

Induction Chemotherapy Using FAP for Patients with Stage II/III Squamous Cell Carcinoma of the Esophagus

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Abstract. *Background:* The aim of this study were to evaluate the feasibility and efficacy of chemotherapy using fluorouracil, adriamycin, and cisplatin (FAP) in patients with clinical stage II/III squamous cell carcinoma of the esophagus (SCCE). *Patients and Methods:* Forty patients were enrolled in the study. They received 30 mg/m² adriamycin and 70 mg/m² cisplatin on day 1, and 700 mg/m² 5-fluorouracil on days 1-5 every four weeks. Following two courses of chemotherapy, eligible patients underwent esophagectomy. *Results:* Twenty-one patients (53%) achieved partial response, and 27 patients underwent surgical resection (resection rate: 68%). Grade 3/4 toxicities developed: 7 patients (18%) with leukopenia, 23 (58%) with neutropenia. The three and five-year survival rates were 55% and 48%. Patients with surgical resection had better prognosis than those without resection, with a three-year survival rate of 68% vs. 25%. *Conclusion:* FAP is effective and feasible and surgery may provide additional benefit for SCCE patients with FAP.

Squamous cell carcinoma of the esophagus (SCCE) is a disease with one of the highest mortality rates and is often diagnosed at a late stage with metastatic spread. Even if SCCE is diagnosed at the T1 to T3 disease, lymph node metastases frequently occur at distant sites. In addition, lymph node metastasis is one of the major prognostic factors of patients who have undergone curative esophagectomy, and the number of lymph node metastases is strongly correlated with the prognosis (1).

A recent randomized control study revealed that postoperative adjuvant chemotherapy with cisplatin and 5-fluorouracil (5-FU)

was better able to prevent relapse in patients with esophageal cancer than surgery-alone in those with lymph node metastasis (2). Moreover, in stage II and III squamous cell carcinoma of the thoracic esophagus, overall survival (OS) of patients treated with neoadjuvant chemotherapy followed by surgery was superior to that of patients with esophagectomy followed by chemotherapy. According to these two studies, preoperative chemotherapy with cisplatin plus 5-FU can be regarded as one of the standard treatment for patients with stage II/III squamous cell carcinoma in Japan. However, in a later report on JCOG9907, a survival benefit of preoperative chemotherapy was observed only in patients with clinical stage II disease, but not in those with stage III (3). Therefore, in order to improve the prognosis of patients with locally advanced SCCE including stage III esophageal cancer, a more intensive and feasible regimen of neoadjuvant chemotherapy is required.

Combination chemotherapy with 5-FU and cisplatin (FP) has been a standard regimen for advanced or metastatic esophageal cancer. However, recently, a triplet regimen, consisting of the addition of another drug to FP, has also been introduced.

For advanced head and neck cancer, and gastric or esophagogastric cancer, chemotherapy using FP combined with docetaxel was reported to achieve better outcomes than FP treatment (4-6). In a randomized phase III trial for advanced gastric cancer that compared therapy with docetaxel, cisplatin and 5-FU (DCF) every three weeks with FP every four weeks, the median time-to-tumor progression (TTP) and median OS (OS) were reported to be significantly higher with DCF every three weeks (7). Docetaxel in addition to FP has been considered one of the standard regimens for head and neck squamous cell carcinoma and gastric or esophagogastric adenocarcinoma (4-7), and also for patients with SCCE (8). On the other hand, adriamycin in addition to FP (FAP) has also been reported as a candidate neoadjuvant chemotherapy for esophageal cancer, with demonstrated response rates of 55.6% and 56.5% in recent reports (9, 10).

We have performed FAP chemotherapy for patients with stage II and III esophageal cancer as induction therapy, which was scheduled mainly as neoadjuvant chemotherapy for esophagectomy. Therefore, the aim of the study was to

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Table I. Patients' characteristics (40 cases).

Gender	
Male	31
Female	9
Mean age, year (range)	69.0 (57-79)
Depth of tumor invasion (T)	
T1b	1
T2	8
T3	30
T4	1
Lymph node metastasis (N)	
N0	3
N1	10
N2	24
N3	3
Stage	
II	5
III	35

Table II. Results of induction chemotherapy (40 cases).

	No of cases
Frequency of chemotherapy	
1 Cycle	10
2 Cycles	27
3 Cycles	3
Tumor response	
CR	0
PR*	21
SD	18
PD	1
Response rate (%)	52.5%
Resection (curability)	
Absolutely curative	25
Relatively curative	2
Non-resection	2
Resectability rate (%)	67.5%

*Including the cases with "PR in" because of resection before confirming response with an interval of four weeks or more. CR: Complete response, PR: partial response, SD: stable disease, PD: progressive disease.

evaluate the feasibility and efficacy of chemotherapy using FAP in patients with clinical stage II and III SCCE.

Patients and Methods

This study was performed for patients with operable clinical stage II and III thoracic or abdominal SCCE at Kansai Rosai Hospital. This protocol was reviewed and approved by Review Committee for chemotherapy regimens. Prior to receiving treatment, each patient provided a written informed consent.

