TREATMENT OUTCOMES OF CHEMORADIOTHERAPY FOR PATIENTS WITH STAGE IVA THORACIC ESOPHAGEAL CANCER AT OUR CENTER

Akira Anbai[1], Makoto Koga[1], Satoru Motoyama[2], Yusuke Sato[2], Mario Jin[3], Tamotsu Matsuhashi[3], Hiroyuki Shibata[4], Kazunori Ohtsuka[4] and Manabu Hashimoto[1]

(received 4 June 2012, accepted 30 July 2012)

[1]*Department of Radiology and Radiation Oncology, Akita University Graduate School of Medicine, Akita 010–8543, Japan*
[2]*Department of Esophageal Surgery, Akita University Graduate School of Medicine, Akita 010–8543, Japan*
[3]*Department of Gastroenterology, Akita University Graduate School of Medicine, Akita 010–8543, Japan*
[4]*Department of Clinical Oncology, Akita University Graduate School of Medicine, Akita 010–8543, Japan*

Abstract
We evaluated the treatment outcomes of chemoradiotherapy for patients with unresectable advanced thoracic esophageal cancer. In total, 103 patients (99 men and 4 women) with unresectable cancer (stage IVA) were treated with chemoradiotherapy between April 2003 and December 2009. They ranged in age from 48 to 89 years, with a median age of 68 years. Two courses of chemotherapy (cisplatin [CDDP] 40 mg/m^2 on Days 1 and 8 plus 5-fluorouracil [5-FU] 400 mg/m^2 on Days 1 through 5 and on Days 8 through 12) and radiotherapy at doses of 59.4 to 66 Gy were administered. The mean follow-up period was 15.3 months (range, 2–88 months). The median overall survival was 13.9 months. The 2-year survival rate was 33.1% and the 3-year survival rate 17.0%. Complete response (CR) was obtained in 18 patients (17.5%). Nine of the 18 patients with CR developed recurrence. Severe hematological toxicities occurred, but were tolerable.

Key words : esophageal cancer, chemoradiotherapy

Introduction

Despite recent progress in combined-modality therapy for cancer, esophageal cancer still carries a poor prognosis. Surgical treatment may be a good option, but radical resection is difficult in patients with progressive disease, characterized by cancer involving the surrounding organs and/or multiple lymph node metastases. Consequently, radiotherapy is generally chosen for such patients.

Correspondence : Akira Anbai, M.D., PhD.
Department of Radiology and Radiation Oncology, Akita University Graduate School of Medicine, Akita 010–8543, Japan
Tel : 81–18–884–6179
Fax : 81–18–836–2623
E-mail : anbai@ doc.med.akita-u.ac.jp

Concurrent chemoradiotherapy has been reported to significantly increase the survival rate of patients with unresectable advanced esophageal cancer as compared with radiation alone[1]. In Japan, conventional radiotherapy has been replaced by chemoradiotherapy. We started administering combined-modality therapy for advanced esophageal cancer in April 2003. However, the total radiation dose, the radiation field, and the regimen of concomitant chemotherapy have not yet been established due to the lack of consensus on these issues. Herein, we describe the treatment outcomes of chemoradiotherapy for patients with unresectable advanced thoracic esophageal cancer.

Patients and Methods

Patients

Two hundred and thirty-one patients with newly diagnosed esophageal cancer were treated with radiotherapy at Akita University Hospital between April 2003 and December 2009. Of these 231 patients, 103 who had a diagnosis of unresectable advanced thoracic esophageal cancer and received definitive chemoradiation as the primary treatment were enrolled in this study. Patients who had cervical esophageal cancer, small cell cancer, or distant metastasis to other organs were excluded.

