TABLE 1. Patient and lesion characteristics

Patient	Age (y)	Gender	Baseline TNM stage*†	Tumor status after CRT	TNM stage before PDT†	Histologic confirmation of residual cancer	Tumor length before PDT (cm)
1	64	Male	T2N0M0	Recurrent	T1N0M0	Positive	1
2	59	Male	T3N1M0	Persistent	T1N0M0	Positive	2
3	74	Male	T3N0M0	Persistent	T2N0M0	Positive	4
4	51	Male	T2N0M0	Recurrent	T1N0M0	Positive	2
5	58	Male	T3N1M0	Persistent	T2N0M0	Positive	2.5
6	74	Male	T2N1M1a	Persistent	T1N0M0	Positive	4
7	68	Male	T3N1M0	Persistent	T2N0M0	Negative	7
8	75	Male	T3N1M0	Recurrent	T2N0M0	Positive	3
9	61	Female	T3N0M0	Persistent	T1N0M0	Negative	2
10	71	Male	T2N1M0	Recurrent	T1N0M0	Positive	2
11	64	Male	T3N0M0	Persistent	T2N0M0	Positive	5
12	67	Male	T3N1M0	Persistent	T2N0M0	Positive	6
13	69	Male	T3N1M0	Persistent	T2N0M0	Negative	5

CRT, Chemoradiotherapy; *PDT*, photodynamic therapy.
*Based on the criteria of the TNM classification of malignant tumors by the International Union Against Cancer.
†The tumor stage was evaluated by EUS.

had uT1 tumors (all of them were assessed as having massive submucosal invasion), and 7 patients had uT2 tumors. Three patients were judged to have persistent tumor without histologic confirmation of carcinoma according to the endoscopic and EUS findings of submucosal tumor-like lesions. The median length of tumor before salvage PDT was 3 cm (range 1-7 cm). Seven patients had ulceration on the lesions before PDT.

Clinical outcomes after salvage PDT are summarized in Table 2. The median total delivered light dose was 750 J (range 300-1000 J). A response of the tumors to salvage PDT was seen in all patients. CR was attained in 8 (62%) of the 13 patients. Among the cases with histologically confirmed residual cancer, the CR rate was 60% (6/10). We show the representative case of a patient who achieved CR after salvage PDT in Figure 1. All patients with uT1 tumors achieved CR, whereas two of 7 patients with uT2 also achieved CR. The median time to confirm CR was 3 months (range 1-4 months). Two patients experienced local recurrence after salvage PDT and were re-treated with PDT; however, their recurrent lesions did not disappear. They died of esophageal cancer progression. Of the 5 patients who did not achieve CR, 3 patients were re-treated with PDT, and the remaining two were followed with appropriate best-supportive care. At a median follow-up period of 12 months (range 6-19 months) after application of salvage PDT, 9 patients were still alive and 6 of them were free of disease. The overall survival rate after salvage PDT after 1 year was 68.4% (Fig. 2).

In all cases, intravenous injection of the Photofrin was well tolerated. There were no allergic reactions or injection site irritation. For all 13 patients, the median hospital stay was 13 days (range 6-20 days), the fasting period was 1 day (range 0-6 days), and the antibiotics-required period was 4 days (range 0-10 days). As for acute complication within the 7 days after salvage PDT, high fever ($>38.5\,^{\circ}C$), and chest pain that needed pain killers was observed in 4 and 7 patients, respectively. White blood count (WBC) and C-reactive protein (CRP) were elevated after initial salvage PDT. Median WBC and CRP at 2 days after salvage PDT were 9400/mm^3 (range 5300-15900/mm^3) (normal 4500-8500/mm^3) and 11.2 mg/dL (range 2.3-18.8 mg/dL); (<0.5 mg/dL), respectively. Six patients experienced significant complications: one mediastinitis, one esophagotracheal fistula, 3 stenosis that required repeated balloon dilation, one cutaneous phototoxicity, and one increase of radiation-induced pericardial effusion that required drainage. The patient who developed mediastinitis was cured by intravenous administration of antibiotics and fasting for 1 week. The patient who developed a fistula died of the progression of esophageal cancer. There were no occurrences of treatment-related death.

DISCUSSION

Definitive CRT is considered the standard non-surgical treatment for esophageal cancer, because it shows

TABLE 2. Clinical outcome after salvage PDT

Patient	Total light dose (J)	Best response for PDT	Time to confirm CR (mo)	Recurrence after PDT (site)	Treatment to persistent or recurrent tumor	Major complications	Outcome	Tumor status	Survival from PDT (mo)
1	600	CR	1	No	—	—	Alive	Disease free	19
2	1000	CR	4	Yes (primary)	PDT	—	Dead	With disease	14
3	840	Non-CR	—	—	Palliation	Fistula	Dead	With disease	3
4	750	CR	3	No	—	Stenosis	Alive	Disease free	15
5	750	Non-CR	—	—	Palliation	Mediastinitis	Dead	With disease	8
6	450	CR	3	No	—	Increase of PE	Alive	Disease free	15
7	900	CR	2	Yes (primary)	PDT	—	Dead	With disease	5
8	525	Non-CR	—	Yes (brain)	PDT	—	Dead	With disease	6
9	300	CR	2	No	—	—	Alive	Disease free	13
10	450	CR	2	No	—	—	Alive	Disease free	11
11	825	Non-CR	—	Yes (primary)	PDT	Stenosis	Alive	With disease	6
12	900	Non-CR	—	Yes (primary)	PDT	—	Alive	With disease	9
13	625	CR	3	No	—	Stenosis, phototoxicity	Alive	Disease free	8

PDT, Photodynamic therapy; *CR*, complete response; *NON-CR*, non-complete response; *PE*, pericardial effusion.

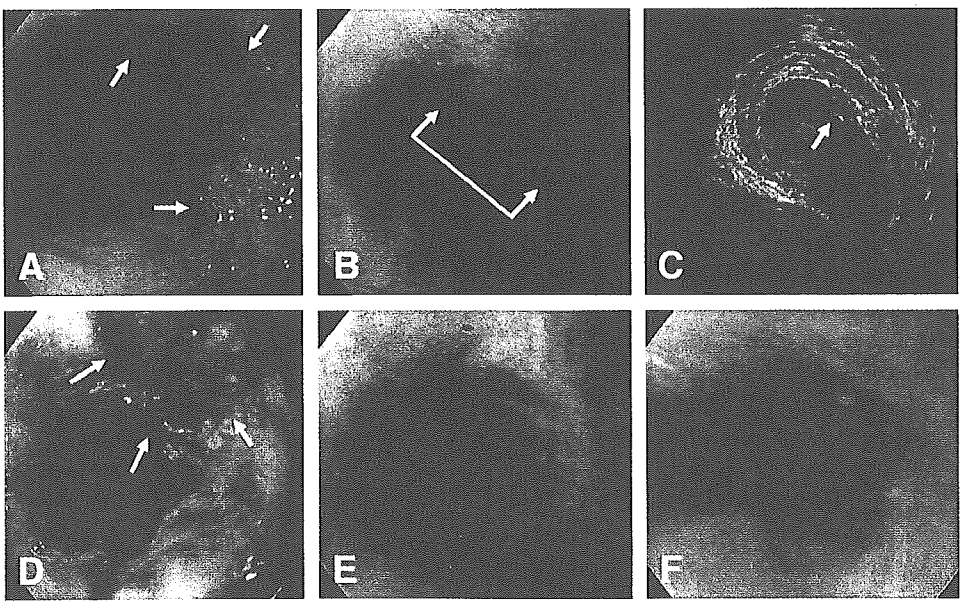

Figure 1. Endoscopic pictures of the patient with esophageal cancer. Baseline clinical stage was assessed as cT2N0M0. **A,** Depressed tumor with surrounding mound *(arrows)* is seen before definitive CRT. **B,** After completion of CRT, a submucosal tumor-like elevation *(arrows)* was persistent at the primary site, and residual cancer was confirmed by biopsy specimen. **C,** EUS image showed a hypoechoic lesion both in the mucosal and submucosal layer *(arrow)*; then, the depth of the residual tumor was assessed as uT1. **D,** At the primary site, tumor necrosis can be recognized by ischemic changes in color *(arrows)*; ulcerative change also can be seen in the background mucosa at 3 days after salvage PDT. **E,** Primary site still shows deep ulceration at 1 month after salvage PDT; however, no cancerous tissue was found by biopsy specimen. **F,** Primary site showed a scar of ulceration at 3 months after salvage PDT; no residual cancer could be found in the biopsy specimen.

comparable survival results to esophagectomy. However, the long-term follow-up results of the prospective randomized trial (Radiation Therapy Oncology Group 85-01) showed that persistence of disease and locoregional failure after definitive CRT were 25% and 13%, respectively.[13] In our previous report, local failure occurred in 34% (18/53)

of the patients treated with definitive CRT.[14] Therefore, improvement of local control is one of the major factors in producing better survival for patients who are treated with definitive CRT.

