Utility of weekly Docetaxel combined with preoperative radiotherapy for locally advanced esophageal cancer from pathologic analysis

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Running head: Chemoradiotherapy for esophageal cancer

Abstract

Purpose: Esophageal squamous cell cancer (ESCC) is a high-grade carcinoma that is treated with multidisciplinary approaches, including chemoradiotherapy (CRT) followed by surgery. Despite some success with these therapies, overall survival remains poor. In order to investigate a newer CRT regimen, we designed a comparative study to evaluate preoperative CRT using docetaxel (DOC) or 5-FU and CDDP (FP therapy) for treatment of resectable ESCC.

Methods: In a retrospective review of patients with resectable, locally advanced ESCC, 95 patients received preoperative CRT between 2001 and 2007. CRT was administered using either FP (n = 40) or DOC (n = 55). Pathological response and clinical outcomes were compared between the two groups. Hazard ratios and time-to-event analyses were used to assess outcomes; the ratios were controlled by multivariate logistic regression analysis of potential prognostic factors, and survival was presented with Kaplan–Meier curves.

Results: In the FP group, a significant curative effect was observed on the basis of pathological examination of postoperative lesions. However, the DOC group presented a significantly better prognosis on the basis of cumulative survival rates. Logistic regression analysis revealed that the presence of five or more lymph node metastases was an independent predictor of reduced survival. Patients with lymph node metastasis exhibited a better prognosis in the DOC group than those in the FP group.

Conclusions: Preoperative CRT for locally advanced esophageal cancer using DOC results in similar or better long-term outcomes compared with FP-based CRT. Therefore, CRT using DOC is a promising therapy option for esophageal cancer.

Introduction

Esophageal cancer is a high-grade carcinoma that requires multidisciplinary therapy for improvement of patient outcome. Since the mid-1980s in Japan, a favorable prognosis has been obtained using three-field lymph node dissection (neck, thoracic cavity, and abdomen), which is now the standard surgical procedure for radical treatment of esophageal cancer.[1-3] At our institution, we have always performed two-or three-incision right transthoracic esophagectomy (TTE) (McKeown procedure) along with standard three-field lymphadenectomy.[4]

Since the 1990s, phase II[5-7] or III[8-10] preoperative chemoradiotherapy (CRT) has been used as the main strategy for the management of advanced esophageal cancer in the United States. Several cases of esophageal cancer in the West are adenocarcinomas of the lower thoracic esophagus and abdominal esophagus, whereas squamous cell carcinomas of the thoracic esophagus are common in Japan.

With regard to surgical procedure, transhiatal esophagectomy (THE) is performed extensively without thoracotomy by the transabdominal approach; the lymph node dissection is believed to have little prognostic significance. Thus, the significance of improving the prognosis using lymph node dissection is viewed with some skepticism in the West.[11-12] In contrast, in Japan, systematic lymph node dissection such as three-field lymph node dissection is commonly used for esophageal cancer; this procedure allows clinicians to gather precise information on cancer staging, including any lymph node metastases.

Complete tumor resection clearly contributes to an improved prognosis and is increasingly used in combination with chemoradiotherapy (CRT).[13-17] In cases with

proven or suspected invasion of adjacent organs or lymph nodes by the primary tumor, we perform CRT before the surgical procedure with the goal of improving the resection rate. The use of 5-FU and CDDP or FP is common in CRT, but FP therapy is difficult to use in patients with renal impairment. In addition, FP therapy can be expensive because hospitalization is mandatory for FP administration. On the other hand, Docetaxel (DOC) has been reported to deliver excellent results in CRT for head and neck cancer[18-20] therefore, we decided to use DOC in CRT for esophageal cancer. The purpose of the current study was to compare the treatment outcomes and the efficacy of preoperative DOC CRT with that of FP CRT in patients undergoing surgical resection of esophageal cancer.

Patients and Methods

The subjects of our study were 95 patients with ESCC with no metastases to distant organs who first received preoperative CRT with FP (n = 40) or DOC (n = 55) and then underwent surgery for resection between 2001 and 2007. At our hospital, we switched from FP to DOC in 2004 because patients could receive this therapy at an outpatient visit.

Squamous cell carcinoma was present in all the 95 patients. Chemoradiotherapy was intended for patients with suspected esophageal invasion or surrounding organ invasion. All the patients had been classified as T2-4N1-3M0 according to the sixth edition of the American Joint Committee on Cancer (AJCC) Staging Manual using computed tomography (CT) scans and endoscopic ultrasounds (EUS). The FP group received a continuous infusion of 5-FU 500 mg/m^2 per day for five days and an intravenous

infusion of CDDP 10 mg/m^2 on days 1–5, repeated every 4 weeks. Cases with renal impairment (Ccr < 30 ml/min) were administered half doses of both the drugs. The DOC group received Docetaxel 10 mg/m^2 by intravenous infusion on day 1; this was repeated every 4 weeks. Radiation therapy was delivered by a two-field technique five days per week at 2 Gy per fraction. Both the patient groups received conventional PA radiotherapy for a total of 40 Gy.