Table 1. Patient characteristics

Characteristic	No. of patients (N=103)	(%)
Age (years)		
Median	68	
Range	48-89	
Sex		
Male	99	96.1
Female	4	3.9
Location of primary tumor		
Upper thoracic (Ut)	23	22.3
Midthoracic (Mt)	64	62.1
Lower thoracic (Lt)	16	15.6
Primary tumor length		
<5 cm	22	21.4
≥5 cm	81	78.6
T factor		
T2	6	5.8
T3	28	27.2
T4	69	70.0
N factor		
N0	0	
N1	17	16.5
N2	26	25.2
N3	12	11.7
N4	48	46.6
Clinical Stage		
IVA	103	

Patient characteristics are shown in Table 1. These patients consisted of 99 men and 4 women whose ages ranged from 48 to 89 years with a median age of 68 years. The primary tumor site was the upper thoracic region (Ut) in 23 patients, middle thoracic region (Mt) in 64, and lower thoracic region (Lt) in 16. Histopathological examination showed adenocarcinoma in one patient and squamous cell carcinoma in the other 102 patients. Clinical staging was performed according to the Japanese Classification of Esophageal Cancer, 10th edition[2].

According to the clinical T-factor, 6 patients had T2, 28 had T3, and 69 had T4. Regional lymph node metastases were observed in all patients. There were 17 patients with N1, 26 with N2, 12 with N3, and 48 with N4. All patients were in stage IVA according to the clinical staging criteria.

Pretreatment evaluation

We discussed our treatment strategy for patients with newly diagnosed esophageal cancer with gastroenterologists, esophageal surgeons, medical oncologists, and radiation oncologists working at our hospital. Before treatment, patients were interviewed to obtain detailed clinical histories, and patients underwent physical, peripheral hematological, and biochemical examinations. Upper gastrointestinal endoscopy was performed in all cases and tumor biopsy specimens were obtained. Clinical stage was determined on the basis of the results obtained by chest X-ray, esophagography, computed tomography (CT), positron emission tomography, magnetic resonance imaging, and radioisotope scintigraphy.

Chemotherapy

Cisplatin (CDDP) and 5-fluorouracil (5-FU) were used for chemotherapy. CDDP (40 mg/m^2/day) was administered on Days 1 and 8 by intravenous infusion over a period of 2 hours or more. 5-FU (400 mg/m^2/day) was administered on Days 1 through 5 and again on Days 8 through 12 by continuous infusion. Patients were given intravenous hydration before and after CDDP administra-

tion. Granisetron hydrochloride and dexamethasone were used as antiemetics. This schedule was started concomitantly with radiotherapy and repeated every fifth week for two cycles.

When grade 3 leukopenia/thrombocytopenia developed, the second course of chemotherapy was delayed until recovery to grade 2 or lower. When grade 4 cytopenia or physical symptoms such as esophagitis occurred, the anticancer drug doses were reduced by 20% to 30%. Patients who had a prolonged bone marrow disorder received a blood transfusion or granulocyte-colony stimulating factor. If they did not recover adequately, the second course of chemotherapy was cancelled.

Maintenance chemotherapy after completion of radiotherapy was performed for patients who were deemed able to receive anticancer drugs. CDDP (80 mg/m^2/day) was administered on Days 1 and 5-FU (800 mg/m^2/day) on Days 1 through 5, starting 4 weeks after the completion of radiation. This treatment was repeated every fourth week for two cycles.

Radiotherapy

High-energy X-rays (6 MV or 10 MV) were used for radiotherapy. All patients underwent three-dimensional radiotherapy planning. After the CT for radiotherapy planning, the data were transferred to the radiation treatment planning system, and then gross tumor volume (GTV), clinical target volume (CTV), and planning target volume (PTV) were determined. The GTV included any lymph node judged to be positive for metastasis, based on the primary tumor, physical examination, and imaging examinations. Upon setting a 1 cm margin around the GTV, the CTV was defined as the prophylactic radiation field including the regional lymph nodes for each patient. The PTV was defined as the CTV plus a 0.5 to 1 cm margin. The dose reference point was at the isocenter.