In our case series, 8 of 13 patients (62%) achieved CR by salvage PDT. Furthermore, the overall survival rate after salvage PDT at 1 year was 68.4%, whereas our previous report showed that overall survival data for patients with non-CR at 3 years was 6%.[2] While, all tumors were assessed as having massive invasion to the submucosal layer or invasion to the muscularis propria layer in this study, salvage PDT showed a relatively high CR rate and excellent short-term survival. These results indicate that carefully selected patients might have a chance of cure by salvage PDT even though they had persistent or recurrent tumor after definitive CRT.

We also previously reported that the overall survival rate of the patients treated by salvage EMR for locoregional failure after definitive CRT was 56% at 3 years.[5] These results might suggest that local treatment by endoscopic modalities such as EMR and PDT could be a treatment option for selected patients.

From a technical point of view, PDT seems to be superior to EMR. If the persistent or the recurrent lesion has an ulceration or severe fibrosis or stenosis, salvage EMR is quite difficult or impossible to perform. If the depth of the residual tumor is limited within the submucosal layer, salvage EMR is relatively difficult and has a risk of being incomplete. Even in such cases, salvage PDT could be indicated in addition to the primary treatment.

Generally, most locoregional failures after definitive CRT are detected at an advanced stage. Endoscopic treatment may not be indicated in such cases because it lacks curative potential. To date, surgical resection is considered to be the only curative treatment in these cases. However, Swisher et al[3] reported that the patients treated by salvage esophagectomy had a significantly higher incidence of anastomotic leaks (39% vs. 7%) and a longer hospital stay (29 days vs. 18 days) than those treated with planned esophagectomy. To treat malignant neoplasms, early detection is very important to cure the patient. Indeed, in our experience, all of the uT1 cases achieved CR. To detect the locoregional failure at earlier stage, the appropriate follow-up schedule after definitive CRT needs to be clarified.

As for the complications of salvage PDT, most of them were manageable with medical treatments. However, one patient developed an esophagotracheal fistula. It is unknown whether the fistula was PDT related or because of the natural progression of disease. Because the tumor in this case was non-CR, we could not deny the possibility of the latter. An esophagotracheal fistula could develop by PDT even for naïve early esophageal cancer cases, and an incidence of 6.5% has been previously reported.[7] Sanfilippo et al[15] reported two patients with esophageal cancer who had developed a fistula after PDT. One received prior external beam irradiation, and the other had intraluminal brachytherapy.[15] Similarly, the reason for mediastinitis or the increase in pericardial effusion occurring after salvage PDT is unknown. One possibility is that radiation-induced esophageal damage and heart disease,[16,17] are potentiated by PDT and that structural damage occurs by transmural necrosis. Nevertheless, it is important to elucidate their mechanism to prevent the potential complications of PDT.

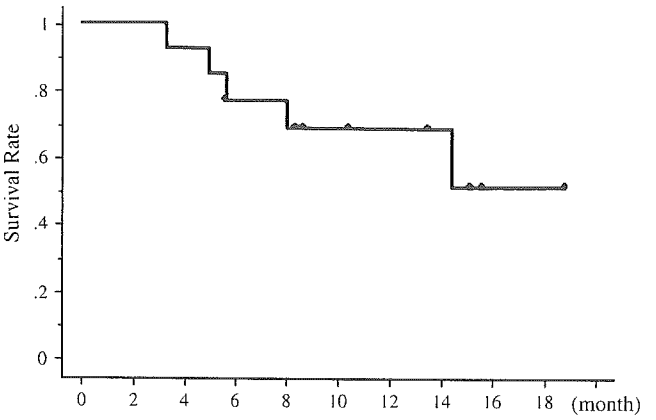

Figure 2. Overall survival of all patients from initiation of salvage PDT.

We have shown the acceptable short-term safety and worthwhile curative properties of salvage PDT when applied to the local failures after definitive CRT. Although further long-term follow-up studies will be required, salvage PDT represents a potentially new and promising treatment option. Large studies will be necessary to define the population of patients who are most likely to benefit from this treatment. Furthermore, we should confirm the efficacy of PDT as a salvage treatment for local failure after definitive CRT.

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ORIGINAL ARTICLE

Efficacy and toxicity of fluorouracil, doxorubicin, and cisplatin/nedaplatin treatment as neoadjuvant chemotherapy for advanced esophageal carcinoma

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Abstract

Objective. Patients with advanced esophageal carcinoma including clinical T4 tumor, extensive lymph node metastasis, or intramural metastasis have a dismal prognosis, despite recent multimodality treatments. The aim of this study was to evaluate the efficacy and toxicity of neoadjuvant chemotherapy using fluorouracil, doxorubicin, and cisplatin or nedaplatin (FAP/N) in these patients. ***Material and methods***. Twenty-six patients were enrolled in this study. The first 9 patients received 600 mg/m^2 fluorouracil on days 1–7 and days 29–35, and 30 mg/m^2 doxorubicin and 60 mg/m^2 cisplatin on days 1 and 29 (FAP). The next 17 patients received modified FAP, in which 50 mg/m^2 nedaplatin was given instead of cisplatin (FAN). ***Results***. Grade 3 or 4 toxicities developed in 6 patients (23.1%) during chemotherapy, but there was no discontinuation of treatment. The clinical response rate was 46.2%. Twenty-one patients (80.8%) underwent esophagectomy, and R0 resection was achieved in 16 patients (61.5%). The 1-year survival rates of 26 patients, 21 patients with resectable tumor, 16 with R0 resection, and 12 clinical responders, were 31.3%, 32.1%, 33.3%, and 45.5%, respectively, each with a median survival time of 9 months. The median progression-free survival time of 26 patients was 6 months; in 16 patients with R0 resection progression-free survival was 6.5 months. There was no correlation between the recurrence pattern and tumor spread before treatment. ***Conclusions***. FAP/N was found to have acceptable toxicities and the ability to control locoregional tumors, but made little contribution to patient survival. The efficacy of this treatment for patients with advanced esophageal carcinoma, however, may not yet be apparent.

Key Words: *Efficacy, esophageal carcinoma, FAP/N, neoadjuvant chemotherapy, toxicity*

Introduction

Most esophageal carcinomas are still diagnosed at an advanced stage, despite efforts being made at early detection [1]. Especially in cases of clinical T4 tumor (cT4), extensive lymph node metastasis (LNM), or intramural metastasis (IM), the prognosis is extremely poor, even after radical esophagectomy including 3-field lymph node dissection [2–4]. Consequently, neoadjuvant therapy has been introduced to down-stage locoregional tumors, to increase the rate of complete resection, and to control micrometastasis [1,5].

Combined neoadjuvant chemotherapy consisting of fluorouracil, doxorubicin, and cisplatin (FAP) for locally advanced esophageal carcinoma was first described by Yasuda et al. [6] in 1995. In their study 4 patients suffering from esophageal carcinoma invading the trachea or main bronchus were treated preoperatively with FAP, and 3 of these 4 patients achieved a clinical response. Subsequently, in 1997, Kabuto et al. [7] reported 12 patients with cT4 esophageal carcinoma who had preoperatively received FAP. The response rate was 75%, and the 1- and 2-year survival rates were 71% and 71%, respectively. They concluded that FAP has the potential to be effective neoadjuvant chemotherapy for locally advanced esophageal carcinoma. However, the numbers of patients in these studies were

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small, and the efficacy of preoperative FAP for advanced esophageal carcinoma remains unclear. Therefore, in the current study we prospectively evaluated the efficacy and toxicity of FAP and its modified regimen, FAN, in which nedaplatin is introduced instead of cisplatin, in patients with advanced esophageal carcinoma, as described above. The primary end-points of this study were the clinical response and toxicity in a neoadjuvant setting. The secondary end-points were the rate of complete resection, survival rate, and recurrence pattern.

Material and methods

Patients

Patients with histologically confirmed squamous cell carcinoma of the esophagus were eligible for this study. Indications for neoadjuvant chemotherapy in our institution were as follow: 1) cT4, 2) extensive LNM, or 3) IM. The inclusion criteria were white blood cell counts $>4000/mm^3$, platelet counts $>100{,}000/mm^3$, hemoglobin >10.0 g/dl, serum total bilirubin <1.2 mg/dl (normal value 0.3–1.1 mg/dl), serum transaminase <2-fold the upper normal limit, serum creatinine <1.2 mg/dl, and creatinine clearance >60 ml/min. The exclusion criterion was previously detected cardiac dysfunction.