Eligibility criteria. The eligibility criteria of this study were as follows: i) histologically proven SCCE; ii) clinical stage II or III esophageal cancer according to the Japanese classification of esophageal cancer (11); iii) age of 20-79 years; iv) Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0-1; v) no previous treatment for esophageal cancer including surgery, chemotherapy and radiotherapy; and vi) adequate organ function including a leukocyte count of between 4,000 mm³ and 12,000 mm³, a neutrophil count of over 2,000mm³, a platelet count of over 100,000 mm³, hemoglobin of over 9.0 g/dl, aspartate aminotranferase (AST) and alanine aminotransferase (ALT) levels within 2.5 times the upper limits of their normal ranges, serum bilirubin level under 1.5 mg/dl, and a serum creatinine level of under 1.2 mg/dl or creatinine clearance of at least 60 ml/min/body.

Induction chemotherapy and evaluation. The administration schedule began with 5-FU at 700 mg/m², which was continuously infused from day 1 to 5. Adriamycin at 30 mg/m² was intravenously infused for 60 to 120 minutes on day 1 and cisplatin at 70 mg/m² was infused for 120 minutes, immediately after adriamycin. The patients generally received two courses of chemotherapy.

Patient evaluation during FAP chemotherapy included hematological tests and assessments of clinical symptoms, which were performed every week. Computed tomographic (CT) scans of

the chest and abdomen were performed two weeks after the first completion of chemotherapy, and esophagography, CT and endoscopy were performed after two cycles of chemotherapy in order to assess the clinical response to induction chemotherapy.

Surgical resection was generally recommended for eligible patients with partial response (PR) and stable disease (SD) after two cycles of chemotherapy. Definitive chemoradiotherapy (CRT) was recommended for patients who refused operation or were judged to have any problem with the surgical procedures, such as poor PS, poor organ function or no family support.

Esophageal resection with lymph node dissection along the bilateral recurrent nerve was performed three to six weeks after the completion of chemotherapy. If lymph node metastasis along the recurrent nerve was confirmed using a frozen section, esophagectomy with three-field lymphadenectomy was performed; otherwise, that with two-field lymph node dissection was carried out.

We judged the anticancer effects in accordance with the Response Evaluation Criteria in Solid Tumours (RECIST) (12) for target lesions and with the tenth edition of the Response Evaluation Criteria in Radiotherapy and Chemotherapy for Esophageal Cancer of the Japanese Society for Esophageal Diseases, (13), for non-target lesions, whereas for safety assessment, we followed the NCI-Common Toxicity Criteria v2.0 (14). Histological effect based on resected tissue specimens was judged according to the tenth edition of the Japanese Society for Esophageal Diseases (13).

Follow-up and statistical analysis. The occurrence of relapse was determined by imaging studies, including ultrasonography, CT and gastrointestinal endoscopy. Follow-up including thoracic and abdominal CT was carried out every four months following chemotherapy or surgery during the first two years and every six months thereafter. In patients with definitive chemo-radiotherapy, endoscopy was performed every six months.

The vital and disease statuses were confirmed by checking the medical records from the date of the last follow-up visit as of December 31, 2014.