Anterior-posterior opposing portal irradiation was initiated at approximately 40 Gy and oblique portal irradiation was then performed to spare the spinal cord from the radiation field. All patients received conventional fractionated radiation of 1.8 to 2.0 Gy per fraction, to a total dose of 59.4 Gy to 66 Gy, five times a week over 6 to 9 weeks.

Between 2003 and 2005, i.e., in the early cases, the radiation dose was approximately 30 Gy and the resting time period was 10 to 14 days. After 2004, the irradiation time period was not limited and irradiation was continued, unless cytopenia of grade 3 or higher (based on leukocyte count, hemoglobin value, and platelet count), lung disorder, or esophagitis symptoms occurred. In patients who had discontinued this treatment, irradiation was restarted as soon as the toxicity grade decreased to 2 or lower.

Response evaluation

Therapeutic effects were evaluated by CT, esophageal barium contrast examination, and endoscopy. Response evaluation criteria were based on those of the World Health Organization[3]. Response evaluation criteria were defined as follows. Complete response (CR) : disappearance of measurable lesions and no appearance of new lesions, lasting 4 weeks or more. Partial response (PR) : 50% or more decrease in measurable lesions and no appearance of new lesions or progression of any lesion, lasting 4 weeks or more. No change (NC) : less than 50% decrease in measurable lesions and no appearance of new lesions or progression of any tumor, lasting 4 weeks or more. Progressive disease (PD) : 25% or more increase in measurable lesions or appearance of new lesions.

The National Cancer Institute Common Terminology Criteria for Adverse Events v. 4.0 was used to evaluate observed toxicity.

Statistical analysis

The survival time was calculated from the date of treatment initiation to that of death from any causes or to the last date of confirmation of survival. We estimated survival curves using the Kaplan-Meier method.

Results

Compliance

A total of 84 patients (81.6%) completed the planned radiation therapy and two courses of chemotherapy. Fourteen patients (13.6%) discontinued the second course of chemotherapy due to prolonged grade 3 cytope-

nia or digestive symptoms after completing the first course and only received the planned radiation therapy. Ninety-eight patients (95.1%) completed the planned radiation therapy.

Three patients discontinued treatment due to the complication of esophagobronchial fistula, which developed during radiation therapy. One patient discontinued treatment due to the complication of pneumonia. One patient discontinued treatment because of cerebral infarction onset.

Response and Survival

Table 2 shows the therapeutic response in 103 patients who were given chemoradiotherapy. Eighteen patients (17.5%) achieved CR. Seventy-four patients (71.8%) achieved PR. Five patients (4.9%) showed NC. Six patients (5.8%) had PD. The response rate was 93.9%.

Table 2. Response results

CR	PR	NC	PD	Response rate
18 (17.5%)	74 (71.8%)	5 (4.9%)	6 (5.8%)	89.3%

Abbreviations : CR=complete response ; PR=partial response ; NC=no change ; PD=progressive disease.

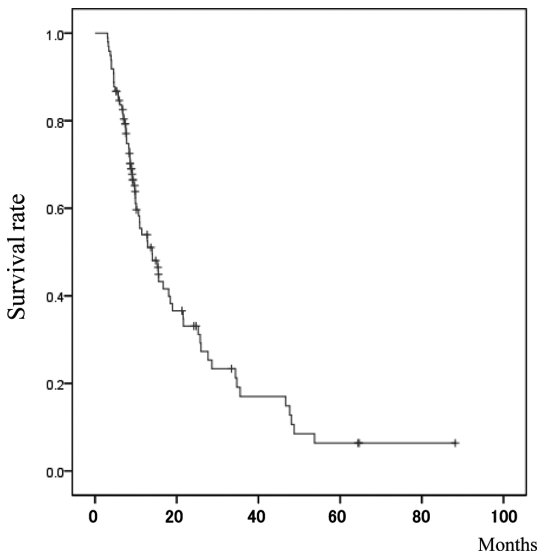

Fig 1. Overall survival curve among all patients (n=103).
The 2-year and 3-year overall survival rates were 33.1% and 17.0%.