All the patients underwent surgery within 4–6 weeks of completing radiochemotherapy. In cases where pathological examinations after surgery detected five or more lymph node metastases, chemotherapy was performed using 5-FU and CDDP and docetaxel as adjuvant therapy.

The cases diagnosed as lymph node (LN) positive by CT and EUS before CRT were evaluated to establish the effectiveness of CRT using the Japanese Classification of Esophageal Cancer (Tenth Edition). The pathological outcomes, which were based on resected specimens and the long-term prognoses, were compared between the two groups. Pathological response to treatment was judged using the "Rules for Classification of Esophageal Cancer in Japan" of the Japan Esophageal Society (Table 1).[21] The prognosis was examined on the basis of both the pathological response and the cancer stage using the Kaplan–Meier method. Disease staging was performed using the sixth edition of the TMN classification.[23] Further, multivariate analysis of the prognostic factors was performed by logistic regression analysis; a difference with a p value of ≤0.05 was considered statistically significant.

Results

In this study, the following parameters did not differ significantly between the DOC and FP groups (Table 2): radical curability, age, gender, smoking, alcohol intake, tumor area, histology, depth of tumor invasion, lymphatic invasion (Ly factor), vascular invasion (V factor), intraepithelial spread, intramural metastasis, lymph node metastasis, ≥5 lymph node metastases, TNM stage, and cause of death.

The clinical effects of CRT on preoperative lymph node metastases revealed no significant differences between the groups. Patients who had been diagnosed as LN negative during preoperative CT and EUS examinations were excluded from the study (Table 3).

Pathological evaluation of the resected lesions revealed a significant curative effect in the FP group because this group had a high percentage of cases with Grade 2 and 3 responses (Table 3). However, on the basis of the cumulative survival rates, the DOC group exhibited a significantly better prognosis compared with that of the FP group (Fig. 1).

Evaluation of the cumulative survival for each pathological grade revealed that cases with Grade 1 and 2 responses in the DOC group exhibited significantly better prognosis compared with those in the FP group (Fig. 2). However, there were no significant prognostic differences between the groups for cases with Grade 3 responses (Fig. 2). The median observation periods for cases with Grade 1, 2, and 3 responses were 85, 93, and 98 months, respectively, and the median observation period for all the cases was 90 months.

Comparison of the cumulative survival on the basis of the postsurgical stage revealed that AJCC Stage IV cases in the DOC group exhibited a significantly better

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prognosis compared with those in the FP group (Fig. 3). There were no significant survival differences between the groups for Stage II and III cases (Fig 3). There was an insufficient number of AJCC Stage I cases for evaluation in our study. The median observation periods for the AJCC Stage II, III, and IV cases were 93, 88, and 98 months, respectively.

Multivariate logistic regression analysis was performed with survival as the dependent variable and the following being used as covariates: sex; tobacco use; alcohol intake; tumor area; histology; depth of tumor invasion; clinical effects on lymph nodes; pathological effects on the primary tumor; Ly factor; V factor; presence of intraepithelial spread; intramural metastasis; pathological lymph node metastasis; and presence of ≥5 lymph node metastases. Among these factors, the presence of ≥5 lymph node metastases and the Ly factor emerged as two independent prognostic factors (P = 0.033, P = 0.026, respectively).

The following adverse events were observed in this study: bone marrow suppression; lung, liver, and kidney damage; and gastrointestinal disorders. Moreover, bone marrow suppression was more common in the FP group patients than in the DOC group patients. However, there was no significant difference in the other observed adverse effects. In both the groups, bone marrow toxicity (mainly grade 1 and 2 with decreased white cells as the primary manifestation) was the primary effect observed after therapy; otherwise, no other significant difference was evident with regard to the side effects between both the groups.

On the basis of this analysis, cumulative survival was compared between the FP and DOC groups for patients with lymph node metastasis and ≥5 lymph node metastases.

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The DOC group revealed better prognosis in cases with lymph node metastasis (Fig. 4) on the basis of the median observation periods of 93 and 89 months for the LN-positive and LN-negative groups, respectively; with regard to cases with ≥5 lymph node metastases, there was no significant difference in survival between the groups (Fig. 5). The median observation periods were 91 and 96 months for cases with <5 and ≥5 lymph node metastases, respectively.

Discussion

Our results showed that patients with esophageal squamous with DOC compared to those who received FP therapy, based on the cumulative survival rate. This result was obtained despite patients demonstrating a better pathological response to FP therapy when compared with DOC therapy, which was primarily administered in patients exhibiting Grade 1 responses. We conclude that FP therapy exhibited a superior pathological response, but DOC therapy resulted in a better long-term prognosis.

