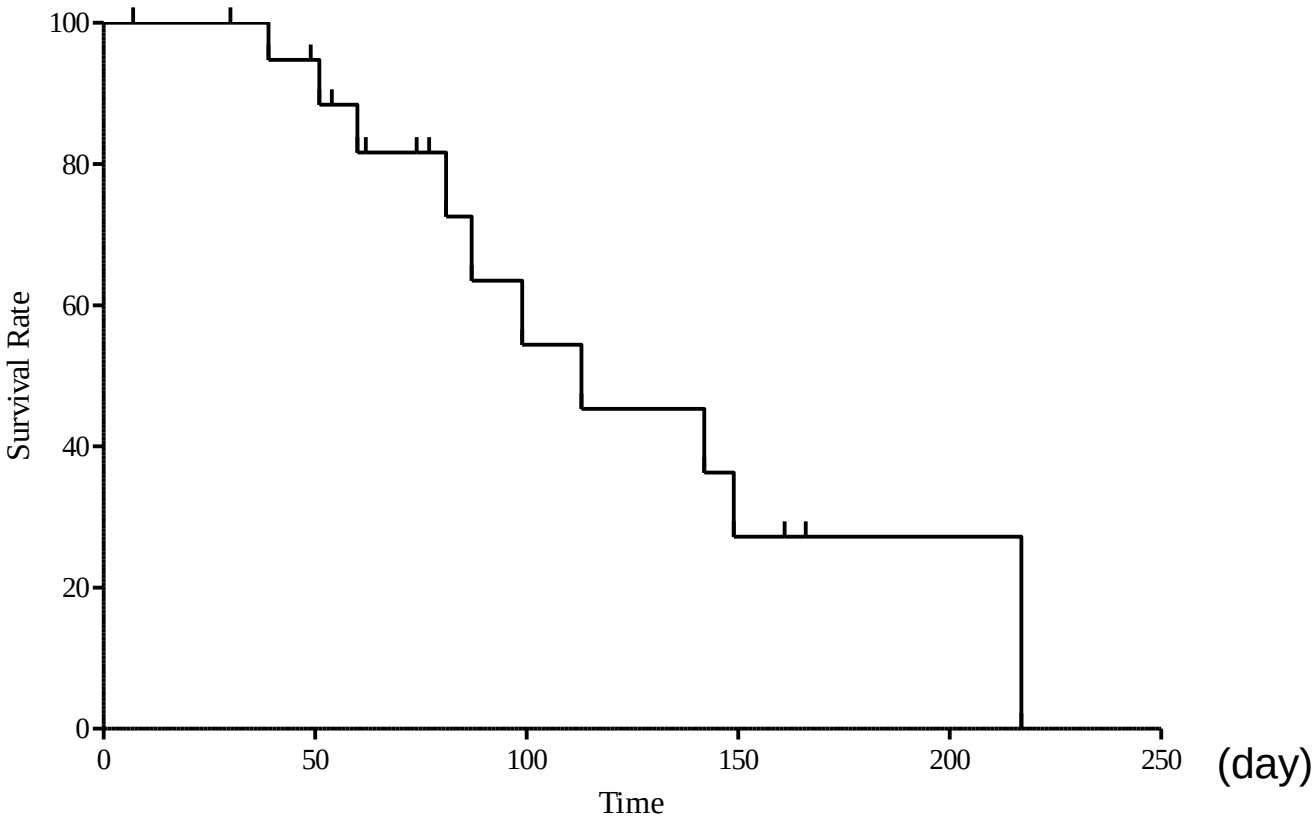



**A median follow-up period: 5.7 months**
**The longest follow-up period: 55.4 months**

**The median OS: 12.3 months (95%CI, 8.8－15.3)**
**1-year survival: 55.7% (95%CI, 37.7－82.2)**

**Survival curve: Kaplan-Meier method**
**95% CI: Greenwood formula**

# Figure 2　Progression free survival




**The median PFS: 3.7 months (95% CI, 2.9－Inf)**

# Table 5 Toxic effects

| Toxicities | Grade1 | 2 | 3 | 4 | %G3-4 |
|---|---|---|---|---|---|
| Hematologic | | | | | |
| Leukopenia | 1 | 5 | 11 | 2 | 62 |
| Neutropenia | 0 | 1 | 2 | 7 | 43 |
| Thrombocytopenia | 2 | 2 | 0 | 0 | 0 |
| Anemia | 4 | 8 | 1 | 0 | 5 |
| GOT | 0 | 0 | 1 | 0 | 5 |
| GPT | 1 | 0 | 0 | 1 | 5 |
| Creatinine | 1 | 0 | 1 | 0 | 5 |
| Gastrointestinal | | | | | |
| Stomatitis | 1 | 1 | 0 | 0 | 0 |
| Anorexia | 4 | 1 | 0 | 1 | 5 |
| Nausea | 7 | 0 | 0 | 1 | 5 |
| Vomiting | 4 | 0 | 0 | 0 | 0 |
| Diarrhea | 3 | 2 | 0 | 0 | 0 |
| Lethargy | 4 | 1 | 0 | 1 | 5 |
| Neurosensory | 0 | 0 | 0 | 0 | 0 |

# Discussion

- **Only 21 patients were registered in this study while a total of 45 patients were required.**
- **The response rate was almost the same as in other phase Ⅱ studies of CF in patients with advanced esophageal cancer.**
- **The results demonstrated favorable survival with a median of 12.3 months compared with other studies.**
- **The Grade3 or 4 hematological and gastrointestinal toxicities were more frequent than in other studies, which were manageable.**
- **The sample size was too small to show statistically whether this regimen is worthy of further phase Ⅲ trials.**

# Conclusion

- **DCF was tolerated in the treatment of metastatic esophageal cancer.**
- **The present study failed to show this regimen has higher response rate than CF.**
- **Further investigations are required to evaluate the efficacy of DCF.**

# References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