The mean follow-up period was 15.3 months (median, 9 months ; range, 2-88 months). Median overall survival time was 13.9 months (95% confidence interval [CI], 9.2-19.4 months). The 2-year survival rate was 33.1% (95% CI, 21.9%-44.3%). The 3-year survival rate was 17.0% (95% CI, 7.2%-26.8%) (Fig. 1).

Of the 18 patients with CR, recurrence was found in 9 during follow-up. Six patients had a local recurrence. One patient had local recurrence and distant metastasis concurrently. One patient had a cervical lymph node recurrence within the irradiated field. One patient had a distant metastasis. Three patients underwent salvage operations (for local recurrence in 2 and for cervical lymph node metastasis in 1) and remain alive to date. Four patients received chemotherapy, but died of disease progression.

Toxicity

Table 3 shows the incidences of acute toxicities associated with chemoradiotherapy. Grade 3 leukopenia was observed in 37 patients (35.9%). Grade 3 neutropenia occurred in 14 patients (13.6%). Seven patients (6.8%) developed grade 3 or higher severe thrombocytopenia. Grade 4 thrombocytopenia was observed in one patient. Grade 3 or higher severe esophageal disorders occurred in 19 patients (18.4%). Grade 3 or higher severe esophageal ulcer and fistula formation were observed in 8 patients (7.8%). In addition, grade 3 or higher severe lung disorders were found in 6 patients (5.8%), pericardial effusion in 10 (9.7%), pleural effusion in 10 (9.7%), and hyponatremia in 7 (6.8%). Toxicities such as esophageal fistula, radiation pneumonitis, pleural effusion, and pericardial effusion may have contributed to the deaths of 6 patients (5.8%).

Discussion

Esophageal cancer is a disease with a poor prognosis, and surgical resection has long been the first choice for curative treatment. Radiation therapy is often performed in patients with unresectable cancer or patients in whom surgery is considered difficult because of older

Table 3. Summary of toxicity

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	≥Grade 3 (%)
White blood cell decreased	8	51	37	0	0	35.9
Neutrophil count decreased	21	26	14	0	0	13.6
Anemia	35	45	13	0	0	12.6
Platelet count decreased	36	25	6	1	0	6.8
Esophagitis	32	45	19	0	0	18.4
Esophageal ulcer, Esophageal fistula	4	2	1	4	3	7.8
Nausea, Vomiting	12	44	11	0	0	10.7
Mucositis oral	11	5	6	0	0	5.8
Diarrhea, Enterocolitis	4	3	0	0	0	0
Dyspnea, Pneumonitis	3	15	2	3	1	5.8
Pleural effusion	15	3	5	4	1	9.7
Pericardial effusion	11	—	7	2	1	9.7
Radiation dermatitis	20	16	0	0	0	0
Hyponatremia	19	—	7	0	0	6.8
Creatinine increased	19	8	0	0	0	0
Myelitis	0	0	0	0	0	0

age or comorbidities and the 5-year survival rate after conventional fractionated radiation at doses of 60 to 69 Gy has been reported to be approximately 10%[4].

However, since 1990, the efficacy of chemoradiotherapy has been well documented. It was reported in western countries that chemoradiotherapy with CDDP/5-FU and a total of 50 Gy radiation was more effective than a total of 60 Gy radiation alone in patients with esophageal cancer of T1-3 N0-1 M0[1,5].

In Japan, the results of chemoradiotherapy for patients with unresectable esophageal cancer of stage T4 N4 or with recurrent esophageal cancer have been reported by Ishida[6] and Ohtsu[7]. These studies (in which the cancer was treated with 60 Gy and CDDP/5-FU) showed CR rates of 8.9% and 33%, respectively, and a 2-year survival rate of 13.3% and a 3-year survival rate of 23%. The phase II clinical study JCOG9516[8], conducted by the Japan Clinical Oncology Group (JCOG), obtained a CR rate of 15% and a 2-year survival rate of 31.5%. Chemoradiotherapy has been clearly shown to improve cure rates compared with radiation alone and the guidelines of the Japan Esophageal Society recommend chemoradiotherapy for unresectable advanced esophageal cancer[9].