These findings suggest that the efficacy of chemoradiotherapy for the primary tumor does not correlate with patient survival because of subsequent R0 resection.DOC might contribute to the micrometastases because AJCC Stage IV cases treated with DOC revealed significantly better survival compared with those that received FP therapy. In the TNM classification,[23] AJCC Stage IV cases are defined as M1a and M1b. All the 95 cases in this study had no apparent distant metastasis and were thus classified as cases with lymph node metastases in the cervical and celiac arterial trunks. DOC therapy results in a better prognosis in these cases. Lymph node metastasis is a key prognostic factor in esophageal cancer[24-26] and might be more important than the size

and invasion depth of the primary lesion. The greater effects of DOC on lymph nodes might be one of the factors contributing to better prognosis with DOC than that with FP therapy. Although we did not evaluate its efficacy for LN metastasis, we plan to evaluate this in our future study. Nevertheless, FP therapy might be more effective for the primary tumor.

To the best of our knowledge, there has been no direct comparison between FP therapy and weekly DOC regimens when combined with radiotherapy in the preoperative management of esophageal cancer. Recently, Zhang and colleagues reported that the median overall survival (OS) of a paclitaxel and CDDP regimen with radiation (16.3 months) was significantly longer than the survival of patients who received a 5-FU plus CDDP regimen alone (9.8 months).[27-28] Although an FP regimen was still listed as the first choice for preoperative radiochemotherapy for esophageal cancer in the latest NCCN guidelines, our data indicates that patients can obtain the same degree of treatment efficacy without hospitalization with weekly DOC.

In the current Japanese medical insurance system, FP therapy is associated with initial hospital costs of 1,100,000 yen, of which 330,000 yen (30%) is the copayment. In contrast, DOC can be administered in an outpatient setting with costs estimated to be 650,000 yen and with a copayment of about 200,000 yen. In addition, all the patients who received FP therapy needed inpatient care for 1–2 weeks—all of which contributed to increased treatment cost. Furthermore, FP therapy can result in many significant adverse events, which also can contribute to both higher costs for the system and a lower quality of life for the patient. Therefore, the use of DOC might reduce the financial burden on patients and might be a superior way to use medical resources as well. Most

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importantly, the use of DOC in preoperative CRT for locally advanced esophageal cancer produced a similar or better treatment outcome compared with that of FP therapy with CDDP and 5-FU; this suggests that DOC might be a promising agent for CRT in this patient population.

References

1. Akiyama H, et al: Lymph node dissection for carcinoma of the esophagus. Jpn Annals Thor Surg 2:645-653, 1982

2. Akiyama H, Tsurumaru M, Udugawa H, et al: Radical lymph node dissection for cancer of the thoracic esophagus. Ann Surg 220:364-373, 1994

3. Turumaru M, Kajiyama Y, Udagawa H, et al: Outcomes of extended lymph node dissection for squamous cell carcinoma of the thoracic esophagus. Ann Thorac Cardiovasc Surg 7:325-329, 2001

4. Hulscher JB, van Sandick JW, van Lanschot JJ, et al: Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the esophagus. N Engl J Med. 347:1662-9, 2002

5. Poplin EA, Fleming T, Leichman L, et al: Combined therapies for squamous-cell carcinoma of the esophagus, a Southwest Oncology Group Study (SWOG-8037). J Clin Oncol 5:622-628, 1987

6. Seydel HG, Leichman L, Byhardt R, et al: Preoperative radiation and chemotherapy for localized squamous cell carcinoma of the esophagus: A RTOG Study. Int J Radiat Oncol Biol Phys 14:33-35, 1988

7. Forastiere AA, Heitmiller RF, Lee DJ, et al: Intensive chemoradiation followed by esophagectomy for squamous cell and adenocarcinoma of the esophagus. Cancer J Sci Am 3:144-152, 1997

8. Walsh TN, Noonan M, Hollywood D, et al: A comparison of multimodal therapy and surgery for esophageal adenocarcinoma. N Engl J Med 335:462-467, 1996

9. Bosset JF, Gignoux M, Triboulet JP, et al: Chemoradiotherapy followed by surgery

compared with surgery alone in squamous-cell cancer of the esophagus. N Engl J Med 337:161-167, 1997

10. Urba SG, Orringer MB, Turrisi A, et al: Randomized trial of preoperative chemoradiation versus surgery alone in patients with locoregional esophageal carcinoma. J Clin Oncol 19:305-313, 2001

11. Hulscher JBF, van Sandick JW, de Boer AGEM, et al: Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the esophagus. N Engl J Med 347:1662-1669, 2002

12. Skinner DB, et al: Recent results of esophageal cancer therapy in North America. Diseases of the Esophagus, Springer-Verlag: 645-651, 1988

13. Leichmann L, Steiger Z, Seydel HG, et al: Preoperative chemotherapy and radiation therapy for patients with cancer of the esophagus: A potentially curative approach. J Clin Oncol 2:75-79, 1984

14. Franklin R, Steiger Z, Vaishampayan G, et al: Combined modality therapy for esophageal squamous cell carcinoma. Cancer 51:1062-1071, 1983