Staging

The tumor stages were classified according to the TNM classification of the International Union Against Cancer (UICC) [8]. Clinical staging was based on chest radiography, esophagography, esophagoscopy, and computed tomography (CT) of the neck, chest, and abdomen. Endoscopic ultrasonography, magnetic resonance imaging, bronchofiberscopy, or bone scintigraphy was additionally performed if indicated for the determination of individual staging. Cases showing definite or strongly suspicious direct involvement of adjacent vital organs by local tumor extension were regarded as cT4. When five or more LNM or non-regional LNM, including cervical and celiac LNM from thoracic esophageal carcinoma, were detected on CT scanning of the neck, chest, and abdomen, these cases were considered to have extensive LNM. IM was defined as a metastatic lesion from a primary tumor of the esophagus to the adjacent esophageal and gastric wall; the criteria for these classifications have been reported previously [4].

Chemotherapy

Between July 1999 and November 2000, 9 patients received neoadjuvant chemotherapy consisting of 600 mg/m^2 fluorouracil administered as a continuous intravenous infusion on days 1–7 and days 29–35, 30 mg/m^2 doxorubicin administered intravenously on days 1 and 29, and 60 mg/m^2 cisplatin administered intravenously for 2 h on days 1 and 29 (FAP). Between December 2000 and July 2003, 17 patients underwent modified FAP in which 50 mg/m^2 nedaplatin was introduced instead of cisplatin (FAN). The toxicity of the chemotherapy was graded according to the National Cancer Institute–Common Toxicity Criteria (NCI-CTC), Version 2.0. For cases in which toxicity higher than grade 3 was observed after the first cycle, the doses of all drugs were decreased by 30% in the second cycle. If there was intolerable toxicity or tumor progression, chemotherapy was discontinued and the patients were referred for surgery.

Response evaluation

Esophagography, esophagoscopy, and CT scanning of the neck, chest, and abdomen were done 3 weeks after completion of every cycle of chemotherapy. The clinical responses in primary or metastatic lesions were evaluated according to the guidelines of the Japanese Society for Esophageal Disease (JSED) [9]. Briefly, the responses were classified as follow: complete response (CR), complete disappearance of all clinical evidence of existing lesions during chemotherapy; partial response (PR), a decrease in tumor size of more than 50% during chemotherapy; or no change (NC), a decrease in tumor size of less than 50%.

The histopathological response to chemotherapy was classified as grade 0, 1, 2, or 3 in accordance with the guidelines of the JSED [9]. The degree of viability of residual tumor cells was assessed as follows: grade 3 (markedly effective), no viable residual tumor cells; grade 2 (moderately effective), less than one-third of the residual tumor cells were viable; grade 1 (slightly effective), more than one-third of the residual tumor cells were viable; grade 0 (ineffective), no change.

Surgery

Resection was performed 3 weeks after the last administration of chemotherapy. Of the 26 patients eligible for this study, 13 underwent thoracic esophagectomy with bilateral cervical, mediastinal, and abdominal lymphadenectomies ($n=3$), or with mediastinal and abdominal lymphadenectomies ($n=10$), and 7 underwent transhiatal esophagectomy with

lower mediastinal and abdominal lymphadenectomies for carcinoma of the lower thoracic esophagus. One patient underwent a total esophagectomy combined with pharyngolaryngectomy through the transhiatal approach with cervical lymphadenectomy for carcinoma of the cervical esophagus. The remaining 5 patients did not undergo esophagectomy and received palliative treatment only. The quality of tumor clearance was determined using the residual tumor (R) classification of the UICC-TNM classification: no residual, microscopic residual, and macroscopic residual tumor states after tumor resection were classified as R0, R1, and R2, respectively [8].

Follow-up and statistical analysis

Patients received follow-up care at regular intervals at our institution or at affiliated hospitals; all patients included in this study underwent routine physical and laboratory examinations after discharge. Chest radiography, ultrasonography, or CT scanning was performed at least once annually to detect possible recurrent disease.

Survival rates were calculated from the time of the first chemotherapy until death or the latest follow-up for surviving patients using the Kaplan-Meier method. Differences between the survival curves were analyzed using the generalized Wilcoxon test. The duration of the follow-up period ranged from 3 to 45 months (median 8.5 months). A p-value of less than 0.05 was considered significant. All analyses were performed with StatView J4.11 (Abacus Concepts Inc., Berkeley, Calif., USA).

Results

Patient characteristics, preoperative chemotherapy, toxicity, and clinical response

Between July 1999 and July 2003, 26 patients with advanced esophageal carcinoma were enrolled in the study and received neoadjuvant chemotherapy at the Department of Surgery, Niigata University Medical Hospital. Patient characteristics are summarized in Table I. In this period, eligible patients were all male, and the patient age ranged from 43 to 76 years (mean 63.4 years). The reasons for neoadjuvant chemotherapy were cT4 in 17 patients, extensive LNM in 7, and IM in 7. Five of the patients had two reasons for receiving chemotherapy: 4 patients had cT4 with IM and 1 patient had extensive LNM with IM. Four patients received only one cycle of chemotherapy; this was due to NC in 2 patients, progressive disease (PD) in 1 patient, and refusal to receive further chemotherapy in 1 patient. The remaining 22 patients completed the planned two cycles.

Table I. Patient characteristics.

	No. of patients (%)
Total patients	26
Age (mean)	43–76 (63.4)
Gender (M:F)	26:0
Location	
Cervical	2 (7.7)
Upper thoracic	1 (3.8)
Middle thoracic	16 (61.5)
Lower thoracic	7 (26.9)
Clinical T	
cT3	9 (34.6)
cT4	17 (65.4)
Clinical N	
cN0	8 (30.8)
cN1	18 (69.2)
Clinical M	
cM0	19 (73.1)
cM1a	3 (11.5)
cM1b	4 (15.4)
Intramural metastasis	
Absence	19 (73.1)
Presence	7 (26.9)
Clinical stage	
IIA	1 (3.8)
III	18 (69.2)
IVA	3 (11.5)
IVB	4 (15.4)
Histology	
GX	2 (7.7)
G1	6 (23.1)
G2	11 (42.3)
G3	7 (26.9)
Resectability	
Resectable	21 (80.8)
R0	16 (61.5)
R1 and R2	5 (19.2)
Unresectable	5 (19.2)

Abbreviations: GX = grade of differentiation cannot be assessed; GI = well differentiated; G2 = moderately differentiated; G3 = poorly differentiated.

Toxic side effects during chemotherapy are summarized in Table II. Grade 3 or 4 toxicities developed in 6 patients (23.1%) after the first cycle of chemotherapy. One patient (3.8%) had grade 4 laryngitis and required tracheostomy. Five patients (19.2%) had grade 3 leukocytopenia, 1 patient (3.8%) had grade 3 anemia, and 3 (11.5%) had grade 3 mucositis. Decreased doses were administered to two patients from the first cycle because of pretreatment complications: one with renal dysfunction and the other with carcinoma of the cervical esophagus with prior adjuvant chemoradiotherapy for carcinoma of the thoracic esophagus. There was

Table II. Toxicity during chemotherapy with fluorouracil, doxorubicin, and cisplatin or nedaplatin (FAP/N) in 26 patients.

	Grade				
Adverse event	0	1	2	3	4
Leukocytopenia	15	0	6	5	0
Hemoglobin	25	0	0	1	0
Anorexia	23	3	0	0	0
Nausea/vomiting	25	1	0	0	0
Diarrhea	25	0	1	0	0
Stomatitis	18	1	4	3	0
Laryngitis	25	0	0	0	1
Infection	25	0	0	1	0
Alopecia	25	0	1	0	0

no patient for whom chemotherapy was discontinued after the first cycle owing to severe toxicity.

The clinical response evaluation demonstrated CR in 1 patient (3.8%), PR in 11 (42.3%), NC in 12 (46.2%), and PD in 2 patients (7.7%). When patients with CR or PR in primary or metastatic lesions were defined as responders, 12 patients (46.1%) were grouped as responders and the remaining 14 (53.9%) as non-responders. Of 12 responders, 5 achieved PR after the first course of chemotherapy, and the remaining 6 showed PR after the second course. One patient had PR after the first course followed by CR after the second course.

Surgical results, operative morbidity and mortality, and pathological response

Of the 21 patients who underwent esophagectomy, complete resection (R0) was obtained in 16 patients (61.5%). In the remaining 5 patients, resection was microscopically (R1) or macroscopically (R2) incomplete. Four patients had to undergo R2 resection because residual tumors were detected on the left main bronchus in 2 patients, the aorta in 1 patient, and the inferior vena cava in 1 patient. One patient had to undergo R1 resection because positive involvement of the external surface was proven histologically.

One patient (4.8%) died on the 26th day of the operation. The cause of death was congestive heart failure, and an autopsy revealed cardiomyopathy that was strongly suspected of being doxorubicin-induced cardiotoxicity. In-hospital mortality was reported in two patients who died of recurrent disease. Major morbidity included paralysis of the vocal cords in 3 patients (14.3%), pneumonia in 1 (4.8%), cardiac tamponade in 1 (4.8%), and osteomyelitis of the sternum in 1 patient (4.8%). In total, 11 patients (52.4%) had at least one of these postoperative complications. Anastomotic leakage developed in 4 patients (19.0%).

