

Chemoradiotherapy using low-dose  
protracted infusion of 5-FU alone is  
as effective as 5-FU combined with  
cisplatin for advanced esophageal  
cancer

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# Background & Purpose

Survival rates of advanced esophageal cancer patients treated by radiotherapy have increased by using concurrent chemotherapy. However, standard-dose chemotherapy leads to a relatively high incidence of hematological toxicity and therefore, some patients can receive chemotherapy only once during the radiation course.

On the other hand, reduced-dose chemotherapy can be given throughout the radiation course and can sensitize the response of tumors to radiation. In 1992, we began protocol treatment using low-dose protracted infusion of 5-FU combined with conventional radiotherapy. Thereafter, the successful local control rate using this treatment encouraged us to add cisplatin (CDDP) to the regimen. The aim of this study was to evaluate the long-term results of this protocol treatment.

# Materials & Methods

- From 1992 to 2002
- Advanced esophageal cancer
- Eligibility criteria

Age < 80

ECOG performance status (PS): 0 - 3

No distant metastasis

No previous treatment

Sufficient organ function

→ 64 patients

# Patient characteristics

Group		o-FU group	FP group	p value
<b>No. of patients</b>		20	28	
<b>Age (median)</b>		63-78 (79)	60-79 (78)	0.205
<b>Male/Female</b>		20/0	28/6	0.027
<b>Tumor site</b>	Cervical	0	2	
	Upper thoracic	2	0	
	Middle thoracic	20	22	
	Lower thoracic	6	2	0.202
<b>T</b>	1	1	1	
(UICC 1997)	2	2	0	
	3	7	9	
	4	20	19	0.512
<b>N</b>	0	12	12	
(UICC 1997)	1	18	21	1.000
<b>M</b>	0	29	29	
(UICC 1997)	1 (supraclav. LN mets.)	1	0	0.202
<b>Stage</b>	IIA	6	7	
(UICC 1997)	IIB	1	2	
	III	22	19	
	IV (supraclav. LN mets.)	1	0	0.788
<b>ECOG PS</b>	0	7	6	
	1	12	18	
	2	0	10	
	3	0	0	0.701
	(Unknown)	(2)	(0)	
<b>Histology</b>	squamous cell carcinoma	20	28	-
<b>Operable</b>	Yes	1	8	
	No	29	26	0.029

- Chemotherapy

5-FU group: 30 patients

Daily continuous infusion of 5-FU

Median dose: 300 mg/m<sup>2</sup>

Median duration: 7 weeks

FP group: 34 patients

Daily continuous infusion of 5FU and  
daily continuous or bolus infusion of CDDP

Median 5-FU dose: 250 mg/m<sup>2</sup>

Median 5-FU duration: 5 weeks

Median CDDP dose: 3 mg/m<sup>2</sup>

Median CDDP duration: 5 weeks

- Radiotherapy

Fractionation: 1.8 - 2 Gy/fraction, once a day

Radiation field:

Large A-P field encompassing elective lymph nodes up to 40-46 Gy followed by booster cord-off oblique field