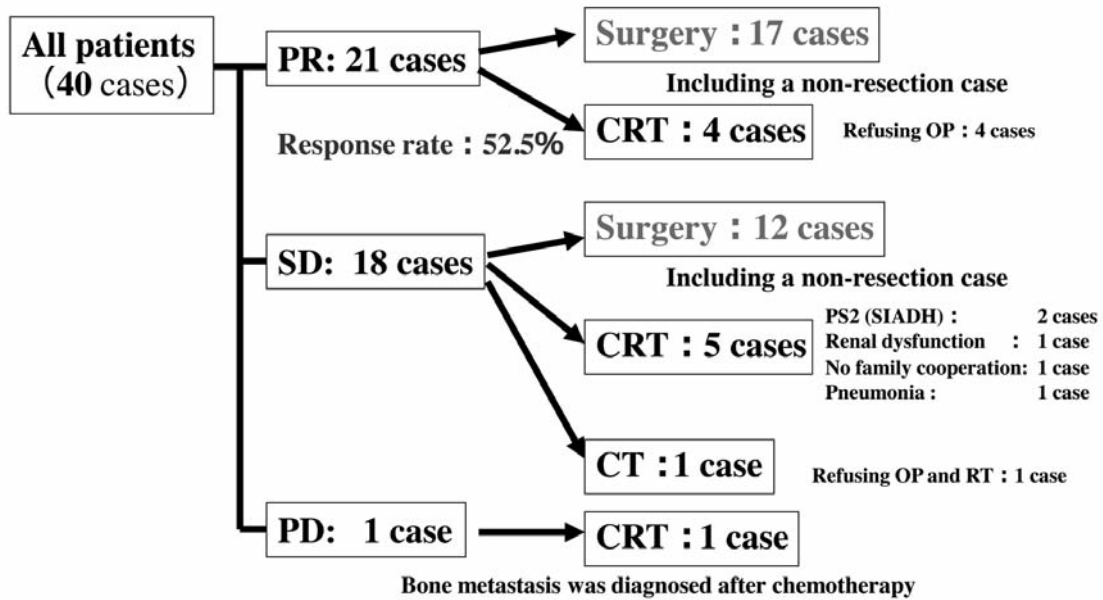


Figure 1. Clinical course of all patients. A total of 17 out of 21 patients with partial response (PR) and 12 out of 18 patients with stable disease (SD) underwent surgery. However, esophagectomy could not be performed in two cases because of severe obsolete pleuritis and severe pleural plaque. The surgical resection rate was 67.5% (27/40). CRT: Chemoradiation therapy, CT: chemotherapy, OP: operation. SIADH: Syndrome of inappropriate secretion of antidiuretic hormone.

All enrolled patients were included in the intention-to-treat analysis of efficacy. OS was measured from the start of chemotherapy until the time of death or last follow-up visit in 2014 and was estimated using the Kaplan–Meier method. The chi-square test was performed to determine statistical differences regarding downstaging and pathological effects in patients with surgical resection between the PR and SD groups. A *p*-value of less than 0.05 was considered as being statistically significant. All statistical analyses were performed using SPSS (SPSS Inc., Chicago, IL, USA).

Results

Patients' characteristics. Forty patients were enrolled in the study between October 2003 and January 2013. These included 31 males and nine females, with an average age of 69.0 (range=57-79) years. All patients but three had lymph node metastases as judged from CT before chemotherapy, with five patients having stage II disease and 35 having stage III disease. The demographic and clinicopathological characteristics of these patients are listed in Table I.

FAP was performed in one cycle in 10 patients, two cycles in 27 patients, and three cycles in three patients. The reasons for performing one cycle of chemotherapy were that four patients had renal dysfunction, one suffered from pneumonia and five hoped for an early operation after one cycle of chemotherapy. One patient with pneumonia chose CRT after pneumonia and one with syndrome of inappropriate secretion of antidiuretic hormone chose radiation therapy.

Efficacy and clinical course. Twenty-one cases of PR, 18 cases of SD, and one case of progressive disease (PD), because of the diagnosis of bone metastasis after initial chemotherapy, were confirmed, giving an overall response rate of 52.5% (Table II).

A total of 17 of 21 patients with PR and 12 of 18 patients with SD underwent surgery. However, esophagectomy could not be performed in two cases because of severe obsolete pleuritis and severe pleural plaque. Eleven patients did not undergo surgery: in five cases due to refusing an operation, in two cases due to down-grading of performance status, in two cases because of a complication during chemotherapy (*i.e.*, pneumonia and renal dysfunction), in one case because of no support from his family, and in one case because of PD (Figure 1).

According to the clinical and pathological stages and pathological responses of the resected cases, a total of nine out of 16 cases of PR (56%) and one out of 11 cases of SD (9%) achieved down-staging, and 14 out of 16 PR (88%) and one out of 11 SD (9%) showed good pathological responses beyond grade 1b: cases with PR had better clinical and pathological effects than those with SD (*p*<0.05 and *p*<0.01, respectively). Two cases had no residual tumor cells in resected specimens of both primary lesion and lymph node of resected specimen, resulting in a rate of pathological CR of 6.7%.

At the median follow-up of 66 months (range=23-119 months), 20 patients were still alive and disease-free but one had upper mediastinal lymph node recurrence, which was

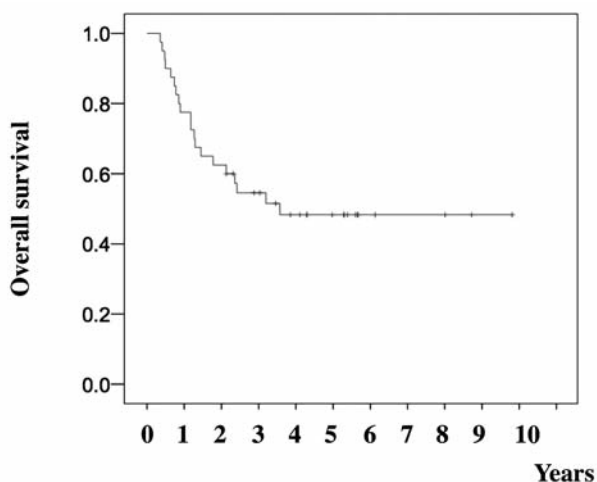


Figure 2. Survival curve for patients overall (40 cases). The median follow-up time was 63 months and the three- and five-year survival rates of patients were 54.7% and 48.4%, respectively.

identified in December 2014. A total of 11 out of 27 patients in the surgical resection group died: four from lymph node metastasis, two from local recurrence in a mediastinal lesion, three from distant metastasis (liver, brain, bone), one from pneumonia without recurrence 41 months after surgery, and one from postoperative complication. In addition, nine out of 13 patients in the non-resection group died: five from locoregional progression, two from distant metastasis to brain or liver, and two from pneumonia and mediastinitis during CRT.