Pathological response evaluated from the resected specimens was grade 2 in 4 patients, grade 1 in 4, and grade 0 in 11. No pathologically complete response was observed. Compared with clinical staging, 10 patients with cT4 had lower pathological T: pT3 in 8 patients, pT2 in 1, and pT1 in 1 patient. Of the 7 patients with extensive LNM based on CT scanning, only 4 underwent esophagectomy and all had 5 or more metastatic nodes. Of the 7 patients with IM before treatment, 6 underwent esophagectomy and all but one had residual metastatic tumors. Two patients, in whom IM was not apparent before esophagectomy, were found to have IM by pathological examination from the resected specimen.

Patient outcome

The 1- and 2-year survival rates of all 26 patients were 29.5% and 12.3%, respectively, with a median survival time (MST) of 9 months (range 3–45 months; Figure 1). The 1- and 2-year survival rates of 5 patients with unresectable esophageal carcinomas were 26.7% and 0%, respectively, with an MST of 10 months (range 6–14 months). In contrast, the 1- and 2-year survival rates of 21 patients with resectable esophageal carcinomas were 30.1% and 15.1%, respectively, with an MST of 9 months (range 3–45 months). There was no significant difference in survival between patients with unresectable and resectable tumors (Figure 2). The 1- and 2-year survival rates of 16 patients who had undergone complete resection were 32.0% and 21.3%, respectively, with an MST of 9 months (range 3–45 months). The 1- and 2-year survival rates of 5 patients who had undergone incomplete resection were 26.7% and 0%, respectively, with an MST of 12 months (range 6–17 months). There was no significant difference in survival between patients who had undergone complete and incomplete resections (Figure 3). In 21 patients with resectable tumors, the 1- and 2-year survival rates of 12 clinically responding patients were 45.5% and

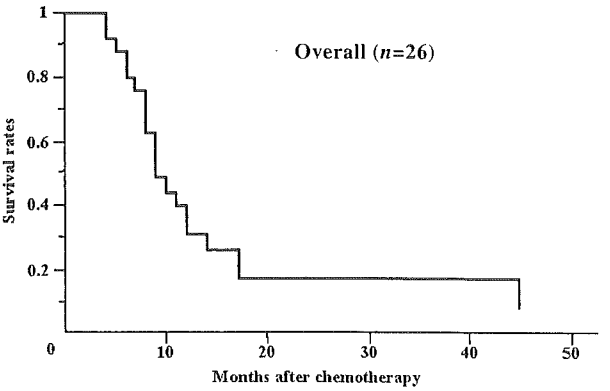

Figure 1. Overall survival curve of 26 patients enrolled.

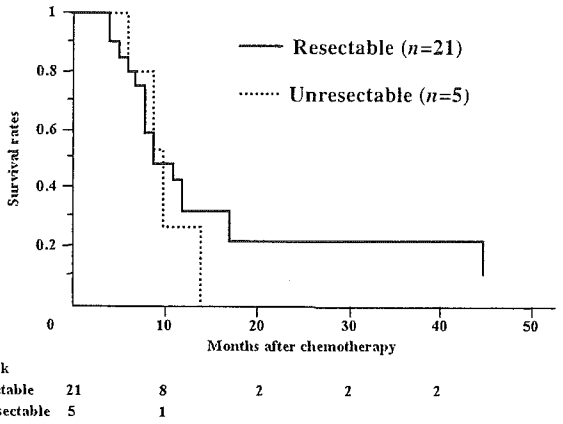

Figure 2. Overall survival for patients with resectable and unresectable esophageal carcinoma.

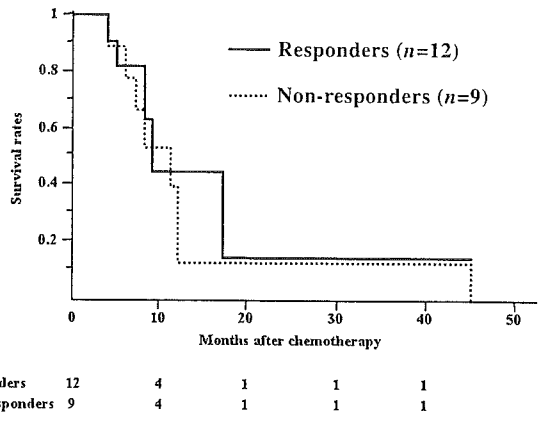

Figure 4. Overall survival for clinically responding and non-responding patients.

15.2%, respectively, with an MST of 9 months (range 3–45 months). In contrast, the 1- and 2-year survival rates of 9 clinically non-responding patients were both 13.3%, with an MST of 11 months (range 4–40 months). There was no significant difference in survival between responders and non-responders (Figure 4).

The progression-free survival of all 26 patients ranged from 1 to 45 months (median 6 months). In 16 patients with complete resection, progression-free survival ranged from 3 to 45 months (median 6.5 months). Only two patients are still alive with no evidence of disease. Three patients are alive but with recurrences, and 10 patients died of metastatic disease. The one remaining patient who had undergone complete resection died of operative mortality. The pattern of recurrence was analyzed for these 13 patients (Table III). No apparent correlation could be found between the tumor spread before treatment and the pattern of recurrence.

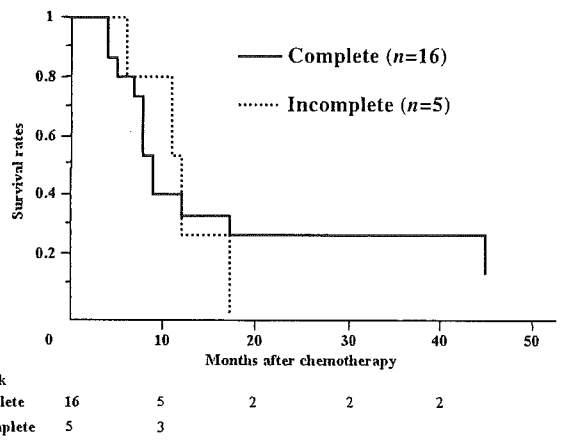

Figure 3. Overall survival for patients who underwent complete and incomplete resection.

Discussion

Neoadjuvant chemotherapy is often performed in patients with advanced esophageal carcinoma with the objective of down-staging locoregional tumors and eradicating micrometastatic disease [5]. A meta-analysis of 11 randomized controlled trials comparing neoadjuvant chemotherapy and surgery with surgery alone for resectable esophageal carcinoma was reported by Urschel et al. [10] in 2002. They concluded as follow: 1) neoadjuvant chemotherapy and surgery are associated with a higher rate of complete (R0) resection; 2) the combination treatment does not increase treatment-related mortality; and 3) there is no apparent survival benefit for the combination of neoadjuvant chemotherapy and surgery. Despite these results, it remains controversial whether neoadjuvant chemotherapy improves outcome in patients with advanced esophageal carcinoma [11,12]. It may be difficult to evaluate the efficacy of neoadjuvant chemotherapy even by randomized controlled trials because the combination of chemotherapeutic agents and the quality and radicalness of cancer surgery vary among trials.

Regarding resectable esophageal cancer, patients with cT4, extensive LNM, or IM are considered to have far-advanced disease and therefore an extre-

Table III. The pattern of recurrences according to tumor spread before treatment.

	Recurrence site		
Tumor spread	Organ	Lymph node	Organ and lymph node
cT4 alone	1	3	1
cT4 with IM	0	2	1
Extensive LNM	2	0	2
IM	0	0	1

Abbreviations: IM = intramural metastasis; LNM = lymph node metastasis.

mely poor prognosis. Between December 1990 and June 1999, combined chemotherapy consisting of fluorouracil and cisplatin (FP) was administered preoperatively in our institution to 14 patients with these far-advanced diseases. The clinical response rate, the rate of esophageal resection, and the rate of complete (R0) resection were 7.1%, 50.0%, and 21.4%, respectively. The overall 1- and 2-year survival rates were 28.1% and 14.3%, respectively, with an MST of 7.0 months (range 2–85 months). Based on these unacceptable results, FAP was introduced in this patient population because of its high response rate and promising long-term outcomes for patients with cT4 esophageal carcinoma, as reported by Yasuda et al. [6] and Kabuto et al. [7]. The response rate was 75%, and 1- and 2-year survival rates were 71% and 71%, respectively. In the current study, 17 patients underwent FAN, modified FAP, in which nedaplatin was used. Nedaplatin is a second-generation platinum complex that has a characteristic property of being approximately 10 times as soluble in water as cisplatin. As such, nedaplatin is considered to have more pronounced activity against solid tumors and less nephrotoxicity and gastrointestinal toxicity than cisplatin [13].