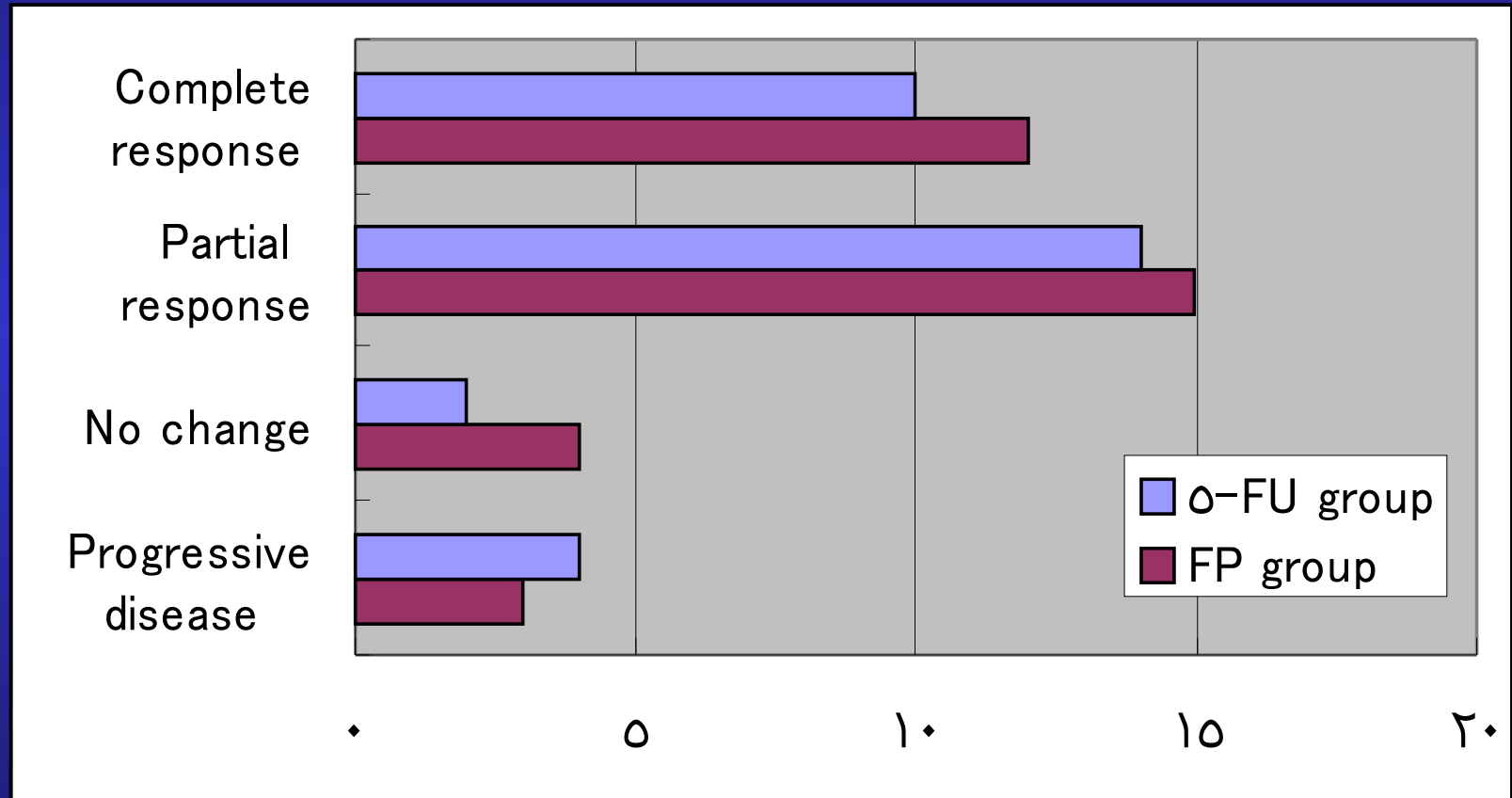
Total dose:

5-FU group: 25-74 (median 70) Gy

FP group: 60-77 (median 69) Gy

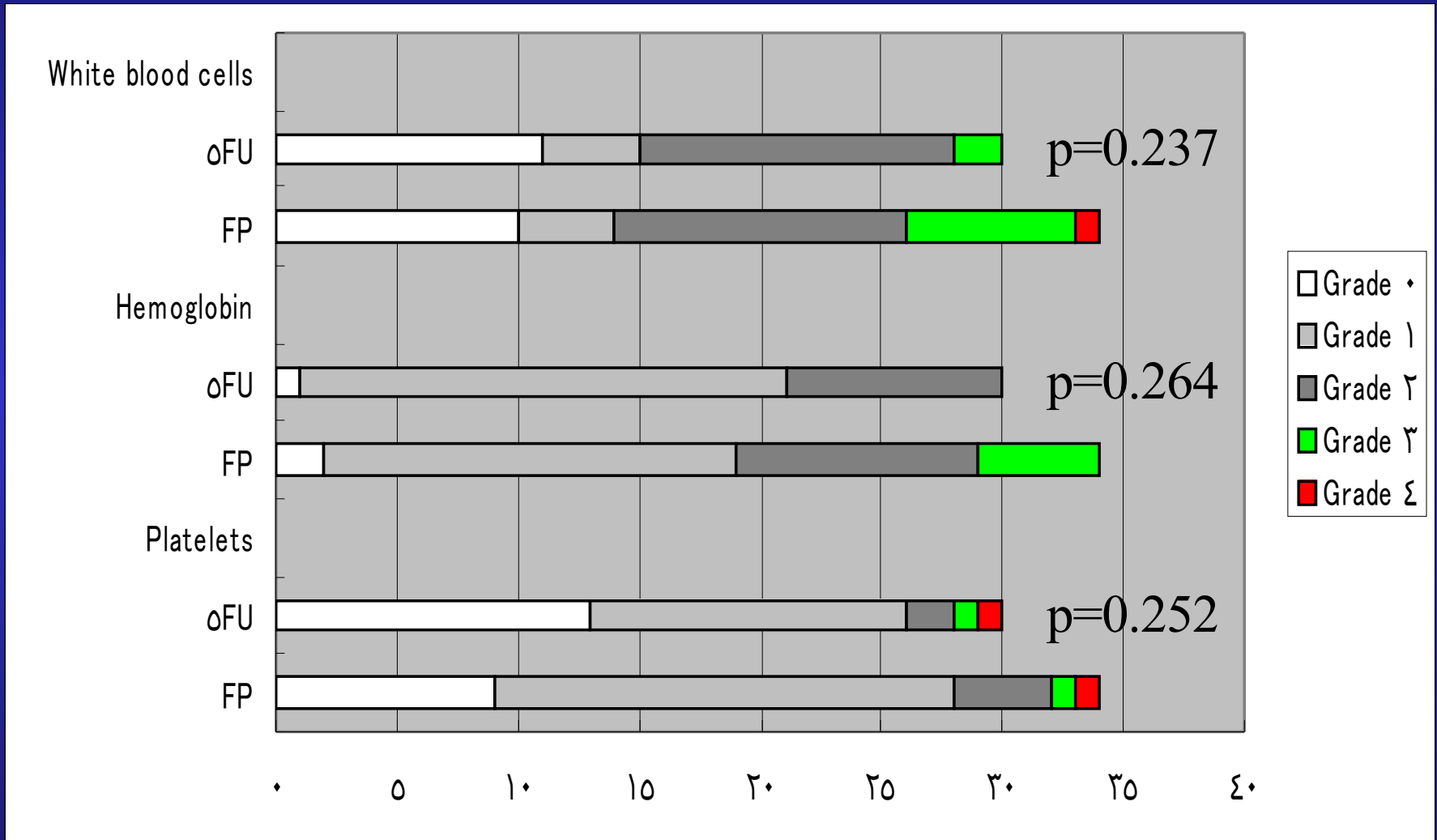