The Kaplan–Meier estimate of the overall five-year survival rate of all patients was 48% (Figure 2).

According to the tumor response, the 3- and 5-year survival rates were 66% and 56%, respectively, for patients achieving PR; those tended to be better than for patients not achieving PR by induction chemotherapy, with three- and five-year survival rates of 42% and 42%, respectively, but these differences were not significant ($p=0.137$) (Figure 3). Regarding the survival rate by surgical intervention, the cumulative survival rate for the patients who underwent esophagectomy was significantly higher than in those without it (Figure 4) (58% vs. 25% at five years, $p=0.023$). Of 18 patients with tumor response of SD, seven out of 11 who underwent surgery were still alive (range=28-119 months), whereas six out of seven patients treated by CRT or chemotherapy died: from locoregional progression in three, liver metastasis in one, and pneumonia and mediastinitis in one each, with a median survival time of nine months. In patients with SD as the tumor response for induction chemotherapy, the cumulative survival rate for those with surgical resection was significantly better than for those with CRT/chemotherapy ($p=0.005$) (Figure 5).

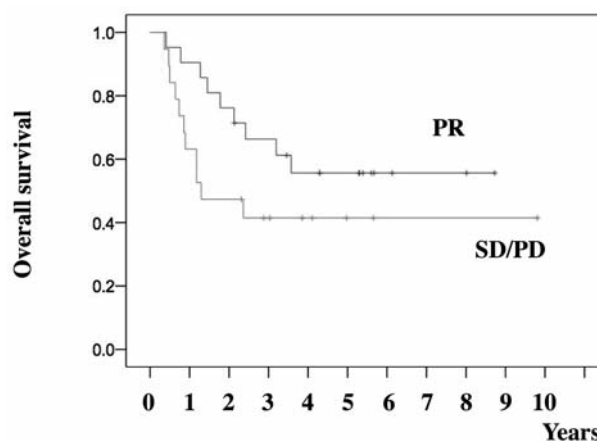


Figure 3. Survival curves according to the tumor response to induction chemotherapy. According to the tumor response, the three- and five-year survival rates (66% and 56%) for patients achieving partial response (PR) tended to be better than those (42% and 42%) for patients not achieving it by induction chemotherapy, but this difference was not significant ($p=0.137$). SD: Stable disease, PD: progressive disease.

Patients undergoing esophagectomy with a good pathological response had better OS than those with a poor pathological response. However, no significant difference was found in OS ($p=0.102$).

Toxicity. Toxicity data are summarized in Table III. Grade 3 leukopenia occurred in seven patients (18%), grade 3 or 4 neutropenia occurred in 23 patients (58%), and grade 3 thrombocytopenia occurred in three cases. Grade 3 or 4 hyponatremia occurred in three patients, to which attention should be paid. Non-hematological toxicity of grade 3 or more involved nausea/vomiting in one case. The hematological and non-hematological toxicities of induction chemotherapy of FAP were as expected and manageable.

No treatment-related deaths occurred during FAP chemotherapy but one patient died after 30 days postoperatively due to surgical complication of pneumonia caused by Methicillin-resistant *Staphylococcus aureus* (MRSA) and hepatic failure.

Discussion

Induction chemotherapy is defined as chemotherapy as the initial treatment for cancer, as the first part of a multidisciplinary therapy, including neoadjuvant chemotherapy. We performed induction chemotherapy not only for patients with clinical stage II or III SCCE as adjuvant chemotherapy but also for patients who hesitated about which therapy to choose, surgery or CRT, or for patients for who it was unclear whether sufficient familial support was available for surgical treatment.

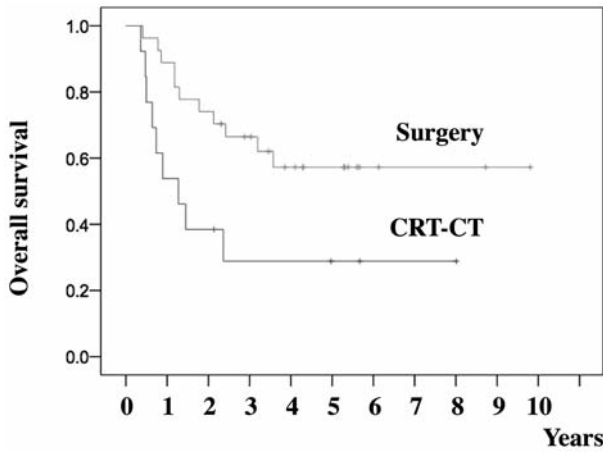


Figure 4. Survival curves comparing patients undergoing surgical resection versus those undergoing CRT or chemotherapy following induction chemotherapy. The cumulative survival rate for the patients who underwent esophagectomy was significantly better than for patients who did not ($p=0.023$).