15. Forastiere AA, Orringer MB, Perez-Tamayo C, et al: Preoperative chemoradiation followed by transhiatal esophagectomy for carcinoma of the esophagus: Final report. J Clin Oncol 1:1118-1123, 1993

16. Urba SG, Orringer MB, Perez-Tamayo C, et al: Concurrent preoperative chemotherapy and radiation therapy in localized esophageal adenocarcinoma. Cancer 69:285-291, 1992

17. Wolfe WG, Vaughn AL, Seigler HF, et al: Survival of patients with carcinoma of the esophagus treated with combined-modality therapy. J Thorac Cardiovasc Surg

105:749-756, 1993

18. Haddad R, Colevas AD, Tishler R, et al: Docetaxel, cisplatin, and 5-fluorouracil-based induction chemotherapy in patients with locally advanced squamous cell carcinoma of the head and neck: the Dana Farber Cancer Institute experience. Cancer 97:412-418, 2003

19. Urba SG, Moon J, Giri PG, et al: Organ preservation for advanced resectable cancer of the base of tongue and hypopharynx: a Southwest Oncology Group Trial. J Clin Oncol 23:88-95, 2005

20. Fujii M, Tsukuda M, Satake B, et al: Phase I/II trial of weekly docetaxel and concomitant radiotherapy for squamous cell carcinoma of the head and neck. Int J Clin Oncol 9:107-112, 2004

21. Japan Esophageal Society: Japanese Classification of Esophageal Cancer Tenth Edition:35-37, 2008

22. Japan Esophageal Society: Japanese Classification of Esophageal Cancer Tenth Edition:112-115, 2008

23. Sobin LH, Gospodarowicz MK, Wittekind Ch: TNM Classification of Malignant Tumors, sixth edition. New York, John Wiley and Sons, 2002.

24. Turumaru M, Akiyama H, Ono Y, et al: Analysis of lymph node metastasis of the intra-thoracic esophageal carcinoma based on prognosis. Gastroenterol Surgery 18:585-588,1985

25. Turumaru M, Akiyama H, Udagawa H, et al: Evaluation of collo-thoraco-abdominal dissection for intrathoracic esophageal carcinoma. J Jpn Surg Soc 90:1612-1615, 1989

26. Kajiyama Y, Iwanuma Y, Tomita N, et al: Indication and limitation of 3-field lymph node dissection surgery for esophageal cancer. J Surg 68:400-404, 2006

27. Zhang J, Peng F, Li N, Liu Y, Xu Y, Zhou L, Wang J, Zhu J, Huang M, Gong Y. Salvage concurrent radio-chemotherapy for post-operative local recurrence of squamous-cell esophageal cancer. Radiat Oncol. 7:93, 2012

28. Clinical Practice Guidelines in Oncology: Esophageal cancer. NCCN guidelines version 1. 2009.

Table 1. Criteria for evaluation of therapeutic efficacy[21]

Grade	Definition	Description
0	Ineffective	No discernible therapeutic effect on cancer tissue or cells.
1	Slightly effective	Apparently "viable" cancer cells (including cells with an eosinophilic cytoplasm, vacuolation, and swollen nuclei) account for 1/3 or more of tumor tissue, but there is some evidence of degeneration of cancer tissue or cells. Grade 1 lesions might be subclassified into Grade 1a (viable cancer cells accounting for 2/3 or more of tumor tissue) and Grade 1b (viable cancer cells accounting for 1/3 or more but less than 2/3 of tumor tissue).
2	Moderately effective	Viable cancer cells account for less than 1/3 of tumor tissue, while other cancer cells are severely degenerated or necrotic.
3	Markedly effective	No viable cancer cells are evident.

Table 2. Preoperative background of the patients in the FP and DOC groups

		FP	DOC	p value
Age	mean (range)	60.4(42–76)	61.9 (46–80)	0.698
Sex	M:F	36:4	48:7	0.472
Smoking	+:−	34:6	52:3	0.113
Alcohol intake	+:−	37:3	53:2	0.351
Tumor area	Ce:Ut:Mt:Lt	4:8:23:5	9:22:17:7	0.057
Histology	well:mod:poor	14:26:0	15:34:6	0.088

Postoperative background of the patients in the FP and DOC groups

		FP	DOC	p value
Depth	T0:T1:T2:T3:T4	6:2:0:22:10	7:5:4:24:15	0.381
Ly	Ly0:Ly1:Ly2:Ly3:unknown	6:12:13:8:1	9:18:19:8:1	0.846
V	V0:V1:V2:V3:unknown	11:16:11:0:2	15:19:17:3:1	0.524
Intraepithelial spread	+:−: unknown	25:13:2	32:22:1	0.558
Intramural metastasis	+:−: unknown	5:35	7:47:1	0.691
LN metastasis	+:−	31:9	42:13	0.549
LN Metastasis ≥5	LN ≥ 5:LN < 5	24:16	35:20	0.441
TNM	0:I:II:III:IV	2:1:6:11:20	4:2:10:19:20	0.771
Curativity	A:B:C	19:13:8	17:16:22	0.095
Cause of death	Surgery-relateddeath: Recurrence:Others(death)	3:30:0	2:37:1	0.529

Curativity[21]
  Curativity A: pStage0~III, pR0
  Curativity B: Neither curativity A nor C
  Curativity C: Pathologically, cancer remains

Table 3. Clinical effects of preoperative CRT using FP or DOC

Lymph node metastases

Group	Effective	Ineffective
	CR and PR	SD and PD
FP	19	17
DOC	29	25
	P = 0.551	

Patients who had been diagnosed as LN negative during preoperative CT and EUS examinations were excluded.