Differences in anti-tumor effects and toxicities between FAP/N and FP were apparent. The clinical response rates of FAP/N and FP were 46.1% and 7.1%, respectively. Consequently, the rate of complete (R0) resection for FAP/N was higher than that for FP (61.5% and 21.4%, respectively). As for toxic side effects, however, grade 3 or 4 toxicities developed in 6 patients (23.1%) who received FAP/N but in none of the patients who received FP. One patient died of cardiomyopathy within 26 days of surgery and was regarded as a treatment-related mortality. These considerable anti-tumor effects and toxicities may result from doxorubicin-containing regimens. Particular attention should be paid to toxicities in cases of FAP/N. Concerning other types of postoperative morbidity, FAP/N did not increase the rate of anastomotic leakage, vocal cord paralysis, or postoperative pulmonary complications compared with FP (data not shown).

Despite the acceptable clinical response rate, long-term outcomes of patients who received FAP/N were unacceptable. There was no significant difference in overall 1-year and 2-year survival rates and MST between FAP/N and FP. To examine whether survival in patients who received FAP/N was related to the clinical response to chemotherapy, esophageal resection, or the quality of tumor clearance, subset analyses were performed and revealed that no subgroup survived longer than its counterpart. Several trials have shown that survival after neoadjuvant chemotherapy and surgery is related to the clinical response to chemotherapy [14–18]. In the present study, the 1-year survival rate of 12 responders was relatively higher than that of 9 non-responders (45.5% and 13.3%, respectively), but the difference was not statistically significant. A discrepancy between the clinical response and long-term outcomes was suggested by the low pathological response of the primary and metastatic disease. Therefore, FAP/N may have the ability macroscopically to control locoregional tumors and to facilitate surgical resection by down-staging, but an inability completely to root out microscopic residual tumor cells. In addition, neoadjuvant chemotherapy using FAP/N was not found to affect the recurrence pattern, thereby suggesting that currently used chemotherapeutic agents may not be sufficiently effective to eradicate micrometastatic systemic disease.

A major criticism of the present study is patient selection, as the patient group consisted of clinically heterogeneous subgroups. There was no significant difference in survival among these subgroups with cT4, extensive LNM, or IM (data not shown). It is possible that the numbers of patients in the respective subgroups were too small to allow detection of modest differences in survival. It is more reasonable, however, to assume that these patients already had micrometastatic systemic disease at the time of diagnosis, even in patients with cT4, which is regarded as a locally advanced disease. Based on their randomized controlled trial, Baba et al. [19] have reported that neoadjuvant chemotherapy did not provide a survival benefit over surgery alone for patients with T3 tumors, which may support our hypothesis described above.

How should patients with far-advanced esophageal carcinoma be treated? Long-term survivors may hold the key to resolving this issue. In the present study, only three patients survived over 2 years. The first patient, who was a non-responder and had no pathological response, died of bone metastasis 45 months after chemotherapy, with a progression-free survival of 39 months. The second patient, in whom lung metastasis developed 45 months after chemotherapy, had been a responder and had a metastatic node. This patient received an additional course of FAN for recurrent disease and is still alive with recurrent disease. The third patient, in whom cervico-mediastinal LNM developed 21 months after chemotherapy, was a responder and had a grade 2 pathological response. This patient received chemoradiation that achieved CR and he is still alive 34 months after chemotherapy, with no evidence of recurrent disease. All underwent complete resection regardless of the operative approach or the extent of lymph node dissection. Neoadjuvant chemotherapy

and surgery certainly provide some survival benefit for these patients, but there is currently no reliable method for predicting who will be long-term survivors. It is therefore essential to obtain novel selection tools for patients who are potentially curable by neoadjuvant chemotherapy and surgery.

In conclusion, FAP/N has acceptable toxicities and the ability to control locoregional tumors, but makes little contribution to patient survival. The efficacy of this treatment for patients with advanced esophageal carcinoma, however, may not yet be apparent. Attempts to control systemic micrometastatic disease are mandatory.

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原 著

根治切除不能進行食道癌に対するNedaplatin/Adriamycin/5-FU (NAF) 併用療法のPhase I Study

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Phase I Study of the Combination of Nedaplatin (NED), Adriamycin (ADM), and 5-Fluorouracil (5-FU) (NAF) for Treatment of Unresectable Advanced Esophageal Cancer: Motohiro Hirao, Kazumasa Fujitani, Toshimasa Tsujinaka (*Dept. of Surgery, Osaka National Hospital*)

Summary

Background: Esophageal cancer has a poor prognosis. Several strategies including chemotherapy (CDDP+5-FU), either alone or with radiotherapy, have been used to improve the prognosis. However, since CDDP itself has substantial toxicities, including renal and gastrointestinal toxicities, newer platinum analogues, such as nedaplatin (NED) have been developed, and it is of interest to test this new platinum analogue in a combination chemotherapy. Methods: We conducted a phase I-II study using a combination of NED (3 levels, 60-80 mg/m² on day 1), ADM (30 mg/m² on day 1), and 5-FU (700 mg/m² on day 1-5) for treatment of previously untreated advanced esophageal squamous cell carcinoma. Cycles were repeated every 28 days. The objectives were to determine dose-limiting toxicity (DLT), maximum-tolerated dose (MTD), recommended dose (RD) for a phase II study, and to determine antitumor effects. Results: Phase I: 12 patients (pts) (male/female=11/1) were evaluable. The median age was 65 (range 46-74), PS 0/1=7/5. At level 1, 1 pt developed DLT (grade 4, neutropenia). At level 2, 2 pts developed DLT (grade 4 neutropenia and grade 3 diarrhea). Level 2 (70 mg/m²) was determined as the MTD, and a level 1 dose (60 mg/m²) was recommended. Phase II: 7 pts (male/female=4/3) are at RD of level 1 at the present time. Median age 62 (range 46-75). The median number of cycles on phase II study at RD was 2 (range 1-3). 4 PRs were obtained. The response rate was 57.1%. Median survival time (MST) was not reached at the time. Conclusions: This combination therapy appears to be highly effective and generally well tolerated for advanced esophageal cancer. Key words: Nedaplatin, Esophageal cancer, Phase I-II (*Received May 1, 2004/ Accepted Jul. 7, 2004*)

要旨 今回われわれは，NED/ADM/5-FU併用療法（NAF療法）に着目し，予後不良な切除不能食道癌に対するfirst-lineとして，この併用化学療法の安全性および有効性の検討を計画した。key drugであるNEDを増量していき，step 2: 70 mg/m²で2例のdose limiting toxicity（DLT）（grade 4血液毒性とgrade 3非血液毒性）が出現したためstep 2を最大耐用量，step 1の60 mg/m²をNEDの推奨投与量とした。grade 1の悪心・嘔吐が最も多い非血液毒性であり，grade 1の腎毒性はstep 2で1例経験したが，すべて保存的に軽快した。また，step 1でのgrade 4好中球減少のDLT症例のみG-CSFを使用した。以上の第I相試験で明らかとなったNED 60 mg/m²，ADM 30 mg/m² day 1，5-FU 700 mg/m²/日 day 1～5の持続点滴静注を推奨投与とした現在までの第II相での奏効率は57.1%と良好な結果が得られており，安全かつ有効なregimenとして十分期待できる。

はじめに

今回われわれは，予後不良な進行食道癌患者を対象としてnedaplatin (NED)，adriamycin (ADM)，および5-fluorouracil (5-FU) とのNAF併用療法（NAF療法）の安全性および有効性の検討を目的にこの研究を行った[1,2]。臨床第I相として[2]，first-line NAF療法の安全性を検討し，NEDをkey drugとした本療法の推奨用量，用法の結果を報告する。また，現在進行中の第II相として，第I相で決定された推奨用量，用法における有効性

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および安全性を評価し，本併用療法のfeasibilityを明らかにする。当研究は当センターIRBにて承認され，患者には十分なインフォームド・コンセントを得てから行っている。以下の記載は，食道癌取扱い規約第9版に準じる。

I. 対　象

2003年1月から2004年3月までの期間，当院消化器科および外科を受診した前治療歴のない根治切除不能進行食道扁平上皮癌。根治切除不能進行食道癌とは，T4もしくはT4疑い，N4，M1，または腹部または頸部の2領域以上に及ぶ明らかなリンパ節転移が認められる症例。評価測定可能病変を有し，年齢は20歳以上75歳以下，performance status (PS): 0～1 (ECOG分類)，十分な心，骨髄，腎，肝機能を有し，重複癌のない患者を対象に施行。なお，選択基準や除外基準の詳細の記述は省略する[2]。