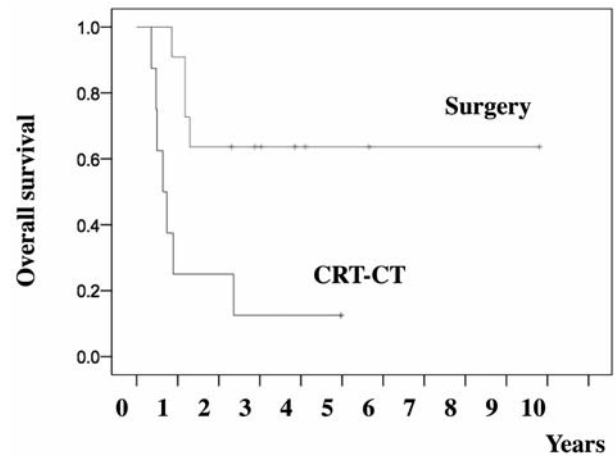


Figure 5. Survival curve comparing patients undergoing surgery versus those undergoing CRT or chemotherapy following induction chemotherapy in those with stable disease (SD) as the tumor response. In patients with SD as the tumor response, the cumulative survival rate for those with surgical resection was significantly better than in those treated with CRT or chemotherapy ($p=0.005$).

Table III. Toxicity due to induction chemotherapy.

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 3/4(%)
Bone marrow					
Leukopenia	8	13	7	0	18
Neutropenia	5	2	17	6	58
Thrombocytopenia	12	3	3	0	8
Anemia	16	11	1	0	3
Gastrointestinal					
Stomatitis	15	6	0	0	0
Diarrhea	13	5	0	0	0
Nausea/vomiting	23	9	1	0	3
Hyponatremia	12	0	2	1	8
Fever	5	0	0	0	0
Alopecia	23	16	0	0	0

This FAP regimen for induction chemotherapy appears to be well tolerated, with manageable hematological toxicities and limited non-hematological ones, and seems more effective for locally advanced esophageal cancer than the standard FP regimen (15-17), with a response rate of 52.5%.

In terms of the rationale for preoperative therapies, this could be consistently thought to be the down-staging or down-sizing of the primary tumor in order to improve the complete resection rate, and to eliminate hematogenous/lymphogenous micrometastases resulting in the prevention of postoperative recurrence. On the other hand, the demerits of induction therapy are that surgical treatment is delayed in patients with a tumor that is increasing in size, regardless of chemotherapy, and which cannot be performed because of the severe side-

effects of chemotherapy. Furthermore, induction chemotherapy may increase postoperative morbidity and mortality.

A meta-analysis reported by Kranzfelder *et al.* revealed no evidence of increased mortality resulting from neoadjuvant chemotherapy and CRT (18). In addition, the mortality of the JCOG9907 study was reported not to increase in association with preoperative chemotherapy: it was 0.6% in the surgical group and 0.6% in the preoperative chemotherapy group (3).

In this study, although one among 27 patients (3.7%) with esophagectomy died 30 days postoperatively due to surgical complication of pneumonia caused by MRSA and hepatic failure, this mortality rate is thought to be within the acceptable range.

Randomized trials of neoadjuvant therapies for SCCE are summarized in Table IV (3, 19-24). In the 1990s, several randomized trials of neoadjuvant chemotherapy followed by surgery vs. surgery alone were conducted for patients with SCCE using combination therapy with cisplatin and other anticancer agents, such as bleomycin, vindesine and 5-FU. However, none of these trials demonstrated the efficacy of neoadjuvant chemotherapy for patients with SCCE.

Boonstra *et al.* demonstrated that preoperative chemotherapy with a combination of etoposide and cisplatin significantly improved OS in patients with SCCE, with the result that five-year survival rates were 26% and 17%, respectively ($p=0.03$, HR=0.17, 95% CI=0.51-0.98) (24). In addition, Ando *et al.* reported in the JCOG9907 study on resectable clinical stageII/III thoracic SCCE that OS in patients with preoperative chemotherapy using two courses of cisplatin and 5-FU followed by surgery was superior to that in patients with postoperative chemotherapy. The five-

Table IV. Randomized trials of neoadjuvant chemotherapies in squamous cell carcinoma of the esophagus.