In our institution, a joint conference consisting of four departments (Surgery, Gastroenterology, Medical Oncology, and Radiology) was held. During this conference, we focused particularly on the usefulness of chemoradiotherapy and we began to actively perform chemoradiotherapy with concomitant administration of CDDP and 5-FU for unresectable advanced esophageal cancer in 2003.

In our hospital, chemoradiotherapy basically aims to achieve a radical cure of cancer in patients without distant metastasis. For this purpose, we believe the radiation doses delivered to the GTV and the CTV should be as high as possible; the optimal standard therapy is to irradiate with a 1.8 Gy dose per fraction 34 times, to achieve a total dose of 61.2 Gy.

The irradiated PTV includes the primary tumor, metastatic lymph nodes, and a prophylactically irradiated lymph node area. Anterior-posterior opposing portal irradiation was applied to the PTV with doses up to approximately 40 Gy. Oblique portal irradiation was performed to avoid radiation-induced spinal cord damage. Even under these circumstances, the radiation field was planned so as to include the prophylactic lymph node area whenever possible.

We obtained a CR rate of 17.5% and a 3-year survival rate of 17% (95% CI, 7.2%-26.8%). Regarding the general therapeutic results for patients with T4 or N4, the

Table 4. Comparison of treatment outcomes

Author (ref.)	Total Patients	CR rate (%)	3-year survival rate (%)
Ohtsu *et al.*[7]*	54	33	23
JCOG9516 (8)†	60	15	31.5 (2-years)
Nishimura *et al.*[10]‡	246	Not stated	21 (10-36)
Present series	103	17.5	17

Abbreviations : *CDDP 40 mg/m^2 Days 1, 8, 36, 43, 5-FU 400 mg/m^2/day Days 1-5, 8-12, 36-40, 43-47, Radiotherapy 60 Gy/30 fraction. †CDDP 70 mg/m^2 Days1, 29, 5-FU 700 mg/m^2/day Days 1-4, Days 29-32, Radiotherapy 60 Gy/30 fraction. ‡Retrospective, multicentric study.

3-year survival rates reportedly ranged from 10% to 36%[7,8,10]. Our results thus appear to be acceptable, considering that we even treat patients with local tumors showing marked progression (Table 4).

With respect to radiation methods and chemotherapy regimens for esophageal cancer, in western countries, the standard consists of radiation with a total dose of 50.4 Gy plus four courses of CDDP/5-FU chemotherapy, based on the INT 0123 (Radiation Therapy Oncology Group [RTOG] 94-05) Phase III trial[11]. However, in Japan, many institutions administer radiation therapy with doses of 60 Gy or higher and two or more courses of CDDP/5-FU chemotherapy[12].

It is well known that esophageal cancer is associated with widespread lymph node metastasis[13]. In some cases, esophageal cancer also spreads over three regions (the neck, chest, and abdomen) regardless of the size of the primary tumor[14]. In such cases, it is essential to carefully determine the radiation field and dose, although PTV determination varies among institutions.

In the RTOG 94-05 study[11], the radiation field did not cover all prophylactic lymph node areas as it does in Japan. The RTOG 94-05 report stated that there were more treatment-related deaths in the high-dose (64.8 Gy) group than in the standard-dose group, but 7 of the 11 deaths occurred in patients who had received 50.4 Gy or less radiation.

The RTOG 0113 study[15] was conducted to determine whether chemotherapy improves the survival rate; it showed that even high-intensity chemotherapy was not associated with survival rate improvement. Therefore, the dose of 50.4 Gy is not necessarily appropriate for all patients.

We speculated that radiation therapy would be more useful for local control and thus have endeavored to include the primary tumor and all lymph node metastases in the PTV. In patients with advanced esophageal cancer, the primary tumor often spreads from one region to another, such as from the Ut to the Mt or from the Mt to the Lt, or shows metastasis from the neck to abdominal lymph nodes. Consequently, in patients with widespread lesions, our radiation field may extend to the neck, from the upper mediastinum to the lower esophagus, or to the abdomen, thus tending to be rather large.