食道癌に対する補助化学療法としてのFAP (5-FU/ADM/CDDP) 併用療法の投与量はそれぞれ50 mg/body，100 mg/body，1,000 mg/body (day 1～5または7持続) と報告されている[3]。今回，NEDの投与量はNED単剤での至適投与量が100 mg/m²であることを考慮し，60 mg/m²を第一投与量とした。ADM，5-FUの投与量はそれぞれ30 mg/m² (day 1)，700 mg/m² (day 1～5持続) とし1日量はほぼ同量としたが，5-FUは5日間の持続投与とし，総投与量として減量した。この理由としてNEDはcisplatin (CDDP) より骨髄障害が強いため，5-FUの総投与量を減らすと同時に，患者のQOLを考えたためである。

II. 方　法

ADM 30 mg/m² day 1，5-FU 700 mg/m²/日 day 1～5の持続点滴静注で4週ごとに投与し，key drugであるNEDの投与量は以下に従い増量する。step 1: 60 mg/m²，step 2: 70 mg/m²，step 3: 80 mg/m²。step 1より試験を開始し，各stepのコースでのdose limiting toxicity (DLT) の発現頻度を評価し，以下に示した基準で投与量stepを移行する。1）同一投与量stepの3例にDLTが認められない場合は，次のstepに移行。2）3例中1例にDLTが認められた場合は3例追加し6例とする。①追加後の3例にDLTが認められない場合には，次のstepに移行する。②追加後の3例中1例にDLTが認められた場合は，その投与量stepを最大耐用量 (MTD) とする)。MTDが判明したのち，MTDより1段階低い投与量stepをRD（推奨投与量）とする。またDLT基準は以下のとおりである。①grade 4の白血球減少または好中球減少が出現，②38°C以上の発熱を伴うgrade 3の好中球減少が出現，③25,000/mm³未満の血小板減少，④悪心・嘔吐，食欲不振，疲労および脱毛を除く，grade 3以上の非血液毒性が出現した場合。中止基準を満たさない限り2コース以上行い，前コースでの発現副作用により減量基準も設けた[2]（詳細省略）。

Table 1　Patient characteristics on phase I study

Total number of patients (step 1/step 2)	12 (6/6)
Sex (M/F)	11/1
Age (years)	65 (46-74)
Stage (III/IV a/IV b)	4/3/5
Performance status (0/1)	7/5

第II相として，第I相で決定された推奨用量，用法における有効性を評価するためSimonのminimax designに従い，期待奏効率を50%，閾値率を30%として ($\alpha=0.05$, $\beta=0.20$)，目標必要症例数を40例に設定した。評価病変に対する臨床的治療効果（腫瘍縮小効果）および奏効度の表現はWHO criteriaに従った。

III. 結　果

第I相は男性11例，女性1例の計12例（平均年齢65歳，46～74歳）が登録(Table 1)。進行度とPSもTable 1を参照されたい。各step 6例ずつでstep 2まで増量。step 1で1例のDLT (grade 4の好中球減少)，step 2で2例のDLT（grade 4の好中球減少とgrade 3の下痢）出現のためstep 2をMTD，step 1の60 mg/m²をNEDの推奨投与量とした（Table 2)。好中球減少のnadirは投与第1日目から9～22日（中央値17日）で，回復に3～4日を要した。grade 1の悪心・嘔吐が最も多い非血液毒性であり，grade 1の腎毒性はstep 2で1例経験したが，すべて保存的に軽快した。また，step 1でのgrade 4好中球減少のDLT症例のみG-CSFを使用した。また，進行中の第II相では，NEDの推奨用量をstep 1の60 mg/m²とし，現在のところ7例（男性4例，女性3例）（平均年齢62歳，46～74歳）を登録。施行コース数中央値は2（1～3）で，PR 4例，NC 3例であり，現在までの奏効率は57.1%であった (Table 3)。生存期間も追跡中である。

IV. 考　察

近年，手術手技の向上，術後管理の進歩，早期癌症例発見の増加などの理由で食道癌全体の治療成績は以前より改善したが，高度進行食道癌や再発食道癌は依然とし

Table 2 Hematologic and nonhematologic toxicities by dose level in the first cycle on phase I

Dose step	No. of patients	Neutropenia				Thrombocytopenia				Anemia				Nausea/vomiting				Diarrhea				Elevation of creatinine				Elevation of transaminase			
		1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
1	6	1	1	2	1	0	0	1	0	3	2	1	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2	6	2	1	1	1	0	0	0	0	4	1	0	0	3	0	0	0	1	0	1	0	1	0	0	0	0	0	0	0

Table 3 Phase II study on going

Pt #	Gender	Age	TNM	Stage	No. of courses	Response	Evaluable sites
1	F	70	T4	IVa	2	PR	Main tumor
2	M	54	H1	IVb	2	PR	Liver
3	M	46	M1 (brain)	IVb	3	NC	Brain
4	M	74	T4	IVa	2	NC	Main tumor
5	F	68	T4, M1 (lung)	IVb	2	PR	Main tumor, Lung
6	M	60	H1	IVb	2	NC	Liver
7	F	61	T4	IVa	1	PR	Main tumor

て予後不良である。1980年代以降の高度進行食道癌や再発食道癌に対する化学療法成績をみると，単剤での奏効率は2～4剤の併用療法よりも低いことは判明している。当初，胃癌に対する効果からADMと5-FUとの併用が期待されたが，1984年のCDDP登場以来，それをkey drugとした多剤併用療法が中心となり効果をあげてきた[4]。1987年以後食道癌の標準併用化学療法となった5-FU/CDDP（FP）は，1992年Japanese Esophageal Oncology Group（JEOG）で行った進行食道癌を対象にしたFP療法の第II相臨床試験にてもその効果が認められ，わが国においても現在標準治療となっている[5]。同時にADMとCDDPの併用効果についても報告されるようになり，ADM，5-FUにCDDPを加えた3剤併用のいわゆるFAP療法の比較的良好な成績が報告されている[3]。しかし，key drugであるCDDPの腎毒性や消化器毒性などの副作用が強いため，QOLの改善が望まれている。

NEDはわが国で開発されたプラチナ誘導体であり，単剤で行われた第II相臨床試験でCDDP同様幅広い抗腫瘍スペクトルを有していることが示され，特に扁平上皮癌（頭頸部癌[6]，食道癌[7]，子宮頸癌[8]）に対する有効性が高いと評価された。また，CDDPに比較し，腎毒性が少なく，消化器障害の程度も低く，患者のQOL向上が期待できる。一方，NEDのDLTは骨髄抑制（白血球減少，血小板減少）であり，MTDは120 mg/m²であった。NED単剤での第II相臨床試験における食道癌に対する奏効率が51.7%（15例/29例）得られている。さらに，NED/5-FU併用療法が基礎的検討からも併用効果が証明されて以来[9]，NED/5-FU併用療法の良好な報告がされている[10]。食道癌と同様にFP療法が標準療法とされる頭頸部癌における報告[11]では，NED+5-FUはCDDP+5-FUと比較して奏効率はほぼ同等で血小板減少の頻度は高いが，腎毒性，悪心・嘔吐の消化器毒性が低いと報告されている。

また，ADMを加えたFAP/N療法の清水らの報告では，高度進行食道癌（高度リンパ節転移およびT4）に対し，抗腫瘍効果50%（FP療法5.9%）で，手術切除率92%（FP療法47%），根治率73%（FP療法25%）と，かなり良好な成績が得られ，毒性ではgrade 2～3の白血球減少と口内炎を認めたが腎毒性や消化器毒性はなく，いずれも保存的に対処可能であったとされている[12]。

taxane系を加えたnew regimenもでているなか[13]，食道癌の標準的治療として現実にはFP療法が行われており，欧米では40～60%の奏効率が報告されている[14,15]が，JEOGにおけるstudyでは奏効率33%（CR 1例+PR 11例/36例）であり，予想を下回る結果であった。以上より，今回われわれは，NED/ADM/5-FU併用療法（NAF療法）に着目し，切除不能進行食道癌に対するfirst-lineとして，この併用化学療法の安全性および有効性の検討を計画した。

NED 60 mg/m²，ADM 30 mg/m² day 1，5-FU 700 mg/m²/日 day 1～5の持続点滴静注を推奨投与法とした，現在までの第II相試験での奏効率は57.1%であり良好な結果が得られた。grade 4の血液毒性がみられたが，保存的に十分対応可能であり，CDDPにみられるような消化器，腎毒性はほとんどなかった。奏効度，安全性およびQOLの面からも期待できるregimenと思われる。治療後予後または生存期間はまだ解析中であるが，今後

症例を登録追加し，さらなる検討を進めたい。

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食道癌に対する根治目的放射線化学療法後のサルベージ手術後に早期再発した3例の検討