Author (Ref.)	Year	Country	Treatment	No. of cases	Resection rate % /Curative resection rate % (No. of cases)	Response rate % (No. of cases)	pCR rate (No. of cases)	Median survival months	Survival % (Years)
Nygaard <i>et al.</i> * (19)	1992	Norway	CDDP/bleo	56	52 (29/56)/44 (22/50)			7	31% (1Y), 3% (3Y)
			Surgery	50	56 (28/50)/37 (15/41)			7	34% (1Y), 9% (3Y)
Schlag (20)	1992	Germany	CDDP/vinblastone/bleo	22	69 (11/16)/43 (7/16)	38 (8/21)52**		10	20% (1Y)
			Surgery	24	79 (19/24)/42 (10/24)			10	32% (1Y)
Maipang <i>et al.</i> (21)	1994	Thailand	CDDP/vinblastone/bleo	24		33 (8/24)/53 (8/15***)		17	58% (1Y), 31% (3Y)
			Surgery	22				17	85% (1Y), 36% (3Y)
Law <i>et al.</i> (22)	1997	China	5-FU/CDDP	74	81 (60/74)/67 (40/60)	58 (35/60***)	6.7 (4/60***)	16.8	38% (3Y), 28% (5Y)
			Surgery	73	95 (69/73)/35 (24/69)			13	14% (3Y), 0% (5Y)
Ancona <i>et al.</i> (23)	2001	Italy	5-FU/CDDP	47	85 (40/47)/79 (37/47)	40****	12.8	25	44% (3Y), 34% (5Y)
			Surgery	47	87 (41/47)/74 (35/47)			24	41% (3Y), 22% (5Y)
Boonstra <i>et al.</i> (24)	2011	Netherlands	CDDP/etoposide	85	81 (69/85)/	40 (32/80)	7	16	42% (2Y), 26% (5Y)
			Surgery	84	83 (70/84)/			12	30 % (2Y), 17% (5Y)
Ando <i>et al.</i> (3)	2012	Japan	5-FU/CDDP/surgery	164	95 (155/164)/96 (149/155)		2.5 (4/155)		55% (5Y)
			Surgery/5-FU/CDDP	166	98 (162/166)/91 (147/162)				44% (5Y)

*Nygaard *et al.* reported four types of therapy, surgery alone, pre-operative chemotherapy, pre-operative radiation therapy, pre-operative chemotherapy+chmo-radiotherapy; **including minor response; ***completed the chemotherapy program; ****assessed by pathological examination. CDDP: cisplatin, bleo: bleomycin, 5-FU: 5-fluorouracil, pCR: pathological complete response

year OSs were 55% and 43% in the preoperative and postoperative chemotherapy groups, respectively (HR=0.73, 95% CI=0.54-0.99, $p=0.04$) (3).

These two studies in the 2000s demonstrated the superiority of preoperative chemotherapy to surgery alone for patients with SCCE. The reason for the favorable results is not clear, but may be due to progress in the management of chemotherapy and in perioperative management and surgical techniques, such as three-field lymphadenectomy.

Two meta-analyses that compared neoadjuvant chemotherapy and surgery with surgery alone for resectable esophageal carcinoma including SCCE and adenocarcinoma performed by Malthaner *et al.* (25) and Urshel *et al.* (26) demonstrated no advantage of neoadjuvant chemotherapy

over surgery alone in terms of short-term OS (at 1 and 2 years, and 1, 2, and 3 years, respectively). On the other hand, a meta-analysis performed by Kaklamanos *et al.* demonstrated improved two-year survival of patients treated with neoadjuvant chemotherapy compared with surgery alone (27). Moreover, a recent meta-analysis by Xu *et al.* showed that there was no evident difference in one-year survival, resection rate, and operative mortality, but there was a statistically significant survival advantage at three and five years for patients with esophageal cancer treated with neoadjuvant chemotherapy compared with that for those treated with surgery alone (28).

On the basis of these results, preoperative chemotherapy followed by esophagectomy has become accepted as a standard

therapeutic strategy for clinical stage II or III SCCE. However, the efficacy of the FP regimen as adjuvant chemotherapy is not satisfactory, especially for patients with stage III disease.

With the development of chemotherapy schedules and drugs for esophageal cancer, the curative effect of neoadjuvant chemotherapy will become more and more pronounced in patients with esophageal cancer. Thus, a triplet regimen, consisting of the addition of another drug to FP, has been introduced. In terms of the FAP regimen reported by Shimokawa *et al.* (9) and Yanagawa *et al.* (10) that the response rates were as high as 55.6% and 56.5%, respectively, our response rate of 52.5% is similar. From these results, the FAP regimen may be one of the most promising regimens for neoadjuvant chemotherapy for SCCE with respect to its usefulness and safety.

On the other hand, docetaxel combined with cisplatin and 5-FU is now regarded as a standard regimen for advanced gastric and esophagogastric adenocarcinoma. And in recent years, several trials of preoperative chemotherapy using DCF have demonstrated a high response rate of over 60% (8, 29).

In Japan, a three-arm phase III trial (JCOG1109 study) started in November 2012, with the aim of confirming whether DCF is superior to FP, and whether FP is superior to CRT, as preoperative therapies for SCCE.

The majority of the available reports reveal that resectable SCCE is likely to benefit from adjuvant chemotherapy. The focus of future trials should be on identification of the optimal regimen to minimize the side-effects of chemotherapy and maximize quality of life, as well as to achieve a higher local control rate and a stronger effect on lymph node metastasis in order to improve the complete resection rate and to prevent postoperative recurrence.

Conflicts of Interest

The Authors declare that they have no conflict of interest with regard to any part of the study.