The incidence of symptoms of acute hematological toxicities or esophagitis tends to correlate with the size of the radiation field. In this study, acute toxicities occurred in the following incidences: grade 3 or higher severe leukopenia, 35.9%; thrombocytopenia, 6.8%; and esophagitis, 18.4%. The incidence of acute toxicities was almost the same as that reported by Toita[16] except for a rather high incidence of esophagitis. All symptoms could be controlled by symptomatic therapy.

It is known that many cases of advanced esophageal cancer develop recurrence after chemoradiotherapy, even if CR is achieved. Half of the cases in this study developed recurrences. If tumor cells remain localized at the site of origin, a salvage operation can be performed. However, some patients had lymph node metastases or distant metastases, resulting in a poor outcome.

To improve patient prognosis, new chemotherapy regimens and radiotherapy techniques have been reported. For example in chemoradiotherapy, Higuchi reported using docetaxel combined with CDDP and 5-FU chemotherapy and concurrent radiotherapy[17]. Li reported chemoradiation in combination with erlo-

tinib[18]. These chemoradiotherapy methods are not yet generally accepted, but suggest a novel approach.

Recently, a new radiation therapy method called intensity-modulated radiation therapy (IMRT) was attempted for the treatment of esophageal cancer in some cases[19]. Dose conformality and sparing of healthy tissues can be improved further by using IMRT, so if this radiation therapy were to be developed for the treatment of esophageal cancer, accelerated dose escalation would be possible and it would be useful for tumor control.

In summary, 103 patients with advanced thoracic esophageal cancer were treated with chemoradiotherapy in our institute. The median overall survival was 13.9 months. The 3-year survival rate was 17.0%. Our treatment outcomes were at the same level as past reports and the toxic appearances were about the same. Thus, chemoradiotherapy seemed to be a useful method for treating advanced esophageal cancer.