# Results

- Initial response

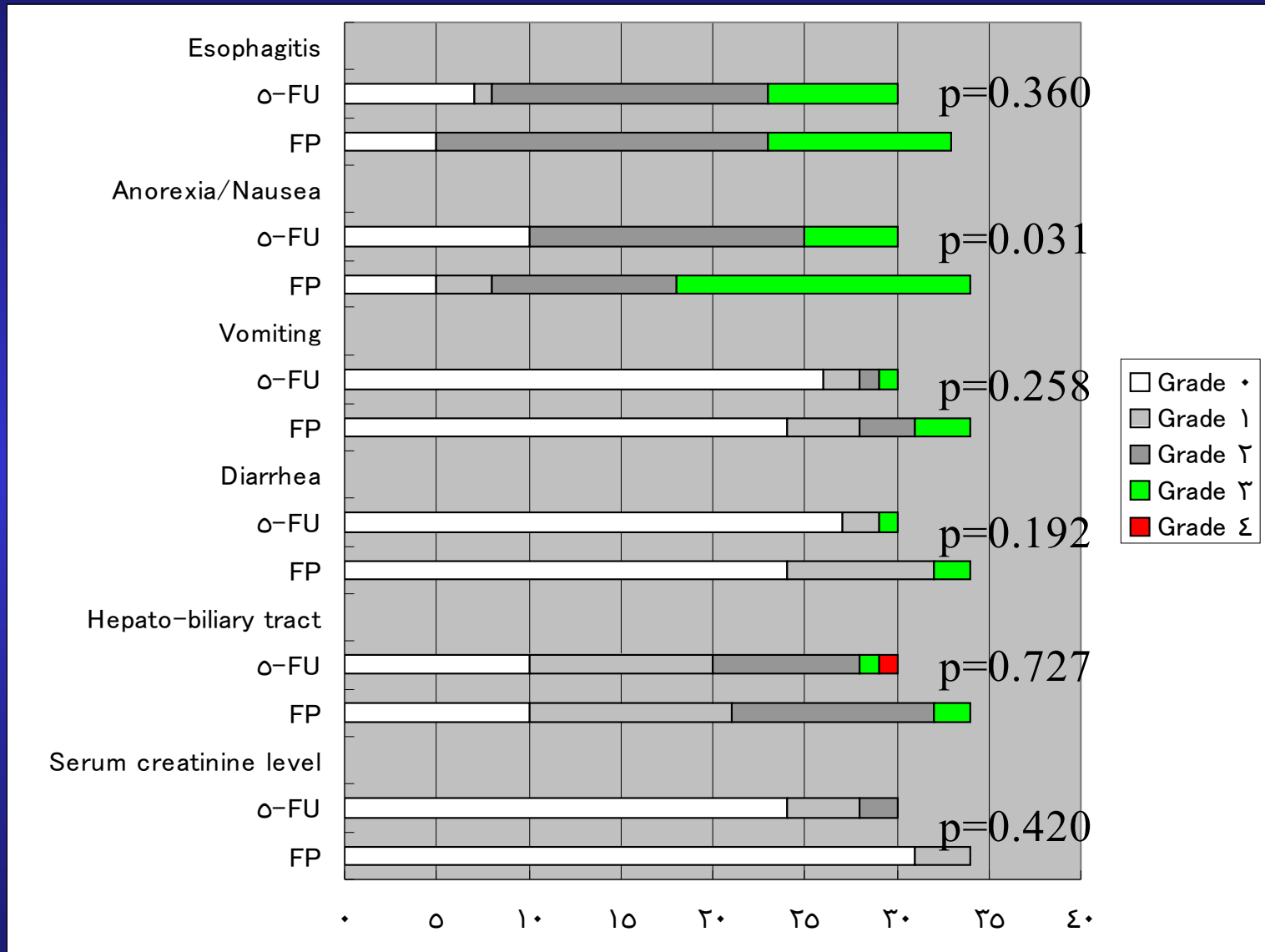


p=0.882

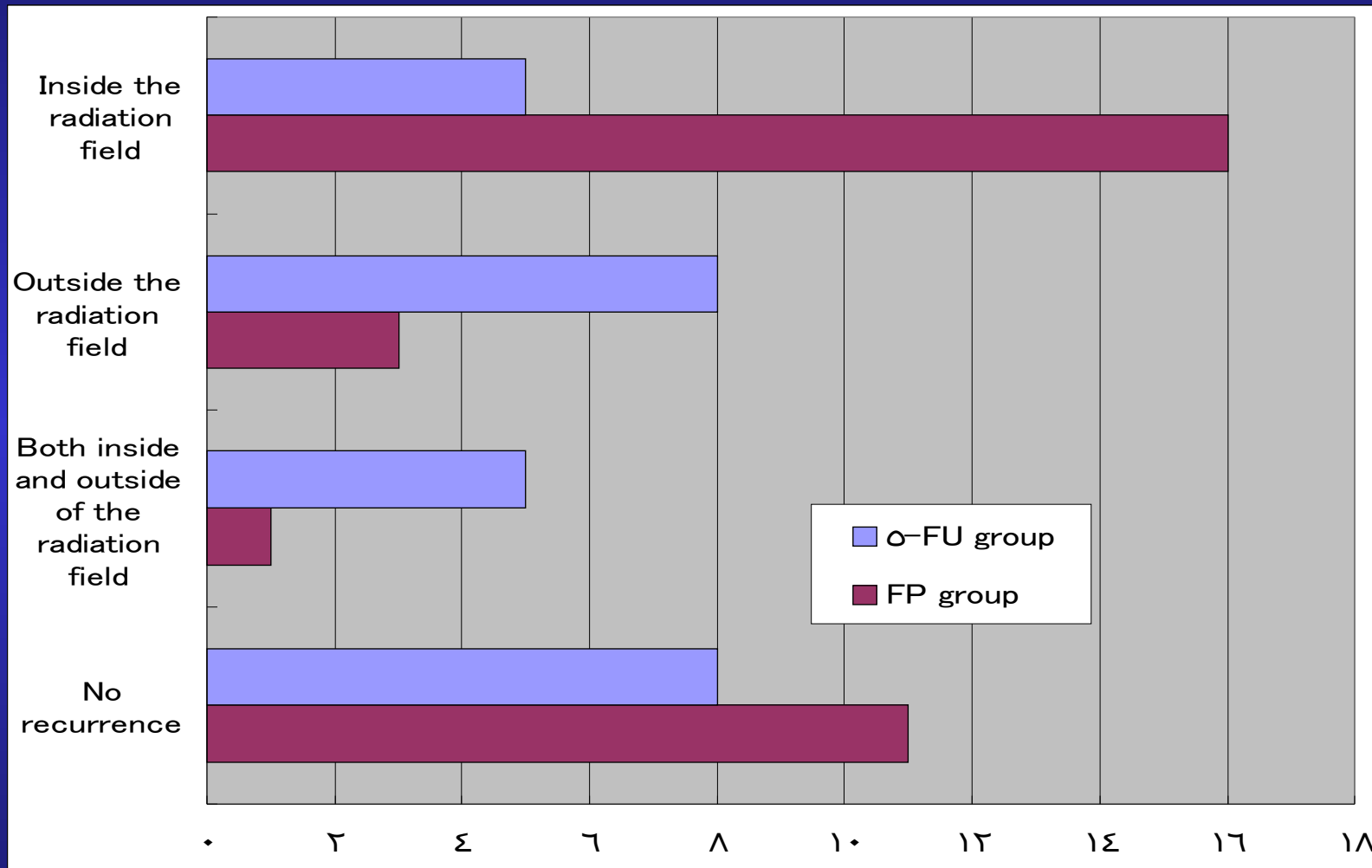
- Hematological toxicities (NCI-CTCAE ver. 3)



- Non-hematological toxicities (NCI-CTCAE ver.3)