Response Evaluation Criteria for Target Lesions[22]

CR: The disappearance of all the target lesions as well as the secondary changes associated with the tumor. With regard to lymph node metastasis, CR is declared when the size decreases to normal size or less.
PR: At least a 30% decrease in the sum of the greatest dimensions of the target lesions; the baseline sum of the greatest dimensions is considered as a reference.
PD: At least a 20% increase in the sum of the greatest dimensions of target lesions; the smallest sum of the greatest dimensions recorded since the initiation of therapy is considered as a reference.
SD: Neither PR nor PD

Pathological effects on the primary tumor

Group	Effective Grade	Ineffective Grade
	2, 3 response	0,1 response
FP	28	12
DOC	28	27
	P = 0.048	

Figure Legends

Figure 1. Cumulative survival rates in the FP and DOC groups.

Figure 2. Cumulative survival rates for cases with pathological grades 1, 2, and 3 in the FP and DOC groups.

Figure 3. Cumulative survival rates for cases with postsurgical stages I, II, and III in the FP and DOC groups.

Figure 4. Cumulative survival rates for cases with and without lymph node metastasis in the FP and DOC groups.
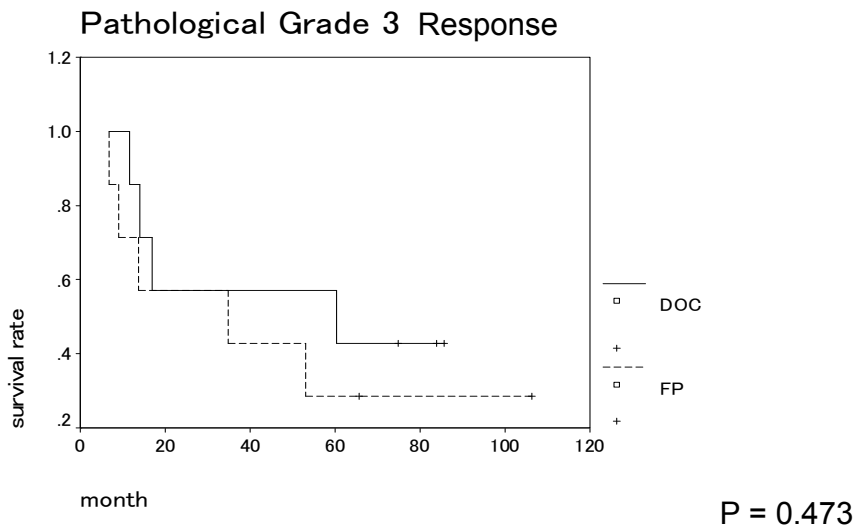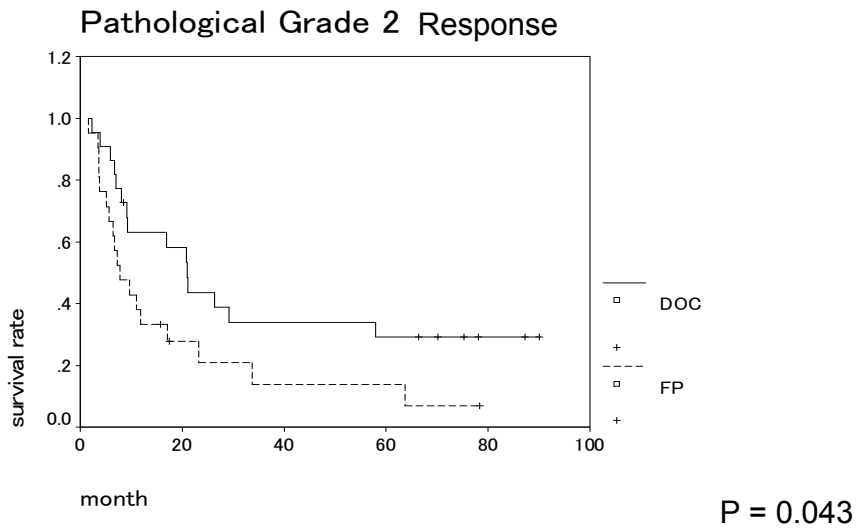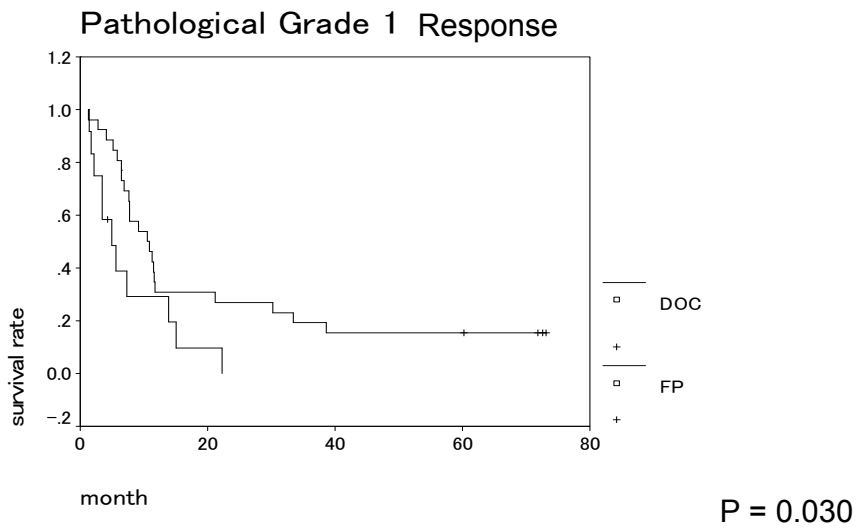
Figure 5. Cumulative survival rates for cases with ≥5 and <5 lymph node metastases in the FP and DOC groups.