References

1) Cooper, J.S., Guo, D.G., Herskovic, A., *et al.* (1999) Chemoradiotherapy of locally advanced esophageal cancer : long-term follow-up of a prospective randomized trial (RTOG 85-01). *JAMA,* **281**, 1623-1627.
2) The Japan Esophageal Society. (2008) *Japanese Classification of Esophageal Cancer, 10th edition, revised version*. Kanehara Shuppan, Tokyo, pp. 7-27.
3) Miller, A.B., Hoogstraten, B., Staquet, M. and Winkler, A. (1981) Reporting results of cancer treatment. *Cancer,* **47**, 207-214.
4) Sun, D.R. (1989) Ten-year follow-up of esophageal cancer treated by radical radiation therapy : analysis of 869 patients. *Int. J. Radiat. Oncol. Biol. Phys.,* **16**, 329-334.
5) Herskovic, A., Martz, K., Al-Sarraf, M., Leichman, L., Brindle, J., Vaitkevicius, V., Cooper, J., Byhardt, R., Davis L. and Emami, B. (1992) Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus. *N. Engl. J. Med.,* **326**, 1593-1598.
6) Ishida, K., Iizuka, T., Ando, N. and Ide, H. (1996) Phase II study of chemoradiotherapy for advanced squamous cell carcinoma of the thoracic esophagus : nine Japanese institutions trial. *Jpn. J. Clin. Oncol.,* **26**, 310-315.
7) Ohtsu, A., Boku, N., Muro, K., *et al.* (1999) Definitive chemoradiotherapy for T4 and/or M1 lymph node squamous cell carcinoma of the esophagus. *J. Clin. Oncol.,* **17**, 2915-2921.
8) Ishida, K., Ando, N., Yamamoto, S., Ide, H. and Shinoda, M. (2004) Phase II study of cisplatin and 5-fluorouracil with concurrent radiotherapy in advanced squamous cell carcinoma of the esophagus : a Japan Esophageal Oncology Group (JEOG)/Japan Clinical Oncology Group trial (JCOG9516). *Jpn. J. Clin. Oncol.,* **34**, 615-619.
9) Japanese Society for Esophageal Diseases. (2007) *Guide Lines for the Esophageal Cancer Diagnosis and Treatment*. Kanehara Shuppan, Tokyo, pp. 51-65.
10) Nishimura, Y., Koike, R., Ogawa, K., Sasamoto, R., Murakami, Y., Ito, Y., Negoro, Y., Itasaka, S., Sakayauchi, T. and Tamamoto, T. (2012) Clinical practice and outcome of radiotherapy for esophageal cancer between 1999 and 2003 : the Japanese Radiation Oncology Study Group (JROSG) Survey. *Int. J. Clin. Oncol.,* **17**, 48-54.
11) Minsky, B.D., Pajak, T.F., Ginsberg, R.J., Pisansky, T.M., Martenson, J., Komaki, R., Okawara, G., Rosenthal, S.A. and Kelsen, D.P. (2002) INT 0123 (Radiation Therapy Oncology Group 94-05) phase III trial of combined-modality therapy for esophageal cancer : high-dose versus standard-dose radiation therapy. *J. Clin. Oncol.,* **20**, 1167-1174.
12) Kenjo, M., Uno, T., Murakami, Y., Nagata, Y., Oguchi, M., Saito, S., Numasaki, H., Teshima, T. and Mitsumori, M. (2009) Radiation therapy for esophageal cancer in Japan : results of the Patterns of Care Study 1999-2001. *Int. J. Radiat. Oncol. Biol. Phys.,* **75**, 357-363.
13) Akiyama, H., Tsurumaru, M., Udagawa, H. and Kajiyama, Y. (1994) Radical lymph node dissection for cancer of the thoracic esophagus. *Ann. Surg.,* **220**, 364-373.
14) Nishimaki, T., Tanaka, O., Suzuki, T., Aizawa, K., Hatakeyama, K. and Muto, T. (1994) Patterns of lymphatic spread in thoracic esophageal cancer. *Cancer,* **74**, 4-11.

15) Ajani, J.A., Winter, K., Komaki, R., Kelsen, D.P., Minsky, B.D., Liao, Z., Bradley, J., Fromm, M., Hornback, D. and Willett, C.G. (2008) Phase II randomized trial of two nonoperative regimens of induction chemotherapy followed by chemoradiation in patients with localized carcinoma of the esophagus : RTOG 0113. *J. Clin. Oncol.,* **26**, 4551–4556.

16) Toita, T., Ogawa, K., Adachi, G., Kakinohana, Y., Nishikuramori, Y., Iraha, S., Utsunomiya, T. and Murayama, S. (2001) Concurrent chemoradiotherapy for squamous cell carcinoma of thoracic esophagus : feasibility and outcome of large regional field and high-dose external beam boost irradiation. *Jpn. J. Clin. Oncol.,* **31**, 375–381.

17) Higuchi, K., Koizumi, W., Tanabe, S., Sasaki, T., Katada, C., Ishiyama, H. and Hayakawa, K. (2008) A phase I trial of definitive chemoradiotherapy with docetaxel, cisplatin, and 5-fluorouracil (DCF-R) for advanced esophageal carcinoma : Kitasato digestive disease and oncology group trial (KDOG 0501). *Radiother. Oncol.*, **87**, 398–404.

18) Li, G., Hu, W., Wang, J., Deng, X., Zhang, P., Zhang, X., Xie, C. and Wu, S. (2010) Phase II study of concurrent chemoradiation in combination with erlotinib for locally advanced esophageal carcinoma. *Int. J. Radiat. Oncol. Biol. Phys.*, **78**, 1407–1412.

19) Nishimura, Y. and Koike, R. (2011) IMRT for esophageal neoplasms. *Gan to Kagaku Ryoho*, **38**, 1421–1423.