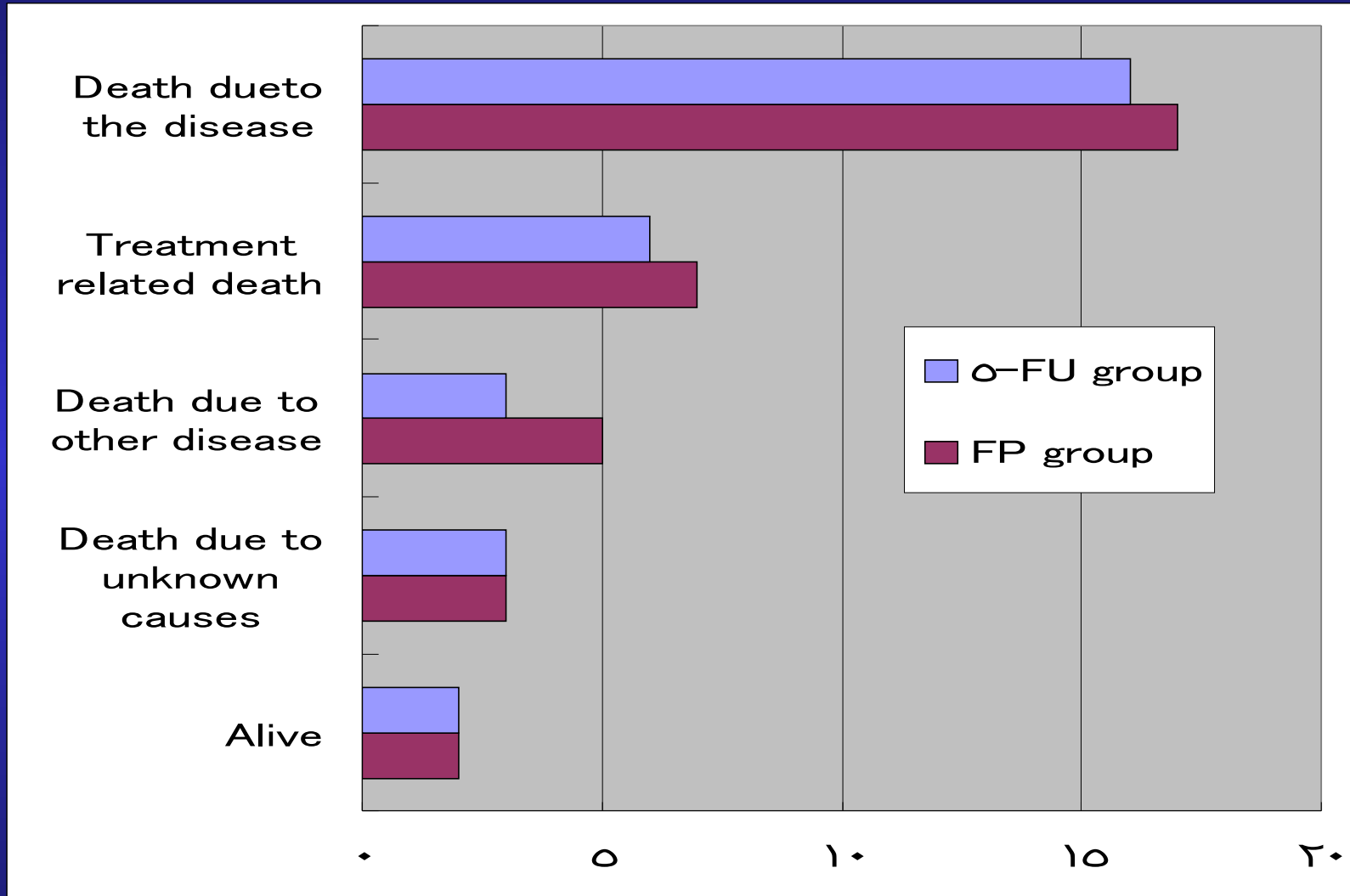


- Patterns of first failure



$p=0.013$

- Causes of death



$p=0.954$

- Acute treatment related deaths: 8 patients

### 5-FU group

Necrotizing enterocolitis	1
MRSA sepsis	1
Radiation pneumonitis	1
Mediastinitis after stenting	2