Figure 1

overall survival

P = 0.030

Figure 2

Pathological Grade 1 Response

P = 0.030

Pathological Grade 2 Response

P = 0.043

Pathological Grade 3 Response

P = 0.473

20
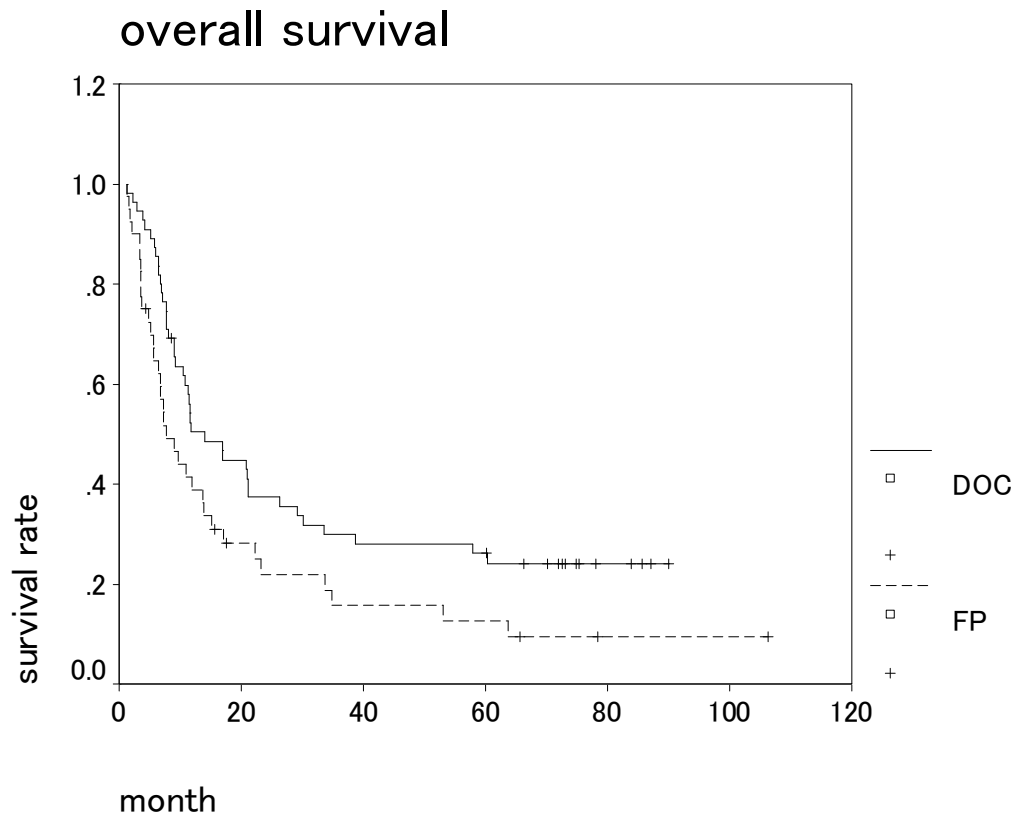