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症例報告

食道癌に対する根治目的放射線化学療法後のサルベージ手術後に早期再発した3例の検討

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2002年9月から2003年12月までに，食道癌に対する根治目的放射線化学療法後のサルベージ手術を5例に施行した．104Rリンパ節転移遺残に対する右頸部郭清術施行例と，胸部中部食道の原発巣遺残と106recRリンパ節転移遺残に対する食道切除再建手術施行例の2例には再発を認めていないが，その他の3例は術後2か月以内の再発を認めた．症例1は，胸部下部の原発巣遺残と腹部リンパ節転移に対し，下部食道切除・胃全摘を施行した．術後1か月後に膵背側のリンパ節再発を認めた．症例2は，胸部中部食道癌の106recRのリンパ節転移遺残に対し，右頸部郭清術を施行．術後1か月後に原発巣の再発を認めた．症例3は，頸部食道癌遺残に対し，咽喉食摘術を施行．術後2か月で肺転移を認めた．再発した症例も術前評価では根治が望めると判断したが，結果的には早期に再発した．現段階ではサルベージ手術の適応・術式・成績などのデーターが不十分であるため，十分なinformed consentが重要である．

はじめに

胸部食道癌に対する根治目的放射線化学療法（chemoradiation therapy：CRT）は，手術治療に匹敵すると報告され[1)~3)]，標準的治療方法の1つになってきている．当院ではJapan Clinical Oncology Group（JCOG）の食道癌に対する放射線化学療法同時併用療法の第II相臨床試験のプロトコールに沿って治療している（Stage I；JCOG 9708, Stage II/III；JCOG9906）．しかしながら，根治に至らず，サルベージ手術を必要とすることもある．ここでいうサルベージ手術とは，根治目的のCRT後の腫瘍残存・再燃に対する根治目的の外科治療をいう．サルベージ手術は，CRT後の腫瘍残存・再燃に対し，唯一の根治を期待できる治療方法であるが，その高い在院死亡率・合併症率が問題である．症例ごとのリスクと腫瘍の進展状況により，適応・術式の選択に苦慮することも多い．サルベージ手術後の早期再発について検討した．

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症　例

当院で2002年9月から2003年12月までに，食道癌に対する根治目的放射線化学療法後のサルベージ手術を5例に施行した．いずれも手術治療で根治を目指した症例である（Table 1）．そのうち胸部中部食道癌で，原発巣は完全寛解（CR）で104Rリンパ節転移の遺残に対する右頸部郭清術施行例と，胸部中部食道の原発巣遺残と106recRリンパ節転移の遺残に対する食道切除再建手術施行例の2例は，それぞれ9か月，8か月間の無再発生存であるが，その他の3例は術後2か月以内に再発した．その3例に検討を加えた．

症例1：57歳，男性

主訴：嚥下困難

既往歴：特記すべきことなし．

現病歴：H14年11月7日腹部食道癌の診断で当院紹介初診．切除可能な食道癌であったが，根治目的CRTを希望され，fluorouracil（5-FU），cisplatin（CDDP）による化学療法と放射線（60Gy）の同時併用療法（FP-R）を2コース行った．さらに化学療法のみ2コースを追加した．その後の評価で，主腫瘍がpartial response（PR）であったの

Table 1　Characteristics of patients with salvage surgery following definitive chemoradiotherapy for esophageal cancer

Case	Age	Sex	Site	Clinical stage	The location of relapse or residual tumor	Surgical methods	Postoperative recurrence	Disease free period
1	57	M	Ae	III	The primary lesion and paragastric lymph node	Lower esophagectomy combined with total gastrectomy	Lymphnode behind the pancreas	1 month
2	74	F	Mt	III	Right recurrent laryngeal nerve lymph node	Right lymph node dissection	The primary lesion	1 month
3	65	M	Ce	IVa	The primary lesion	Pharyngolaryngoesophagectomy	Multiple lung metstasis	2 months
4	65	M	Mt	III	The primary lesion and right recurrent laryngeal nerve lymph node	Right transthoracic esophagectomy with 2-field lymph node dissection	None	9 months
5	55	M	Mt	IVb	The right subclavian lymph node	Right lymph node dissection	None	8 months

で，サルベージ手術目的に当科紹介受診.

当科入院時現症：身長171.4cm　体重52.2kg

上部消化管内視鏡検査所見：胸部下部食道から腹部食道にかけて，Type 2病変を認める．潰瘍の辺縁より生検でpoorly differentiated squamous cell carcinomaを認めた．治療効果はGrade2であった.

頸胸腹造影CT所見：胸部下部食道から腹部食道にかけて食道壁が全周性に肥厚．胃小弯にリンパ節再発疑われた.心嚢液が軽度貯留していたが，膵周囲にリンパ転移は疑われなかった(Fig. 1a).

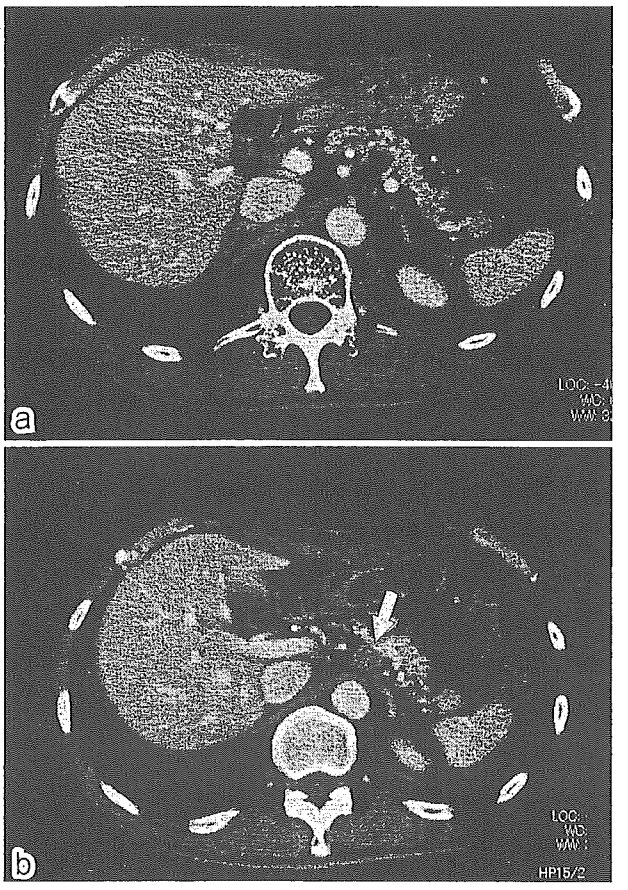
手術術式は，開胸食道切除が標準的であると考えられたが，安全性を重視し，開腹下部食道胃全摘＋Roux-Y再建予定とした.

手術所見：H15年8月26日手術施行.開腹でアプローチした．胸部下部食道から腹部食道は硬く腫大していたが，周囲から剥離は可能であった．胃小彎の転移が疑われるリンパ節が膵との境界が不明であった．膵を切り込まない切離線で結紮しながら離断した．左胃動脈は細い索状物のようになり血流は途絶していた．下部食道胃全摘＋Roux-Y再建を施行した．食道は放射線治療の影響で血流低下が予想されたので，栄養管理用に空腸瘻を造設した.

病理所見：原発巣にviable cellは残存．胃壁に固着したリンパ節と膵との剥離面がpositiveであった.

臨床経過：術後経過は順調で9月11日（15 POD）に軽快退院．9月29日経過観察のCTで膵体部上部から背側にLN再発を認めた(Fig. 1b).

Fig. 1　a：Abdominal enhanced CT before salvage surgery showed no lymph node metastasis behind the pancreas. b：Abdominal enhanced CT about one month after the operation showed local recurrence behind the pancreas (arrows).



再発に対し，他院で化学療法を施行中である．

症例2：74歳，女性

主訴：嚥下時狭窄感

既往歴：特記すべきことなし．

現病歴：H15年5月上旬頃より前胸部痛・嚥下時狭窄感あり．前医で上部消化管内視鏡で食道癌と診断．5月22日当院紹介初診．胸部中部食道癌（cT3N1M0）と診断．リンパ節転移は106recRに1つ転移が疑われた．手術治療と根治目的放射線化学療法の選択肢から，放射線化学療法を選択された．FP-R 2コース施行．化学療法のみもう1コース追加したが，106recRのリンパ節はPRのままであった．9月10日サルベージ手術目的で当科紹介．