References

- Ozawa S, Tachimori Y, Baba H, Fujishiro M, Matsubara H, Mumasaki H, Oyama T, Shinoda M, Takeuchi H, Teshima T, Udagawa H, Uno T and Barron JP: Comprehensive registry of esophageal cancer in Japan, 2004. *Esophagus* 9: 75-98, 2012.
- Ando N, Iizuka T, Ide H, Ishida K, Shinoda M, Nishimaki T, Takiyama W, Watanabe H, Isono K, Aoyama N, Makuuchi H, Tanaka O, Yamana H, Ikeuchi S, Kabuto T, Nagai K, Shimada Y, Kinjo Y and Fukuda H: Japan Clinical Oncology Group: Surgery plus chemotherapy compared with surgery alone for localized squamous cell carcinoma of the thoracic esophagus: a Japan Clinical Oncology Group Study-JCOG9204. *J Clin Oncol* 21(24): 4592-4596, 2003.
- Ando N, Kato H, Igaki H, Shinoda M, Ozawa S, Shimizu H, Nakamura T, Yabusaki H, Aoyama N, Kurita A, Ikeda K, Kanda T, Tsujinaka T, Nakamura K and Fukuda H: A randomized trial comparing postoperative adjuvant chemotherapy with cisplatin and 5-fluorouracil *versus* preoperative chemotherapy for localized advanced squamous cell carcinoma of the thoracic esophagus (JCOG9907). *Ann Surg Oncol* 19(1): 68-74, 2012.
- Vermorken JB, Remenar E, van Herpen C, Gorlia T, Mesia R, Degardin M, Stewart JS, Jelic S, Betka J, Preiss JH, van den Weyngaert D, Awada A, Cupissol D, Kienzer HR, Rey A, Desautels I, Bernier J and Lefebvre JL; EORTC 24971/TAX 323 Study Group: Cisplatin, fluorouracil, and docetaxel in unresectable head and neck cancer. *N Engl J Med* 357: 1695-1704, 2007.
- Posner MR, Hershock DM, Blajman CR, Mickiewicz E, Winkler E, Gorbounova V, Tjulandin S, Shin DM, Cullen K, Ervin TJ, Murphy BA, Racz LE, Cohen RB, Spaulding M, Tishler RB, Roth B, Viroglia Rdel C, Venkatesan V, Romanov I, Agarwala S, Harter KW, Dugan M, Cmelak A, Markoe AM, Read PW, Steinbrenner L, Colevas AD, Norris CM Jr. and Haddad RI: TAX 324 Study Group: Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer. *N Engl J Med* 357: 1705-1715, 2007.
- Ajani JA, Fodor MB, Tjulandin SA, Moiseyenko VM, Chao Y, Cabral Filho S, Majlis A, Assadourian S and Van Cutsem E: Phase II multi-institutional randomized trial of docetaxel plus cisplatin with or without fluorouracil in patients with untreated, advanced gastric, or gastroesophageal adenocarcinoma. *J Clin Oncol* 23: 5660-5667, 2005.
- Van Cutsem E, Moiseyenko VM, Tjulandin S, Majlis A, Constenla M, Boni C, Rodrigues A, Fodor M, Chao Y, Voznyi E, Risse ML and Ajani JA; V325 Study Group: Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group. *J Clin Oncol* 24: 4991-4997, 2006.
- Yamasaki M, Miyata H, Tanaka K, Shiraishi O, Motoori M, Peng YF, Yasuda T, Yano M, Shiozaki H, Mori M and Doki Y: Multicenter phase I/II study of docetaxel, cisplatin and fluorouracil combination chemotherapy in patients with advanced or recurrent squamous cell carcinoma of the esophagus. *Oncology* 80: 307-313, 2011.
- Shimakawa T, Naritaka Y, Asaka S, Isohata N, Murayama M, Konno S, Yoshimatsu K, Shiozawa S, Katsube T and Ogawa K: Neoadjuvant chemotherapy (FAP) for advanced esophageal cancer. *Anticancer research* 26: 2321-2326, 2008.
- Yanagawa M, Tatsumi M, Miyata H, Morii E, Tomiyama N, Watabe T, Isohashi K, Kato H, Shimosegawa E, Yamasaki M, Mori M, Doki Y and Hatazawa J: Evaluation of Response to Neoadjuvant Chemotherapy for Esophageal Cancer: PET Response Criteria in Solid Tumors Versus Response Evaluation Criteria in Solid Tumors. *J Nucl Med* 53: 872-880, 2012.
- Japan Esophageal Society: Japanese Classification of Esophageal Cancer, Tenth Edition: Part I. *Esophagus* 6: 1-25, 2009.
- Therasse P, Eisenhauer EA and Verweij J: RECIST revisited: a review of validation studies on tumour assessment. *Eur J Cancer* 42: 1031-1039, 2006.
- Japan Esophageal Society: Japanese Classification of Esophageal Cancer, Tenth Edition: Part II and Part III. *Esophagus* 6: 71-94, 2009.
- National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 2.0. published: 30th April 1999. US Department of Health and Human Services, National Institute of Health. National Cancer Institute, 1999.
- De Besi P, Sileni VC, Salvagno L, Tremolada C, Cartei G, Fossier V, Paccagnella A, Peracchia A and Fiorentino M: Phase II study of cisplatin, 5-FU, and allopurinol in advanced esophageal cancer. *Cancer Treat Rep* 70: 909-910, 1986.