Figure 3 Postoperative stage

AJCC Stage Ⅱ
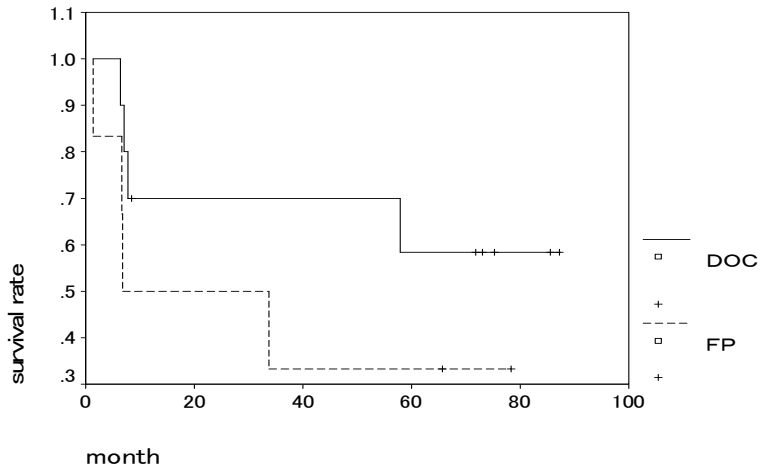
P = 0.242

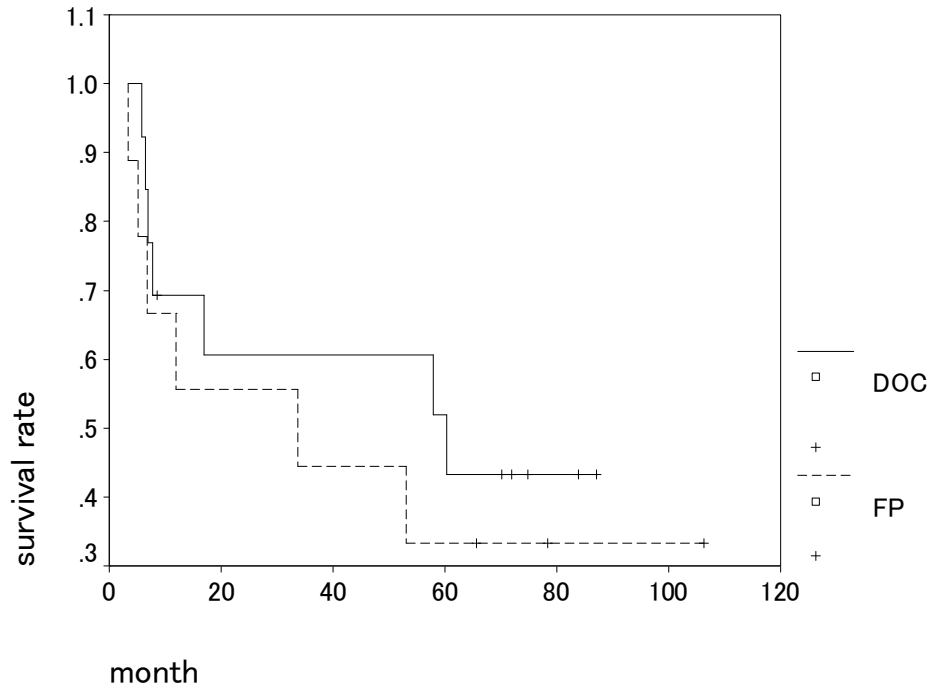AJCC Stage Ⅲ
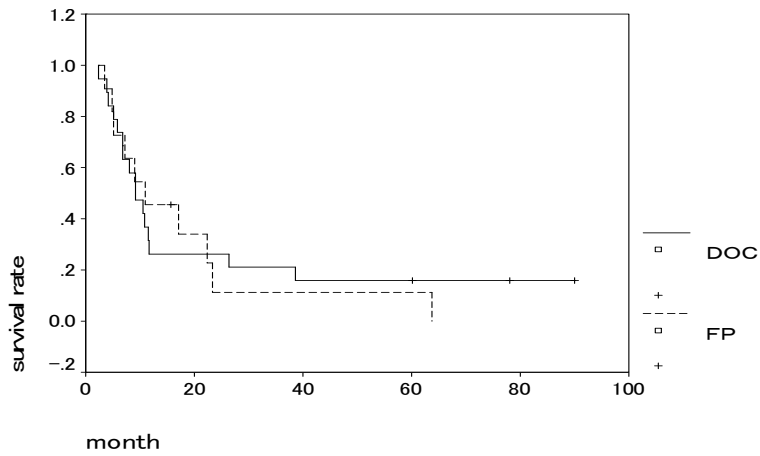
P = 0.828