当科入院時現症：身長151.4cm，体重53.8kg．表在リンパ節は触知しなかった．

上部消化管内視鏡検査：門歯30cmにCRT後の潰瘍瘢痕を認めるが，明らかな再発所見は認めなかった（Fig. 2a）．原発巣は完全寛解（CR）と診断した．

頸胸腹造影CT：106recRリンパ節は増大傾向にあった（Fig. 3）．食道Mtの腫瘍部分はわずかに壁肥厚を認めるのみであった．

PET検査：106recRリンパ節に一致した集積像あり．食道には集積像は認めず．

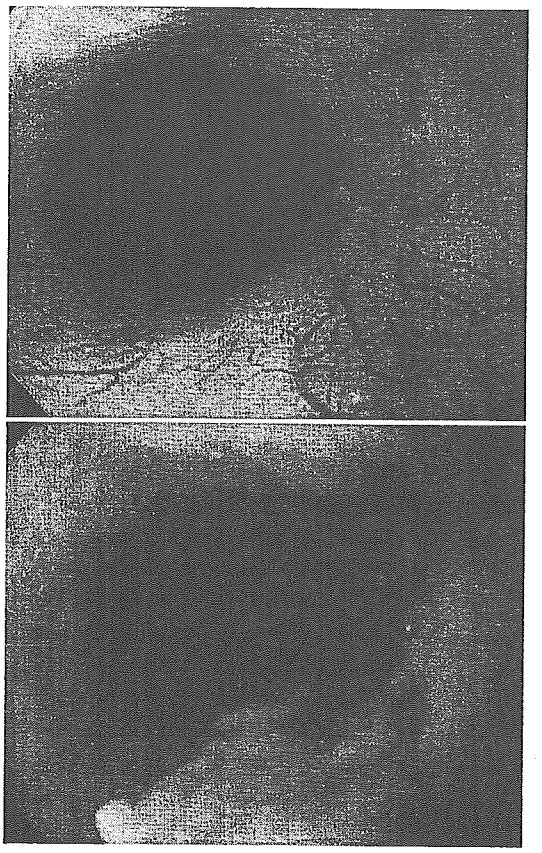
上記所見より106recRリンパ節のみに癌が遺残していると考えた．しかしながら追加の抗がん剤治療では，根治に至る可能性は低いと考え，同リンパ節の切除術のみ施行の方針とした．

手術所見：全身麻酔下右頸部切開施行．101Rと106recRを郭清し，術前指摘のリンパ節を摘出．その他104Rも郭清した．

病理所見：総郭清リンパ節9個のうち，術前指摘の106recRリンパ節1個のみ転移を認めた．

術後経過：9月22日（6POD）に軽快退院した．経過観察目的の上部消化管内視鏡検査を10月16日に施行したところ，前回瘢痕であった病変が，周堤を伴う潰瘍性病変に変化しprogressive disease（PD）と診断した（Fig. 2b）．頸胸腹造影CTでは，明らかな再発病変は認めなかった．開胸食道切除術を勧めたが拒否され，他院で免疫療法を施行中である．

Fig. 2 a：Endoscopy showed only a scar, about 30cm from the incisors. Complete response (CR) was expected. b：Endoscopy showed ulcerative change with randwall in the same location. Recurrence of esophageal carcinoma was suspected.



症例3：65歳，男性

主訴：嗄声

既往歴：特記すべきことなし．

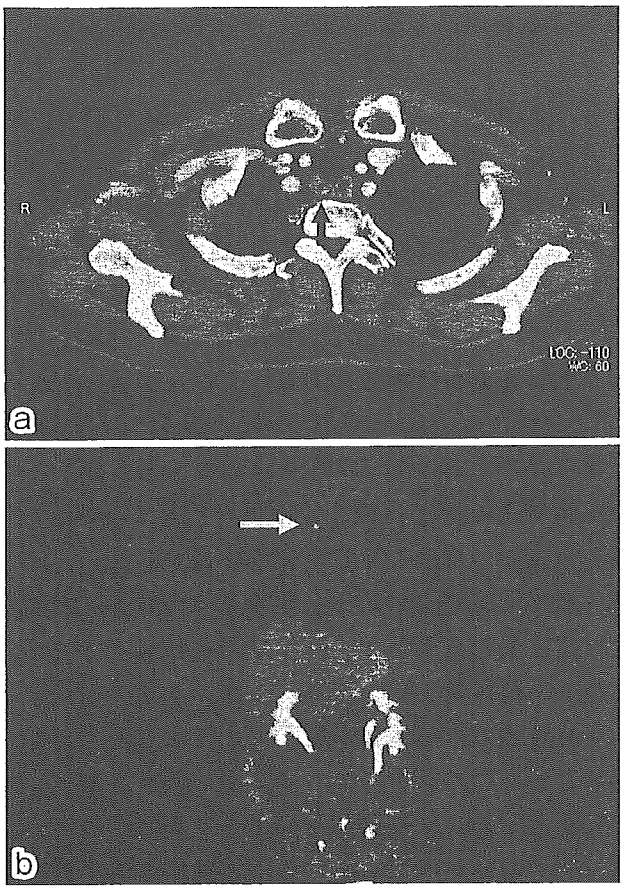
現病歴：H14年5月頃より嗄声出現．前医で頸部食道癌を指摘され（cT4N1M0），CRTを施行（放射線治療：58Gy，CDDP 200mg，5FU 5,000 mg）．その後PRと診断．10月30日追加治療目的で当院紹介受診．

当科入院時現症：身長163cm，体重51kg．気管切開が前医で施行されている．

上部消化管内視鏡検査：食道入口部直下に潰瘍性病変を認め，腫瘍が残存していると考えられた．

頸胸腹造影CT所見：食道入口部レベルより胸骨上縁1cm頭側まで気管浸潤が疑われた．101Lリンパ節も腫瘍残存が疑われた（Fig. 4）．

Fig. 3　a : Enhanced CT after chemoradiotherapy (CRT) showed the possibility of metastasis to the right recurrent laryngeal nerve lymph node (arrows). b : Positron emission tomography (PET) with fluorodeoxyglucose (FDG) after CRT showed increased FDG uptake of the right recurrent laryngeal nerve lymph node (arrow).



上記所見よりPRと診断し，手術治療を選択した．

手術所見：11月19日咽喉食摘・食道抜去・咽頭胃吻合・永久気管孔造設術施行．

病理所見：原発巣にsquamous carcinoma cell gohstは認められたが，viable cellは認められなかった（Fig. 5）．リンパ節転移も認められずCRと診断された．

術後経過：術後経過はおおむね順調で，12月19日（30POD）に軽快退院した．1月31日の経過観察のCTで多発肺転移を指摘された．術前のCTを振り返って診断しても，肺転移は指摘できなかった．3月6日Nedaplatin＋Vindesinを用いた化学療法を施行．以後は前医で，化学療法施行中

Fig. 4　Enhanced CT before the operation showed cervical esophageal carcinoma with suspected invasion to the trachea (arrow) and metastasis to the right cervical paraesophageal lymph node (arrow head).

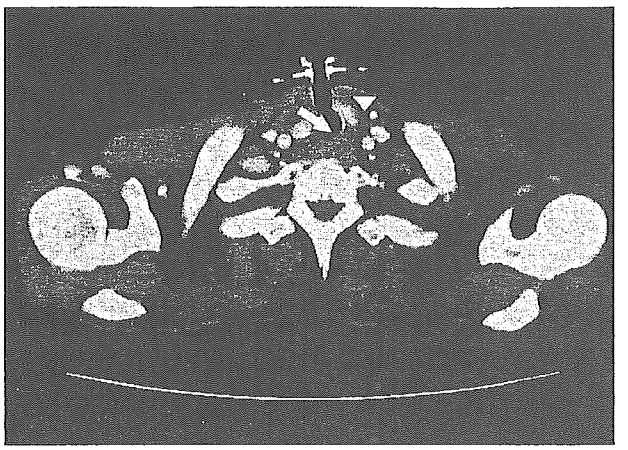
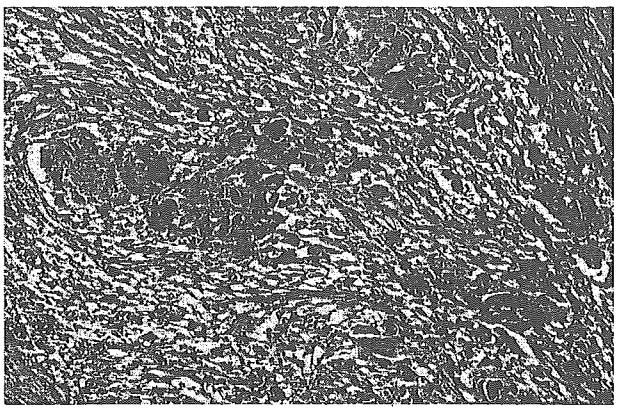


Fig. 5　Microscopic findings revealed squamous cell carcinoma of the cervical esophagus with no viable cells. Therapeutic effect : grade 3. (HE staining, 40×)



である．

考　察

放射線化学療法は切除不可能な症例ばかりでなく，切除可能な症例にも適応拡大され，手術治療に匹敵する成績が報告されてきている[1)~3)]．現段階においては，切除可能症例は手術治療が標準的治療と言えるが，根治目的放射線化学療法も治療選択肢の1つとして位置付けられてきている[1)~3)]．しかし，CRTの症例が増えることにより，根治に至らなかった症例の2nd lineの治療が問題になってきている．2nd lineの化学療法も行われているが，