### FP group

Mediastinitis after stenting	1
General collapse	1
Aspiration pneumonia	1

- Late treatment related deaths: 5 patients

5-FU group

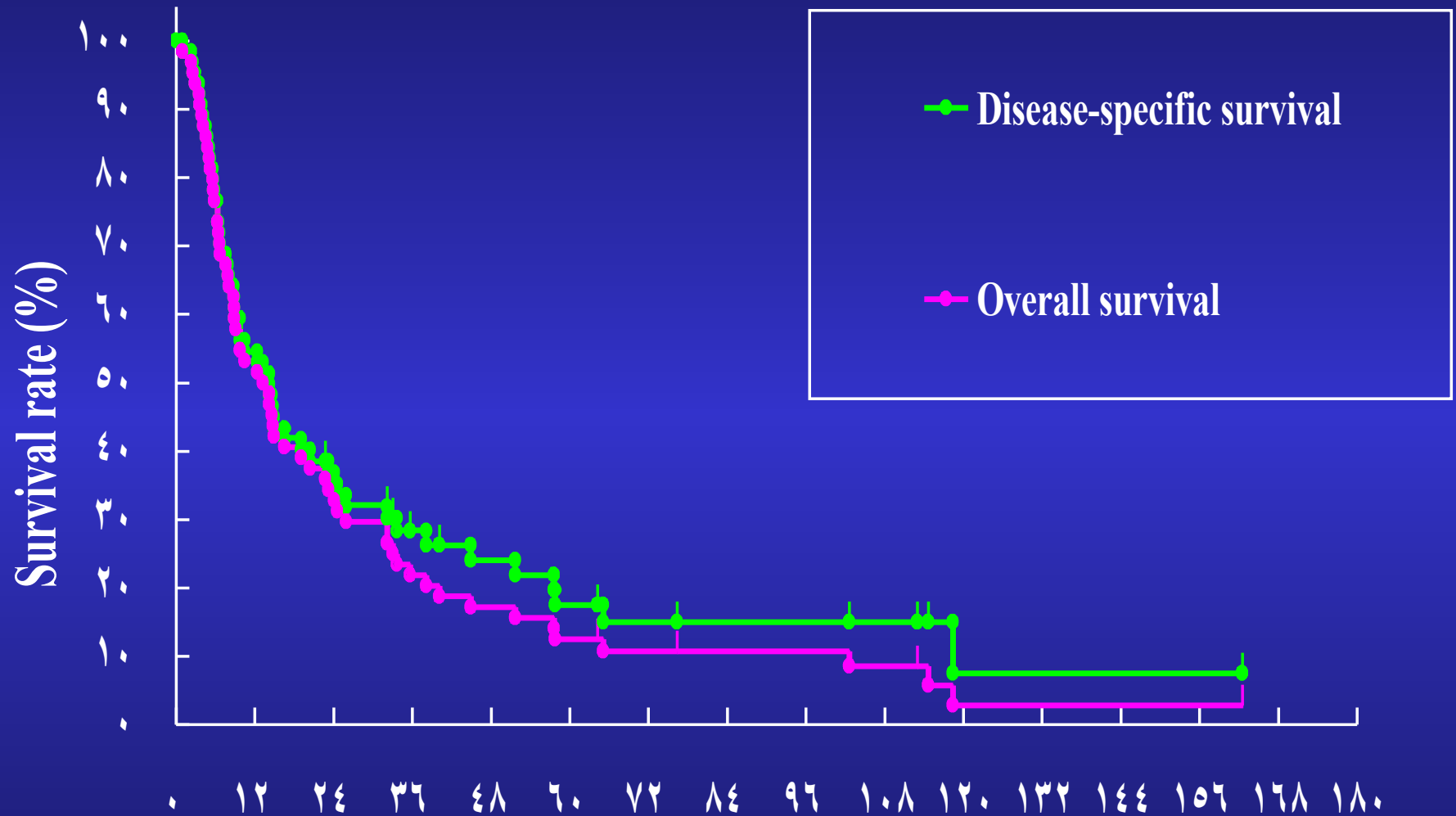
Massive pleural effusion 1

FP group

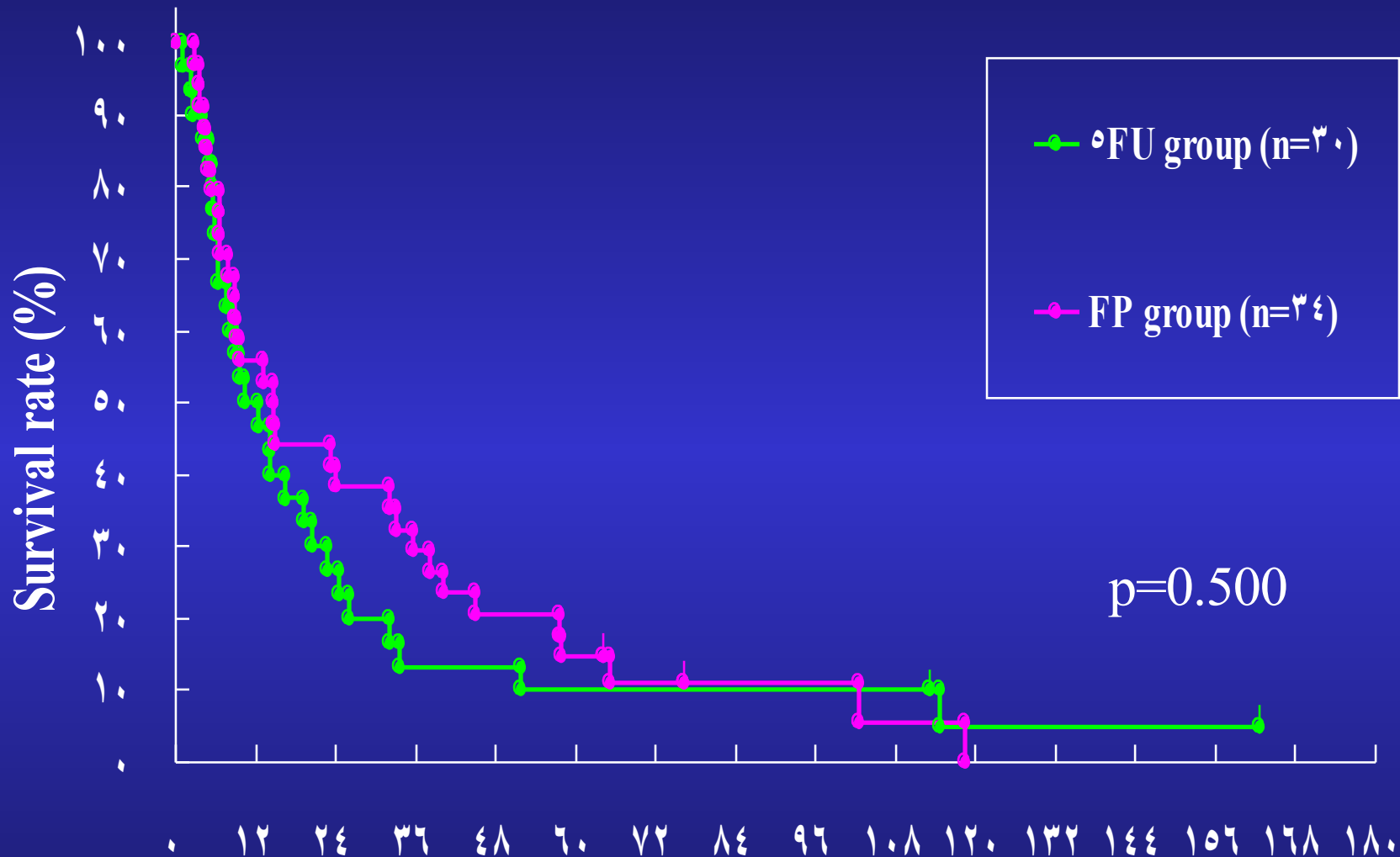
Acute myocardial infarction 2

Heart failure 2

- Survival rate for all patients



- 5-FU vs. FP (Overall survival)



Survival period (months)

# Discussion

Low-dose protracted chemotherapy is often administered with radiotherapy for esophageal cancer in Japan, because many practitioners think this approach will lessen the incidence of acute toxicities. The rationale for low-dose chemotherapy is to exploit cytotoxic cooperation, with the assumption that there may be radiosensitization or radioenhancement by the drug.

Given the large population of patients in this study with unresectable disease or other medical problems, our treatment seemed to provide a comparable efficacy with standard-dose chemoradiotherapy.

Our protocol showed less acute hematological toxicities. However, rates of treatment related death were relatively high. This may be related to the high rate of the inoperable status and large radiation field.

Results of two Japanese randomized controlled studies comparing low-dose chemotherapy and standard-dose chemotherapy are currently being compiled for publication.

The rate of inoperable status in the 5-FU group was higher than that in the FP group. However, the initial response, causes of death, and overall survival rates were similar. The incidence of high grade anorexia in the 5-FU group was lower, and the rates of other toxicities were similar.

Although the CDDP dose in our protocol was low (median: 3 mg/m<sup>2</sup>), the rate of recurrence outside the radiation field was lower in the FP group. On the other hand, the rate of recurrence inside the radiation field in FP group was higher.

Overall, the role of low-dose CDDP combined with low-dose 5-FU remains controversial.

# Conclusion

Treatment for esophageal cancer using radiotherapy combined with either low-dose 5-FU alone or that adding cisplatin demonstrated similar results.