AJCC Stage Ⅳ
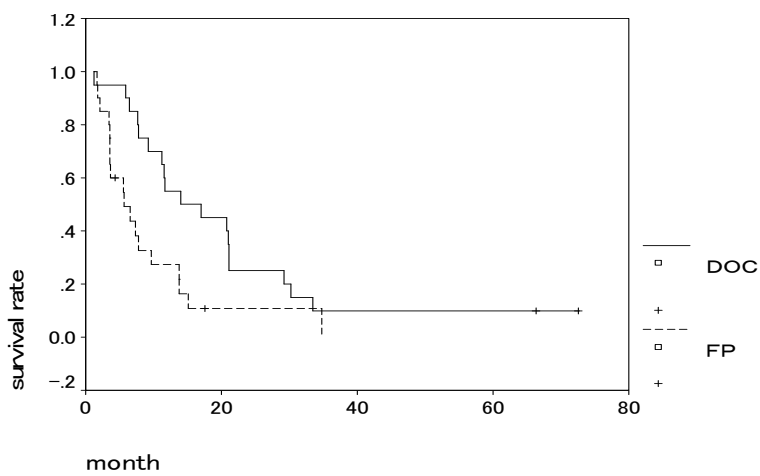
P = 0.011

Figure 4
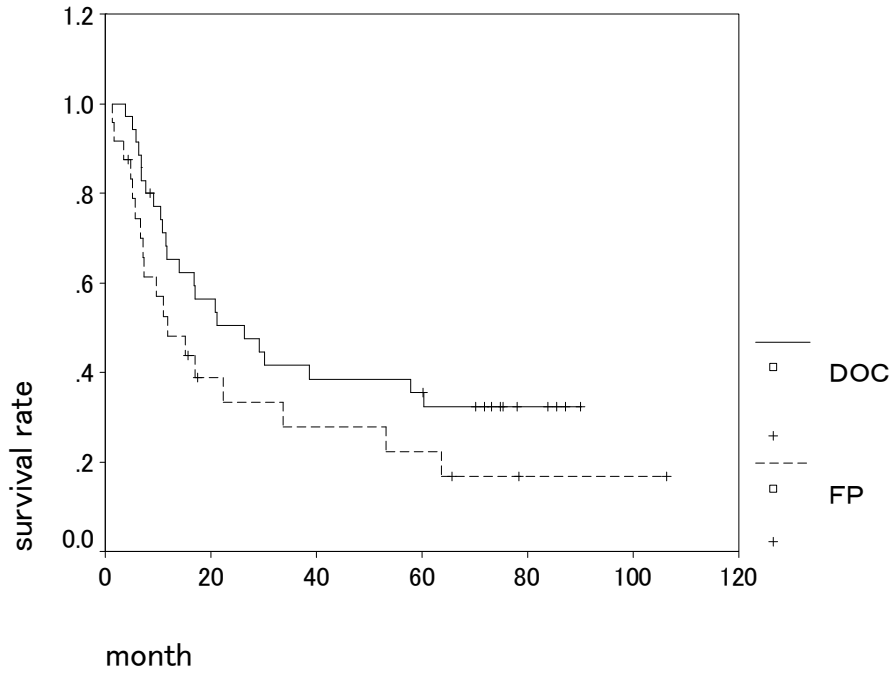
Pathological LN negative

P = 0.509

Pathological LN positive
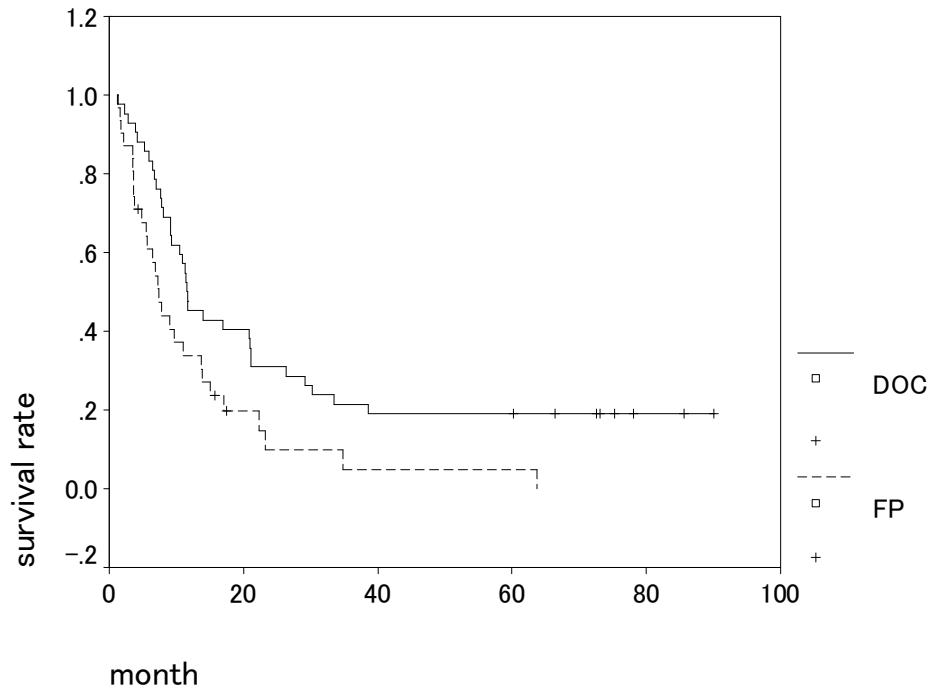
P = 0.011

Figure 5

Pathological　LN metastases＜5

month

P = 0.123

Pathological　LN metastases≧5

month

P = 0.200