- 16 Kies MS, Rosen ST, Tsang TK, Shetty R, Schneider PA, Wallenmark CB and Shields TW: Cisplatin and 5-fluorouracil in the primary management of squamous esophageal cancer. *Cancer* 60: 215-216, 1987.
- 17 Bleiberg H, Conroy T, Paillot B, Lacave AJ, Blijham G, Jacob JH, Bedenne L, Namer M, De Besi P, Gay F, Collette L and Sahmoud T: Randomised phase II study of cisplatin and 5-fluorouracil (5-FU) *versus* cisplatin alone in advanced squamous cell oesophageal cancer. *Eur J Cancer* 33: 1216-1220, 1997.
- 18 Kranzfelder M, Schuster T, Geinitz H, Friess H and Büchler P: Meta-analysis of neoadjuvant treatment modalities and definitive non-surgical therapy for oesophageal squamous cell cancer. *Br J Surg* 98(6): 768-783, 2011.
- 19 Nygaard K, Hagen S, Hansen HS, Hatlevoll R, Hultborn R, Jakobsen A, Mäntyla M, Modig H, Munck-Wikland E, Rosengren B, Tausjo J and Eligen K: Preoperative radiotherapy prolongs survival in operable esophageal carcinoma: a randomized, multicenter study of preoperative radiotherapy and chemotherapy. The second Scandinavian trial in esophageal cancer. *World J Sur* 16(6): 1104-1109, 1992.
- 20 Schlag PM: Randomized trial of preoperative chemotherapy for squamous cell cancer of the esophagus. The Chirurgische Arbeitsgemeinschaft Fuer Onkologie der Deutschen Gesellschaft Fuer Chirurgie Study Group. *Arch Surg* 127(12): 1446-1450, 1992.
- 21 Maipang T, Vasinanukorn P, Petpichetchian C, Chamroonkul S, Geater A, Chansawwaang S, Kuapanich R, Panjapiyakul C, Waeanaarepomchai S and Punperk S: Induction chemotherapy in the treatment of patients with carcinoma of the esophagus. *J Surg Oncol* 56(3): 191-197, 1994.
- 22 Law S, Fok M, Chow S, Chu KM and Wong J: Preoperative chemotherapy *versus* surgical therapy alone for squamous cell carcinoma of the esophagus: a prospective randomized trial. *J Thorac Cardiovasc Surg* 114(2): 210-217, 1997.
- 23 Ancona E, Ruol A, Santi S, Merigliano S, Sileni VC, Koussis H, Zaninotto G, Bonavina L and Peracchia A: Only pathologic complete response to neoadjuvant chemotherapy improves significantly the long term survival of patients with resectable esophageal squamous cell carcinoma: final report of a randomized, controlled trial of preoperative chemotherapy *versus* surgery alone. *Cancer* 91(11): 2165-2174, 2001.
- 24 Boonstra JJ, Kok TC, Wijnhoven BP, van Heijl M, van Berge Henegouwen MI, Ten Kate FJ, Siersema PD, Dinjens WN, van Lanschot JJ, Tilanus HW and van der Gaast A: Chemotherapy followed by surgery *versus* surgery alone in patients with resectable oesophageal squamous cell carcinoma: long-term results of a randomized controlled trial. *BMC Cancer* 2011;11:181. doi: 10.1186/1471-2407-11-181.
- 25 Multhaner R and Fenlon D: Preoperative chemotherapy for resectable thoracic esophageal cancer. *Cochrane Database Syst Rev* 4, CD001556, 2003.
- 26 Urschel JD, Vasan H and Blewett CJ: A meta-analysis of randomized controlled trials that compared neoadjuvant chemotherapy and surgery to surgery alone for resectable esophageal cancer. *Am J Surg* 183: 273-279, 2002.
- 27 Kaklamanos IG, Waker GR, Ferry K, Franceschi D and Livingstone AS: Neoadjuvant treatment for resectable cancer of the esophagus and the gastroesophageal junction: a meta-analysis of randomized clinical trials. *Ann Surg Oncol* 10: 754-761, 2003.
- 28 Xu XH, Peng XH, Yu P, Xu XT, Cai EH, Guo P and Li K: Neoadjuvant chemotherapy for resectable esophageal carcinoma: A meta-analysis of randomized clinical trials. *Asian Pac J Cancer Prev* 13: 103-110, 2012.
- 29 Watanabe M, Nagai Y, Kinoshita K, Saito S, Kurashige J, Karashima R, Hirashima K, Sato N, Imamura Y, Hiyoshi Y, Baba Y, Iwagami S, Miyamoto Y, Iwatsuki M, Hayashi N and Baba H: Induction chemotherapy with docetaxel/cisplatin/5-fluorouracil for patients with node-positive esophageal cancer. *Digestion* 83: 146-152, 2011.

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